A Phase 2 Study of Apalutamide in Active Surveillance Patients

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Sponsor-Investigator: Michael T. Schweizer, MD

Title: A Phase 2 Study of Apalutamide in Active Surveillance Patients

Objective: To determine if a 90-day course of apalutamide will lead to a negative repeat prostate biopsy in active surveillance patients.

Study Design: This is an open label, multi-site, Phase II study to evaluate the combination of apalutamide in men followed on active surveillance.

Participating Institutions: University of Washington Medical Center

Financial and Medication Support: Janssen Scientific Affairs, LLC

Timeline: This study is planned to complete enrollment within one year, with all patients followed for a total of five years.

Treatment Plan: This is an open label, multi-site, Phase II study designed to determine the negative repeat prostate biopsy rate following 90-days of treatment with apalutamide. All subjects must be enrolled in the active surveillance program at the University of Washington Medical Center. All eligible patients will initiate therapy with apalutamide, which will be administered at the FDA approved dose for treating non-metastatic castration-resistant prostate cancer (i.e., 240 mg daily by mouth). Note that apalutamide is FDA approved only for the treatment of patients with non-metastatic castration-resistant prostate cancer, and is under development as an investigational product for other types of prostate cancer. Subjects will have either 1) an MRI detectable cancer of PIRADS 3 or more >5mm, and pathologically documented by MRI/TRUS fusion biopsy with coordinates of biopsy site stored for repeat biopsy; or 2) a systematic 12 core biopsy pathologically documenting prostate cancer with the coordinates of the biopsy sites stored for repeat biopsy. This biopsy may be done up to 12-months prior to enrollment.

Following 90-days of treatment with apalutamide, patients will undergo a repeat prostate biopsy selectively targeting sites of prior positive biopsies (3 from each positive biopsy site) plus a 12 core systematic prostate biopsy without targeting. All patients will continue on active surveillance per the standard practice of the treating urologist.

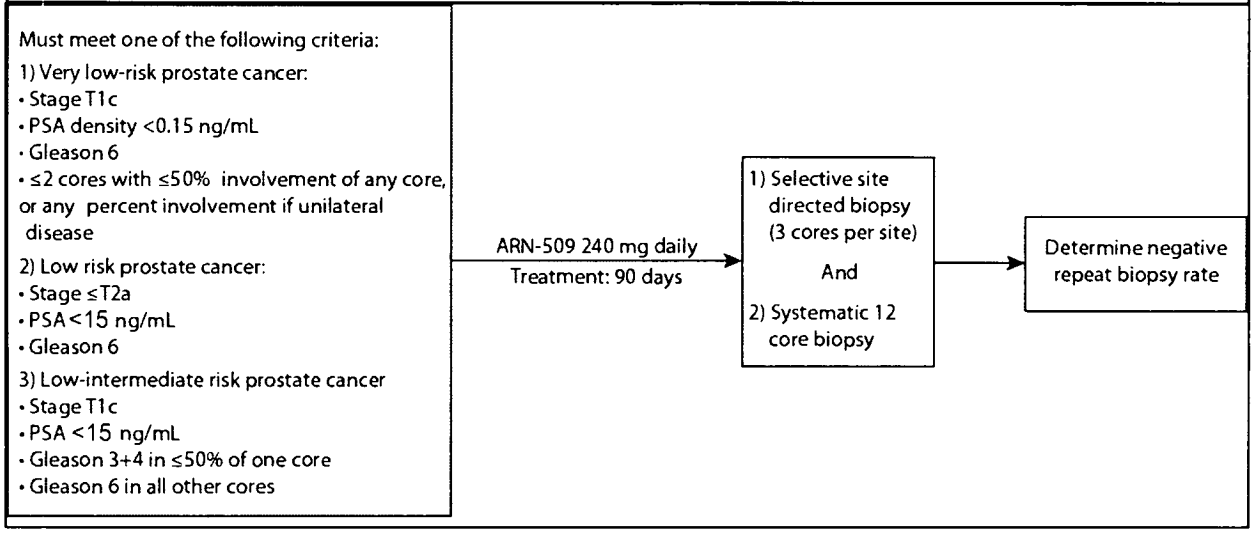
The primary endpoint for this trial will be the absence of residual carcinoma (i.e., a negative repeat biopsy) as determined by targeted and systematic biopsies following 90-days of apalutamide. Secondary endpoints will include: exit from active surveillance due to pathologic progression or otherwise at 2 years, receipt of local treatment for prostate cancer at 2 years, local treatment free survival, PSA progression at 2 years, PSA PFS as defined by Prostate Cancer Working Group 2 (PCWG2) criteria, radiographic disappearance of MRI detectable

nodules following treatment, quality of life changes and safety (as assessed by the revised National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE], version 4.03).[1]

Biopsy specimens, blood and plasma samples will be stored at -80°C. These specimens will be labeled with a subject's unique study ID, and will not have personal identifiers imprinted on them. Samples (i.e., prostate tissue, blood and plasma) will be obtained pre- and post-treatment with apalutamide. These biologic specimens will be used for additional correlative work. Examples of studies to be conducted may include, but are not limited to: assessment for PTEN loss via immunohistochemistry (IHC), assessment for alteration in MYC/chromosome 8q24 via FISH, whole blood RNA expression panel, and tumor mRNA expression profiling/risk classification (e.g., Decipher [GenomeDX Biosciences, San Diego, CA], Oncotype DX Prostate Cancer Assay [Genomic Health, Inc., Redwood City, CA], or RNA-seq).[2-6]

Subject enrollment requires a baseline systematic 12 core biopsy with pathologically documented prostate cancer and with the coordinates of the biopsy sites stored for repeat biopsy. Subjects can include men with newly diagnosed prostate cancer or those already enrolled in active surveillance, but baseline prostate biopsy must have occurred within 12-months of enrolling onto this study. Subjects may have had a multiparametric MRI of the prostate performed at least 6 months from any prior prostate biopsy. If an MRI detectable cancer of PIRADS 3 or more and >5mm was pathologically documented by MRI/TRUS fusion biopsy with coordinates of biopsy site stored, this lesion will be targeted for repeat biopsy. Otherwise, coordinates should be stored using a standard sextant prostate biopsy diagram (Appendix A) to aid in targeted repeat biopsy. Ninety days after treatment with apalutamide, all subjects will undergo 1) selective biopsy targeting cancer positive sites based on stored coordinates (3 biopsy cores per positive site); and 2) a 12 core non targeted systematic biopsy. PSA will be measured at baseline (i.e., within 30 days of initiating treatment per the study) and again within one week of completing combination therapy. PSA progression will be determined based on PCWG2 criteria (i.e., confirmed rising PSA ≥2 ng/mL at least one week apart).[1]

Study Schema



All samples collected as part of this research study will be stored at University of Washington and access to these samples will be limited to the Sponsor-Investigator, Co-Investigators,

Janssen Scientific Affairs, LLC or their designees. These biologic samples will be retained for up to 5 years following the last patient completing the study, and any remaining samples will be destroyed after that time. Likewise, data generated as part of this study will be stored on secure servers at University of Washington and/or Janssen Scientific Affairs, LLC and access will be limited to the Sponsor-Investigator, Co-Investigators, Janssen Scientific Affairs, LLC or their designees. The identity of enrolled subjects will remain confidential, and only the treating physician, research team, and/or Sponsor-Investigator will have access to this information. Patient identifiers will not be made available to the Janssen Scientific Affairs, LLC.

Study Population:

Men with very low-risk to low-intermediate risk prostate cancer (see 'risk' definitions under inclusion criteria) enrolled (or planning to enroll) on active surveillance.

Number of Patients: Up to 33 patients at University of Washington Medical Center.

