NCT03098836

Prospective study of **A**palutamide and Abiraterone Acetate i**N** Chemo**TH**erapy-Naïve m**E**n with mCRPC Stratified by **R**ace (PANTHER)

DUKE CANCER INSTITUTE

A National Cancer Institute-designated Comprehensive Cancer Center

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Principal Investigator
Daniel George, MD
[redacted]

Sub-Investigators
Andrew Armstrong, MD
Michael Harrison, MD

Statistician
Susan Halabi, PhD
[redacted]

Correlative Science Investigators
Andrew Nixon, PhD (Duke University)
Jennifer Freedman, PhD (Duke University)
Nima Sharifi, MD (Cleveland Clinic)
Rick Kittles, PhD (City of Hope)
Elahe Mostaghel, MD, PhD (Fred Hutch Cancer Center and University of Washington)
Robert Montgomery, MD (Fred Hutch Cancer Center and University of Washington)
Massimo Loda, MD (Weill Cornell Medicine)
Sara Bleve, MD (Weill Cornell Medicine)
David Nanus, MD (Weill Cornell Medicine)

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Responsible Study Personnel

Principal Investigator	Daniel George, MD [redacted]
Regulatory Coordinator	Steven Gray, PhD, RAC [redacted]

Duke Cancer Network (DCN) Participating Sites

Clinical Sites

Site PI : Dr. Daniel George, MD

Lumberton: Southeastern Regional Medical Center / Gibson Cancer Center

Laurinburg: Scotland Health Care System

Smithfield: Johnston Memorial Hospital Authority:
Johnston Cancer Center, Smithfield, NC
Johnston Hem/Onc of Clayton, NC

Research Affiliates

Virginia Oncology Associates
Site Lead Inv: Dr Mark Fleming, MD
[redacted]

Spartanburg Regional
Gibbs Cancer Center & Research Institute
Site Lead Inv: Michael Humeniuk, MD
[redacted]

External Sites Participating in This Study

Barbara Ann Karmanos Cancer Institute
Site PI: Elizabeth Heath, MD
[redacted]

Tulane University
Site PI: Brian Lewis, MD
[redacted]

University of North Carolina at Chapel Hill
Site PI: Young Whang, MD
[redacted]

Chesapeake Urology
Site PI: Ronald Tutrone
[redacted]

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LIST OF ABBREVIATIONS

ADT	Androgen Deprivation Therapy
AE	Adverse Event
AKT	See PKB (protein Kinase B)
ALT	Alanine aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate aminotransferase
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
cfDNA	Cell-free DNA
CK	Creatine Kinase
CR	Complete Response
CRF	Case report forms
CRPC	Castration resistant prostate cancer
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
ECHO	Echocardiogram
FFPE	Formalin-fixed, paraffin-embedded
GCP	Good Clinical Practice
GWAS	Genome Wide Association Study
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
mCRPC	Metastatic castration-resistant prostate cancer
MRI	Magnetic Resonance Imaging
PC	Prostate cancer
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression free survival
PIN	Prostatic intraepithelial neoplasia
PK	Pharmacokinetic
PKB	Protein Kinase B (or AKT)
PR	Partial response
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
QTc	QT interval (corrected)
RBC	Red Blood Cells
REB	Research Ethics Board
RECIST	Response Evaluation in Solid Tumors
SAE	Serious adverse event
SD	Stable disease
SNP	Single Nucleotide Polymorphism
TTP	Time to Progression
ULN	Upper Limit of Normal
WBC	White Blood Count

1. SYNOPSIS

Study Title: Prospective study of Apalutamide and Abiraterone Acetate iN ChemoTHerapy-Naïve mEn with mCRPC Stratified by Race					
Protocol Number	Pro00075097	**Phase**	II	**Type**	Interventional
Condition/Disease: Castration resistant metastatic prostate cancer, chemo-naïve					
Number of Evaluable Subjects	100	**Duration of Subject Participation**			Up to 24 months on study drug
Number of Study Centers	6 total	**Duration of Study 3 years (exclusive of survival follow-up)**			Anticipated 20 months accrual time, up to 24 month follow up

Rationale: African American men have a 60% greater incidence of being diagnosed with prostate cancer and nearly a 2.5 fold greater chance of mortality from the disease, yet the underlying cause for this increased mortality remains controversial [1]. Hormonal levels vary in men by race, with African American men having higher dihydrotestosterone (DHT), androstenedione (ASD) and sex hormone-binding globulin (SHBG) than Caucasian men with localized prostate cancer [2, 3]. Historically, African American men with prostate cancer have a worse overall survival than Caucasian men, however, this is confounded by the timing of androgen deprivation therapy (ADT) and access to other therapies [4, 5]. To what extent race affects response to therapy in prostate cancer is not clear.

Germline polymorphisms of genes involved in androgen signaling have been shown to vary significantly by race and may have important implications with regard to response to therapy targeted towards this pathway. Polymorphisms within the promoter region of the androgen receptor (AR) (specifically CAG repeats) have been well documented and vary significantly according to race, with African American men having significantly shorter CAG repeats resulting in greater AR activity [6]. These CAG repeats have been associated with more aggressive disease characteristics [6]. Recently, germline polymorphisms in androgen metabolism genes have been shown to have prognostic value in regards to the time to development of castration-resistant prostate cancer (CRPC) in men with prostate cancer on ADT. Ross et al tested 129 polymorphisms across 20 genes associated with androgen metabolism and identified three polymorphisms in separate genes (*CYP19A1*, *HSD3B1*, and *HSD17B4*) that were significantly associated with prolonged time to progression (TTP) on ADT [7]. Specifically, individuals carrying more than one of the polymorphisms were associated with *improved* time to CRPC than individuals carrying zero or one ($P < .0001$). More recently this group identified polymorphisms in two androgen transporter genes, *SLCO2B1* and *SLCO1B3* that were associated with a significantly *shorter* time to CRPC alone and in combination [8]. Incidences of these polymorphisms ranged from 15 to 81%; unfortunately, the cohort of patients used to identify these polymorphisms had limited numbers of African American patients or other racial and ethnic groups.

Recent studies by our laboratory and others have focused on discovering molecular mechanisms underlying prostate cancer disparities using microarrays and bioinformatics. These studies have compared the gene expression profiles between African American and Caucasian American cancers and between prostate cancer and patient-matched normal prostate from African Americans and Caucasian Americans. By integrating gene expression profiling and pathway analyses, multiple components within the androgen receptor signaling pathway were revealed to be up-regulated in African American prostate cancer specimens along with the up-regulation of genes within other signaling pathways that converge on androgen receptor signaling, portending that androgen receptor pathway activation is a key component of prostate cancer health disparities. Overall the comparison of African American and Caucasian American prostate cancer specimens has led to the identification of a number of differentially expressed genes, including CYP19A1, AMFR, CXCR4, MMP9, SRD5A2, ADIPOQ, AKT1, ALOX12, ALOX15, ALOX15B, BMP2, CGA, ERG, FASN, IL1B, IL6, IL8, NFKB1, PIK3C3, PIK3CA, PI3K3R1, PLA2G2A, TGFB1, TIMP3, TNF, P38MAPK, STAT1, RHOA, ITGB5, MAPKAPK2, CSNK2A1, PIK3CB, ARA55, GNA01, GNB3, POLR2L, PRKCE, PRKD1, TBP, CALR, GNG2, GNG11, GNG12, CALM1, NFKB2, STAT2, RHOU, FGF13, EIF3B, and GIT1

[9-12]. Thus, germline polymorphisms of these differentially expressed genes also may have important implications with regard to response to therapy targeted towards the androgen signaling pathway. In addition, our laboratory has identified a number of novel alternatively spliced genes in African American versus Caucasian prostate cancer and have shown that African American variants track with more aggressive cancer invasion characteristics of prostate cancer in African American men (Bi-Dar Wang, Jennifer A. Freedman, Daniel J. George, Norman H. Lee and Steven R. Patierno, manuscript in preparation). Moreover, we have identified novel single nucleotide polymorphisms located in splicing regulatory regions of such genes that associate with prostate cancer risk, aggressiveness and survival (Jennifer A. Freedman, Yanru Wang, Hongliang Liu, Patricia G. Moorman, Terry Hyslop, Daniel J. George, Norman H. Lee, Qingyi Wei and Steven R. Patierno, manuscript in preparation). Subsets of these genes are androgen receptor targets. Therefore, germline polymorphisms of these alternatively spliced genes also may have important implications with regard to response to therapy towards the androgen signaling pathway.

To what extent racial differences affect response and time to progression on secondary hormonal therapies in the CRPC setting are unknown. A retrospective analysis of the COU-AA-302 study included only 28 black patients but demonstrated trends in favor of median rPFS and 90% decline from baseline PSA in this subpopulation vs the entire population [79]. Similarly, a retrospective case-controlled analysis of patients treated at Duke University with abiraterone prednisone pre or post docetaxel chemotherapy revealed statistically significant improved PSA response rate in African American vs Caucasian patients by 30% decline (77.8% vs 54.4%; p=0.008) and 50% decline (68.9% vs 48.9%; p=0.028) with trends in favor of 90% PSA decline (37.8%, vs. 28.9%) [80]. In addition, primary abiraterone-refractory disease (PSA increase as best response) trended to be more in Caucasian than in African American patients (31.1% vs 15.6%; p=0.052). Based upon these findings we hypothesized that African American CRPC patients may be more sensitive to abiraterone prednisone than Caucasian patients. We have conducted a prospective Phase II study of abiraterone acetate and prednisone in patients with mCRPC, stratified by self-described race in order to test this hypothesis (Abi Race Clinicaltrials.gov NCT01940276). Secondarily, to what extent differences in systemic hormonal levels as well as androgen transport gene polymorphisms affect response to abiraterone acetate is unknown. Understanding any potential differences in response to therapy by race and/or by hormonal/genetic factors could impact on both our clinical use of abiraterone acetate as well as future clinical trial design. Finally, as other agents targeting the androgen/androgen receptor pathways become available, it will be important to differentiate their activity according to race, genetics and hormonal milieu.

Apalutamide is a competitive AR inhibitor that is fully antagonistic to AR overexpression, lacking significant agonist activity, , or inducing activity for AR nuclear localization or DNA binding [81]. In Phase I testing apalutamide was dosed between 30 mg and 480 mg once daily, resulting at all dose levels and a median 50% decline from baseline PSA at 12 weeks of 47% [82]. The most frequently reported adverse event was grade 1/2 fatigue (47%). A phase II multicenter study evaluated the clinical efficacy of apalutamide at 240 mg daily in non-metastatic (nm) CRPC patients. In 51 evaluable patients 89% had ≥50% PSA decline at 12 weeks. Median time to PSA progression was 24.0 mo (95% confidence interval [CI], 16.3 months - not reached [NR]); median metastasis-free survival was NR (95% CI, 33.4 months - NR). The most common AE was fatigue (any grade, n=31 [61%]) [83]. A Phase III Study of apalutamide versus placebo in men with nmCRPC showed that apalutamide prolonged metastasis-free survival and time to symptomatic progression. [89]

Abiraterone acetate and apalutamide are not FDA approved in combination. The concept of combining apalutamide with abiraterone prednisone derives from their potentially complimentary mechanisms of action in which apalutamide functions as a pure androgen receptor antagonist while abiraterone inhibits cholesterol metabolism into androgen, thus lowering the functional levels of ligand for the receptor. Since most patients who progress on abiraterone do so with a rising PSA we believe the androgen receptor remains a driver of disease progression in patients treated with abiraterone prednisone alone. Together, apalutamide and abiraterone may be able to more completely inhibit the androgen – androgen receptor axis and provide greater clinical benefit. An ongoing Phase III study (ACIS) is evaluating whether the combination of apalutamide, abiraterone acetate and prednisone improves radiographic progression-free survival compared to abiraterone acetate, prednisone and placebo (clinicaltrials.gov NCT02257736). Like the COU-AA-302 study, the ACIS trial is international and not likely to contain a significant proportion of African American patients, leaving

unanswered the question of whether African American patients may have a genetic propensity for response and clinical benefit to this combination.

We propose a Phase II Multisite, prospective study to evaluate radiographic PFS in men with mCRPC stratified by self-described race and treated with apalutamide, abiraterone acetate and prednisone. Secondary endpoints will describe the response to apalutamide, abiraterone acetate and prednisone, PSA kinetics, as well as safety and tolerability. Exploratory endpoints will describe the incidence and associations of key hormone and lipid levels, germline polymorphisms in androgen signaling genes and genes that have been shown to be differentially expressed and/or alternatively spliced in African American versus Caucasian prostate cancer, cell-free plasma DNA profiles, pharmacokinetics of abiraterone acetate and plasma-based biomarkers in both African American and Caucasian cohorts.

Primary Objective: The primary goal is to estimate the radiographic PFS distribution separately in African American and Caucasian men with mCRPC treated with apalutamide, abiraterone acetate and prednisone.

Secondary Objectives:

1) PSA kinetics: to determine the duration of PSA response, time to nadir, and percent of men who achieve a PSA < 0.1

2) Radiographic assessments: to estimate the rate of objective response and incidence of bone flares

3) Safety (NCI CTC v4.0) and tolerability, particularly incidence and grade of hypertension in the two populations

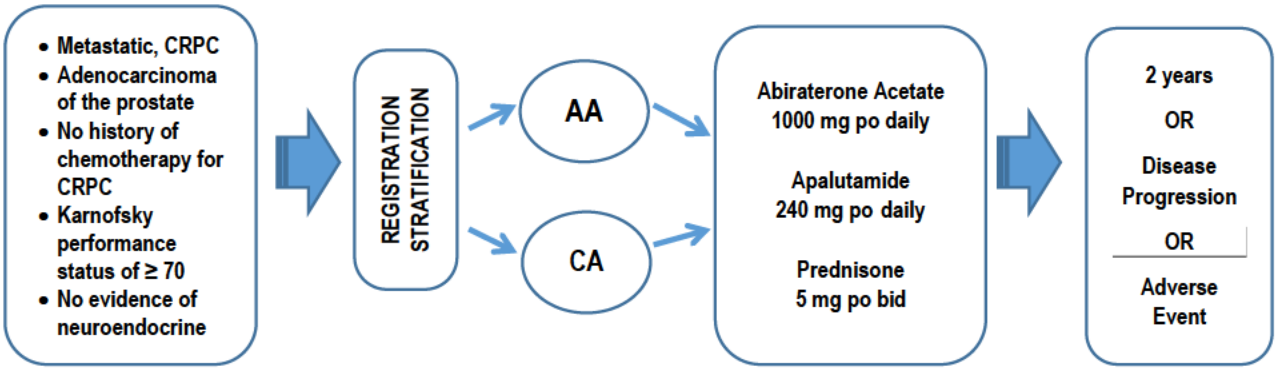
4) Overall survival

Exploratory Objectives:

1. Perform ancestral genotyping to obtain genetically estimated indicators of race using DNA isolated from whole blood at baseline.
2. Describe the baseline profile of serum hormone levels (including but not limited to testosterone, DHT, DHEA, DHEAS, estradiol) and lipids, the change in levels with subsequent therapy (Cycle 4), and their correlation with response to abiraterone acetate plus apalutamide.
3. Abiraterone Pharmacokinetics (PKs) drawn at cycle 1 d1 at 1, 2, 4, 8 hours post dose and cycle 2 d1 at (24 hour trough), 1, 2, 4, 8 hours post dose
4. Describe the germline SNP profiles of the androgen receptor gene, target genes involved in androgen metabolism and signaling and target genes that have been shown to be differentially expressed in African American and in Caucasian prostate cancer and their associations with response to abiraterone acetate, prednisone plus apalutamide. The status of the aforementioned targets will also be assessed in archival tumor tissue, if available.
5. Describe the expression and splicing profiles of the androgen receptor gene, target genes involved in androgen metabolism and signaling and target genes that have been shown to be differentially expressed and/or spliced in African American and in Caucasian prostate cancer and their associations with response to abiraterone acetate, prednisone plus apalutamide. The status of the aforementioned targets will also be assessed in archival tumor tissue, if available.
6. Describe cell-free plasma DNA profiles and their associations with response to abiraterone acetate, prednisone plus apalutamide.
7. To explore the associations between baseline levels and treatment-related changes of plasma-based protein markers with response in patients treated with abiraterone acetate, prednisone plus apalutamide.
8. Describe abiraterone metabolism by race with particular attention to active metabolites including D4A and 3-keto-5α-abiraterone.
9. To assess the concordance between the genomic alterations identified in cfDNA to the genomic alterations identified in the tumor-derived DNA

Design: This is a Phase II, open-label, multicenter study of apalutamide, abiraterone acetate and prednisone in African American and Caucasian men with mCRPC. The primary goal is to estimate the median radiographic PFS in African American and Caucasian men with mCRPC cancer treated with apalutamide, abiraterone acetate and prednisone. 50 patients per group is expected to be enrolled. Patients will be treated on open-label treatment and investigational product until evidence of disease progression as defined by modified Prostate Cancer Working Group Three (PCWG3) definition [13] or until two years at which point they will roll over to the standard of care at that time.

Study schema is shown below.



Study Population: This will be a Duke Cancer Institute sponsored multicenter study. It is anticipated that the Duke Cancer Institute, the Duke Cancer Network and up to six external sites will be needed to accrue evaluable 100 subjects (50 African American and 50 Caucasian) over a 20 month accrual period. We anticipate that once all sites are open, approximately 7 subjects total will be enrolled each month.

