Statistical Analysis Plan (SAP)

Title	Prospective study of Apalutamide and Abiraterone Acetate iN ChemoTHerapy-Naïve mEn with mCRPC Stratified by Race (PANTHER)
IRB Number	Pro00075097 (NCT03098836)
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Project Goal(s)	abstract, manuscript

1 Study Overview

Background/Introduction:

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 Black patients, leaving unanswered the question of whether Black 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 Black versus White prostate cancer, cell-free plasma DNA profiles, pharmacokinetics of abiraterone acetate and plasma-based biomarkers in both Black and White cohorts.

1.1 Study Objectives

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

Secondary:

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

2 Study Population

2.1 Inclusion/Exclusion Criteria

- See protocol

2.2 Data Acquisition

Fill in all relevant information:

Study design	Phase II, open-label, multicenter study
Data source/how the data were collected	In Rave and Advarra
Contact information for team member responsible for data collection/acquisition	Marco Reyes

3 Outcomes, Exposures, and Additional Variables of Interest

3.1 Primary Outcome(s)

Outcome	**Specifications**
Radiographic progression-free survival	Time from study enrollment to disease progression or death - defined as Radiologic progression by RECIST 1.1 and/or bone scan progression by modified PCWG3 criteria

3.2 Secondary Outcome(s)

Outcome	**Specifications**
Overall survival	Time from study enrollment to date of death due to any cause
PSA recurrence/ biochemical progression	Time from study enrollment to date of PSA progression as defined by the modified PCWG3:

	After decline from baseline: record time from start of therapy to first PSA increase that is ≥ 25% and ≥ 2 ng/mL above the nadir, and which is confirmed by a second value ≥ 3 weeks later (ie, a confirmed rising trend) No decline from baseline: PSA progression ≥ 25% increase and ≥ 2 ng/mL increase from baseline beyond 12 weeks
PSA nadir	Lowest PSA value achieved during the study
PSA decline	PSA decline of 30%, 50% and 90%
PSA <0.1	Percentage of men who achieve a PSA <0.1
Radiographic assessments	
Toxicity	Standard toxicity summary (NCI CTC v4.0)

3.3 Additional Variables of Interest (Table 1)

Variable	**Specifications**
Age at enrollment	Age at date of study enrollment
BMI	Using height and weight from C1 or screening
Time from diagnosis to enrollment (years)	Years from prostate cancer diagnosis to study enrollment
Gleason score at diagnosis	Unknown, ≤7, 8-10
Tumor classification at diagnosis	TX, ≤T2, T3-T4
Lymph node classification	NX, N0, N1-N3
Extent of metastasis	MX, M0, M1
KPS	80-70, 100-90
Comorbidities at baseline	Y/N: Hypertension Hyperglycemia Insomnia Fatigue Hypercholesterolemia Diabetes
Pain at baseline	Y/N
Opioid use at baseline	Y/N
Site of metastasis	Y/N: Bone Lung Liver Lymph node

	Visceral
Median PSA at enrollment	Continuous
Years from prostate cancer diagnosis to enrollment	Continuous
Months from ADT start to enrollment	Continious
Prior radiation	
Prior primary radiation	Y/N
Prior prostatectomy	Y/N
Prior bicalutamide	Y/N
Prior sipuleucal-T	Y/N
Prior docetaxel	Y/N

4 Statistical Analysis Plan

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.

4.1 Demographic and Clinical Characteristics ("Table 1")

Demographic and clinical characteristics in table 3.3 will be summarized among all patients and stratified by race. For continuous variables, we will report median, minimum, and maximum. For categorical variables, we will report count and percent within each category.

4.2 Analyses Plan for Primary Objective - estimate the radiographic PFS distribution separately in Black and White men

The Kaplan-Meier product limit method will be used to estimate the rPFS in Black and White men separately. Estimates will be graphed, and median rPFS along with 95% CIs will be reported within each race. We will also report 1-year and 2-year rPFS rates.

4.3 Analyses Plan for Secondary Objective 1 – PSA kinetics

The proportion of patients who experience no PSA decline, PSA decline of 30%, 50% and 90% within 3 months on study, PSA <0.1 will be estimated by race 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 biochemical PFS (confirmed PSA progression) in Black and White men separately. Estimates will be graphed, and median rPFS along with 95% CIs will be reported within each racial group. We will also report 1-year and 2-year rPFS rates.

A waterfall plot will be created to show the best % change in PSA from baseline by race. Spaghetti plots will be used to show PSA trajectories over the study by race.

4.4 Analyses Plan for Secondary Objective 2 – radiographic assessments

The percentage of patients with bone flares will be reported within each race group. Radiographic assessments: to estimate the rate of objective response and incidence of bone flares

4.5 Analyses Plan for Secondary Objective 3 – safety and tolerability

The standard toxicity summaries will be reported by race. First, all toxicities will be summarized by grade. Next, toxicities that are possibly, probably, and definitely related to study drugs/procedures will be summarized by grade. A butterfly plot will be created to show the most prevalent study-related AEs by race.

4.6 Analyses Plan for Secondary Objective 4 – overall survival

The Kaplan-Meier product limit method will be used to estimate OS in Black and White men separately. Estimates will be graphed, and median rPFS along with 95% CIs will be reported within each race. We will also report 2-year and 3-year rPFS rates.