Inclusion Criteria:

1. Have signed an informed consent document.
2. Be willing/able to adhere to the prohibitions and restrictions specified in this protocol
3. Written authorization for use and release of health and research study information has been obtained (i.e., HIPAA authorization)
4. Male aged 18 to 75 years or life expectancy ≥10 years (as determined by the treating physician)
5. Eastern cooperative group (ECOG) performance status ≤1
6. Histologically confirmed adenocarcinoma of the prostate as documented by a minimum 12 core prostate biopsy completed within 1-year of enrollment (Note: most recent prostate biopsy must have demonstrated prostatic adenocarcinoma)
7. Favorable risk prostate cancer as defined by:

Very low-risk

a. Clinical stage T1c disease
b. PSA density (PSAD) <0.15 ng/mL
c. Gleason score 6
d. ≤2 core biopsies with ≤50% involvement of any biopsy core with cancer, or unilateral disease ≤2 core biopsies with any percentage involvement

or

Low risk

a. Clinical stage ≤ T2a
b. PSA < 15 ng/mL
c. Gleason score 6

or

Low-intermediate risk

a. Clinical stage T1c
b. PSA <15 ng/ml
c. Gleason 3+4 present in ≤50% of one core/site as detected by systematic biopsy or MRI/TRUS fusion guided biopsy
d. Gleason 6 disease in all other cores

8. Willing and qualified for active surveillance at University of Washington
9. Serum testosterone ≥150 ng/dL
10. Able to swallow the study drugs whole as a tablet
11. Clinical laboratory values at screening:

    a. Hemoglobin ≥9.0 g/dL, independent of transfusion and/or growth factors within 3 months prior to randomization
    b. Platelet count ≥100,000 x 10^9/μL independent of transfusion and/or growth factors within 3 months prior to registration
    c. Serum albumin ≥3.0 g/dL
    d. GFR ≥45 mL/min
    e. Serum potassium ≥3.5 mmol/L
    f. Serum total bilirubin ≤1.5 × 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)
    g. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) <2.5 × ULN

12. Medications known to lower the seizure threshold (see list under prohibited meds) must be discontinued or substituted at least 4 weeks prior to study entry.
13. 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.

Exclusion Criteria:

1. Prior local therapy to treat prostate cancer (e.g., radical prostatectomy, radiation therapy, brachytherapy)
2. Prior use of ARN-509 (apalutamide)
3. Have known allergies, hypersensitivity, or intolerance to ARN-509 (apalutamide) or its excipients
4. Prior or ongoing systemic therapy for prostate cancer including, but not limited to:
    a. Hormonal therapy (e.g., leuprolide, goserelin, triptorelin)
    b. CYP-17 inhibitors (e.g., abiraterone, ketoconazole)
    c. Antiandrogens (e.g., bicalutamide, nilutamide)
    d. Second generation antiandrogens (e.g., enzalutamide)
    e. Immunotherapy (e.g., sipuleucel-T, ipilimumab)
    f. Chemotherapy (e.g., docetaxel, cabazitaxel)
5. Have any condition that, in the opinion of the investigator, would compromise the well-being of the subject or the study or prevent the subject from meeting or performing study requirements
6. History of any of the following:

    a. Seizure or known condition that may pre-dispose to seizure (including but not limited to prior stroke, transient ischemic attack, loss of consciousness within 1 year prior to registration, brain arteriovenous malformation; or intracranial

masses such as schwannomas and meningiomas that are causing edema or mass effect)

b. 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 registration.
c. Any condition that in the opinion of the investigator, would preclude participation in this study

7. Current evidence of any of the following:

    a. Uncontrolled hypertension
    b. Gastrointestinal disorder affecting absorption
    c. Active infection (e.g., human immunodeficiency virus [HIV] or viral hepatitis) or other medical condition that would make prednisone/prednisolone (corticosteroid) use contraindicated
    d. Any condition that in the opinion of the investigator, would preclude participation in this study

8. The use of drugs known to lower the seizure threshold, including: atypical antipsychotics (e.g., clozapine, olanzapine, risperidone, ziprasidone), bupropion, lithium, meperedine, pethidine, phenothiazine antipsychotics (e.g., chlorpromazine, mesoridazine, thioridazine), and tricyclic antidepressants (e.g., amitriptyline, desipramine, doxepin, imipramine, maprotiline, mirtazapine) (see Appendix C for a more complete list of prohibited concomitant medications).
9. The use of strong CYP3A4 inhibitors, including: itraconazole, clarithromycin, erythromycin, diltiazem, verapamil, delavirdine, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole, grapefruit juice (or grapefruits) (see Appendix C for a more complete list of prohibited concomitant medications). Note: If a patient is on a strong CYP3A4 inhibitor, they can be reconsidered for enrollment if they can safely stop said medication. A two week or 5 half-lives, whichever is longer, washout will be required prior to enrolling on study. Subject may not resume medication while receiving apalutamide.
10. Strong CYP3A4 inducers, including: phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, efavirenz, tipranivir, St. John's wort (see Appendix C for a more complete list of prohibited concomitant medications). Note: If a patient is on a strong CYP3A4 inducer, they can be reconsidered for enrollment if they can safely stop said medication. A two week or 5 half-lives, whichever is longer, washout will be required prior to enrolling on study. Subject may not resume medication while receiving apalutamide.
11. Any psychological, familial, sociological, or geographical condition that could potentially interfere with compliance with the study protocol and follow-up schedule.

Primary Objective: Determine the negative repeat biopsy rate by site directed and systematic prostate biopsy after 90-days of apalutamide.

Secondary Objectives:

1. Determine the rate of exit at 2 years from active surveillance due to pathologic reclassification.
2. Determine the overall rate of exit at 2 years from active surveillance.

3. Determine the rate of local treatment (e.g., radical prostatectomy, radiation therapy, brachytherapy) at 2 years and the local treatment free survival.
4. Determine PSA progression rates and PSA progression free survival (PFS), as defined by the Prostate Cancer Working Group 2 (PCWG2) criteria.
5. Determine the rate of radiographic disappearance of MRI detectable prostate cancer following treatment (only in patients with a baseline nodule that is PIRADS 3 or more and >5mm).
6. Investigate the safety of apalutamide in men undergoing active surveillance.
    a. Safety will be evaluated by the incidence, severity, duration, causality, seriousness, and type(s) of adverse events as assessed by the revised National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03 published 14 June 2010.
7. Track quality of life utilizing the FACT-P and SF36 surveys for each cohort.
8. Exploratory biomarker Assessment. Examples of these may include, but are not limited to: assessment for genomic PTEN loss via fluorescence in situ hybridization (FISH), PTEN immunohistochemistry (IHC), assessment for alteration in MYC/chromosome 8q24 via FISH and tumor mRNA expression profiling/risk classification (e.g., Decipher, Oncotype DX Prostate Cancer Assay, or RNA-seq).

Primary Endpoint: Negative (i.e., no residual carcinoma) site directed and systematic prostate biopsy following 90-days of apalutamide.

Secondary Endpoints:

1. Exit from active surveillance due to pathologic reclassification at 2 years.
2. Exit from active surveillance for any reason at 2 years.
3. Local treatment (e.g., radical prostatectomy, radiation therapy, brachytherapy) at 2 years and the local treatment free survival.
4. PSA progression and PSA progression free survival (PFS), as defined by the Prostate Cancer Working Group 2 (PCWG2) criteria [Scher *et al*, 2008].
5. Radiographic disappearance of MRI detectable prostate cancer following treatment (in patients with a baseline nodule that is PIRADS 3 or more and >5mm).
6. Safety of apalutamide in men undergoing active surveillance.
    a. Safety will be evaluated by the incidence, severity, duration, causality, seriousness, and type(s) of adverse events as assessed by the revised National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03 published 14 June 2010.
7. Quality of life as assessed using the FACT-P and SF36 surveys.
8. Exploratory biomarkers assessment. Examples of these may include, but are not limited to: assessment for genomic PTEN loss via fluorescence in situ hybridization (FISH), PTEN immunohistochemistry (IHC), assessment for alteration in MYC/chromosome 8q24 via FISH and tumor mRNA expression profiling/risk classification (e.g., Decipher, Oncotype DX Prostate Cancer Assay, or RNA-seq).