Prohibited Concomitant Treatment:
(see full list of prohibited and restricted concomitant treatments in Section 8.3.2 and 8.3.3)

- Chemotherapy, radiation therapy, or immunotherapy, or any systemic anti-cancer therapy other than abiraterone acetate, apalutamide and prednisone and those described as permitted concomitant treatment.
- Avoid strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, and phenobarbital) during abiraterone acetate treatment.
- Avoid strong CYP3A4 inhibitors (e.g., itraconazole, clarithromycin, erythromycin, diltiazem, verapamil, delavirdine, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole, grapefruit juice (or grapefruits); co-administration with any of these agents may increase apalutamide plasma concentrations
- Immunosuppressive doses of systemic corticosteroids greater than prednisone 5mg twice daily or the equivalent. Short term use of systemic corticosteroids are allowed for side effect management.
- 5 alpha reductase inhibitors (example dutasteride, finasteride, aminoglutethamide); estrogens given for cancer therapy: 2-week washout required and no concomitant treatment
- Atypical antipsychotics (e.g. clozapine, olanzapine, risperidone, ziprasidone)
- Bupropion
- Lithium
- Meperidine and pethidine
- Phenothiazine antipsychotics (e.g., chlorpromazine, mesoridazine, thioridazine)
- Tricyclic antidepressants (e.g., amitriptyline, desipramine, doxepin, imipramine, maprotiline, mirtazapine

Permitted Concomitant Treatment:
(see full list of permitted concomitant treatments in Section 8.3.1)

- Standard therapies for preexisting conditions, medical/surgical complications including nausea and diarrhea, and palliation.
- Non-potent P450 CYPs isoenzyme inhibitors and/or inducers (Appendix 3).
- LHRH agonists or antagonists.
- Anti-hypertensive medications.
- Diabetic medications.
- Antidepressants or other medications for mood disorders.
- Analgesics including opioids are allowed provided KPS remains 70 or greater.
- Bisphosphonates and/or denosumab.
- Erythropoietic agents.
- Systemic anticoagulation with Coumadin and low molecular weight heparin.
- Focal therapies for localized non-prostate cancers
- Provenge, after the first 3 cycles on treatment are completed

Study Intervention and Administration: The study agent abiraterone acetate will be administered at a dose of 1000 mg orally once daily and apalutamide 240 mg orally once daily with prednisone 5 mg BID in 4-week cycles throughout the treatment period. Abiraterone acetate must be taken on an empty stomach. No food should be consumed for at least two hours before the dose of abiraterone acetate is taken and for at least one hour after the dose of abiraterone acetate is taken. Abiraterone acetate should be taken with a glass of water and consumed over as short a time as possible. Patients should swallow the tablets whole and not chew them. There are no specific requirements with respect to dosing and food for taking the apalutamide. The subject must have the ability to swallow, retain, and absorb oral medication. Apalutamide and abiraterone acetate will be provided by Janssen Scientific Affairs, LLC and distributed by DCI Investigational Chemotherapy Service. The study drug provided must be dispensed in the original packaging. Patients will be instructed to take a 5-mg prednisone tablet, twice daily. Prednisone will be obtained commercially. It is not required for the prednisone to be taken at the same time as abiraterone acetate or apalutamide. The dose of prednisone will remain unchanged in the event that the study drug dose is changed. If a prednisone dose is missed, it should be omitted and will not be made up. Should a dose modification of the prednisone be needed due to toxicities, the site will need to discuss this with the Sponsor-Investigator.

Study Assessments:
Vital signs, performance status, and physical exam will be assessed at each visit. The following laboratory studies will be obtained at intervals specified in the study flow chart to assess subject safety, specifically the risk of infection, hyperglycemia, and/or bone marrow, liver, thyroid and kidney abnormalities: complete blood count, TSH, blood urea nitrogen (BUN), creatinine, sodium, potassium, calcium, glucose, albumin, total protein, total bilirubin, alkaline phosphatase, AST (SGOT), ALT (SGPT) LDH.

For efficacy assessment, a PSA will be drawn at screening and prior to each scheduled study visit per the schedule of events. A CT scan with contrast of chest, abdomen, and pelvis, and a bone scan will be performed within 42 days prior to cycle 1 day 1 visit and every 3 cycles (12 weeks).

Correlative Science:
Whole blood will be collected in purple top EDTA tubes at baseline for DNA isolation. Isolated DNA will be used for ancestral genotyping to obtain genetically estimated indicators of race and for characterization of SNPs of androgen metabolism and signaling genes as well as genes that have been shown to be differentially expressed in African American versus Caucasian prostate cancers. A genome wide association study (GWAS) is planned in both African American and Caucasian men with mCRPC and their association with response to abiraterone acetate plus apalutamide, in line with the specified endpoints and biomarkers defined in the trial. In addition, blood will be collected in PAXgene Blood RNA Tubes at baseline, Cycle 4, and at progression or end of treatment for RNA isolation and characterization of differential expression and/or splicing of

the androgen receptor gene, TMPRSS2-ERG gene fusion, androgen metabolism and signaling genes and genes that have been shown to be differentially expressed and/or spliced in African American versus Caucasian prostate cancer. Blood will also be collected at baseline, Cycle 2, and at progression or end of treatment in EDTA tubes for cell-free plasma DNA isolation and characterization. Moreover, baseline assessments of lipidomics and hormonal levels, including but not limited to testosterone, DHT, DHEA, DHEAS and estradiol and their change after 12 weeks on therapy will be evaluated from collected serum. Furthermore, abiraterone pharmacokinetics (PKs) will be drawn on C1D1 at 1, 2, 4 and 8 hours post dose of study drug and C2D1 at 24 hour trough, 1, 2, 4 and 8 hours post dose of study drug. Finally blood will be collected at baseline, cycle 2 and at progression or end of treatment in EDTA tubes and plasma samples will be isolated to explore additional biomarkers that may have prognostic or predictive value. In addition to blood, paraffin-embedded archival tumor tissue will be collected whenever available from all patients having undergone a diagnostic core biopsy or a surgery (prostatectomy or metastatic sampling).

Safety Evaluation:

Subjects receiving at least one dose of apalutamide and/or abiraterone acetate will be evaluable for safety.

- Safety will be assessed by physical exam, laboratory assessments, review of concomitant medications, adverse event (AE) and serious adverse event (SAE) evaluations every cycle throughout the study.
- Electrocardiogram prior to initiation and subsequently at the discretion of the treating physician
- NCI Common Toxicity Criteria (v 4.0) will be used to record and monitor for adverse events (Appendix 3).

Treatment will be held and/or dose reduced for certain specified grade 3 or 4 adverse events until resolution to grade 1 as specified in the protocol

Efficacy Evaluation:

The primary endpoint will be radiographic **progression free survival** (rPFS) based on modified PCWG3 criteria or based on the onset of a skeletal related event. Imaging will be obtained every 12 weeks.

Secondary endpoints will include:

1. PSA kinetics: to determine the duration of PSA response, time to nadir, and percent of men who achieve a PSA < 0.1;
2. Radiographic assessments: to estimate the rate of objective response and incidence of bone flares
3. Safety (NCI CTC v4.0) and tolerability, particularly incidence and grade of hypertension in the two populations

Statistical Considerations:

Sample Size justification Based on Ryan et al. the median time to radiographic progression free survival (rPFS) for Abiraterone acetate in mCRPC patients is 16.5 months [14]. This trial is non-comparative. Fifty (50) patients will be enrolled in each group (AA and Caucasians). With an accrual rate of 50 patients/group over 20-month accrual period, 24-months follow-up, and assuming that rPFS follows an exponential distribution, based on 5000 simulations the average width of a two-sided 95% confidence interval for the median rPFS is 16.

Data Analysis Point estimates (median rPFS and proportion) and 95% confidence limits for the rPFS and the proportion of patients who experience PSA decline of 30%, 50% and 90% will be calculated. In addition, post therapy changes in PSA will be explored as a continuous outcome. The Kaplan-Meier product limit method will be used to estimate the PSA PFS and rPFS.

The GWAS analysis will be mostly exploratory as the trial limited sample size will not permit definitive analyses. Call rate, patterns of missing data, and departures from the Hardy-Weinberg equilibrium will be performed using exact test to identify SNPs that will not be used in analysis. Allele frequencies will be estimated within each racial group separately. Although race is self reported, admixture estimates and will be adjusted for in the analysis. Test for association will be performed under an additive model.

Ethical Considerations:

This study will be conducted in accordance with applicable laws and regulations including, but not limited to, the ICH GCP and the ethical principles that have their origins in the Declaration of Helsinki. The IRB must review and approve the protocol and ICF before any subjects are enrolled. Before any procedures specified in the protocol are performed, the subject must sign and date the IRB-approved ICF.

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2. SCHEDULE OF EVENTS

Procedure	Screening[a]	On-treatment visits 28 day cycle				Post-treatment			
	Within 30 days of dosing	Cycle 1 Day 1[r]	Cycle 1 Day 15	Cycle 2, 3 Day 1	Cycle 4 Day 1 & every 3rd cycle (Cycles 7, 10, 13, etc.)	End of Treatment[c]	Follow-up - safety[d]	Follow up - progression[d]	Follow up – survival[d]
		-2 days	+/- 5 days	+/- 7 days	+/- 7 days			+/- 7 days	+/- 1 month
Informed consent	X								
Inclusion / exclusion criteria	X								
Demographic data	X								
Prior and concomitant medications	X	X	X	X	X	X	X		
Medical history and AE assessment[e]	X	X	X	X	X	X	X		
Vital signs, height, and weight[f]	X	X	X	X	X	X	X	X	
Karnofsky performance status[g]	X	X	X	X	X	X	X	X	
Physical examination[e]	X	X	X	X	X	X	X	X	
Electrocardiogram[h]	X								
Tumor Site Assessments: CT scans (chest, abdomen, pelvis) and bone scans[i]	X[i]				X[i]		X[d]	X	
Abiraterone acetate & apalutamide dispensed[j]		X		X	X				
Phone call or chart review									X[d]
Standard-of-care laboratory assessments[k]									
CBC with differential[k]	X	X[b]	X	X	X	X	X		
Serum chemistries[k]	X	X[b]	X	X	X	X	X		
PSA	X	X[b]		X[k]	X	X			
Testosterone[k]	X				X[r]				
TSH[k]	X[s]			X	X	X			
Lactate dehydrogenase (LDH)[k]	X[s]			X	X	X			
Correlative/research studies									
Serum Hormone Levels[l]	X[s]				X[r]	X			
Serum Lipidomics[l]	X[s]				X[r]	X			
Plasma biomarkers[m]	X[s]			X[m]		X			
Whole blood DNA isolation, ancestral genotyping and characterization of SNPs[n]	X[s]								
PAXgene Blood RNA isolation and characterization of expression and/or splicing[o]	X[s]				X[r]	X			
PKs[p]		X		X					
Archival tissue collection[q]		X							

Footnotes to Schedule of Events:

a. Screening/ evaluations must be completed within 30 days prior to Cycle 1 Day 1 (C1D1) dosing, with the exception of informed consent and scans (42 days).
b. If the CBC with differential, Serum Chemistries, and PSA are performed within 7 days of Cycle 1 Day 1 visit, do not repeat these at the Cycle 1 Day 1 visit unless requested by the site's PI.
c. The end of treatment visit is to occur no more than 7 days after the last dose of study agent or within 7 days of the decision to stop drug.
d. The follow-up safety visit is to occur 28 days (+/- 7 days) after the last dose of study agent. This may be combined with the end of treatment visit if the window allows. CT and bone scan will be done at the safety follow up visit if scans have not been done within the last 8 weeks of the visit. Subjects who discontinue treatment due to reasons other than radiographic progressive disease will be followed every 3 months (+/- 14 days) until a new treatment is started or disease progression (for up to 24 months from the start of study therapy). Disease progression will be obtained through Standard of Care scans. All subjects will be followed for survival every 6 months +/- 1 month (by phone or chart review).
e. Medical history, physical examination and AE assessments will be performed prior to dispensing each supply of study drug to patient. An end-of-study medical history, physical exam, and AE assessment will be performed at the end of treatment or at progression. In addition, one safety follow-up visit with medical history, physical exam, and AE assessment will occur 30 +/- 7 days of the last dose of study drug
f. Vital signs (BP, pulse, respirations, temperature and weight) will be recorded at each visit. Height will be measured at screening only. Patients will check their blood pressures at least monthly (independent at home) and more often if elevated, as directed by the study team. An elevated blood pressure is >140/90. Blood pressure CTCAE grading will be done based on the blood pressure reading, not the number of blood pressure medications the subject is taking.
g. Karnofsky performance status (Appendix 1) will be evaluated and recorded at all clinic visits on study.
h. Electrocardiogram prior to initiation and subsequently at the discretion of the treating physician.
i. As part of routine tumor assessment, CT and bone scans will be performed within 42 days prior to C1D1visit and every 3 cycles (approximately every 12 weeks) thereafter (i.e., Screening, Day 1 of cycles 4, 7, 10 and every 3 cycles). The timing of the scans will be within 7 days of the next planned cycle initiation. A CT scan will be performed at the above described time points with contrast as per radiology protocol of chest, abdomen, and pelvis. If the chest CT at screening is clear, chest x-rays may be used for subsequent assessments at the enrolling physician's discretion. <u>These tumor assessments will be performed locally, in strict accordance with the RECIST 1.1 guidelines</u>. A total body bone scan will be performed at the above described time points and interpreted according to modified PCWG3 guidelines (Appendix 4). CT and bone scan modalities per standard institutional practices may be used, but the same modality should be used throughout the study for each subject. Note: during screening, metastatic disease may be confirmed by prostate cancer-specific imaging without meeting RECIST 1.1 criteria.
j. Abiraterone acetate and apalutamide will be dispensed directly from clinic. Both study drugs should be kept in the original packaging at all times. For C1D1 and C2D1, abiraterone acetate will be taken in the presence of the coordinator. This will allow the coordinator to document the exact time of dosing (abiraterone acetate) and to time the PKs accurately. Subject may take prednisone and apalutamide with food 2 hours before abiraterone acetate dose. Abiraterone acetate is taken without food. Alternatively, prednisone and apalutamide may be taken 1 hour after abiraterone acetate dose, with food.
k. Standard-of-care laboratory assessments at the times indicated include:

   <u>Complete blood count (CBC) with differential</u>: WBC count with differential, platelet count, hemoglobin, and hematocrit at screening, Cycle 1 Day 15, Day 1 of cycles 1, 2, 3, 4 etc. every 3 cycle visits scheduled per protocol, at the end of treatment visit and at safety follow-up visit.

   <u>Serum chemistries:</u> Sodium, potassium, chloride, blood urea nitrogen (BUN), creatinine, glucose, carbon dioxide or bicarbonate, calcium, total protein, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, and alkaline phosphatase at screening, Cycle 1 Day 15, Day 1 of cycles 1, 2, 3, 4 etc. every 3 cycle visits scheduled per protocol, at the end of treatment visit, and at the end of Safety Follow-up Visit.

   <u>LDH</u> can be drawn at screening (or C1D1 prior to first dose) then day 1 of each cycle that has a visit scheduled per protocol and end of treatment.

   <u>TSH</u> at screening, every day 1 of cycles 2, 3, 4, then every 3 cycles and end of treatment. If TSH is abnormal obtain a T3/T4.

   <u>PSA</u>: Drawn at screening, Day 1 of Cycle 1 and cycles 1, 2, 3, 4, etc. and every cycle that has a visit scheduled per protocol, and at the end of treatment visit.

   <u>Testosterone</u>: Drawn at screening and at C4D1.

   Note: Cycle 1 Day 1 CBC, Serum Chemistries, & PSA lab tests do not have to be repeated if screening lab tests are obtained within <u>7 days</u> prior to Cycle 1 Day 1 visit.
l. Serum hormone levels including but not limited to testosterone (ultrasensitive) DHT, DHEA, DHEAS, and estradiol: One 5ml gold top tube will be collected at screening (or C1D1 prior to first dose), at Cycle 4 Day 1, and at the end of treatment visit (end of treatment research labs may be drawn at safety follow up visit if needed). Serum

lipidomics will also be assessed at screening (or C1D1 prior to first dose). C4D1 and end of treatment (EOT). Lipidomic samples should be collected after fasting. See lab manual for detailed instructions.

m. Plasma for blood-based biomarkers and cfDNA: Two 10ml lavender top tubes will be collected at screening (or C1D1 prior to first dose), C2D1, and end of treatment (end of treatment research labs may be drawn at safety follow up visit if needed. Cell-free DNA (cfDNA) will be analyzed at screening (or C1D1 prior to first dose) and end of treatment.

n. Whole blood DNA isolation ancestral genotyping and characterization of SNPs: One 4ml lavender top tube will be collected at screening (or C1D1 prior to first dose), See lab manual for detailed instructions.

o. PAXgene blood RNA isolation and characterization: One 2.5 ml PAXgene Blood RNA tube will be collected at screening (or C1D1 prior to first dose), C4D1, and at end of treatment (end of treatment research labs may be drawn at safety follow up visit if needed. See lab manual for detailed instructions.

p. PKs drawn at C1D1 at 1, 2, 4, 8 hours post dose and cycle 2 D1 at 0 (24 hour trough), 1, 2, 4, 8 hours post dose. Document timing of abiraterone acetate doses for C1D1, C1D28, and C2D1 on the Duke Research PK Sample Flowsheet. There is a +/-15 minute window for all PKs that are drawn except for the 8 hour time point. The 8 hour time point has a +/-1 hour window.

q. If available and consistent with local regulations, banked tumor tissue will be obtained (in accordance with the lab manual) and evaluated to assess somatic expression and/or splicing and mutation of the androgen receptor gene, target genes involved in androgen metabolism and signaling and/or target genes that have been shown to be differentially expressed and/or spliced in African American versus Caucasian prostate cancer potentially predictive of abiraterone acetate plus apalutamide antitumor activity. See lab manual for detailed instructions.

r. C4D1 only (do not collect on C7D1, C10D1, etc.).

s. May be collected on C1D1 prior to first dose.

3. CURRENT TREATMENT FOR METASTATIC CRPC

Metastatic Castrate Resistant Prostate Cancer

Globally, 307,000 men die of prostate cancer each year (87). In the United States, with an estimated 180,890 new cases of prostate cancer and 26,120 deaths (88). Prostate cancer has the second highest death rate of any cancer, almost all of which occurs as a result of the development of metastatic castration-resistant prostate cancer. Optimizing treatments for the management of advanced prostate cancer is urgently needed.

Prostate cancer is hormone sensitive at the time of initial diagnosis. Although most patients with advanced metastatic disease initially respond to conventional androgen deprivation with medical or surgical castration, the median duration of disease control has been 13-22 months and historically overall survival may be as short as 28-36 months from starting androgen deprivation therapy [1-3]. The clinical status of patients after failure of castration is commonly referred to as castration-resistant prostate cancer (CRPC). Patients with metastatic CRPC have a very limited life expectancy of 1-5 years and most often die of their prostate cancer.