1. Introduction

1.1. Overview and Rationale

Prostate cancer is highly curable when caught at an early stage, with 10-year overall survival (OS) rates following radical prostatectomy (RP) or radiation therapy reported at >80%.[7,8] While this data is encouraging, it is now recognized that a large number of men with localized, low grade prostate cancer are being over treated. Large population based screening programs conducted in Europe have reported that the number of men with prostate cancer who need to be treated in order to save one life may be as high as 48.[9] A similar study conducted in the United States did not find that prostate cancer screening efforts led to any improvement in overall survival (OS).[10]

A logical conclusion from the aforementioned screening data is that only a subset of higher risk men may stand to benefit from localized prostate cancer treatment. One strategy to mitigate this over treatment entails the expectant management of men with favorable risk prostate cancer (i.e., active surveillance), where only patients with pathologic upstaging are referred for local therapy (e.g., prostatectomy or radiation therapy).[11-13] Active surveillance can lead to approximately 45% to 70% of men with favorable risk disease avoiding local therapy, with approximately 25 to 35% leaving the program due to pathologic upstaging.[13,14] Medical strategies to further decrease the rate of exit from active surveillance due to pathologic upstaging are needed given the morbidity associated with RP or prostatic radiation therapy. The need for intervention in this group is further bolstered by the fact that in spite of presenting with favorable risk disease, a subset of these patients will still go on to die from metastatic prostate cancer.[14,15]

Androgen/androgen receptor (AR) targeted therapies remain the backbone of advanced prostate cancer therapy.[16] The initial treatment paradigm typically involves driving testosterone levels down to the castrate range (i.e., <50 ng/dL), most often through chemical castration with an LHRH agonist or antagonist. This approach is successful in controlling the disease in upwards of 85% of men; however, responses are typically transient and at the time of progression men are labeled as having castrate resistant prostate cancer (CRPC).[17,18] The observation that even in a castration-resistant state AR regulated genes (e.g., PSA) remain expressed has led to the further

exploration of the AR-signaling axis as a therapeutic target in men with CRPC. Subsequently, newer AR-directed agents like abiraterone and enzalutamide, which inhibit AR-signaling in men with CRPC through disrupting the ligand-AR interaction (Abi through ligand depletion and Enza through receptor antagonism) have been developed.[19-23] The next-generation pure AR-antagonist apalutamide builds on the success of enzalutamide, with improved pharmacokinetics/pharmacodynamics (PK/PD), and is currently under clinical investigation.[24]

Given the proven track record of targeting the androgen/AR axis in the more advanced setting, AR-signaling inhibitors are the logical choice to evaluate at an earlier stage. Indeed, twenty-four weeks of neoadjuvant abiraterone acetate in combination with an LHRH agonist (leuprolide) has been reported to result in a 24% total/near total pathologic complete response (pCR) rate as documented in prostatectomy specimens.[25] Monotherapy with apalutamide may have the theoretical advantage of not causing prolonged testosterone suppression. This is in contrast to the LHRH agonists which have been documented to cause prolonged testosterone suppression following their discontinuation.[26-29]

The *hypothesis* of this trial is that apalutamide will lead to negative repeat biopsies as determined through systematic and site directed biopsies in active surveillance patients, which should in turn lead to decreased rates of pathologic progression and attrition from active surveillance.

1.2. Androgen/Androgen Receptor Directed Therapies

The initial management of advanced prostate cancer, as well as higher risk localized prostate cancer being treated with radiation therapy, typically involves targeting the androgen/androgen receptor (AR) signaling axis through lowering serum testosterone levels.[16,30] This is accomplished either through surgical castration or now more commonly with an LHRH agonist/antagonist (i.e., hormonal therapy [HT]). Hormonal therapy is initially highly effective in those with metastatic prostate cancer, leading to objective responses in >85% of individuals.[17] Unfortunately, after a variable period of symptom relief, androgen ablation invariably ceases to suppress prostate cancer growth and patients eventually succumb to their disease. This disease state defined by progression in spite of androgen ablation has been termed castrate resistant

prostate cancer (CRPC).[18] More recently it has come to light that CRPC is still largely dependent on androgen/AR axis signaling. This realization has led to the development of multiple newer AR directed therapies.[19-23] Mechanistically these agents primarily work either through ligand depletion (e.g., abiraterone acetate) or through interference with AR trafficking and signaling (e.g., apalutamide, enzalutamide).

Traditional HTs have several unwanted side effects, making their use in an otherwise healthy population of men somewhat disadvantageous. Specifically, these agents have been shown to increase one's risk of diabetes and cardiovascular disease, lead to weight gain, and cause serum total cholesterol levels to increase.[31-34] While one could argue that brief periods of LHRH agonist therapy are unlikely to produce such unwanted effects, it has been well documented that the use of HT for even a transient period of time can lead to prolonged periods of testosterone suppression – potentially putting these men at risk for the aforementioned side effects.[26-29] After approximately 8 months of HT only ~35% of men will recover their testosterone to baseline and only 70-80% of men will recover their testosterone to within a normal range.[35]

1.2.1. APALUTAMIDE

Apalutamide works through competitive AR inhibition and unlike the older anti-androgens (e.g., bicalutamide, nilutamide), is a pure AR antagonist. It additionally has the ability to prevent AR nuclear translocation and DNA binding to nuclear response elements.[24] It is generally felt to function similarly to enzalutamide, another AR targeted therapy approved for men with mCRPC pre- and post-docetaxel. In docetaxel pre-treated patients enzalutamide was shown to result in a 37% reduced risk of death compared to placebo (HR 0.63, 95% CI, 0.53-0.75; P<0.001), and in docetaxel naïve patients it led to a 29% reduction in the risk of death compared to placebo (HR 0.71, 95% CI, 0.60 to 0.84; P<0.001).[22,23] Preclinical work comparing apalutamide to enzalutamide, however, demonstrated that apalutamide may have several theoretical advantages over enzalutamide.[36] Namely, in mouse models apalutamide was able to achieve a maximal therapeutic effect at 30 mg/kg/day compared to 100 mg/kg/day of enzalutamide (Figure 1). Apalutamide is also able to achieve equivalent intra-tumoral concentrations at a lower plasma steady state concentration compared to enzalutamide. Finally, while high-dose Apalutamide

(i.e., 3-fold higher than the Phase II dose of 240 mg/day based on dose per m^2 body surface area and standard species conversion factors) has resulted in tremors and seizures in dogs, apalutamide is less effective than enzalutamide at crossing the blood-brain barrier. This may result in decreased CNS toxicities in those treated with apalutamide compared to enzalutamide. For instance, while enzalutamide has been implicated in causing seizures in a minority of patients, possibly through off target inhibition of GABA-A, no seizure have occurred in subjects treated on the Phase I/II studies of apalutamide (see apalutamide Investigator's Brochure).[22,37]

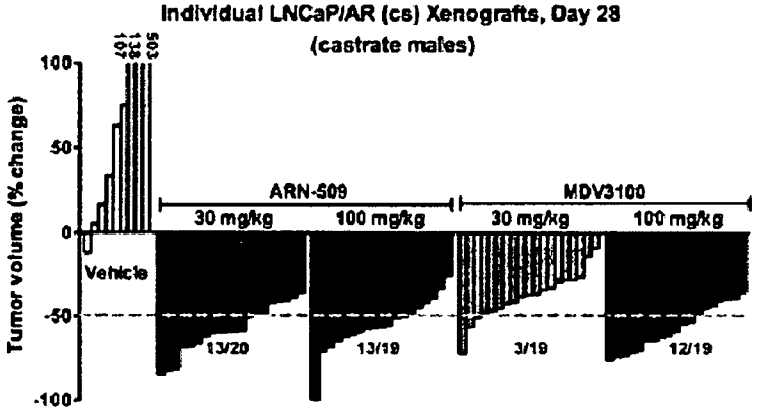


Figure 1: Apalutamide comparative efficacy to enzalutamide (MDV-3100) in mouse xenograft models. Apalutamide is able to achieve maximal therapeutic effect at 30 mg/kg/day compared to 100 mg/kg/day of enzalutamide.