In the castrate state, remaining ligands to the AR have been thought to be derived primarily from the adrenal glands. Conventional androgen deprivation therapy removes 90% of circulating androgens produced in the gonads. As much as 10% of circulating testosterone remains, in part due to the peripheral conversion of adrenal steroids to testosterone. In addition, several recent studies suggest that androgen levels in the microenvironment of prostate cancer may be maintained in spite of reduced systemic levels [4, 5]. In patients with castrate levels of testosterone, the tissue levels of dehydroepiandrosterone, dihydrotestosterone, and androstenedione all remain sufficient to activate the AR. Furthermore, the ARs are predominately located in the nucleus in biopsy tissue, indicating ligand-binding and the activation of androgen-dependent gene expression. Increased expression of the AR is common in advanced prostate cancer, and allows lower ligand levels to more strongly activate the AR [6]. A recent investigation made the observation that in high risk primary prostate tumors and in metastatic biopsies, CYP17A1 gene expression is highly upregulated, suggesting the possibility of in situ production of androgens as autocrine or paracrine growth factors despite castration.[7, 8] Similarly, investigators at MD Anderson Cancer Center also detected CYP17 expression by immunohistochemistry in bone marrow metastasis in CRPC [9]. Although these preliminary findings require further corroborating evidence, the need to suppress androgen production in adrenal glands and possibly at tissue levels persists in CRPC.

Complete androgen independence in CRPC is thought to be rare. A few patients (9%) have mutations in the AR; these changes could allow the AR to be activated by non-androgen ligands, or might allow ligand-independent AR association with coactivator molecules.[10]

Although gene fusions are well known to drive the development of blood cancers and sarcomas, only rarely have they been detected in the common solid cancers. Recent evidence indicates that a gene fusion may be important in the pathogenesis of prostate carcinoma.[11-15] Chromosomal translocations involving the androgen-responsive gene transmembrane protease serine 2 (TMPRSS2) and erythroblast transformation–specific (ETS)-related transcription factors ETV1, ETV4, and ETV5, have been identified in 50% to 70% of prostate cancer cases.[11, 12] Translocation of TMPRSS2 to the ERG gene, found in a high proportion of human prostate cancer, results in overexpression of the 3'-ERG sequences joined to the 5'-TMPRSS2 promoter. ERG and other ETS family members are transcription factors that are implicated in the control of cell growth and differentiation and the chimeric protein product of the gene translocation appears to retain hormone responsiveness.[13] Specific translocations in primary tumors have been associated with more aggressive natural clinical history, more advanced disease at diagnosis and greater lethality.[14-17] These gene rearrangements may be associated with tumor response to androgen deprivation therapy, including abiraterone acetate [18].

4. RATIONALE FOR CURRENT STUDY

4.1 ABIRATERONE ACETATE

Abiraterone Acetate and Mechanism of Action

Abiraterone acetate is [17-(3-pyridyl)androsta-5,16-dien-3β-ol] and is a steroidal inhibitor of CYP17 (17α hydroxylase/C17,20-lyase) that blocks two important enzymatic activities in the synthesis of testosterone (Figure 1), based on the observation that nonsteroidal 3 pyridyl esters improve selectivity for inhibition of 17α-hydroxylase/C17,20 lyase. Abiraterone acetate is a potent inhibitor with an apparent inhibition constant of 0.5 nM. Pharmacodynamic studies demonstrated that its effects on adrenal steroid synthesis were consistent with its mechanism of action. Antitumor effects were evident with PSA response and durable objective responses using Response evaluation criteria in solid tumors (RECIST) criteria in Phase 1 and Phase 2 studies conducted to date.[19] Abiraterone acetate in combination with prednisone is FDA approved for the treatment of patients with metastatic castration-resistant prostate cancer and metastatic high-risk castration-sensitive prostate cancer.

Abiraterone acetate is the 3-acetylated analog of abiraterone and thus a pro-drug of abiraterone. The chemical nomenclature of abiraterone acetate is 3β acetoxy-17-(3- pyridyl) androsta-5, 16-diene; its empirical formula is C26H33NO2 and molecular weight is 391.55. Once absorbed after oral administration, abiraterone acetate is rapidly converted to the active form, abiraterone (Figure 2). In initial research studies, abiraterone acetate was the predominant, if not the only, metabolite of abiraterone acetate detected in blood, both in preclinical studies and in previously conducted clinical studies.[20, 21]

More recently, metabolitic analyses of abiraterone in mice and in humans reveal that abiraterone is converted to Δ (4)-abiraterone (D4A), which inhibits additional enzymes, involved in androgen synthesis (CYP17A1, 3βHSD and SRD5A) and directly antagonizes the androgen receptor [84]. Furthermore, D4A is converted to at least three 5α-reduced and three 5β-reduced metabolites in human serum [85]. The initial 5α-reduced metabolite, 3-keto-5α-abiraterone, is present at higher concentrations than D4A in patients with prostate cancer taking abiraterone, and is an androgen receptor agonist, which may promote prostate cancer progression [85].

Figure 1. The Enzyme Complexes Inhibited by Abiraterone acetate

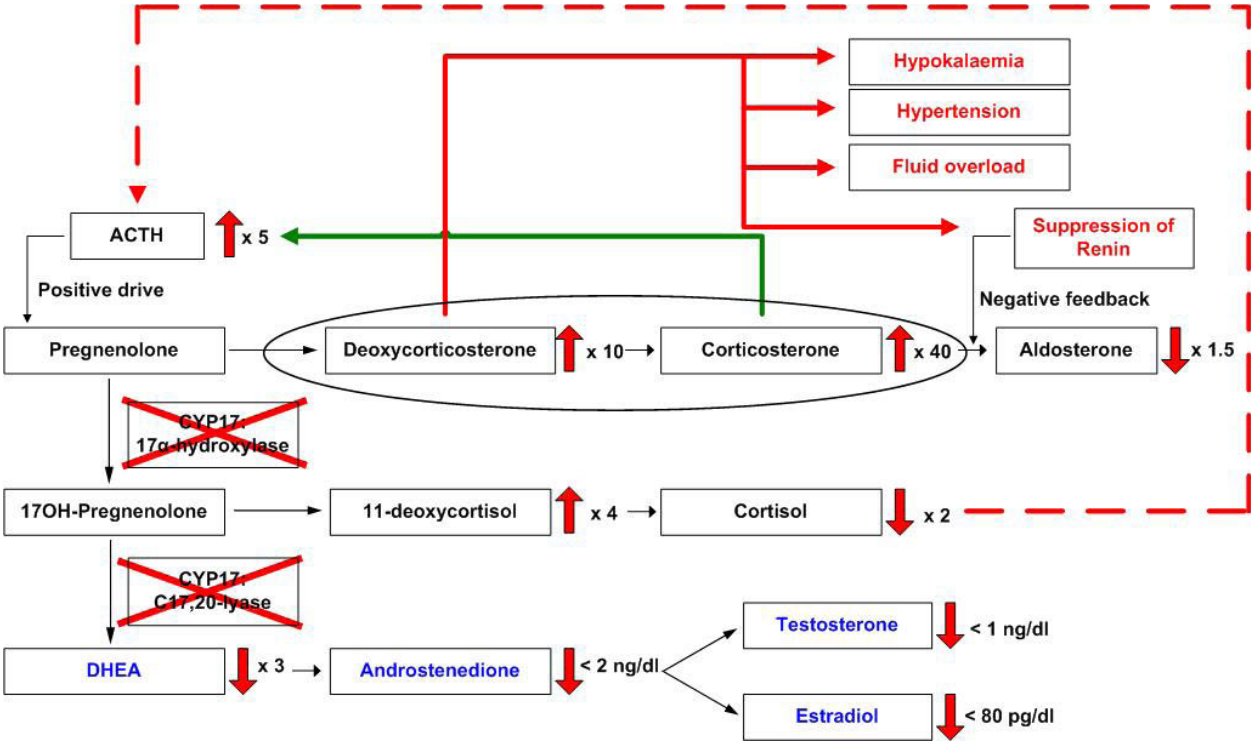
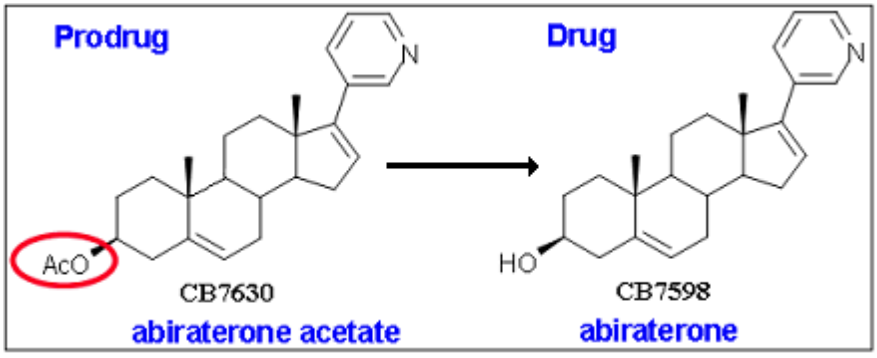


Figure 2. Prodrug Abiraterone Acetate is Converted to Abiraterone after Absorption



Clinical Trials with Abiraterone Acetate and Prednisone

COU-AA- 301 was a randomized, double-blind, International Phase III study comparing abiraterone acetate, given at 1000 mg once daily with prednisone 5 mg BID to placebo and prednisone 5 mg BID in men with mCRPC previously treated with docetaxel-based chemotherapy [22]. Overall survival was the primary endpoint and 1195 patients were enrolled. A planned interim analysis after 534 patients met the primary endpoint revealed a statistically significant difference in overall survival between the abiraterone acetate and prednisone arm (median OS 14.8 months; 95% CI 14.1- 15.2) and the placebo and prednisone arm (median OS 10.9 months; 95% CI 10.2-12.0) with a hazard ratio of 0.646 and a $p < 0.0001$ [22]. Secondary endpoints were all statistically significant in favor of abiraterone acetate including time to PSA progression, radiographic progression, and PSA response. Subgroup analysis revealed all parameters in favor of abiraterone acetate. Side effects in this large phase III heavily pre-treated population were relatively low and balanced in both arms except for fluid retention, hypokalemia, hypertension and cardiac disorders; however, grade 3 or greater incidence of these toxicities were less than 5%. These results have led to the FDA-approval of abiraterone acetate with prednisone for patients with mCRPC who have failed docetaxel-based chemotherapy.

In chemotherapy-naïve mCRPC, the COU-AA-302 study was a randomized, double blind, international phase III study comparing abiraterone acetate and prednisone to placebo and prednisone [23]. 1088 patients were randomized in a 1:1 ratio and treated until radiographic progression. Radiographic progression-free survival and overall survival were co-primary endpoint. Three interim analyses were pre-planned. At the time of the second interim analysis, following after 311 events (43% of events) the independent data safety monitoring committee recommended halting the study and unblinding the patients due to a statistically significant positive effect in favor of abiraterone acetate for radiographic progression-free survival (HR 0.43; 95% CI 0.35-0.52; $p < 0.0001$), a strong trend in favor of overall survival (HR: 0.75; 95% CI 0.61-0.93; $p = 0.0097$) and positive secondary endpoints as well [23]. A final analysis confirmed a statistically significant clinical benefit in median overall survival in favor of abiraterone acetate with prednisone (34.7 months [95% CI 32.7-36.8] vs 30.3 months [28.7-33.3]; hazard ratio 0.81 [95% CI 0.70-0.93]; p=0.0033) [86]. These results led to the FDA-approval of abiraterone acetate with prednisone for patients with mCRPC in December 2012.

For the most comprehensive clinical information regarding the efficacy and safety of abiraterone acetate, refer to the latest version of the Package Insert for abiraterone acetate.

4.2 APALUTAMIDE

Apalutamide has been approved by the US Food and Drug Administration (FDA) for the treatment of non-metastatic castration resistant prostate cancer and metastatic castration-sensitive prostate cancer, but not for metastatic castration resistant prostate cancer. It is a

competitive AR inhibitor developed to optimally antagonize AR transcriptional activity and prostate cancer cell proliferation, pharmacokinetics, and in vivo efficacy [81]. In contrast to bicalutamide, apalutamide lacks significant agonist activity in preclinical models of CRPC. Moreover, apalutamide does not induce AR nuclear localization or DNA binding. In a clinically valid murine xenograft model of human CRPC, apalutamide showed greater efficacy than MDV3100. Maximal therapeutic response in this model was achieved at 30 mg/kg/d of apalutamide, whereas the same response required 100 mg/kg/d of MDV3100 and higher steady-state plasma concentrations. Thus apalutamide exhibits characteristics predicting a higher therapeutic index with a greater potential to reach maximally efficacious doses in man than current AR antagonists. Our findings offer preclinical proof of principle for apalutamide as a promising therapeutic in both castration-sensitive and castration-resistant forms of prostate cancer.

In Phase I testing apalutamide was dosed between 30 mg and 480 mg once daily, resulting in PSA declines at all dose levels and a median 50% decline from baseline PSA at 12 weeks of 47% [82]. The most frequently reported adverse event was grade 1/2 fatigue (47%). A phase II multicenter study evaluated the clinical efficacy of apalutamide at 240 mg daily in non-metastatic (nm) CRPC patients. In 51 evaluable patients 89% had ≥50% PSA decline at 12 weeks. Median time to PSA progression was 24.0 mo (95% confidence interval [CI], 16.3 months - not reached [NR]); median metastasis-free survival was NR (95% CI, 33.4 months - NR). The most common AE was fatigue (any grade, n=31 [61%]) [83]. A Phase III Study of apalutamide versus placebo in men with nmCRPC has showed that apalutamide prolonged metastasis-free survival and time to symptomatic progression. [89]

Additional details of the preclinical and clinical testing of apalutamide conducted thus far can be found in the apalutamide investigator's brochure or package insert.

4.3 Rationale

African American men have a 60% greater incidence of being diagnosed with prostate cancer and nearly a 2.5 fold greater chance of mortality from the disease, yet the underlying cause for this increased mortality remains controversial [24]. Hormonal levels vary in men by race, with African American men having higher dihydrotestosterone (DHT), androstenedione (ASD) and sex hormone-binding globulin (SHBG) than Caucasian men with localized prostate cancer [5, 25]. Historically, African American men with prostate cancer have a worse overall survival than Caucasian men, however, this is confounded by the timing of androgen deprivation therapy (ADT) and access to other therapies [26, 27]. To what extent race affects response to therapy in prostate cancer is not clear.

Germline polymorphisms of genes involved in androgen signaling have been shown to vary significantly by race and may have important implications with regard to response to therapy targeted towards this pathway. Polymorphisms within the promoter region of the androgen receptor (AR) (specifically CAG repeats) have been well documented and vary significantly according to race, with African American men having significantly shorter CAG repeats resulting in greater AR activity [28]. These CAG repeats have been associated with more aggressive disease characteristics [28]. Recently, germline polymorphisms in androgen metabolism genes have been shown to have prognostic value in regards to the time to development of CRPC in men with prostate cancer on ADT. Ross et al tested 129 polymorphisms across 20 genes associated with androgen metabolism and identified three polymorphisms in separate genes (*CYP19A1*, *HSD3B1*, and *HSD17B4*) that were significantly associated with prolonged time to progression (TTP) on ADT [29]. Specifically, individuals carrying more than one of the polymorphisms were associated with *improved* time to CRPC than individuals carrying zero or one ($P<$ .0001). More recently this group identified polymorphisms in two androgen transporter genes, *SLCO2B1* and *SLCO1B3* that were associated with a significantly *shorter* time to CRPC alone and in combination [30]. Incidences of these polymorphisms ranged from 15 to 81%; unfortunately, the cohort of patients used to identify these polymorphisms had limited numbers of African American patients or other racial and ethnic groups.

Recent studies by our laboratory and others have focused on discovering molecular mechanisms underlying prostate cancer disparities using microarrays and bioinformatics. These studies have compared the gene expression profiles between African American and Caucasian cancers and between prostate cancer and patient-matched normal prostate from African American and Caucasian. By integrating gene expression profiling and pathway analyses, multiple components within the androgen receptor signaling pathway were revealed to be up-regulated in African American prostate cancer specimens along with the up-regulation of genes within other signaling pathways that converge on androgen receptor signaling, portending that androgen receptor pathway activation is a key component of prostate cancer health disparities. Overall the comparison of African American and Caucasian prostate cancer specimens has led to the identification of a number of differentially expressed genes, including CYP19A1, AMFR, CXCR4, MMP9, SRD5A2, ADIPOQ, AKT1, ALOX12, ALOX15, ALOX15B, BMP2, CGA, ERG, FASN, IL1B, IL6, IL8, NFKB1, PIK3C3, PIK3CA, PI3K3R1, PLA2G2A, TGFB1, TIMP3, TNF, P38MAPK, STAT1, RHOA, ITGB5, MAPKAPK2, CSNK2A1, PIK3CB, ARA55, GNA01, GNB3, POLR2L, PRKCE, PRKD1, TBP, CALR, GNG2, GNG11, GNG12, CALM1, NFKB2, STAT2, RHOU, FGF13, EIF3B, and GIT1 [31-34]. Thus, germline polymorphisms of these differentially expressed genes also may have important implications with regard to response to therapy targeted towards the androgen signaling pathway. In addition, our laboratory has identified a number of novel alternatively spliced genes in African American versus Caucasian prostate cancer and have shown that African American variants track with more aggressive cancer invasion characteristics of prostate cancer in African American men (Bi-Dar Wang, Jennifer A. Freedman, Daniel J. George, Norman H. Lee and Steven R. Patierno, manuscript in preparation). Moreover, we have identified novel

single nucleotide polymorphisms located in splicing regulatory regions of such genes that associate with prostate cancer risk, aggressiveness and survival (Jennifer A. Freedman, Yanru Wang, Hongliang Liu, Patricia G. Moorman, Terry Hyslop, Daniel J. George, Norman H. Lee, Qingyi Wei and Steven R. Patierno, manuscript in preparation). Subsets of these genes are androgen receptor targets. Therefore, germline polymorphisms of these alternatively spliced genes also may have important implications with regard to response to therapy towards the androgen signaling pathway.