1.2.1.1. APALUTAMIDE Clinical Trial Experience

The first in human Phase I/II study of apalutamide is currently ongoing [Clinicaltrials.gov, NCT01171898]. This study is evaluating men with mCRPC. Results from the Phase I portion of this study (N=30) demonstrated that apalutamide is generally safe and well tolerated. At the maximum tested dose of 300 mg daily by mouth only 1/4 subjects experienced a grade 3 adverse event (AE) (abdominal pain). The other three individuals receiving a dose of 300 mg daily did not experience dose limiting toxicities (DLT) (see apalutamide Investigator's Brochure); [Rathkopf, ASCO GU 2012]. Common grade 1-2 AEs observed in the Phase I study included: fatigue (47%), nausea (30%), abdominal pain

(20%), arthralgias (13%), diarrhea (17%), dyspnea (13%) and peripheral sensory neuropathy (13%). Five patients experienced serious adverse events and one patient discontinued the study due to an adverse event (atrial fibrillation) deemed unrelated to study treatment. PSA declines ≥50% were observed in 12 (55%) patients. ^{18}F-16β-fluoro-5α-dihydrotestosterone (FDHT) PET evaluation demonstrated AR blockade at four weeks across multiple doses. Given promising activity observed across all doses in conjunction with no appreciable difference in FDHT-PET uptake at 240 mg compared to 300 mg of apalutamide, a dose of 240 mg has been selected for Phase II testing.[22,24]

The Phase II portion of this study is ongoing and will evaluate three expansion cohorts with a total enrollment of 97 patients (see apalutamide Investigator's Brochure).[22] The primary endpoint of the Phase II study is PSA response at 12 weeks according to Prostate Cancer Working Group 2 (PCWG2) Criteria.[1] All cohorts will consist of men who are chemotherapy naïve and have CRPC. Specific cohorts are: 1) non-metastatic CRPC, 2) mCRPC pre-abiraterone acetate and 3) mCRPC post-abiraterone acetate. Preliminary results for the non-metastatic CRPC cohort, mCRPC pre-abiraterone acetate cohort and the mCRPC post-abiraterone acetate cohort demonstrated ≥50% PSA declines at 12-weeks in 91% (41/45), 88% (22/25) and 29% (4/14) subjects, respectively (see apalutamide Investigator's Brochure).[38] The most frequent, treatment-emergent, all causality, adverse events observed in > 10% of patients were fatigue (43%), diarrhea (32%), abdominal pain (25%), and nausea (23%). Table 6 in the apalutamide Investigator's Brochure lists all Phase II AEs reported in more than 3 patients by cohort. In Phase II, as of 20 August 2012, there were three Grade 3 treatment-related AEs: diarrhea, abdominal pain, and rash. Both diarrhea and rash occurred in NM-CRPC patients, with start dates approximately one month after the start of treatment and both were ongoing at the time of the data cut. The third Grade 3 AE (abdominal pain) occurred in a metastatic treatment-naïve CRPC patient, starting 29 days after the start of treatment. It resolved after eight days of study

treatment interruption with no further recurrence or sequelae. Table 7 in the apalutamide Investigator's Brochure lists all Phase II treatment-related Grades ≥ 3 AEs.

Apalutamide was recently approved by the FDA for use in men with non-metastatic CRPC on the basis of Phase III data showing that it significantly prolonged the time to development of metastatic disease[39]. In the pivotal Phase III study, patients with a PSA doubling time ≤10 months were randomized 2:1 between apalutamide or placebo. Men in the apalutamide group had a median metastasis-free survival of 40.5 months vs. 16.2 months in the placebo group (HR = 0.28; 95% CI 0.23 to 0.35; P<0.001). Several additional studies evaluating apalutamide are ongoing, including a Phase I trial evaluating it in combination with abiraterone acetate in a mCRPC population [clinicaltrials.gov, NCT01792687].

1.3. Active Surveillance

While watchful waiting is primarily focused on avoiding treatment in those with advanced prostate cancer and a minimal life expectancy, active surveillance is geared towards individualizing management in those with favorable risk disease who are otherwise fit for local therapy – the intent being to not sacrifice overall cure rates while minimizing overtreatment.[11] Those individuals felt most appropriate for this strategy have traditionally had low to very low-risk localized prostate cancer, usually as defined by the criteria proposed by Epstein or D'Amico; however, several cohorts now allow men with favorable-intermediate risk disease (i.e., low-volume Gleason 3+4 disease).[14,40-42] By focusing on those with favorable risk disease, active surveillance has been able to achieve comparable survival rates compared to those receiving immediate treatment while allowing approximately 45% to 70% of men to avoid local therapy (Table 2).[13,14] Furthermore, given that upward of 45% of men may qualify for active surveillance (i.e., have at least low risk disease), if management of patients per this paradigm becomes more widely accepted, the number of men avoiding unnecessary local therapy could reach nearly 50,000 per year in the United States alone.[43,44]

					Inclusion Criteria							
Center	Total number enrolled	Number meeting all inclusion criteria (%)	Median age (years)	Median follow-up (months)	Gleason	PSA criteria	cT	Total positive cores	Any given core positivity (%)	Number receiving local therapy (%)	OS (%)	Prostate Cancer Specific OS (%)
Johns Hopkins[13]	769	633 (82)	66	32	Gleason ≤3+3	PSA density ≤0.15 ng/ml/ml	1	≤2	≤50%	255 (33.2)	98	100
University of Miami[45]	230	230 (100)	64	32	Gleason ≤6	PSA ≤10 ng/ml	≤2	≤2	≤20%	32 (14)	100	100
University of California San Francisco[46]	640	376 (59)	62	47	Gleason ≤3+3	PSA ≤10 ng/ml	≤2	≤33%	≤50%	Low-risk (n=376): 104 (28) Intermediate risk (n=90): 27 (28)	97	100
University of Toronto[14]	993	993 (100)	68	77	Gleason ≤6 Gleason ≤3+4 (select patients only)	Before year 2000: Men ≤70 years-old: PSA ≤10 ng/ml Men >70 years-old: PSA ≤15 ng/ml After year 2000: PSA ≤10 ng/ml Life expectancy <10 years/significant comorbidities: PSA 10-20 ng/ml	-	-	-	267 (27)	85	98.5
Memorial-Sloan Kettering[47]	238	238 (100)	64	22	≤3+3	PSA ≤10 ng/ml	≤2a	≤3	≤50%	-	-	

able 2: Key North American active surveillance cohorts. Abbreviations: OS, overall survival; cT, clinical tumor stage.

Enrollment criteria vary across active surveillance cohorts, but in general enrollment is offered only to those with favorable risk prostate cancer, which can be defined as very low-risk to low-intermediate risk disease (i.e., low-volume Gleason 3+4 disease).[40,41,48] In general, local intervention is recommended upon pathologic reclassification (i.e., increased tumor volume or Gleason score), with some also recommending intervention following a change in PSA kinetics.[13,14,46] The reported reasons men leave active surveillance in pursuit of treatment include: Gleason grade change (8% to 38%), PSA increase (14% to 26%) and anxiety (3% to 9%).[49]

As conducted at Johns Hopkins, active surveillance focuses on men with very low-risk disease as defined per the Epstein criteria (i.e., T1c stage, PSA density <0.15 ng/mL, PSA <10 ng/mL, Gleason ≤6, ≤2 cores involved and ≤50% cancer in any given core).[11,13,41] Approximately 80% of men enrolled in the active surveillance program at Johns Hopkins met all criteria for very low-risk disease, with the other 20% failing to meet the PSA <10 ng/mL requirement only. Surveillance has entailed semiannual PSA measurements with digital rectal exam (DRE) and an annual 12 to 14 core biopsy. Curative local therapy is in turn only recommended upon pathologic upgrade from the enrollment criteria. To date, 1,134 men have enrolled in active surveillance, with 508 (45%) men exiting the program. Out of those who have exited, 298 (26%) were secondary to pathologic upstaging, 99 (9%) elected to undergo treatment in spite of stable pathology and 113 (10%) electively withdrew from the program (Figure 2). Out of the 113 that electively withdrew from active surveillance, 66 (58.4%) were lost to follow-up. In regard to those who exited active surveillance due to pathologic upstaging, 130 (44%) exited due to Gleason score upgrading, 168 (56%) exited due to an increase in disease volume (i.e. total number of effected cores >2 or >50% involvement in any given core). Within two years 143 (12.6%) exited; 65 (45%) due to Gleason score upgrading and 78 (55%) due to an increase in disease volume. Only one of the subjects on active surveillance at Johns Hopkins has died as a result of prostate cancer Unpublished data).[13]

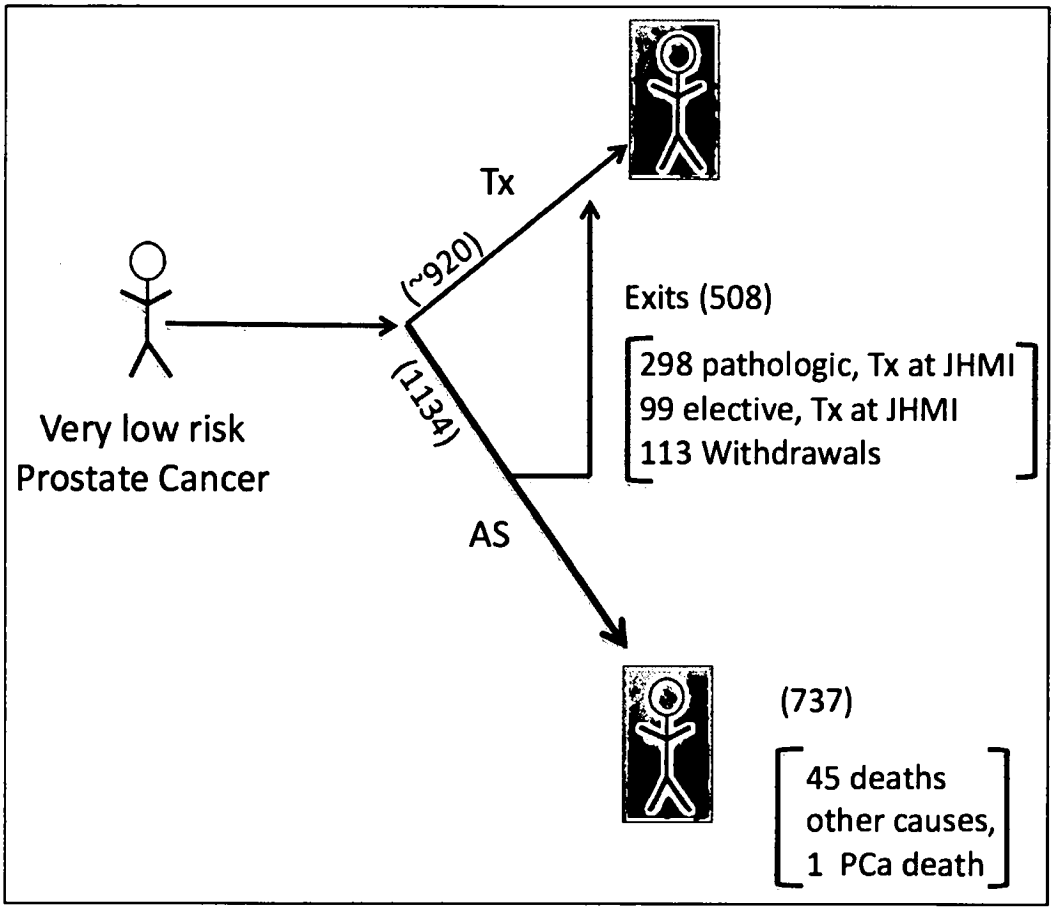


Figure 2: Johns Hopkins active surveillance schematic. AS, active surveillance; Tx, local treatment (e.g. prostatectomy, radiation therapy); JHMI, Johns Hopkins Medical Institution; PCa, prostate cancer.

In contrast to the Johns Hopkins active surveillance cohort, the University of Toronto cohort allows select patients with intermediate-risk prostate cancer to enroll.[14] Prior to the year 2000, patients >70 years-old who had a PSA up to 15 ng/ml or a Gleason score ≤3+4 were allowed to enroll. After 2000, any patient could enroll if they had a PSA of 10-20 ng/ml and/or a Gleason score ≤3+4 as long as they had a life expectancy of <10 years and significant comorbidities. Gleason 7 patients with primary pattern 4 disease were excluded given that these patients have been shown to have poorer outcomes compared to primary pattern 3 patients.[48] Out of 993 men enrolled onto this cohort, 25% fulfilled the D'Amico criteria for intermediate risk.[40] After a median follow up of 6.4 years, 27% of men have received intervention for their prostate cancer. Reasons for leaving the program include: short PSA doubling time (11.7%), grade

progression (9.5%), patient preference (1.6%), stage progression (0.8%) and biopsy volume progression (0.6%). Prostate cancer-specific mortality remains low, with only 6% of patients having died from metastatic prostate cancer at 15-years. There does, however, appear to be an increased risk of death for those with intermediate risk disease compared to those with low-risk disease (15 year OS: 50.3% vs. 68.8%, P<0.0001; 15 year prostate cancer-specific survival: 88.5% vs. 96.3%, P<0.01).[15]

One area in need of further study is how to best manage minority patients with prostate cancer. For instance, African American men have been reported to have a 1.6 fold increased age-adjusted incidence of prostate cancer and a 2.4 fold increased age-adjusted prostate cancer mortality.[44] While some of the observed disparities in outcomes can be attributed to socioeconomic factors, a difference in tumor biology cannot be excluded, with some data pointing to African Americans harboring faster growing tumors compared to Caucasians.[50,51] It has recently been reported that amongst a cohort of men with very low-risk prostate cancer being followed with active surveillance, African Americans were more likely to experience pathologic upgrading post-prostatectomy compared to Caucasians (27.3% vs. 14.4%; P<0.001).[52] This data indicates that current means of risk stratifying based on clinical parameters alone may not be sufficient for certain patient populations interested in enrolling in active surveillance programs. Incorporating additional variables into pre-operative predictive models, such as prostatic MRI data, may help to overcome some of these limitations.

1.3.1. Androgen-directed Therapy in Active Surveillance

Two trials have assessed the clinical effects of androgen-directed therapy (e.g., LHRH agonist, 5α-reductase inhibitor) in men with prostate cancer enrolled on active surveillance. The first trial reported by Fleshner and colleagues randomized men with low-risk prostate cancer on active surveillance (T1c-T2a, Gleason score ≤6, PSA ≤11 ng/mL and a life expectancy of >5 years) to dutasteride 0.5 mg PO daily (N=144) vs. placebo (N=145).[53] The primary endpoint was time to prostate cancer progression, defined as the time to pathological or therapeutic (i.e., radical prostatectomy, radiation therapy or drug therapy) progression. The dutasteride group had significantly fewer patients with prostate cancer progression at 3 years compared to the placebo group (38% vs. 48%, P=0.009) and a higher negative 12-core TRUS repeat biopsy rate (36% vs.

23%, P=0.024). It should be noted, however, that the rates of pathological progression were the same for the dutasteride and placebo groups (29% vs. 33%, P=0.079).

The second trial by Cussenot and colleagues evaluated combination leuprolide 22.5 mg SC and bicalutamide 50 mg PO daily in men enrolled on active surveillance.[54] Subjects were required to have low-risk prostate cancer (Gleason ≤6, PSA < 10 ng/mL, ≤3 positive cores and ≤T2a). Ninety-eight subjects were enrolled and received a single 3-month depot injection of leuprolide plus 15 days of oral bicalutamide around the time of their injection. The primary endpoint was the negative 10-core TRUS biopsy rate approximately one year after initiation of therapy. They reported a negative re-biopsy rate of 45% (11-19 months post-medical therapy). The investigators noted that this was higher than the 36% negative biopsy rate reported in the trial by Fleshner and colleagues.