To what extent racial differences affect response and time to progression on secondary hormonal therapies in the CRPC setting are unknown. A retrospective analysis of the COU-AA-302 study included only 28 black patients but demonstrated trends in favor of median rPFS and 90% decline from baseline PSA in this subpopulation vs the entire population [79]. Similarly, a retrospective case-controlled analysis of patients treated at Duke University with abiraterone prednisone pre or post docetaxel chemotherapy revealed statistically significant improved PSA response rate in African American vs Caucasian patients by 30% decline (77.8% vs 54.4%; p=0.008) and 50% decline (68.9% vs 48.9%; p=0.028) with trends in favor of 90% PSA decline (37.8%, vs. 28.9%) [80]. In addition, primary abiraterone-refractory disease (PSA increase as best response) trended to be more in Caucasian than in African American patients (31.1% vs 15.6%; p=0.052). Based upon these findings we hypothesized that African American CRPC patients may be more sensitive to abiraterone acetate with prednisone than Caucasian patients. We have conducted a prospective Phase II study of abiraterone acetate with prednisone in patients with mCRPC, stratified by self-described race in order to test this hypothesis (Abi Race Clinicaltrials.gov NCT01940276). Secondarily, to what extent differences in systemic hormonal levels as well as androgen transport gene polymorphisms affect response to abiraterone acetate is unknown. Understanding any potential differences in response to therapy by race and/or by hormonal/genetic factors could impact on both our clinical use of abiraterone acetate as well as future clinical trial design. Finally, as other agents targeting the androgen/androgen receptor pathways become available, it will be important to differentiate their activity according to race, genetics and hormonal milieu.

The concept of combining apalutamide with abiraterone acetate and prednisone derives from their potentially complimentary mechanisms of action in which apalutamide functions as a pure androgen receptor antagonist while abiraterone acetate inhibits cholesterol metabolism into androgen, thus lowering the functional levels of ligand for the receptor. Since most patients who progress on abiraterone acetate do so with a rising PSA we believe the androgen receptor remains a driver of disease progression in patients treated with abiraterone acetate and prednisone alone. Together, these apalutamide and abiraterone acetate may be able to more completely inhibit the androgen – androgen receptor axis and provide greater clinical benefit. An ongoing Phase III study (ACIS) is evaluating whether the combination of apalutamide, abiraterone acetate and prednisone improves radiographic progression-free survival compared to abiraterone acetate, prednisone and placebo (clinicaltrials.gov NCT02257736). Like the COU-AA-302 study, the ACIS trial is international and not likely to contain a significant proportion of

African American patients, leaving unanswered the question of whether African American patients may have a genetic propensity for response and clinical benefit to this combination. We propose a Phase II open label, prospective study to evaluate, radiographic PFS in men with mCRPC stratified by self-described race and treated with apalutamide, abiraterone acetate and prednisone. Secondary endpoints will describe the response to apalutamide, abiraterone acetate and prednisone, PSA kinetics, pharmacokinetics of abiraterone acetate as well as safety and tolerability. Exploratory endpoints will describe the incidence and associations of key hormonal levels as well as germline polymorphisms in androgen signaling genes and genes that have been shown to be differentially expressed in African American versus Caucasian prostate cancers in both African American and Caucasian cohorts.

5. STUDY OBJECTIVES AND ENDPOINTS

5.1 Study objectives

5.1.1 Primary objective

The primary goal is to estimate the radiographic PFS distribution of African American and Caucasian men with mCRPC treated with apalutamide, abiraterone acetate, and prednisone.

5.1.2 Secondary objectives

1) PSA kinetics: to determine the duration of PSA response, time to nadir, and percent of men who achieve a PSA < 0.1 ng/mL;
2) Radiographic assessments: to estimate the rate of objective response and incidence of bone flares
3) Safety (NCI CTC v4.0) and tolerability, particularly incidence and grade of hypertension in the two populations
4) Overall survival

5.1.3 Exploratory objectives

1) Perform ancestral genotyping to obtain genetically estimated indicators of race using DNA isolated from whole blood at baseline.
2) Describe the baseline profile of serum hormone levels (including but not limited to testosterone, DHT, DHEA, DHEAS, estradiol) and lipids, the change in levels with subsequent therapy (Cycle 4), and their correlation with response to abiraterone acetate plus apalutamide.
3) Abiraterone Pharmacokinetics (PKs) drawn at cycle 1 d1 at 1, 2, 4, 8 hours post dose and cycle 2 d1 at (24 hour trough), 1, 2, 4, 8 hours post dose.

4) Describe the germline SNP profiles of the androgen receptor gene, target genes involved in androgen metabolism and signaling and target genes that have been shown to be differentially expressed in African American versus Caucasian prostate cancer and their associations with response to abiraterone acetate plus apalutamide. The status of the aforementioned targets will also be assessed in archival tumor tissue, if available.
5) Describe the expression and splicing profiles of the androgen receptor gene, target genes involved in androgen metabolism and signaling and target genes that have been shown to be differentially expressed and/or spliced in African American versus Caucasian prostate cancer and their associations with response to abiraterone acetate plus apalutamide. The status of the aforementioned targets will also be assessed in archival tumor tissue, if available.
6) Describe cell-free plasma DNA profiles and their associations with response to abiraterone acetate plus apalutamide.
7) To explore the associations between baseline levels and treatment-related changes of plasma-based protein markers with response in patients treated with abiraterone acetate plus apalutamide.
8) Describe abiraterone metabolism by race with particular attention to active metabolites including D4A and 3-keto-5α-abiraterone.
9) To assess the concordance between the genomic alterations identified in cfDNA to the genomic alterations identified in the tumor-derived DNA

5.2 Study endpoints

5.2.1 Primary endpoint

The primary endpoint will be radiographic **progression free survival** (rPFS) based on modified PCWG3 criteria or based on the onset of a skeletal related event. Imaging will be obtained every 12 weeks.

5.2.2 Secondary endpoints

Secondary endpoints will include:

1) PSA kinetics: to determine the duration of PSA response, time to nadir, and percent of men who achieve a PSA < 0.1 ng/mL;
2) Radiographic assessments: to estimate the rate of objective response and incidence of bone flares
3) Safety (NCI CTC v4.0) and tolerability, particularly incidence and grade of hypertension in the two populations
4) Overall survival

5.2.3 Exploratory correlative sciences endpoints

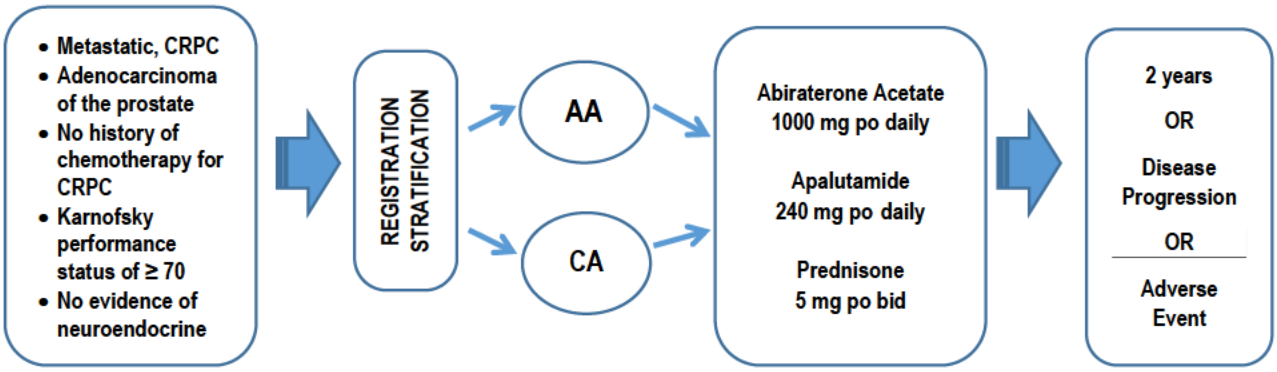
Whole blood will be collected in purple top EDTA tubes at baseline for DNA isolation. Isolated DNA will be used for ancestral genotyping to obtain genetically estimated indicators of race and for characterization of SNPs of androgen metabolism and signaling genes as well as genes that have been shown to be differentially expressed in African American versus Caucasian prostate cancer. A genome wide association study (GWAS) is planned in both African American and Caucasian men with mCRPC and their association with response to abiraterone acetate plus apalutamide, in line with the specified endpoints and biomarkers defined in the trial. In addition, blood will be collected in PAXgene Blood RNA Tubes at baseline, cycle 4, and at progression or end of treatment for RNA isolation and characterization of differential expression and/or splicing of the androgen receptor gene, TMPRSS2-ERG gene fusion, androgen metabolism and signaling genes and genes that have been shown to be differentially expressed and/or spliced in African American versus Caucasian prostate cancer. Blood will also be collected at baseline, cycle 2 and at progression or end of treatment in EDTA vacutainers for cell-free plasma DNA isolation and characterization. Moreover, baseline assessments of lipidomics and hormonal levels, including but not limited to testosterone, DHT, DHEA, DHEAS and estradiol and their change after 12 weeks on therapy will be evaluated from collected serum. Furthermore, abiraterone pharmacokinetics (PKs) will be drawn on day 1 and day 29 (C2d1) at 24 hour trough, 1, 2, 4 and 8 hours post dose of study drug. Finally, baseline, Cycle 2 and at progression or end of treatment in EDTA vacutainers will be drawn to explore additional circulating protein biomarkers that may have prognostic or predictive value. In addition to blood, formalin-fixed, paraffin-embedded archival tumor tissue will be collected whenever available from all patients having undergone a diagnostic core biopsy or a surgery (prostatectomy or metastatic sampling).

6. INVESTIGATIONAL PLAN

6.1 Overall study design

This is a phase II open-label, multicenter study of apalutamide, abiraterone acetate and prednisone in African American and Caucasian men with mCRPC. The primary goal is to prospectively estimate the median radiographic PFS in African American and Caucasian men with mCRPC cancer treated with apalutamide and abiraterone acetate. Patients will self-report on race and 50 patients will be enrolled into each group. Patients will be treated on open-label treatment until evidence of disease progression as defined by Prostate Cancer Working Group Three (PCWG3) modified definition [35] or until two years at which point they will roll over to the standard of care at that time.

Study schema is shown below.



6.2 Study population

Study Population: This will be a Duke Cancer Institute sponsored multicenter study. It is anticipated that the Duke Cancer Institute, the Duke Cancer Network and six external sites will be needed to accrue 100 subjects (50 African American and 50 Caucasian) over a 20 month accrual period. Up to 130 men may be consented to this study to reach the target accrual of 100. We anticipate that once all sites are open, approximately 7 subjects total will be enrolled each month.

6.3 Inclusion and exclusion criteria

Patients must have screening evaluations performed prior to the first dose of study drug and must meet all inclusion and exclusion criteria. Results of the screening evaluations, which assure that all inclusion and exclusion criteria have been satisfied, must be reviewed by the Principal Investigator at Duke University, or his/her designee prior to enrollment of that patient. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained from the patient prior to any screening procedures being performed. The following criteria apply to all patients enrolled onto the study unless otherwise specified.

Inclusion Criteria:

1. Male, age ≥ 18 years
2. Karnofsky performance status ≥ 70 (Appendix 1)
3. Life expectancy of ≥ 12 months as determined by treating investigator

4. Written Authorization for Use and Release of Health and Research Study Information (HIPAA authorization per institutional requirements)
5. Willing/able to adhere to the prohibitions and restrictions specified in this protocol
6. Willing to take abiraterone acetate on an empty stomach, and should be able to swallow tablets whole, without crushing/chewing tablets. Must have the ability to swallow, retain, and absorb oral medication.
7. Medications known to lower the seizure threshold (see list under prohibited meds, appendix 2) must be discontinued or substituted at least 4 weeks prior to study entry
8. 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. Abstinence is an acceptable method of birth control.
9. Adequate bone marrow function as shown by: ANC ≥ 1.0 x 10^9/L, Platelets ≥ 100 x 10^9/L, Hb≥9 g/dL, (independent of transfusion and/or growth factors within 3 months prior to Cycle 1 Day 1)
10. Serum potassium ≥ 3.5 mEq/L
11. Serum albumin of ≥ 3.0 g/dl
12. AST/SGOT and ALT/SGPT <2.5 x Institutional Upper Limit of Normal (ULN)
13. Serum total bilirubin ≤ 1.5 x Institutional ULN (Note: In subjects with Gilbert's syndrome, if total bilirubin is >1.5 × ULN, measure direct and indirect bilirubin and if direct bilirubin is ≤1.5 × ULN, subject may be eligible)
14. GFR ≥30 mL/min
15. Confirmation of diagnosis of adenocarcinoma of the prostate through either histological methods or tissue, or diagnosis clinically consistent with prostate cancer. Histologic variants of prostate cancer comprising of >50% of the tumor including neuroendocrine features and small cell carcinoma of the prostate are excluded
16. Radiographic evidence of metastatic disease based on RECIST 1.1 Criteria OR by prostate cancer-specific PET imaging. Evaluable non-target lesions and/or bone only metastasis are permitted per RECIST 1.1 and PCWG3 guidelines. Non-target, pathological lymph nodes ≥ 10 mm and less than 15 mm in the short axis are permitted.
17. Ongoing ADT using an LHRH agonist (e.g. leuprolide, goserelin) or antagonist (e.g. degarelix) must continue on therapy unless prior bilateral orchiectomy has been performed.
18. PSA ≥ 2.0 ng/mL
19. Evidence of castration resistant disease in the setting of ongoing ADT (medical or surgical) as evidenced by at least one of the following:
    - Absolute rise in PSA of 2.0 ng/mL or an increase >25% from the nadir, minimum 2 consecutive rising PSA levels with an interval of ≥ 1 week between each PSA level, **OR**
    - CT or MRI based evidence of disease progression (soft tissue, nodal or visceral disease progression) according to RECIST 1.1 criteria, **OR**

- At least 1 new bone scan lesion as compared to the most immediate prior radiologic studies.

20. A minimum of 2 weeks elapsed off of antiandrogen therapy prior to start of study drug (i.e. flutamide, nilutamide, bicalutamide.)
21. A minimum of 2 weeks elapsed off of sipuleucel-T and radiation therapy prior to start of study drug
22. A minimum of 4 weeks from any major surgery prior to start of study drug.
23. Self-reported race of either African American/Black or Caucasian.
24. Ability to understand and the willingness to sign a written informed consent document. If the subject is unable to understand the consent due to comorbidity, such as Alzheimer's disease, consent by a legally authorized representative and assent by the subject will be obtained.

Exclusion Criteria:

1. Prior treatment with abiraterone acetate, enzalutamide, apalutamide, galaterone (TOK-001), orteronel (TAK-700), or similar agent
2. Active infection or other medical condition that would make prednisone/prednisolone (corticosteroid) use contraindicated
3. Active or symptomatic infection including HIV, viral hepatitis or chronic liver disease
4. Any chronic medical condition requiring a higher dose of corticosteroid than 5mg prednisone/prednisolone bid
5. Have known allergies, hypersensitivity, or intolerance to abiraterone acetate, apalutamide or prednisone or their excipients.
6. Pathological finding consistent with small cell carcinoma of the prostate
7. Symptomatic liver or visceral organ metastasis
8. Have a history of gastrointestinal disorders (medical disorders or extensive surgery) that may interfere with the absorption of the study agents
9. Known brain metastasis
10. Prior cytotoxic chemotherapy or biologic therapy for the treatment of CRPC. Note: sipuleucel-T is permitted with a 2-week washout.
11. Previously treated with ketoconazole for prostate cancer for greater than 7 days
12. Prior systemic treatment with an azole anti-fungal drug (e.g. fluconazole, itraconazole) within 4 weeks of Cycle 1, Day 1.
13. Uncontrolled hypertension (systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg). Patients with a history of hypertension are allowed provided blood pressure is controlled by anti-hypertensive treatment
14. Poorly controlled diabetes, FBS ≥200 mg/dL
15. History of pituitary or adrenal dysfunction
16. Symptomatic Atrial Fibrillation, or other symptomatic cardiac arrhythmia
17. Other malignancy, except non-melanoma skin cancer, with a ≥ 30% probability of recurrence within 24 months
18. History of any of the following:

- Seizure or known condition that may pre-dispose to seizure (e.g. prior stroke within 6 months of Cycle 1 Day 1, brain arteriovenous malformation, Schwannoma, meningioma, or other benign CNS or meningeal disease which may require treatment with surgery or radiation therapy)
- Severe or unstable angina, myocardial infarction, symptomatic congestive heart failure, arterial or venous thromboembolic events (e.g., pulmonary embolism, cerebrovascular accident including transient ischemic attacks), or clinically significant ventricular arrhythmias within 6 months prior to first dose of study drug. Venous thrombolic events within 6 months are permitted IF they are not attributed to prostate cancer (in the opinion of the treating physician).

19. Baseline administration of concomitant strong CYP3A4 inducers and planned to continue during abiraterone acetate treatment.
20. Baseline administration of and planned co-administration of abiraterone acetate with CYP2D6 substrates that have a narrow therapeutic index. If an alternative treatment cannot be used, exercise caution and consider a dose reduction of the concomitant CYP2D6 substrate
21. Baseline moderate or severe hepatic impairment (Child Pugh Class B & C)
22. Use of herbal products that may decrease PSA levels (i.e., saw palmetto) refer to section 8.3.2 (no washout period required)
23. Administration of an investigational therapeutic within 30 days prior to Cycle 1, Day 1
24. Any condition which, in the opinion of the investigator, would preclude participation in this trial

7. PATIENT REGISTRATION

After signing informed consent and completing eligibility screening, patients who are selected to participate will be registered with the lead site (Duke) and with their study site/institution. A record of patients who fail to meet entry criteria (i.e., screen failures) will be maintained. Patient registration must be complete before beginning any treatment.

7.1 Informed Consent

Authorized study personnel should fully explain the scope of the study to each patient before obtaining informed consent. If the patient is not able to fully understand the informed consent due to a known comorbidity, such as Alzheimer's disease, a legally authorized representative will be included in the consent process. Patients, and a legally authorized representative if appropriate, should be advised of any known risks inherent in the planned procedures, of any alternative treatment options, of their right to withdraw from the study at any time for any reason, and of their right to privacy. If a legally authorized representative signs the consent, the patients' assent will also be documented.

When obtaining informed consent, study personnel should:

First: Confirm that the patient is a potential candidate for study participation.

Next: Obtain dated and signed informed consent.
Finally: Confirm that the patient is eligible as defined in Section 6.3 (Inclusion/Exclusion Criteria). A record of patients who fail to meet entry criteria (i.e., screening failures) will be maintained.

For patients consented at the lead site ONLY, registration in the Duke clinical trial subject registry must be completed within 1 business day of the patient providing informed consent.