Neither of the aforementioned studies documented the development of metastatic prostate cancer or prostate cancer related death. Both of these trials demonstrate the feasibility and safety of an androgen-directed medical intervention in men enrolled on active surveillance. While the randomized trial by Fleshner and colleagues does report a decreased rate for the composite therapeutic and pathological progression endpoint, the fact that the rate of pathologic progression between groups is the same may indicate that 5α-reductase inhibitor therapy alone is inadequate to alter the natural course of low-risk prostate cancer. The report by Cussenot and colleagues interestingly reported a higher negative repeat biopsy rate when men were treated with combined leuprolide plus bicalutamide; however, caution should be taken in comparing data across studies. It is notable that there were a substantial number of false negatives in the Fleshner study, as evidenced by the high number of men (23%) with a negative repeat biopsy on the placebo arm.

1.3.2. MRI in Active Surveillance

While most centers have not formally incorporated MRI into their active surveillance guidelines, it does appear that MRI may play a role in determining

whether higher risk prostate cancer is present – be it through guiding prostate biopsies or improving upon predictive nomograms. Indeed, it has been shown that current clinical models used to determine the probability of insignificant prostate cancer pre-prostatectomy can be improved upon through incorporating endorectal prostatic MRI data.[55,56] MRI has also been shown to be useful in planning prostate biopsies, with the cancer detection rate in those with and without detectable prostate lesions being 70.1% and 13.1% respectively ($P<0.001$).[57] The multiparametric MRI (mMRI) is most useful in excluding presence of clinically significant disease defined as tumor volume >0.5 cm^3. Turkbey et al reported that at 3.0 T mMRI can accurately estimate the index tumor volume sized above 0.5 cm^3 compared with prostatectomy histological findings. MRI could detect 127 of 135 (94%) index tumors. Mean volume of tumors detected on MRI was 2.02 cm^3 (median 0.98, range 0 to 21). Eight tumors were missed by MRI, the mean tumor histological volume 0.19 cm^3 (median 0.11, range 0.0046 to 0.58) .[58] In a study by Rosenkrantz et al, it has been shown that mMRI can accurately (82.7-89%) detect tumor foci measuring more than 3 mm on prostatectomy histological exam. The median diameter of tumors detected by MRI was 9 mm (range, 4–20 mm). They only considered tumor foci of larger than 3 mm on histopathology as tumor positive.[59] Lee et al have also reported the mean diameter of tumor suspicious lesions in a subgroup of patients with lesions less than 1 cm on DWI (8.26±1.51mm).[60]

Recent advances in mMRI employ both morphologic and functional MR techniques, which allow extending the obtainable imaging information beyond anatomical assessment. Diffusion-weighted imaging (DWI) interrogates the tissue microstructure at the microscopic scale of water self-diffusion and by measuring the Brownian motion of water molecules provides information about the functional environment of water in tissue and reflecting cellular status of normal and pathological tissue.[61] Furthermore, DWI is sensitive to changes in the micro-diffusion of water within the intra-cellular space and extracellular space and cytotoxic edema due to alterations in the ATP dependent sodium-potassium pumps.[62] The quantitative biomarker of water diffusivity is apparent diffusion coefficient (ADC). In general, water movement is restricted by compacted or proliferating cells, which enables the ADC to be a marker of tumor density or

cellularity, such that, a highly dense malignant region will have low ADC and an area with low cellular density will exhibit a high ADC value. Malignant lesions have a lower ADC values (about 20-40%) than benign or normal prostatic tissue. Preliminary results suggest that DWI-MRI has the potential to not only increase the specificity of PCa detection but also to support prediction of tumor aggressiveness.[62] Dynamic contrast-enhanced MR imaging (DCE-MRI) dynamically captures the distribution of intravenously administered Gadolinium-based contrast agents between tissue and blood pool, and allows characterizing the microvascular environment alterations resulting from tumor angiogenesis, reflecting changes in perfusion and capillary permeability.[63] DCE-MRI uses pharmacokinetic (PK) modeling to describe the microscopic processes leading to the distribution of contrast agent molecules between the vascular and extravascular spaces over time. Tissue enhancement therefore contains information about the microvascular properties, the extravascular space and the exchange rate between these compartments. The parameters in the PK model are: the leakage space (v_e), efflux rate constant (k_{ep}), and the influx volume transfer constant (K^{trans}). These parameters are connected by the equation: $v_e=K^{trans}/k_{ep}$. Limited data are available on the application of MRI in monitoring treatment response in prostate cancer, such as the study of monitoring response to androgen deprivation therapy.[64] These investigators reported significant reduction in all DCE-MRI parameters in the region of tumor, while normal-appearing tissue showed no significant change after 3-month therapy.[64]

The significance of MRI detectable prostate lesions in men who have low to very-low risk prostate cancer as defined by standard clinical criteria (i.e. the Epstein criteria) is illustrated in data from men enrolled in the active surveillance program at Johns Hopkins (unpublished data).[65] In total, 98 active surveillance patients had follow-up data and underwent prostatic MRI (endorectal MRI in 83.8%). Thirteen (13.3%) had MRI invisible tumors and 85 (86.7%) had MRI visible tumors. After a median follow-up post-MRI of 13 months (range, 1-42 months), none of those with MRI invisible tumors had pathologic reclassification while 34 (40%) of those with MRI visible tumors did. Taken in total, the above data point to MRI detectable prostate nodules having clinical significance, with

their presence perhaps indicating an underlying significant cancer – even when otherwise classified as low to very low-risk.

1.4. Exploratory Biomarkers

1.4.1. PTEN

PTEN is a tumor suppressor gene implicated in the tumorigenesis and progression of prostate cancer.[66-69] It plays an important role in the modulation of phosphatidylinositol-3-kinase (PI3K) signaling, most likely though preventing the activation of the protein kinase Akt.[70] Loss or inactivation of PTEN can in turn lead to the upregulation of PI3K/AKT signaling as well as downstream mTOR signaling.[71] Genomic PTEN loss as determined through Fluorescence in situ hybridization (FISH) as well as lost PTEN expression as determined by immunohistochemistry (IHC) have been associated with adverse pathological markers as well as increased risk of recurrence following prostatectomy.[72-76]

1.4.2. MYC

MYC is an onco-protein that functions as a transcription factor, regulating cell proliferation, metabolism, protein synthesis, mitochondrial function and stem cell renewal.[77] Like PTEN, its expression has been associated with prostate cancer initiation and progression.[77-79] Indeed, MYC has been shown to be able to transform benign prostate cancer cells in a single step and its overexpression has been documented at the earliest stages of transformation in prostatic intraepithelial neoplasia samples.[78,80] The region on chromosome 8q24 that encompasses the MYC locus is often altered (e.g. amplified, deleted) in more advanced disease.[77,81-83] Interestingly, while alterations in chromosome 8q24 have been documented in more advanced cases of prostate cancer, MYC protein expression seems to be higher in Gleason 3 disease compared to Gleason 4-5 disease.[77]

1.4.3. ERG

Gene fusions between the androgen receptor regulated TMPRSS2 gene and members of the ETS family of nuclear transcription factors (primarily ERG)

are frequently recognized in prostate cancer specimens.[84] Furthermore, these gene fusions may synergize with PTEN loss, leading to more aggressive prostate cancer behavior.[72,85]

1.4.4. KI-67

KI-67 (Ki67) is a nuclear protein complex that is present during all active phases of the cell cycle, but absent during the G0 phase, making it a marker of cellular proliferation [Gerdes et al, 1984].[86] In men with localized prostate cancer, Ki67 has been found to independently associate with the risk of developing progressive disease following both radiation therapy and radical prostatectomy.[72,87]

1.4.5. AR-axis liquid biopsy assay

Expression of a panel of RNA markers will be evaluated from whole blood collected in PAXgene RNA tubes. These cancerous RNA transcripts are involved in AR-signaling, steroidogenesis, proliferation, neuroendocrine and other pathways important in prostate cancer. Detection of differential expression levels may associate with response to drug treatment.

1.4.6. Prostate Cancer mRNA Expression Profiling/Risk Classifier

There are several commercially available mRNA expression assays designed to assess the risk of prostate cancer recurrence/progression (e.g., Decipher [GenomeDX Biosciences, San Diego, CA] and Oncotype DX Prostate Cancer Assay [Genomic Health, Inc., Redwood City, CA]).[2-6] In addition, whole transcriptome sequencing (i.e., RNA-seq) can provide detailed assessment of the landscape of genes being transcribed within a population of cancer cells, and provide insights into potential resistance mechanisms. One or more of these approaches will be used on prostate core biopsy specimens obtained pre- and post-treatment with apalutamide. The goal will be to develop predictive biomarkers for response to apalutamide.

2. Study Objectives

2.1. Primary Objective

Determine the negative repeat biopsy rate by site directed and systematic prostate biopsy after 90-days of apalutamide.

2.2. Secondary Objectives

1. Determine the rate of exit at 2 years from active surveillance due to pathologic reclassification.
2. Determine the overall rate of exit at 2 years from active surveillance.
3. Determine the rate of local treatment (e.g., radical prostatectomy, radiation therapy, brachytherapy) at 2 years and the local treatment free survival.
4. Determine PSA progression rates and PSA progression free survival (PFS), as defined by the Prostate Cancer Working Group 2 (PCWG2) criteria.[1]
5. Determine the rate of radiographic disappearance of MRI detectable prostate cancer following treatment (only in patients with a baseline nodule that is PIRADS 3 or more and >5mm).
6. Investigate the safety of apalutamide in men undergoing active surveillance.
    a. Safety will be evaluated by the incidence, severity, duration, causality, seriousness, and type(s) of adverse events as assessed by the revised National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03 published 14 June 2010.
7. Track quality of life utilizing the FACT-P and SF36 surveys for each cohort.
8. Exploratory biomarker Assessment. Examples of these may include, but are not limited to: assessment for genomic PTEN loss via fluorescence in situ hybridization (FISH), PTEN immunohistochemistry (IHC), assessment for alteration in MYC/chromosome 8q24 via FISH and tumor mRNA expression profiling/risk classification (e.g., Decipher, Oncotype DX Prostate Cancer Assay, or RNA-seq).

2.3. Primary Endpoint

Negative (i.e., no residual carcinoma) site directed and systematic prostate biopsy following 90-days of apalutamide.

2.4. Secondary Endpoints

1. Exit from active surveillance due to pathologic reclassification at 2 years.
2. Exit from active surveillance for any reason at 2 years.
3. Local treatment (e.g., radical prostatectomy, radiation therapy, brachytherapy) at 2 years and the local treatment free survival.
4. PSA progression and PSA progression free survival (PFS), as defined by the Prostate Cancer Working Group 2 (PCWG2) criteria [Scher *et al*, 2008].
5. Radiographic disappearance of MRI detectable prostate cancer following treatment (in patients with a baseline nodule that is PIRADS 3 or more and >5mm).
6. Safety of apalutamide in men undergoing active surveillance.
    a. Safety will be evaluated by the incidence, severity, duration, causality, seriousness, and type(s) of adverse events as assessed by the revised National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03 published 14 June 2010.
7. Quality of life as assessed using the FACT-P and SF36 surveys.
8. Exploratory biomarkers assessment. Examples of these may include, but are not limited to: assessment for genomic PTEN loss via fluorescence in situ hybridization (FISH), PTEN immunohistochemistry (IHC), assessment for alteration in MYC/chromosome 8q24 via FISH and tumor mRNA expression profiling/risk classification (e.g. Decipher, Oncotype DX Prostate Cancer Assay, or RNA-seq).

3. Patient Population and Selection

Up to 33 patients will be enrolled at University of Washington Medical Center, in a 2-stage design. The target population will be men with very low-risk to low-intermediate risk prostate cancer (see 'risk' definitions under Inclusion Criteria) enrolled (or planning to enroll) on active surveillance.

3.1. Inclusion Criteria

1. Have signed an informed consent document .
2. Be willing/able to adhere to the prohibitions and restrictions specified in this protocol
3. Written Authorization for Use and Release of Health and Research Study Information has been obtained
4. Male aged 18 to 75 years or life expectancy ≥10 years (as determined by the treating physician)
5. Eastern cooperative group (ECOG) performance status ≤1
6. Histologically confirmed adenocarcinoma of the prostate as documented by a minimum 12 core prostate biopsy completed within 1-year of enrollment (Note: most recent prostate biopsy must have demonstrated prostatic adenocarcinoma)
7. Favorable risk prostate cancer as defined by:

Very low-risk

a. Clinical stage T1c disease
b. PSA density (PSAD) <0.15 ng/mL
c. Gleason score 6
d. ≤2 core biopsies with ≤50% involvement of any biopsy core with cancer, or unilateral disease ≤2 core biopsies with any percentage involvement

or

Low risk

a. Clinical stage ≤ T2a
b. PSA < 15 ng/mL
c. Gleason score 6

or

Low-intermediate risk

a. Clinical stage T1c
b. PSA <15ng/ml
c. Gleason 3+4 present in ≤50% of one core/site as detected by systematic biopsy or MRI/TRUS fusion guided biopsy
d. Gleason 6 disease in all other cores/sites

8. Willing and qualified for active surveillance at the University of Washington
9. Serum testosterone ≥150 ng/dL
10. Able to swallow the study drugs whole as a tablet
11. Clinical laboratory values at screening:
    a. Hemoglobin ≥9.0 g/dL, independent of transfusion and/or growth factors within 3 months prior to registration
    b. Platelet count ≥100,000 x 10^9/μL independent of transfusion and/or growth factors within 3 months prior to registration
    c. Serum albumin ≥3.0 g/dL
    d. GFR ≥45 mL/min
    e. Serum potassium ≥3.5 mmol/L
    f. Serum total bilirubin ≤1.5 × 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)
    g. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) <2.5 × ULN
12. Medications known to lower the seizure threshold (see list under prohibited meds) must be discontinued or substituted at least 4 weeks prior to study entry.
13. Agrees to use a condom (even men with vasectomies) and another effective method of birth control if he is having sex with a woman of childbearing potential or agrees to use a condom if he is having sex with a woman who is pregnant while on study drug and for 3 months following the last dose of study drug. Must also agree not to donate sperm during the study and for 3 months after receiving the last dose of study drug.

3.2. Exclusion Criteria:

1. Prior local therapy to treat prostate cancer (e.g., radical prostatectomy, radiation therapy, brachytherapy)
2. Prior use of ARN-509 (apalutamide)
3. Have known allergies, hypersensitivity, or intolerance to ARN-509 (apalutamide) or its excipients
4. Prior or ongoing systemic therapy for prostate cancer including, but not limited to:
    a. Hormonal therapy (e.g., leuprolide, goserelin, triptorelin)
    b. CYP-17 inhibitors (e.g., abiraterone, ketoconazole)
    c. Antiandrogens (e.g., bicalutamide, nilutamide)
    d. Second generation antiandrogens (e.g., enzalutamide)
    e. Immunotherapy (e.g., sipuleucel-T, ipilimumab)
    f. Chemotherapy (e.g., docetaxel, cabazitaxel)
5. Have any condition that, in the opinion of the investigator, would compromise the well-being of the subject or the study or prevent the subject from meeting or performing study requirements
6. History of any of the following:
    a. Seizure or known condition that may pre-dispose to seizure (including but not limited to prior stroke, transient ischemic attack, loss of consciousness within 1 year prior to registration, brain arteriovenous malformation; or intracranial masses such as schwannomas and meningiomas that are causing edema or mass effect)
    b. 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 registration.