7.2 Lead Site Registration

Patient registration for all patients signing informed consent will be completed by Duke University Genitourinary Oncology Group. Following consent and completion of the Eligibility Checklist, de-identified documents will be submitted for review and registration of subject. All subjects will be assigned a unique study ID.

Refer to Subject Registration Instructions for details. See coordinator manual.

Patients will be enrolled only after all pre-treatment screening evaluations are completed and all eligibility criteria are met. Once the patient has signed consent and been found to meet all eligibility criteria, the subject will be registered. The date of enrollment is the date the patient starts study drug. A unique patient study identification number will be assigned by the enrolling site upon consenting. This number will include the site # and subject number such as 01-001. 01 being the site number and 001 being the first subject enrolled at that site. The numbers will be assigned sequentially and include all subjects that are consented. Minimal amount of information will be entered into the database for subjects that consent but do not enroll. Treatment must not commence until the study team has received the approved documentation from the lead site. Treatment will commence according to the guidelines in the protocol. Should a patient present on Cycle 1 Day 1 with an adverse event that is in conflict with the eligibility criteria, the subject may be treated for the adverse event and started on study drug as scheduled per the treating provider's discretion. The event must be reviewed and approved by the Sponsor-Investigator prior to starting therapy.

7.3 Institutional Registration

Patient registration at each study site/institution will be conducted according to the institution's established policies. Prior to registration, patients will be asked to sign and date an Institutional Review Board (IRB)-approved consent form. Patients must be registered with their local site/institution and with the lead site before beginning any treatment or study activities.

8. TREATMENTS

8.1 Abiraterone acetate

8.1.1 Abiraterone acetate Formulation

Abiraterone acetate 250-mg tablets are oval, white to off-white and contain abiraterone acetate and compendia (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 tableting).

8.1.2 Handling 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. Women who are pregnant or who may be pregnant should wear gloves if they need to touch abiraterone acetate tablets**.** You should notify any caregivers and staff personnel of this information, to ensure the appropriate precautions are taken.

8.1.3 Abiraterone acetate administration

The study agent abiraterone acetate will be administered by the patient at a dose of 1000mg orally once daily with prednisone 5 mg BID in 4-week cycles throughout the treatment period. Abiraterone acetate must be taken on an empty stomach. No food should be consumed for at least one hour before the dose of abiraterone acetate is taken and for at least two hours after the dose of abiraterone acetate is taken. Abiraterone acetate should be taken with a glass of water and consumed over as short a time as possible. Patients should swallow the tablets whole and not chew them. Study drug will be provided by Janssen Scientific Affairs and distributed by DCI Investigational Chemotherapy Service, which will be distributing drug to the satellite sites. Study drug should at all times be kept in the original packaging.

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. The safety of these increased exposures when multiple doses of abiraterone acetate are taken with food has not been assessed.

Patients will be instructed to take a 5mg prednisone tablet, twice daily with food. It is not required for the prednisone to be taken at the same time as abiraterone acetate. The dose of prednisone will remain unchanged in the event that the study drug dose is changed. If a prednisone dose is missed, it should be omitted and will not be made up. Should a dose modification of the prednisone be needed due to toxicities, the site will need to discuss this with the Sponsor-Investigator.

Each treatment cycle consists of 28 consecutive days. No cycle will be delayed. If doses of study drug are held or missed, they will not be made up. The subject could complete a maximum of 26 cycles during the 24 month duration of the study. Patients may take apalutamide with abiraterone acetate plus prednisone until radiographic disease progression (as defined in Section 12.5); at which time study treatment will be discontinued.

If vomiting occurs during the course of treatment, no redosing of the patient is allowed before the next scheduled dose. If > 6 hours after the subject's regularly scheduled dose then the dose should be withheld that day and abiraterone acetate should be restarted the following day.

8.1.4 Effects of Abiraterone Acetate on Drug Metabolizing Enzymes

Abiraterone acetate is an inhibitor of the hepatic drug-metabolizing enzyme CYP2D6. In a CYP2D6 drug-drug interaction trial, the Cmax and AUC of dextromethorphan (CYP2D6 substrate) were increased 2.8- and 2.9-fold, respectively, when dextromethorphan was given with abiraterone acetate 1,000 mg daily and prednisone 5 mg twice daily. Avoid co-administration of abiraterone acetate with substrates of CYP2D6 with a narrow therapeutic index (e.g., thioridazine). If alternative treatments cannot be used, exercise caution and consider a dose reduction of the concomitant CYP2D6 substrate drug.

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

Drugs that Inhibit or Induce CYP3A4 Enzymes

Based on in vitro data, abiraterone acetate is a substrate of CYP3A4. In a clinical pharmacokinetic interaction study of healthy subjects pretreated with a strong CYP3A4 inducer (rifampin, 600 mg daily for 6 days) followed by a single dose of abiraterone acetate 1000 mg, the mean plasma AUC∞ of abiraterone was decreased by 55%.

Strong inducers of CYP3A4 (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital) during treatment with abiraterone acetate are to be avoided, or used with careful evaluation of clinical efficacy.

In a separate clinical pharmacokinetic interaction study of healthy subjects, coadministration of ketoconazole, a strong inhibitor of CYP3A4, had no clinically meaningful effect on the pharmacokinetics of abiraterone.

All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded. If a patient requires an abiraterone acetate or apalutamide dose delay of >21 days from the previous dose or 28 days in cases of rash, the patient must be discontinued from treatment (unless unrelated to study drug and approved by the Sponsor-Investigator) with the delayed drug but remain on study for other study treatments as planned.

Medication labels will comply with US legal requirements and be printed in English. Labels of subjects at Duke will include their name and medical record number. External sites will include information according to their institutional guidelines. The storage conditions for study drug will be described on the medication label.

8.2 Apalutamide

Apalutamide has been approved by the FDA for the treatment of nonmetastatic castrate resistant prostate cancer and metastatic castration-sensitive prostate cancer at a dose of 240 mg. Apalutamide has not been approved by the FDA for metastatic castration resistant prostate cancer and, consequently, is investigational in the context of this study.
Tablets: The apalutamide drug substance is an almost white to slightly brown powder that is formulated in tablets at a strength of 60 mg.
Apalutamide is administered orally on a continuous once daily dosing schedule. Each cycle of drug administration consists of 28 days. Doses from 30 to 480 mg were tested in the Phase 1 portion of the first clinical study (Study ARN-509-001). The therapeutic dose is 240 mg once daily. Apalutamide can be taken with or without food.

8.2.1 Apalutamide Tablets

Apalutamide tablets (60 mg) are packaged in 120-count bottles, and should at all times be kept in the original packaging.
Detailed information on handling and storage conditions will accompany the clinical drug supplies to the clinical study site(s). The storage conditions and expiry will be indicated on the label of the drug product.

8.2.2 Apalutamide Pharmacology

The mechanism of action of apalutamide is through antagonism of the androgen receptor and inhibition of AR nuclear translocation and DNA binding to AREs. Unlike bicalutamide, apalutamide shows no significant agonist properties in a model of CRPC
(e.g., AR-over-expressing prostate cancer cells; LNCaP/AR cells). Gene transcription of PSA and TMPRSS2 is inhibited by apalutamide and results in concentration-dependent reduction of these protein levels in vitro. Apalutamide was also shown to reduce proliferation of CRPC cells as well as increase apoptosis and necrosis in vivo. These effects are supported by the anti-tumor activity observed in murine tumor CRPC models, where apalutamide showed

dose-dependent tumor growth inhibition and tumor regression over a dose range of 0.1 to 10 mg/kg/day, with effects that were superior to bicalutamide.

8.3 Concomitant therapy

All medications (excluding prior chemotherapy and biologic, immunologic or radiation therapy) taken within 4 weeks prior to the administration of apalutamide and abiraterone acetate and all concomitant therapy administration during the study with reasons for therapy should be recorded.
Patients on chronic medications that can be given concomitantly with apalutamide and abiraterone acetate should be maintained on the same dose and dose schedule throughout the study period, as medically feasible. The investigator should instruct the patient to notify the study site about any new medications he takes after the start of the study drug. All new medications, changes in medication dosing, and significant non-drug therapies (including herbal medicines, physical therapy and blood transfusions) administered after the patient starts treatment with study drug and 30 days after end of treatment will be recorded in the database (during the safety follow up period).

8.3.1 Permitted Concomitant Medications

The following concomitant medication/therapies are permitted if deemed necessary for the care of the patient:

- Standard therapies for preexisting conditions, medical/surgical complications including nausea and diarrhea, and palliation.
- Non-potent CYP3A4 isoenzyme inhibitors and/or inducers.
- LHRH agonists or antagonists.
- Anti-hypertensive medications.
- Diabetic medications.
- Antidepressants or other medications for mood disorders.
- Analgesics including opioids.
- Bisphosphonates and/or denosumab.
- Erythropoietic agents.
- Systemic anticoagulation with low molecular weight heparin.
- Focal therapies for localized non-prostate cancers
- Provenge, after the first 3 cycles on treatment are completed.

8.3.2 Prohibited Concomitant Medications

- Other investigational therapies must not be used while the patient is on the study.
- Site pharmacist or physician should review subject's concomitant medication list while subject is in screening and once enrolled on study, for any drug interaction.

- Chemotherapy, radiation therapy, or immunotherapy, or any anti-cancer therapy other than apalutamide and abiraterone acetate and prednisone and those described above or below.
- Herbal preparations/medications are not allowed throughout the study. These herbal medications include, but are not limited to: St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications, with no washout delay required prior to first dose of study drug.
- In lieu of surgical castration, the use of an LHRH agonist or antagonist must continue while on this study. However, antiandrogens, ketoconazole, estrogens, and all other forms of hormonal manipulation are not permitted for the treatment of cancer.
- Investigators should keep in mind the possibility that abiraterone acetate may interact with concomitant medications, particularly those that are metabolized or activated by P450 CYPs 2D6 and 1A2 (see Appendix 2 for a list of such medications to be used with caution). Please see comments above regarding interactions. If at any time an investigator suspects a drug-drug interaction due to abiraterone acetate therapy, an adverse event report should be completed and Duke University notified.
- Immunosuppressive doses of systemic corticosteroids greater than prednisone 5 mg twice daily or the equivalent. Short term use of systemic corticosteroids are allowed for side effect management with notification to the Sponsor-Investigator.
- As a class effect, AR antagonists have been associated with seizures due to an off-target mechanism of action (gamma amino butyric acid chloride channel [GABAA] inhibition). Drugs known to lower the seizure threshold or cause seizures are prohibited. See appendix 2.A representative list is included below:
  - Atypical antipsychotics (e.g. clozapine, olanzapine, risperidone, ziprasidone)
  - Bupropion
  - Lithium
  - Meperidine and pethidine
  - Phenothiazine antipsychotics (e.g., chlorpromazine, mesoridazine, thioridazine)
  - Tricyclic antidepressants (e.g., amitriptyline, desipramine, doxepin, imipramine, maprotiline, mirtazapine

8.3.3 Restricted Concomitant Medications

Apalutamide is metabolized primarily by human CYP3A4, thus co-administration with strong inhibitors or inducers of CYP3A4 should be avoided as much as possible (see Appendix 2 for a list of these medications to be used with caution). Apalutamide may also induce CYP3A4; therefore, caution should be taken when administered in conjunction with CYP3A4 substrates that have a narrow therapeutic index. Examples of the strong CYP3A4 inhibitors and inducers include the following:

- Strong CYP3A4 inhibitors: itraconazole, clarithromycin, erythromycin, diltiazem, verapamil, delavirdine, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir,

telithromycin, voriconazole, grapefruit juice (or grapefruits); co-administration with any of these agents may increase apalutamide plasma concentrations

- Strong CYP inducers: phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, efavirenz, tipranivir, St. John's wort; co-administration with any of these agents may decrease apalutamide plasma concentrations

The potential for drug-drug interaction between apalutamide and warfarin (e.g., Coumadin) is unknown at present. If a subject is taking warfarin, re-assess PT (prothrombin time) /international normalized ratio (INR) as clinically indicated and adjust the dose of warfarin accordingly.

Based on in vitro data, abiraterone acetate is a substrate of CYP3A4. In a dedicated drug interaction trial, co-administration of rifampin, a strong CYP3A4 inducer, decreased exposure of abiraterone by 55%. Avoid concomitant strong CYP3A4 inducers during abiraterone acetate treatment. If a strong CYP3A4 inducer must be co-administered, increase the abiraterone acetate dosing frequency. In a dedicated drug interaction trial, co-administration of ketoconazole, a strong inhibitor of CYP3A4, had no clinically meaningful effect on the pharmacokinetics of abiraterone. Abiraterone acetate is an inhibitor of the hepatic drug-metabolizing enzymes CYP2D6 and CYP2C8. In a CYP2D6 drug-drug interaction trial, the Cmax and AUC of dextromethorphan (CYP2D6 substrate) were increased 2.8- and 2.9-fold, respectively, when dextromethorphan was given with abiraterone acetate 1,000 mg daily and prednisone 5 mg twice daily. Avoid co-administration of abiraterone acetate with substrates of CYP2D6 with a narrow therapeutic index (e.g., thioridazine). If alternative treatments cannot be used, exercise caution and consider a dose reduction of the concomitant CYP2D6 substrate drug. In a CYP2C8 drug-drug interaction trial in healthy subjects, the AUC of pioglitazone (CYP2C8 substrate) was increased by 46% when pioglitazone was given together with a single dose of 1,000 mg abiraterone acetate. Therefore, patients should be monitored closely for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used.

8.4 Treatment compliance

Participating sites will be provided with a medication diary for each patient to document his self-administration of apalutamide, abiraterone acetate, and prednisone per cycle. A current and accurate account of the number of study treatment tablets the investigator received from Duke University, dispensed to the patients, the number of units returned to the investigator by the patient, and the number of units returned to Duke University during and at the completion of the study must be maintained. A detailed inventory must be completed for the study treatment. Records of study medication used, dosages administered, and intervals between visits will be recorded during the study. Drug accountability will be noted and patients will be asked to return all unused study medication.

9. STUDY ASSESSMENTS

9.1 Vital signs, performance status, and physical exam

Vital sign assessment consists of height (first visit), pulse, blood pressure, respiration rate, temperature and weight per the visit schedule.

The patient will be asked to check his blood pressure at home at least monthly between clinic appointments and notify the coordinator of elevated blood pressures grade 2 and above. This will be recorded on the medication diary provided to the patient and collected at the end of each cycle. Elevated blood pressure readings should be confirmed with a second reading taken after the patient has rested.

Performance status will be assessed at screening and per the visit schedule using the Karnofsky performance status scale (Appendix 1).

Physical examination will comprise a total body examination (general appearance, skin, including eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities and basic nervous system). Significant findings made after the start of study drug which meet the definition of an Adverse Event must be recorded.

9.2 Laboratory evaluations

The following laboratory studies will be obtained at specified intervals to assess subject safety, specifically the risk of infection, hyperglycemia, thyroid and/or bone marrow, liver, and kidney abnormalities. Abnormalities will be captured as AEs only if deemed clinically significant by the treating physician/provider/investigator.

- **Hematology:** Complete blood count (CBC) consisting total white blood cell count (WBC) with differential (total neutrophil count, lymphocyte, monocyte, eosinophil, and basophil counts), hemoglobin, hematocrit, and platelet count.
- **Blood chemistry:** Blood urea nitrogen (BUN), creatinine, sodium, potassium, calcium, chloride, bicarbonate (CO_2), glucose, albumin, total protein, total bilirubin, alkaline phosphatase, AST (SGOT), ALT (SGPT).
- **LDH** at screening (or C1D1 prior to first dose) then every day 1 of all cycles scheduled per protocol and end of treatment.
- **TSH** to be obtained screening, every day 1 of cycles 2, 3, 4, and then every 3 cycles and end of treatment. If TSH is abnormal complete a T3/T4.
- **PSA** to be obtained at screening, Day 1 of Cycle 1 and cycles 2, 3, 4, and every 3rd cycle going forward and at the end of treatment visit.

- **Testosterone** to be obtained at screening (or C1D1 prior to first dose) and C4D1.

9.3 ECG

A standard 12-lead ECG is to be performed at screening and significant findings must be recorded. Additional ECGs may be performed at the discretion of the treating physician.

9.4 Imaging

A CT scan with contrast of chest, abdomen, and pelvis will be performed within 42 days prior to C1D1 visit, and every 3 cycles (approximately every 12 weeks) as part of routine tumor assessment. These scans are to be performed on day 1 of every 3 cycles (i.e. screening, Day 1 of cycles 4, 7, 10, etc.) within 7 days prior to starting the next cycle. If the chest CT at screening is clear, chest x-rays may be used for subsequent assessments at the enrolling physician's discretion. The tumor assessments will be performed locally, in strict accordance with the RECIST 1.1 guidelines (Note: during screening, metastatic disease may be confirmed by prostate cancer-specific PET imaging without meeting RECIST 1.1 criteria). A total body bone scan will be performed within 42 days of C1D1 visit and every 3 cycles (approximately every 12 weeks) and interpreted according to modified PCWG3 guidelines. CT and bone scan modalities per standard institutional practices may be used, but the same modality should be used throughout the study for each subject.

Because the primary endpoint is progression free survival based upon radiographic disease progression, patients will continue to have CT scans and Bone Scans performed according to standard clinical practice even if study treatment is discontinued for reasons other than radiographic disease progression.

9.5 Exploratory correlative studies

9.5.1 Ancestral Genotyping and SNP Analysis

Human whole blood will be collected at baseline for DNA isolation. Isolated DNA will be used for ancestral genotyping and characterization of SNPs. To obtain genetically estimated indicators of race, ancestral genotyping will be performed. In addition, characterization of SNPs of the androgen receptor gene, androgen metabolism genes (including *CYP19A1*, *HSD3B1*, *HSD17B4, SLCO2B1* and *SLCO1B3*), androgen signaling genes and 147 genes that we have shown to be differentially expressed in African American versus Caucasian prostate will be performed using targeted DNA sequencing. Associations with response to abiraterone acetate

plus apalutamide will be evaluated. A genome wide association study (GWAS) is planned in both African American and Caucasian men with mCRPC and their associations with response to abiraterone acetate plus apalutamide. The local site will process these samples and prepare them for shipment to the lead site per shipping instructions below. The lead site will perform the laboratory analysis. Neither the local sites nor the patients will receive information regarding individual subjects' results.

9.5.2 Hormone Levels and Metabolomics Profile Including Lipid Levels

To assess hormone and lipid levels, serum will be collected at baseline, the end of cycle 3 (at Cycle 4 Day 1) and the end of treatment visit. A metabolomics profile will be conducted to assess lipids level. The metabolomics profile labs will be drawn fasting. The hormone analysis labs will be drawn fasting, when available. The hormone analysis labs may be performed with non-fasting samples when fasting is not available.

Lipidomic analysis will be performed by Dr. Massimo Loda, Dr. Sara Bleve and Dr. David Nanus at Weill Cornell Medicine. As part of their analysis, samples may be sent to Lipometrix. This work will aim to identify a minimally invasive lipid biomarker of response to ARSI in Black and White men with mCRPC. Through liquid chromatography and mass spectrometry, we will detect lipidomic signatures associated with ARSI response in mCRPC and correlate the lipid alterations profiles with prostate racial disparity.

9.5.2.1 Steroid Hormone Analysis

Steroid hormone analysis will occur at baseline, Cycle 4 Day 1 and end of treatment and be performed by Dr. Elahe Mostaghel and Dr. Bruce Montgomery as previously described. [36-38] This analysis will include up to 100 patients from this study and up to 100 patients from the Abi Race study (Pro00046383, NCT01940276). Abi Race enrolled 50 White patients receiving abiraterone acetate + prednisone and 50 Black patients receiving abiraterone acetate + prednisone.

We will quantify steroid hormones, covering the full range of testicular and adrenal derived steroids (over 20 metabolites offered in 5 panels: androgens, estrogens, corticosteroids, 11-hydroxy steroids, and sulfates) in serum specimens. The primary metabolites measured will include androstenedione (AED), testosterone, progesterone, pregnenolone, androsterone, dehydroepiandrosterone (DHEA), dihydrotestosterone (DHT), and dehydroepiandrosterone sulfate (DHEAS). Using these data and clinical data from the Abi Race and PANTHER studies, we will assess race- and genetic ancestry-related steroid hormones and response to abiraterone and combination abiraterone and apalutamide in metastatic castration-resistant prostate cancer (mCRPC).

9.5.3 Pharmacokinetics assessment

For the pharmacokinetics assessment, we will analyze abiraterone acetate and metabolites produced by conversion of abiraterone acetate by steroid metabolizing enzymes. Specifically, we will analyze concentrations of Abi, D4A, 5α-Abi, 5β-Abi, 3-keto-5α-Abi, 3α-OH-5α-Abi, 3β-OH-5α-Abi, 3-keto-5β-Abi, 3α-OH-5β-Abi and 3β-OH-5β-Abi. Concentrations of abiraterone acetate and the aforementioned metabolites will be analyzed in serum samples collected at two time points. Specifically, samples will be drawn on cycle 1 day 1 at 1, 2, 4, 8, hours post dose and cycle 2 day 1 at 24 hour trough, 1, 2, 4, and 8 hours post dose. Drug, drug metabolites and internal standard will be extracted from serum and analyzed using mass spectrometry as described by Li Z et al.[84,85] There is a +/- 15 minute window for all PK lab draws, except for the 8 hour timepoint. There is a +/- 1 hour window for the 8 hour timepoint. Should a subject require a study drug hold during the two weeks prior to cycle 2 day 1, the PK draws will be delayed until the next cycle. The subject should have taken two weeks of study drug prior to cycle 2 (or later) PK. Subject may miss two doses in the two weeks prior to PK draw, if not on drug hold. . The Sponsor-Investigator must be notified of the delay.

9.5.4 Plasma samples for blood-based biomarkers

Plasma samples will be assessed by multiplex ELISA for circulating cytokines and growth factors related to angiogenesis, immune response and inflammation. Samples will be collected at baseline, at Cycle 2 Day 1, and end of treatment to define levels, patterns of expression and pharmacodynamics change during treatment. These additional biomarker analyses will be in support of the specified endpoints in the protocol.

9.5.5 Expression and Splicing Analysis

RNA samples will be collected at baseline, cycle 4, and at progression or end of treatment to determine expression and splicing status of the androgen receptor gene, genes involved in androgen metabolism and signaling and genes that we have shown to be differentially expressed and/or spliced in African American versus Caucasian prostate cancer. Associations with response to abiraterone acetate plus apalutamide will be evaluated.

9.5.6 Cell-Free Plasma DNA Analysis

Cell-free plasma DNA profiles will be investigated at baseline and at progression or end of treatment. Associations with response to abiraterone acetate plus apalutamide will be evaluated.

9.5.7 Collection of Tumor Tissue for Somatic SNP, Expression and/or Splicing Assessments

FFPE archival tumor tissue will be collected whenever available from all patients having undergone a diagnostic core biopsy or a surgery (prostatectomy or metastatic sampling). Fresh frozen or FFPE samples will be batched and evaluated collectively by targeted sequencing, IHC, and/or QRT-PCR for the status of the androgen receptor gene, target genes involved in androgen metabolism and signaling, and target genes that have been shown to be differentially expressed and/or spliced in African American versus Caucasian prostate cancer. Tumor content of samples will be confirmed using H&E. The relationship between germline and somatic DNA and RNA variants will be defined.

In patients without target SNP alterations, it will be important to confirm that there are not somatic tumor alterations within these genes. Discrepancies between germline and somatic mutations will be further evaluated. Methodologies used and evaluations performed will be determined by the yield, tumor content and time points of specimens and DNA/RNA obtained.

Samples will be stored by Dr. Jennifer Freedman, PhD with access limited to key personnel. DUHS will maintain these samples for up to 20 years. Upon completion of this protocol, these samples will be kept in long-term storage at the Duke BioRepository and Precision Pathology Center (BRPC) under the protocol designated IRB# Pro00035974. Any future analyses not specified in this protocol will be agreed upon by prior approval from Janssen Scientific Affairs, LLC.

9.5.8 Sample Collection, Storage and Shipping Instructions

See Laboratory Manual for further details regarding sample collection, storage and shipping.

Once complete, these samples will be analyzed for their appropriate endpoints, as indicated in the study (i.e. ancestral genotyping, SNPs, lipidomics, hormone levels, RNA transcripts, cell-free plasma DNAs and plasma biomarkers). Access to these samples will be limited to Drs. George, Freedman, Nixon, Sharifi, Mostaghel, Montgomery, Loda, Bleve, Nanus and their proxy staff and Lipometrix. These samples will be maintained for up to 20 years, and managed as described above. Any future analyses not specified in this protocol will be agreed upon by prior approval from Janssen Scientific Affairs, LLC.

Ancestral genotyping will be done in collaboration with Rick Kittles, PhD, [redacted] SNP and RNA transcript analysis will be done in collaboration with the Duke Center for Genomic and Computational Biology Sequencing and Genomic Technologies Shared Resource, [redacted] determination of lipid and hormone levels will be done in collaboration with Biocrates Life Sciences AG, Eduard-Bodem-Gasse 8, 6020 Innsbruck, Austria, and investigation of cell-free plasma DNA and plasma biomarkers will be done in collaboration with Andrew Nixon, PhD, [redacted] Pharmacokinetic and cell-free plasma DNA analysis will be done in collaboration with Dr Nima Sharifi, [redacted] Steroid hormone analysis will be performed in collaboration with Dr. Elahe Mostaghel and Dr. Bruce Montgomery at the V.A. [redacted] Lipidomic analysis will be performed in collaboration with Dr. Massimo Loda, Dr. Sara Bleve and Dr. David Nanus at Weill Cornell Medicine, [redacted] Dr. Loda may send samples for lipidomic analysis to Lipometrix, [redacted]

9.6 End of treatment

The end of treatment visit will occur within 7 days (+/- 7days) of the last dose of study drug or 7 days from the decision to remove the subject from the study if the subject has been off study drug more than 7 days.

9.7 Follow up safety visit

The safety follow up visit will occur within 30 days (+/- 7 days) of the last dose of study drug. Adverse events must be followed for 30 days of the last dose of study drug. SAEs that remain open at the end of the follow up safety visit must be followed as detailed in section 11.5.1.

9.8 Follow-Up for Radiographic Progression

During the Follow-up Period, subsequent therapy for prostate cancer should be assessed every 3 months (+/- 14 days) for up to 24 months after the first dose of study drug. Since the primary endpoint is progression free survival based upon radiographic disease progression, patients will continue to have CT scans and Bone Scans performed according to standard clinical practice until they have radiographic progression or until they have started another therapy for prostate cancer.

9.9 Follow-Up for Overall Survival

All subjects will be followed for survival every 6 months +/- 1 month by phone or chart review. This will begin 6 months from the safety follow up visit or last active study visit if a safety follow up visit was not completed.

10. MONITORING AND MANAGEMENT OF SUSPECTED ABIRATERONE ACETATE AND APALUTAMIDE TOXICITY

10.1 Management of Drug-Related Adverse Events

Should a patient present on Cycle 1 Day 1 with an adverse event that is in conflict with the eligibility criteria, the subject may be treated for the adverse event and started on study drug as scheduled per the treating provider's discretion. The event must be reviewed and approved by the Sponsor-Investigator prior to starting therapy.

The most common adverse drug reactions (≥10%) reported in clinical studies were fatigue, joint swelling or discomfort, edema, hot flush, diarrhea, vomiting, urinary tract infection, cough, hypertension, dyspnea, and contusion. The administration of prednisone is expected to mitigate these side effects by supplementing cortisol and abrogating ACTH drive.

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

For guidance on management of side effects of glucocorticoid usage, symptoms related to castration (androgen deprivation), severe and refractory headaches, fatigue, or other toxicities the Principal Investigator at Duke University should be contacted.

AA=abiraterone acetate; ALT=alanine aminotransferase; AST=aspartate aminotransferase; LFT=liver function tests; ULN=upper limit of normal

10.1.1 Dose Modifications for Hypokalemia Attributed to Abiraterone Acetate

Toxicity	Dose of abiraterone acetate	Dose of apalutamide	Dose of prednisone

Grade 1 or 2	Initiate oral potassium supplementation, titrate to ≥3.5 to ≤5.0 mmol/L, maintenance at ≥4.0 mmol/L recommended	No change	No change
≥Grade 3	Hold and initiate IV potassium and cardiac monitoring, resume only after discussion and approval by the Sponsor-Investigator	No change	No change or consider tapering once AA is discontinued

Correct hypokalemia before and during treatment with abiraterone acetate. Monitor serum potassium at as required by schedule of events. Hypokalemia may need to be monitored more frequently until resolved.

10.1.2 Dose Modifications for Hypertension and Edema/Fluid Retention Attributed to Abiraterone Acetate/Apalutamide

Toxicity grading will be done on the blood pressure reading and not the number of medications taken for the hypertension

Toxicity	Dose of abiraterone acetate	Dose of apalutamide	Dose of prednisone
Grade 1 or 2	No change	No change	No change
≥Grade 3	Hold until Grade 1 or baseline, resume at full dose	No change	No change
First Recurrence ≥Grade 3	Hold until Grade 1 or baseline, resume at 750 mg (3 tablets)	No change	No change
Second Recurrence ≥Grade 3	Hold until Grade 1 or baseline, resume at 500 mg (2 tablets)	Hold until Grade 1 or baseline, resume at 180 mg (3 tablets)	No change
Third Recurrence ≥Grade 3	Discontinue	Hold until Grade 1 or baseline, resume at 120 mg (2 tablets)	Consider tapering once AA is discontinued
Fourth Recurrence ≥Grade 3	n/a	Discontinue	Discontinue

10.1.3 Dose Modifications for LFT Abnormalities Attributed to Abiraterone Acetate/Apalutamide

Dose modifications are provided as guidance and should not replace the investigator's own clinical judgment.

Toxicity	Dose of abiraterone acetate	Dose of apalutamide	Dose of prednisone
Grade 1 or 2	No change	No change	No change
Grade 3	Hold until return to baseline AST and ALT or ≤1.5 x ULN and ≤2.5 x ULN total bilirubin, resume at 750 mg (3 tablets) only after discussion and agreement with Sponsor-Investigator	Hold until return to baseline	No change
Recurrence Grade 3	Hold until return to baseline AST and ALT or ≤1.5 x ULN and ≤2.5 x ULN total bilirubin, resume at 500 mg (2 tablets) only after discussion and agreement with Sponsor-Investigator	Hold until return to baseline then dose reduce to 180 mg (3 tablets) only after discussion and agreement with Sponsor-Investigator	No change
Grade 4	Discontinue AA treatment	Discontinue apalutamide treatment	No change or consider tapering once AA discontinued
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 AA treatment	Discontinue apalutamide treatment	No change or consider tapering once AA discontinued

10.1.4 Dose Modifications for Other Toxicities Attributed to Abiraterone Acetate/Apalutamide

Dose modifications are provided as guidance and should not replace the investigator's own clinical judgment. Note that if abiraterone is stopped then prednisone can also be stopped.

Toxicity	Dose of abiraterone acetate	Dose of apalutamide	Dose of prednisone
Grade 1 or 2	No change	No change	No change
≥Grade 3	Hold until Grade 1 or baseline, resume at full dose	No change	No change
First Recurrence ≥Grade 3	Hold until Grade 1 or baseline, resume at 750 mg (3 tablets)	Hold until Grade 1 or baseline, resume at 180 mg (3 tablets)	No change
Second Recurrence ≥Grade 3	Hold until Grade 1 or baseline, resume at 500 mg (2 tablets)	Hold until Grade 1 or baseline, resume at 120 mg (2 tablets)	No change
Third Recurrence ≥Grade 3	Discontinue	Discontinue	Consider tapering once AA is discontinued
First occurrence of seizure of any grade or Grade 4 neurotoxicity	No change	Discontinue	No change

10.1.5 Dose Modifications for Other Rash Attributed to Apalutamide

Dose modifications are provided as guidance and should not replace the investigator's own clinical judgment.

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 of Rash	Intervention

Grade 1	• Continue apalutamide at current dose
	• Initiate dermatological treatment[a]
	  ○ Topical steroid cream AND
	  ○ 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] o If rash or related symptoms improve, reinitiate apalutamide when rash is Grade≤1. Consider dose reduction at a 1 dose level reduction[c].
Grade ≥3[d]	• Hold apalutamide for up to 28 days • Initiate dermatological treatment[a] o Topical steroid cream AND o Oral Antihistamines AND o 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 o Reinitiate apalutamide at a 1 dose level reduction[e] when rash is Grade≤1. o 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 Sponsor-Investigator 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 1 dose level reduction = 60mg (1 apalutamide tablet)

d If there is blistering or mucosal involvement, stop apalutamide dosing immediately and contact Sponsor-Investigator

e 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 Sponsor-Investigator.

10.1.6 Modified Dose levels for all study drugs

General guidelines for modified study drug doses, to be applied per classification of adverse events in sections 10.1.1 – 10.1.5. Dosing of study drug will not be re-escalated once the dose has been modified (reduced).

Study Drug	Starting Dose	1st Dose modification	2nd Dose modification
Abiraterone acetate	1000 mg (4 tablets)	750 mg (3 tablets)	500 mg (2 tablets)
Apalutamide	240 mg (4 tablets)	180 mg (3 tablets)	120 mg (2 tablets)
Prednisone	5 mg twice daily	Per physician discretion	Per physician discretion

10.2 Interruption or discontinuation of treatment

All interruptions or changes to study drug administration must be recorded.

It will be documented whether or not each patient completed the clinical study. If for any patient either study treatment or observations were discontinued the reason will be recorded.

Reasons that a patient may discontinue participation in a clinical study are considered to constitute one of the following:

i. Disease progression by modified PCWG3 criteria
ii. Clinical progression by the discretion of the treating physician
iii. Need for radiation or new systemic therapy for prostate cancer
iv. Unacceptable toxicity requiring cessation of therapy, including adverse event(s), abnormal laboratory value(s), or abnormal test/procedure result(s): Patients, who have sustained toxicities that do not return to NCI CTCAE (version 4.0) baseline grade with appropriate medical management, may be discontinued from the study treatment.
v. Protocol violation
vi. Patient withdrawal of consent - the reason(s) for withdrawal must be documented and clarification requested whether withdrawal of consent applies only to the Treatment Phase (i.e. patient has not withdrawn consent for data collection during the post-treatment Follow-Up Phase) or to both the Treatment and Follow-Up Phases. A patient's decision to take part in the study is voluntary, and he may choose not to take part in the study or to stop taking part at any time. If he chooses not to take part or to stop at any time, it will not affect his future medical care.
vii. Death

Patients whose treatment is interrupted or permanently discontinued due to an adverse event must be followed at 4-week intervals or closer until resolution to Grade I or less. For clinically significant laboratory changes resulting in treatment interruption or discontinuation, patients must have their values monitored at least once a week for 4 weeks, and subsequently at 4-week intervals, until resolution to < Grade II or stabilization of the event, whichever comes first. If a patient requires an apalutamide dose delay of >21 days, or 28 days in cases of rash, from the day of the next scheduled dose, then the patient should discontinue treatment with apalutamide but remain on study for other study treatments (abiraterone acetate and prednisone as planned). Similarly, if a patient requires an abiraterone acetate dose delay of >21 days, or 28 days in cases of rash, from the day of the next scheduled dose, then the patient should discontinue treatment with abiraterone acetate but remain on study for other study treatments (apalutamide as planned). All patients must be followed for adverse events and serious adverse events for 30 days following the last dose of apalutamide and/or abiraterone acetate. All SAEs must be reported to Duke University as detailed in section 11.2-3.

An investigator may withdraw a patient from the study Treatment Phase at any time based on clinical judgment or for any of the following reasons listed above.

11. SAFETY ASSESSMENTS AND REPORTING

Safety assessments will consist of monitoring and recording all adverse and serious adverse events, the regular monitoring of hematology and blood chemistry values, regular measurement of vital signs, and the performance of physical examinations.

These assessments should be performed within the windows as indicated on the schedule of events except for adverse events that will be evaluated continuously through the study. Safety and tolerability will be assessed according to the NIH/NCI CTCAE v. 4.0.

11.1 Definitions

Adverse Event (AE)

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event 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 Harmonisation [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

There are no adverse events of special interest identified for apalutamide or abiraterone acetate.

Definition of Adverse Drug Reaction (ADR)

A noxious and unintended response to any dose of the drug (or biological) product for which there is a reasonable possibility that the product cause the response. ‘‘Reasonable possibility’’ means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

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

Product Quality Complaint (PQC)

A product quality compliant 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

Serious Adverse Event (SAE)

A serious adverse event 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.

11.2 Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event 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:

http://www.zytiga.com/sites/default/files/pdf/full_product_information.pdf

For Apalutamide, the link to the package insert is:

http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/ERLEADA-pi.pdf

11.3 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 a JANSSEN perspective, 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 as described in section 11.8 REPORTING TIMELINES.

11.3.1 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 PRINCIPAL INVESTIGATOR within 24 hours 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.

11.4 Maintenance of Safety Information

All safety data should be maintained in a clinical database in a retrievable format. The INSTITUTION and PRINCIPAL INVESTIGATOR 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 the request of JANSSEN Scientific Affairs, LLC.

11.5 Procedures for Reporting to JANSSEN SCIENTIFIC AFFAIRS

Procedures for Reporting Adverse Events (AE), Serious Adverse Events (SAE), Special Reporting Situation, and Product Quality Complaints (PQCs) to JANSSEN SCIENTIFIC AFFAIRS

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.

Suspected theft, loss, or misplacement of any Janssen supplied study drug from either Duke or the subject's supply should also be reported to Janssen.

The sequence and timing of reporting requirements is described in section 11.8 Reporting Timelines.

11.5.1 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)

The INSTITUTION and the PRINCIPAL INVESTIGATOR will transmit all SAEs and special situations following exposure to a Janssen product under study in a form provided by JANSSEN in English as described in section 11.8 REPORTING TIMELINES.

In the event the study is blinded, the PRINCIPAL INVESTIGATOR will submit an unblinded SAE or pregnancy exposure report to JANSSEN.

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 PRINCIPAL INVESTIGATOR, as described in section 11.8 REPORTING TIMELINES.

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

- The INSTITUTION and/or PRINCIPAL INVESTIGATOR 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 JANSSEN as described in section 11.8 REPORTING TIMELINES.

11.5.2 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.

11.5.3 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 PRINCIPAL INVESTIGATOR as described in section 11.8 REPORTING TIMELINES. 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 PRINCIPAL INVESTIGATOR 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.

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 PRINCIPAL INVESTIGATOR 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.

Transmission Methods
The following methods are acceptable for transmission of safety information to JANSSEN SCIENTIFIC AFFAIRS:

- Electronically via Janssen SECURE Email service (preferred) to secure email box: [redacted]
- For business continuity purposes, if SECURE Email is non-functional:
  - Facsimile (fax), receipt of which is evidenced in a successful fax transmission report to [redacted]
- Telephone, if fax is non-functional: [redacted]

Please use the contact information and process information provided by JANSSEN SCIENTIFIC AFFAIRS.

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

In general, the PI or designate must immediately report to JANSSEN SCIENTIFIC AFFAIRS any serious adverse event and Special Reporting Situations, whether or not considered drug related. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the drug and the event (e.g., death as a result of anaphylactic reaction or fatal hepatic necrosis). In that case, the investigator must immediately report the event to JANSSEN. The PI must record non-serious adverse events and report them to JANSSEN following completion of the accrual and follow up period or to fulfill regulatory reporting requirements.

A Serious Adverse event or Special Reporting Situations must be reported if it occurs during a subject's participation in the Study (whether receiving Study Product or not) starting with the date of signed consent and continuing until 30 days after receiving the last dose of Study Product.

An Adverse Event or Product Quality Complaint must be reported starting with the first dose of Study Product and continuing until 30 days after receiving the last dose of Study Product.
Any theft, loss, or misplacement of any Janssen supplied study drug from either Duke or the subject's supply must be reported to Janssen starting with initial distribution of the study drug

until the end of the study. This applies even if there is no suspicion of misuse or overdose on the part of the subject.

11.7 Recording of Adverse Events, Serious Adverse Events and Special Reporting Situations

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

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

Preexisting conditions that worsen in severity or frequency during the Study should also be recorded (a preexisting condition that does not worsen is not an adverse event).

Further, a procedure or surgery is not an adverse event; rather, the event leading to the procedure or surgery is considered an adverse event. Any event requiring in-patient hospitalization that occurs during the course of a subject's participation in a trial must be reported as an SAE. Hospitalizations that do not meet the criteria for SAE reporting are:

A: Reasons described in the Protocol, e.g. drug administration, Protocol-required testing

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

If, in the PRINCIPAL INVESTIGATOR's judgment, a clinical significant worsening from baseline is observed in any laboratory or other test parameter (e.g. electrocardiogram (ECG), angiogram), physical exam finding, or vital sign, a corresponding clinical adverse event should be recorded.

If a specific medical diagnosis has been made, that diagnosis or syndrome should be recorded as the adverse event, whenever possible. However, a complete description of the signs, symptoms and investigations which led to the diagnosis should be provided. For example, if clinically significant elevations of liver function tests are known to be secondary to hepatitis, "hepatitis" and not "elevated liver function tests" should be recorded. If the cause is not known, the abnormal test or finding should be recorded as an adverse event, using appropriate medical terminology (e/g/ thrombocytopenia, peripheral edema, QT prolongation).

11.8 Reporting Timelines

Serious safety information (SAEs, Special Reporting Situations, and PQCs), whether or not considered drug related, should be sent via the REDCap survey system using the web link provided by the Duke multisite coordinators. For more information on and access to the REDCap system, please contact the GU multisite team: [redacted]

If Duke staff cannot be reached within 24 hours, the Sponsor-Investigator should be contacted:
Dr. Daniel George [redacted]

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

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

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

Upon receipt of the Serious Adverse Event Reporting form by Duke, the PI will be notified and be required to complete the PI assessment of the DCI Safety SAE Report Review Form. Within 24 hours of notification from the site, Duke staff will, in turn, send the Janssen SAE Report Form to Janssen. Safety information will be sent to Janssen by encrypted email using Cisco Registered Envelope Service to [redacted] Delivery and read receipt of the secure email will serve as evidence of successful communication.

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

11.9 FDA Reporting Requirements

The Sponsor-Investigator (Duke) is responsible for reporting serious adverse events to the FDA in accordance with applicable IND Safety Requirements (21 CFR 312.32).

11.10 Dissemination of Safety Information from JANSSEN SCIENTIFIC AFFAIRS to INSTITUTION/PRINCIPAL INVESTIGATORS

JANSSEN will provide to the INSTITUTION/PRINCIPAL INVESTIGATOR IND safety reports/SUSAR (Serious Unexpected Suspect Adverse Reaction) reports generated by the JANSSEN for the

Study Product as they become available until all subjects in the Protocol have completed their last Study visit according to the Protocol (i.e. Last Subject Last Visit has occurred).

12. EFFICACY ASSESSMENTS

12.1 Baseline tumor evaluation

Response and progression will be evaluated in this study using a combination of the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [39]and the modified guidelines for prostate cancer endpoints developed by the Prostate Cancer Clinical Trials Working Group (PCWG3) [35].

Traditional measures of response reflect when a treatment is working and measures of progression indicate when a drug should be stopped. Because assessing response in bone (the most common site of prostate cancer spread) is uncertain and the clinical significance of PSA changes in response to therapy is not a reliable predictor of response, measures of response have been expanded in consortium trials to include measures of progression.
Patients will be reevaluated for response every cycle according to the guidelines below:

Measurable disease: According to RECIST 1.1, measurable disease is defined as at least 1 lesion ≥ 10 mm in its longest diameter as measured by CT scan with slice thickness ≤ 5 mm, ≥ 10 mm by clinical exam with caliper measurement, or ≥20 mm by CXR. A lymph node is measurable if it is ≥ 15 mm in the short axis when assessed by CT scan. All tumor measurements will be taken using a ruler or calipers and recorded in millimeters.

Nonmeasurable disease: Following RECIST 1.1, all other lesions (or sites of disease) will be considered nonmeasurable disease. This includes small lesions (longest diameter < 10 mm) and any of the following:

1. Leptomeningeal disease
2. Ascites
3. Pleural or pericardial effusion
4. Lymphagitic involvement of the skin or lung
5. Abdominal mass or organomegaly identified by physical exam but not by imaging techniques
6. Bone lesions
7. Lesions occurring within a previously irradiated area unless they are documented as new lesions since the completion of radiation therapy

Target (nodal and visceral) lesions: Following RECIST 1.1, progression in a nodal or visceral site (i.e., liver and lung) is sufficient to document disease progression. The presence or absence of nodal and visceral disease before and after treatment should be recorded separately. All measurable lesions (up to a maximum of 2 lesions per organ and 5 lesions in total) will be

identified as target lesions to be measured and recorded at baseline. The target lesions should be representative of all involved organs. Target lesions will be selected on the basis of size (i.e., the largest area) and suitability for accurate, repeated measurements. Lymph nodes can be considered a target lesion if the short axis is ≥ 15 mm by CT. The sum of diameters (long-axis for non-nodal lesions and short-axis for nodal lesions) of all target lesions will be calculated and reported as the *baseline sum diameter*. The baseline sum diameter will be used as a reference by which to characterize the objective tumor response.

Non-target lesions: All other lesions (or sites of disease) will be identified as nontarget lesions and recorded at baseline. Nontarget lesions will include measurable lesions that exceed the maximum number per organ (2) or total of all involved organs (5), as well as nonmeasurable lesions. The presence or absence of these lesions will be recorded on the CRF and should be evaluated at the same assessment time points as all target lesions.

PSA: Because the rate of rise has known prognostic significance, estimate a pretreatment PSA doubling time (PSA-DT) if at least 3 values are available, but do not delay either treatment or enrollment onto a trial simply to estimate PSA-DT.

12.2 Response Criteria

12.2.1 Evaluation of target lesions:

Table 5 RECIST 1.1 response criteria for target (soft tissue)lesions

Response	Evaluation of Target Lesions
Complete response (CR)	The disappearance of all target lesions. Any pathologic lymph nodes (target or non-target) must have reduction in short axis to <10 mm.
Partial response (PR)	A ≥30% decrease in the sum diameter of target lesions as compared to the baseline sum diameter.
Progressive disease (PD)	A ≥20% increase in the sum diameter of target lesions as compared to the smallest sum diameter on study. This must show an absolute increase of at least 5 mm. The appearance of one or more new lesions.
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD based on the smallest sum diameter on study.

Target lesions that are too small to measure will be given a measurement of either 0 mm, if the radiologist believes the lesion has disappeared, or 5 mm, if the lesion is felt to be present. In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, the residual lesion

will be investigated with a fine needle aspirate or biopsy before confirming the complete response status.

If lymph nodes have been identified as target lesions, the short axis measurement will be recorded even if the nodes regress to < 10 mm. Therefore, the sum diameter may not be zero even if complete response criteria are met.

12.2.2 Evaluation of non-target lesions:

*Table 6 RECIST 1.1 response criteria for **non-target** lesions*

Response	Evaluation of Non-target Lesions
Complete response (CR)	The disappearance of all non-target lesions. All lymph nodes must be <10 mm by short axis.
Non-CR, Non-PD	The persistence of one or more non-target lesions.
Progressive disease (PD)	Unequivocal progression of existing non-target lesions and/or the appearance of one or more new lesions.

A clear progression of nontarget lesions only is exceptional. In such circumstances, the progression status, as assigned by the investigator, may be reviewed by a PCCTC panel.

New lesions: If unequivocal, the appearance of new lesions denotes disease progression. If a new lesion is equivocal, therapy will be continued and this lesion will be reevaluated on follow-up imaging as planned in the study flow chart. If repeat scans confirm the new lesion, progression will be documented using the date of the initial equivocal scan. New brain metastases identified while on study are considered new even if there was no baseline brain imaging.

12.2.3 Bone lesions

Record post-treatment changes as either “no new lesions” or “new lesions.” When the bone scan is the sole indicator of progression, disease progression in bone is defined as 2 or more new lesions seen on bone scan compared with the baseline scan used for trial entry. In situations where scan findings suggest a flare reaction or where new lesion(s) may represent trauma, confirm these results with other imaging modalities. In the absence of clearly worsening soft-tissue (nodal and visceral) disease or disease-related symptoms, progression at the first scheduled assessment should be confirmed on a second scan performed 6 or more weeks later. The first post treatment bone scan (the cycle 4 bone scan) will be used as the baseline bone scan with which all future bone scans are compared per PCWG3.

12.2.4 PSA

To report PSA-based outcomes, PCWG3 recommends that the percent of change in PSA from Cycle 1 day 1 to 12 weeks (or earlier for those who discontinue therapy) and the maximum decline in PSA that occurs at any point after treatment be reported for each patient using a waterfall plot. Because declines in serum PSA, if they occur, may not do so for several weeks, PSA measurements obtained during the first 12 weeks should not be used as the sole criterion for clinical decision making. As long as patient safety is the primary concern, in the absence of other indicators of disease progression, therapy should not be discontinued solely on the basis of a rise in PSA.

12.2.5 Symptoms

Transient increases in pain may occur before improvement, and those occurring in the first 12 weeks should not affect the course of treatment in the absence of other compelling evidence of disease progression. Changes in symptoms should be documented and confirmed as per other outcome measures.

12.2.6 Evaluating best overall response

The best overall response is the best response recorded from the start of treatment until the end of treatment. The investigator's determination of best overall response will be based both on response criteria and on confirmation criteria. To be assigned a status of partial response or complete response, changes in tumor measurements must be confirmed by repeat assessment performed 6-8 weeks after the criteria for response are first met. To confirm stable disease, follow-up measurements must meet SD criteria at a minimum interval of 6 weeks after SD was first documented. Table 7 will be used as an assessment tool.

Table7. Assessing Overall Response

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

Patients with global deterioration of health status who require treatment to be discontinued without objective evidence of disease progression should be classified as having symptomatic deterioration. Every effort should be made to document their objective progression, even after discontinuing treatment.

Patients who do not have tumor response assessment due to rapid progression or toxicity will be considered nonresponders, will be included in the denominator for the response rate, and will be classified into one of the categories listed below:

- Death attributed to disease progression
- Early discontinuation attributed to disease progression
- Death attributed to drug toxicity
- Early discontinuation attributed to drug toxicity

Note: If a patient receives subsequent therapy before tumor progression is documented, the reason for changing therapy must be reported. Reasons include clinical progression, drug toxicity, or secondary therapy for maintaining tumor response.

12.3 Confirming time-to-event outcomes

Any on treatment change in disease status, be it favorable or unfavorable (PR, CR, SD, or PD), should be confirmed using a second assessment at a later time point, either 6 weeks later or at the next scheduled scan.

12.4 Duration of overall response

Duration of overall response is measured from the time when partial response or complete response is first noted until the date when recurrent or progressive disease is objectively documented. Duration of overall complete response is measured from the time the criteria for complete response are first met until the first date that recurrent disease is objectively documented. Duration of stable disease is measured from the start of treatment until the criteria for progression are met.

12.5 Radiographic Progression-free survival

The primary endpoint is radiographic progression-free survival (rPFS), a composite endpoint using the time from study entry to disease progression.

Progression is defined as Radiologic progression by RECIST 1.1 [39] and/or bone scan progression by modified PCWG3 criteria [35](Appendix 4).
A rise in PSA alone in the absence of radiologic or symptomatic indicators of disease progression, will not be considered disease progression. Increased pain alone, in the absence of changes in imaging or need for radiation therapy, will not be considered disease progression.

All assessments of disease should be collected at the same time interval. Post-treatment changes will be confirmed based on measurable target lesions, radionuclide bone scans, and symptoms as indicated below. Patients who withdraw from study treatment for reasons other than radiographic disease progression should continue to have results of their CT and Bone scans collected and recorded during the Follow-Up phase until demonstration of radiographic progression.

12.6 Secondary endpoint assessments

12.6.1 RECIST 1.1 defined radiologic response rates

Tumor assessments by CT chest/abdomen/pelvis and bone scan will be made at baseline and every 12 weeks while on therapy. If the chest CT at baseline is clear, chest x-rays may be used for subsequent assessments at the enrolling physician's discretion. Response rates will be calculated based on RECIST 1.1 criteria, as detailed in section 12.2 above centrally. Response rates will be analyzed using objective (defined as CR or PR) parameters.

12.6.2 Safety and toxicity monitoring

National Cancer Institute Common Toxicity Criteria (v 4.0) will be used to record and monitor for adverse events (Appendix 4). Data for safety and severe adverse events will be monitored on an ongoing basis through monthly investigator and staff meetings, including data from all centers involved.

Summary statistics will be provided for the adverse events found in the common group of adverse events (≥10%). This will include: GI disorders; fatigue; decreased appetite; hypokalemia; Dysgeusia; hot flush; rash; falls; and hypertension. Less common adverse events (≤10%) include; insomnia; increase in blood cholesterol and triglycerides; and alanine aminotransferase increased and aspartate aminotransferase increased. Rare but serious adverse events (may occur in less than 1 subject in 100) would include seizures. This will include: mineralocorticoid excess (hypertension, hypokalemia, fluid retention); hepatotoxicity; cardiac disorders; osteoporosis-related fractures; rhabdomyolysis/myopathy; drug-drug interaction (CYP2D6); allergic alveolitis and seizures. Refer to section 11.1.

TSH

Changes in TSH have been observed in the ongoing early phase and blinded Phase 3 studies. The changes in TSH from baseline have been observed both in subjects with and without a history of thyroid disorders, however, the largest numerical increases in TSH have been observed in subjects on thyroid hormone replacement. Increases in TSH are at times associated with decreases in T3 or T4 or both. The mechanism for this observed TSH change and the associated alterations in thyroid function are still under investigation. Thyroid function should be monitored and doses of replacement hormones should be started or adjusted based on laboratory findings.

12.7 Exploratory endpoints

i. Hormone Levels and Metabolomics Profile including Lipid Levels

We will describe the baseline profile of serum hormone levels (including but not limited to testosterone, DHT, DHEA, DHEAS, estradiol) and lipids, the change in levels with subsequent therapy (Cycle 4), and their correlation with response to abiraterone acetate plus apalutamide.

Steroid Hormone Analysis

We will use the Random Lasso approach to assess race- and genetic ancestry-related steroid hormones and response to abiraterone and combination abiraterone and apalutamide in metastatic castration-resistant prostate cancer (mCRPC).[40] In our preliminary work on Abi Race, we recognized that the modest sample size suggested the use of the Random Lasso. In our current collaborative work with this team, we have set up the code required to implement this approach, which utilizes a two-step approach across bootstrap samples. This method has been shown to select all relevant targets, even in the presence of high correlation, eliminating targets with a trivial role. Another advantage of the approach is that internal validation using bootstrap avoids the small sample sizes that would occur with cross-validation. We will implement this approach, incorporating global genetic ancestry (non-penalized), critical clinical covariates and steroid hormone levels.

This analysis will include samples from both this study and Abi Race (Pro00046383, NCT01940276). We expect to analyze up to 200 samples: 50 White patients receiving abiraterone, 50 Black patients receiving abiraterone, 50 White patients receiving combination abiraterone and apalutamide, 50 Black patients receiving combination abiraterone and apalutamide. Using the steroid hormone analysis data and clinical data from the Abi Race and PANTHER studies, we will assess race- and genetic ancestry-related steroid hormones and response to abiraterone and combination abiraterone and apalutamide in metastatic castration-resistant prostate cancer (mCRPC).

ii. **Abiraterone pharmacokinetics**

Abiraterone acetate is metabolized to an active metabolite (D4A), that may function as an androgen receptor antagonist. It is unknown whether this metabolism is linked to race, therefore we will explore abiraterone acetate and active metabolite drug levels in this study. (PKs) will be drawn on cycle 1d1 (at 1, 2, 4 and 8 hours post dose) and cycle 2d1 (at 24 hour trough, 1, 2, 4 and 8 hours post dose) of study drug.

iii. Ancestral Genotyping and SNP Analyses

We will perform ancestral genotyping to obtain genetically estimated indicators of race. In addition, we will describe the germline SNP profiles of the androgen receptor gene, target genes involved in androgen metabolism and signaling and target genes that have been shown to be differentially expressed in African American versus Caucasian prostate cancer and their associations with response to abiraterone acetate plus apalutamide. The status of the aforementioned targets will also be assessed in archival tumor tissue, if available.

iv. Expression and Splicing Analysis

We will describe the expression and splicing profiles of the androgen receptor gene, target genes involved in androgen metabolism and signaling and target genes that have been shown to be differentially expressed and/or spliced in African American versus Caucasian prostate cancer and their associations with response to abiraterone acetate plus apalutamide. The status of the aforementioned targets will also be assessed in archival tumor tissue, if available.

v. Cell-Free Plasma DNA Analysis

We will describe cell-free plasma DNA profiles and their associations with response to abiraterone acetate plus apalutamide.

vi. Plasma-Based Biomarker Analysis

We will describe the profile of plasma blood-based biomarkers that may have prognostic or predictive value and their associations with response to abiraterone acetate plus apalutamide.

13. STATISTICAL METHODS

The primary endpoint is radiographic progression-free survival (rPFS), as assessed by the investigator, which is defined as the duration from the date of study enrollment to the date of first documentation of radiographic progressive disease or death due to any cause, whichever occurs first. Secondary endpoints are overall survival (OS), 12 month PSA PFS and other PSA changes, radiographic assessments and safety. OS is defined from the date of study enrollment to date of death due to any cause. Biochemical progression is defined from date of study enrollment to date of PSA progression as defined by the modified PCWG3.

Sample Size Justification

This trial is non-comparative. Based on Ryan et al. the median time to radiographic progression free survival (rPFS) is 16.5 months [41]. Fifty (50) patients will be enrolled in each group (AA and Caucasians). With an accrual rate of 50 patients/group over 20-month accrual period, 24-months follow-up, and assuming that rPFS follows an exponential distribution, based on 5000 simulations the average width of a two-sided 95% confidence interval for the median rPFS is 16. Because of the small sample size and short follow-up period, 26 radiographic PFS events/group are expected. Consequently, the radiographic PFS distribution by racial group will not be estimated with high precision.

Data Analysis

An intent-to-treat approach will be used for the analyses within each racial group of all clinical outcomes except safety where patients who have received at least one dose of study treatment will be included in the analysis. The proportion of patients who experience PSA decline of 30%, 50% and 90% within 3 months on study will be estimated with 95% confidence intervals based on the binomial distribution. In addition, post therapy changes in PSA will be explored as a continuous variable. The Kaplan-Meier product limit method will be used to estimate the rPFS, biochemical PFS and OS distributions.

Serum hormone, serum lipid, SNP, gene expression, alternative splicing, cell-free plasma DNA and plasma-based biomarker profiles will be summarized using descriptive statistics.

The GWAS analysis will be mostly exploratory as the trial limited sample size will not permit definitive analyses. Call rate, patterns of missing data, and departures from the Hardy-Weinberg equilibrium will be performed using exact test to identify SNPs that will not be used in analysis. Allele frequencies estimated within each racial group separately. Although race is self-reported, admixture estimates and will be adjusted for in the analysis. Test for association will be performed under an additive model.

14. DATA REPORTING AND REGULATORY REQUIREMENTS

14.1 Data Entry

Data collected during this study will be entered into a secure Medidata Rave database. Staff at Duke University will be responsible for the initial study configuration and setup in the electronic database as well as for any future changes.

14.1.1 Case report forms

Electronic case report forms (CRFs) will be generated by Duke University for the collection of all study data. Site Investigators or designee will be responsible for ensuring that the CRFs are kept up-to-date. Each site will enter their own data into CRFs from source documents on site.

14.1.2 Source documents

Study documentation includes all paper case report forms, data correction forms, source documents, monitoring logs and appointment schedules, sponsor-investigator correspondence and regulatory documents (e.g., signed protocol and amendments, Ethics or Institutional Review Committee correspondence and approval, approved and signed subject consent forms, Statement of Investigator form, and clinical supplies receipts and distribution records).

The investigator will prepare and maintain complete and accurate study documentation in compliance with Good Clinical Practice standards and applicable federal, state, and local laws, rules and regulations; and, for each subject participating in the study, promptly complete all original case report forms and such other reports as required by this protocol following completion or termination of the clinical study or as otherwise required pursuant to any agreement with the Sponsor-Investigator.

By signing the protocol, the investigator acknowledges that, within legal and regulatory restrictions and institutional and ethical considerations, study documentation will be promptly and fully disclosed to the Sponsor-Investigator/Regulatory Specialist by the investigator upon request and also shall be made available at the investigator's site upon request for inspection, copying, review and audit at reasonable times by representatives of Sponsor-Investigator or responsible government agencies as required by law. The investigator agrees to promptly take any reasonable steps that are requested by Sponsor-Investigator as a result of an audit to cure deficiencies in the study documentation and case report forms.

14.1.3 Record retention

The investigator will maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. After study closure, each participating site's PI will maintain all source documents, study-related documents, and CRFs. Because the length of time required for retaining records depends upon a number of regulatory and legal factors, documents should be stored until the investigator is notified that the documents may be destroyed. In this study, records are to be retained and securely stored for a minimum of 6 years after the completion of all study activities.

14.2 Study monitoring and quality assurance

The Sponsor-Investigator is responsible for monitoring the protocol to ensure that the investigation is conducted in accordance with the general investigational plan and all applicable

regulatory requirements. In addition, the protocol will be monitored independently via the Duke Cancer Center (DCI) Monitoring Team.

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

The DCI Safety Oversight Committee (SOC) will perform reviews on findings from the DCI Monitoring Team visit and additional safety and toxicity data submitted by the Principal Investigator.

Additional monitoring may be prompted by findings from monitoring visits, unexpected frequency of serious and/or unexpected toxicities, or other concerns and may be initiated upon request of DUHS and DCI leadership, the CPC, the Safety Oversight Committee (SOC), the Duke OARC, the sponsor, the Principal Investigator, or the IRB. All study documents must be made available upon request to the DCI Monitoring Team and other authorized regulatory authorities, which may include but is not limited to the National Institute of Health, National Cancer Institute, and the FDA. Every reasonable effort will be made to maintain confidentiality during study monitoring.

14.3 Data Safety and Monitoring

Data for safety and severe adverse events will be monitored on an ongoing basis through monthly investigator and staff meetings, including data from all centers involved.

In addition a recruitment and withdrawal summary will be discussed at these meetings. Withdrawals will be broken down into those due to AEs and what they were.

In terms of internal review, the Investigator will continuously monitor and tabulate adverse events. Appropriate reporting to the DUHS IRB will be made. If an unexpected frequency of Grade III or IV events occurs, depending on their nature, action appropriate to the nature and frequency of these adverse events will be taken. This may require a protocol amendment, dose de-escalation, or closure of the study. The Investigator of this protocol will also continuously monitor the conduct, data, and safety of this protocol to ensure that:

- Risk/benefit ratio is not altered to the detriment of the subjects
- Appropriate internal monitoring of adverse events and outcomes is done

- Over-accrual does not occur
- Under-accrual is addressed with appropriate amendments or actions
- Data is being appropriately collected in a reasonably timely manner

This protocol is being conducted at additional sites external to Duke University Health Systems. The Sponsor-Investigator is responsible for monitoring these sites to assure the safety and protection of all subjects, and to assure that the study is conducted, recorded, and reported in accordance with the protocol and applicable regulations. To assure that the investigator obligations are fulfilled and all applicable regulations and guidelines are being followed, the Sponsor-Investigator will designate the DCI Monitoring Team to assure that the external site facilities are acceptable, the protocol and investigational plan are being followed, the IRB/IEC has been notified of approved protocol changes as required, complete records are being maintained, appropriate and timely reports have been made to the Sponsor-Investigator and the IRB/IEC, study drug and study drug inventory are controlled and the Investigator is carrying out all agreed activities. Monitoring also includes review of regulatory and eligibility, conduct, data quality and adverse event reporting for select cases.

As pre-arranged by the Sponsor-Investigator, DCI Monitoring Team will monitor 1-3 subjects twice annually at external sites until closed to enrollment or subjects are no longer receiving study drug or other interventions that are more than minimal risk. Study teams will provide requested data for remote monitoring when possible. If feasible, the first visit will be conducted on site. Additional on-site visits will be completed as deemed necessary and as requested. Additional review will be performed on a site-by-site basis, as warranted by the findings of previous monitoring visits. Key variables (demographics, inclusion/exclusion criteria, and safety) on the CRFs will be compared with select subject's source documents. Any discrepancies will be noted and resolved.

15. PROTOCOL AMENDMENTS OR CHANGES IN STUDY CONDUCT

Any change or addition to this protocol requires a written protocol amendment that must be reviewed by Duke University and Janssen Scientific Affairs before implementation.

16. PROCEDURES AND INSTRUCTIONS

16.1 Disclosure and confidentiality

The investigator agrees to keep all information provided by participating sites and by Janssen Scientific Affairs in strict confidence and to request similar confidentiality from his/her staff and the IRB/IEC/REB. Study documents provided by participating sites and Janssen Scientific Affairs (investigators' brochures and other material) will be stored appropriately to ensure their

confidentiality. The information provided by participating sites and Janssen Scientific Affairs to the investigator may not be disclosed to others without direct written authorization from Janssen Scientific Affairs, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial.

16.2 Discontinuation of study

Duke University or Janssen Scientific Affairs reserves the right to discontinue any study under the conditions specified in the clinical trial agreement.

16.3 Ethics and Good Clinical Practice

This study must be carried out in compliance with the protocol and the principles of Good Clinical Practice, as described in ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996. Directive 91/507/EEC, The Rules Governing Medicinal Products in the European Community. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations). The investigator agrees to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

16.3.1 Institutional Review Board/Independent Ethics Committee

Before implementing this study, the protocol, the proposed informed consent form and other information to subjects, must be reviewed by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB). A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB must be given to Janssen before study initiation. Any amendments to the protocol, other than administrative ones, must be reviewed by Janssen Scientific Affairs, and approved by this committee.

16.3.2 Informed consent

The investigator or designee must explain to each subject (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject must be informed that participation in the study is voluntary and that he may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it, and should be given a copy of the signed document. If the subject cannot read or sign the documents, oral presentation may be made or signature given by the subject's legally appointed representative, if witnessed by a person not involved in the study, mentioning that the patient could not read or sign the documents. No patient can enter the study before his/her informed consent has been obtained. The informed consent form is considered to be part of the protocol, and must be submitted by the investigator with it for IRB/IEC/REB approval.

16.3.3 Declaration of Helsinki

The investigator must conduct the trial in accordance with the principles of the Declaration of Helsinki and amendments, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects). Copies of the Declaration of Helsinki and amendments will be provided upon request or can be accessed via the website of the World Medical Association at http://www.wma.net/e/policy/17-c_e.html.

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APPENDIX 1: PERFORMANCE STATUS CRITERIA

Karnofsky Performance Scale	
%	**Description**
100	Normal, no complaints, no evidence of disease
90	Able to carry on normal activity, minor signs or symptoms of disease
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
60	Requires occasional assistance but is able to care for most needs
50	Requires considerable assistance and frequent medical care
40	Disabled, requires special care and assistance
30	Severely disabled, hospitalization indicated. Death not imminent.
20	Very sick, hospitalization indicated. Death not imminent.
10	Moribund, fatal processes progressing rapidly
0	Dead

APPENDIX 2: CYP450 ISOENZYME INHIBITORS AND INDUCERS TO BE USED WITH CAUTION

Strong CYP3A4,5,7 inhibitors	Moderate CYP3A 4,5,7 inhibitors	CYP3A4 inducers
Clarithromycin	Amprenavir	Avasimibe
Conivaptan	Aprepitant	Bosentan
grapefruit juice	Atazanavir	Carbamazepine
Indinavir	Cimetidine	Efavirenz
Itraconazole	Darunavir	Modafinil
	Diltiazem	Nafcillin
Lopinavir	Elvitegravir	Oxcarbazepine
Mibefradil	Erythromycin	Phenobarbital
Nefazodone	Fluconazole	Phenytoin
Nelfinavir	Fosamprenavir	pioglitazone
Posaconazole	Tofisopam	Rifabutin
Ritonavir	Tipranavir	Rifampin
Saquinavir	Verapamil	Topiramate
Telithromycin		
Troleandomycin		
Voriconazole		

This database of CYP inhibitors was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table and from the University of Washington's Drug Interaction Database based on *in vitro* studies. Strong inhibitors are predicted to increase Abiraterone acetate AUC > 5-fold, and moderate inhibitors are predicted to increase Abiraterone AUC ≥ 2-fold but < 5-fold.

This database of CYP inducers was compiled from the FDA's "Guidance for Industry, Drug Interaction Studies;" from the Indiana University School of Medicine's "Clinically Relevant" Table; and from (Pursche et al. 2008).

Note: Site pharmacist or physician should review subject's concomitant medication list while in screening and once on study for drug to drug interactions. This is a not an all-inclusive list.

CYP450 SUBSTRATES TO BE USED WITH CAUTION

CYP2C8	CYP2C9	CYP2C19	CYP3A4,5,7**	
amodiaquine	celecoxib	amitriptyline	Adinazolam	fentanyl[2]
cerivastatin	diclofenac	citalopram	alfentanil[1,2]	flunitrazepam
pioglitazone	flurbiprofen	clobazam	alpha-dihydroergocryptine[1]	fluticasone[1]
repaglinide	fluvastatin	clomipramine	alprazolam	lovastatin[1]
rosiglitazone	glibenclamide (glyburide)	clopidogrel	amlodipine	maraviroc[1]
torsemide	gliclazide	diazepam	aripiprazole	midazolam[1]
troglitazone	glimepiride	fluoxetine	atorvastatin	nifedipine
	glipizide	imipramine	brotizolam[1]	nisoldipine
	indomethacin	lansoprazole	budesonide[1]	nitrendipine
	irbesartan	moclobemide	buspirone[1]	perospirone[1]
	ketobemidone	omeprazole	cerivastatin	quinine
	lornoxicam	pantoprazole	chlorpheniramine	sildenafil[1]
	losartan	progesterone	cyclosporine[2]	simvastatin[1]
	meloxicam	propranolol	darifenacin[1]	sirolimus[1,2]
	naproxen	quazepam	Diazepam	tipranavir[1]
	nateglinide	rabeprazole	diergotamine[2]	trazodone
	piroxicam	sertraline	ebastine[1]	triazolam[1]
	S-ibuprofen	S-mephenytoin	eletriptan[1]	
	sulfamethoxazole		eplerenone[1]	
	tenoxicam		ergotamine[2]	
	tolbutamide		Estazolam	
	torsemide		everolimus[1]	
	valdecoxib			

* This database of CYP substrates was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table, and from (Zhou et al. 2009)

** CYP3A4,5,7 substrates were compiled from the Indiana University School of Medicine's "Clinically Relevant" Table; and supplemented by the FDA's "Guidance for Industry, Drug Interaction Studies" and the University of Washington's Drug Interaction Database.

[1] Sensitive substrates: Drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a potent inhibitor of the respective enzyme.

[2] Substrates with narrow therapeutic index (NTI): Drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (*e.g.*, Torsades de Pointes).

Note: Site pharmacist or physician should review subject's concomitant medication list while in screening and once on study for drug to drug interactions. This is a not an all-inclusive list.

Medications Prohibited while on active treatment with apalutamide

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: Site pharmacist or physician should review subject's concomitant medication list while in screening and once on study for drug to drug interactions. This is a not an all-inclusive list.

APPENDIX 3: NCI COMMON TOXICITY CRITERIA

NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 can be found here:

http://evs.nci.nih.gov/ftp1/CTCAE/About.html

APPENDIX 4: CRITERIA FOR DISEASE PROGRESSION

***Prostate Cancer Clinical Trials Working Group 3 (PCWG3) Outcome Measures* (13)**

Variable	*Prevent/Delay Endpoints*
PSA	***Decline from baseline:*** *record time from start of therapy to first PSA increase that is ~25% and ~2.0 ng/mL above the nadir, and which is confirmed by a second value 3 or more weeks later (i.e., a confirmed rising trend)†* *Recording the duration of PSA decline of little value* ***No decline from baseline:*** *PSA progression ~25% and ~2.0 ng/mL after 12 weeks*
Soft-tissue lesions	*Use RECIST criteria for progression, with additional requirement that progression at first assessment be confirmed by a second scan 6 or more weeks later* *Note that for some treatments, a lesion may increase in size before it decreases*
Bone	*The appearance of ~2 new lesions, and, for the first reassessment only, a confirmatory scan performed 6 or more weeks later that shows at least 2 or more additional new lesions* *The date of progression is the date of the first scan that shows the change*