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

7. Current evidence of any of the following:
   a. Uncontrolled hypertension
   b. Gastrointestinal disorder affecting absorption
   c. Active infection (e.g., human immunodeficiency virus [HIV] or viral hepatitis) or other medical condition that would make prednisone/prednisolone (corticosteroid) use contraindicated
   d. Any condition that in the opinion of the investigator, would preclude participation in this study
8. The use of drugs known to lower the seizure threshold, including: atypical antipsychotics (e.g., clozapine, olanzapine, risperidone, ziprasidone), bupropion, lithium, meperedine, pethidine, phenothiazine antipsychotics (e.g., chlorpromazine, mesoridazine, thioridazine), and tricyclic antidepressants (e.g., amitriptyline, desipramine, doxepin, imipramine, maprotiline, mirtazapine) (see Appendix C for a more complete list of prohibited concomitant medications).
9. The use of strong CYP3A4 inhibitors, including: itraconazole, clarithromycin, erythromycin, diltiazem, verapamil, delavirdine, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole, grapefruit juice (or grapefruits) (see Appendix C for a more complete list of prohibited concomitant medications).

   Note: If a patient is on a strong CYP3A4 inhibitor, they can be reconsidered for enrollment if they can safely stop said medication. A two week or 5 half-lives, whichever is longer, washout will be required prior to enrolling on study. Subject may not resume medication while receiving apalutamide.
10. Strong CYP3A4 inducers, including: phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, efavirenz, tipranivir, St. John's wort (see Appendix C for a more complete list of prohibited concomitant medications).

Note: If a patient is on a strong CYP3A4 inducers, they can be reconsidered for enrollment if they can safely stop said medication. A two week or 5 half-lives, whichever is longer, washout will be required prior to enrolling on study. Subject may not resume medication while receiving apalutamide

11. Any psychological, familial, sociological, or geographical condition that could potentially interfere with compliance with the study protocol and follow-up schedule.

3.3. Inclusion of Women and Minorities

This study is focused on prostate cancer; therefore the treatment cohort is only applicable to men. Men from all ethnic and race groups are eligible for this study.

4. Treatment Plan

4.1. Study Design

This is an open label, multi-site, Phase II study designed to determine the negative repeat prostate biopsy rate following 90-days of treatment with apalutamide. All subjects must be enrolled in the active surveillance program at the University of Washington Medical Center. All eligible patients will initiate therapy with apalutamide, which will be administered at the FDA approved dose for treating non-metastatic castration-resistant prostate cancer (i.e., 240 mg daily by mouth). Note that apalutamide is FDA approved only for the treatment of patients with non-metastatic castration-resistant prostate cancer, and is under development as an investigational product for other types of prostate cancer. Subjects will have either 1) an MRI detectable cancer of PIRADS 3 or more >5mm, and pathologically documented by MRI/TRUS fusion biopsy with coordinates of biopsy site stored for repeat biopsy; or 2) a systematic 12 core biopsy pathologically documenting prostate cancer with the coordinates of the biopsy sites stored for repeat biopsy. This biopsy may be done up to 12-months prior to enrollment.

Following 90-days of treatment with apalutamide, patients will undergo a repeat prostate biopsy selectively targeting sites of prior positive biopsies (3 from each positive biopsy site) plus a 12 core systematic prostate biopsy without targeting. All patients will continue on active surveillance per the standard practice of the treating urologist.

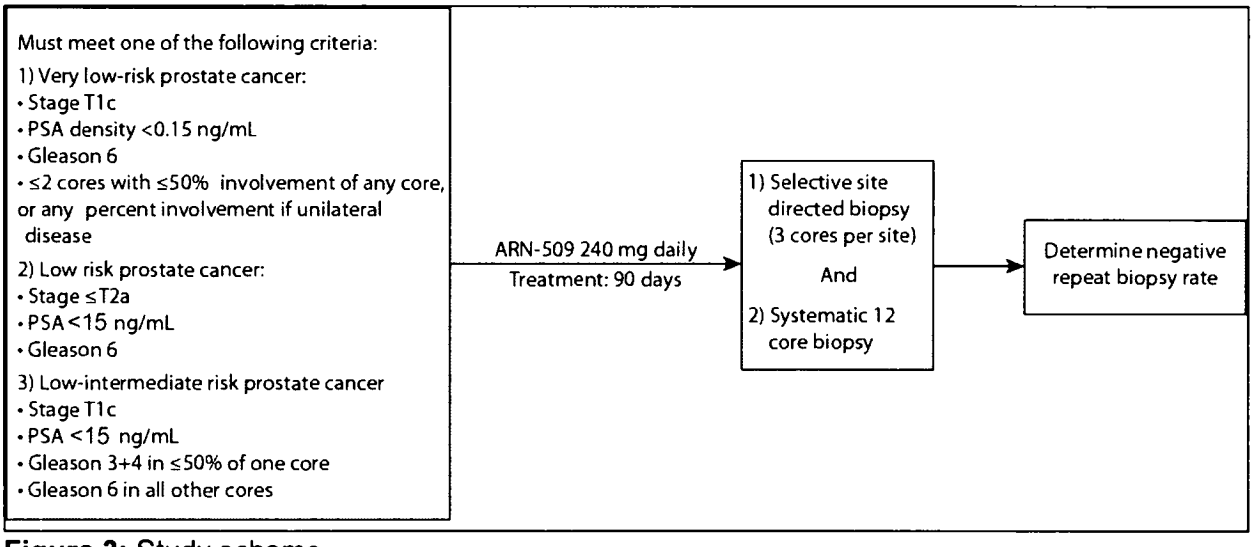


Figure 3: Study scheme.

The primary endpoint for this trial will be the absence of residual carcinoma (i.e. a negative repeat biopsy) as determined by targeted and systematic biopsies following 90-days of apalutamide. Secondary endpoints will include: exit from active surveillance due to pathologic progression or otherwise at 2 years, receipt of local treatment for prostate cancer at 2 years, local treatment free survival, PSA progression at 2 years, PSA PFS as defined by Prostate Cancer Working Group 2 (PCWG2) criteria, radiographic disappearance of MRI detectable nodules following treatment, quality of life changes and safety (as assessed by the revised National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE], version 4.03).[1]

Biopsy specimens, blood and plasma samples will be stored at -80°C. These specimens will be labeled with a subjects unique study ID, and will not have personal identifiers imprinted on them. Samples (i.e., prostate tissue, blood, and plasma) will be obtained pre- and post-treatment with apalutamide. These biologic specimens will be used for additional correlative work. Examples of studies to be conducted may include, but are not limited to: assessment for PTEN loss via immunohistochemistry (IHC), assessment for alteration in MYC/chromosome 8q24 via FISH and tumor mRNA expression profiling/risk classification (e.g., Decipher [GenomeDX Biosciences, San Diego, CA], Oncotype DX Prostate Cancer Assay [Genomic Health, Inc., Redwood City, CA], or RNA-seq).[2-6]

Subject enrollment requires a baseline systematic 12 core biopsy with pathologically documented prostate cancer and with the coordinates of the biopsy sites stored for repeat biopsy. Subjects can include men with newly diagnosed prostate cancer or those already enrolled in active surveillance, but baseline prostate biopsy must have occurred within 12-months of enrolling onto this study. Subjects may have had a multiparametric MRI of the prostate performed at least 6 months from any prior prostate biopsy. If an MRI detectable cancer of PIRADS 3 or more and >5mm was pathologically documented by MRI/TRUS fusion biopsy with coordinates of biopsy site stored, this lesion will be targeted for repeat biopsy. Otherwise, coordinates should be stored using a standard sextant prostate biopsy diagram (Appendix A) to aid in targeted repeat biopsy. Ninety days after treatment with apalutamide, all subjects will undergo 1) selective biopsy targeting cancer positive sites based on stored coordinates (3 biopsy cores per positive site); and 2) a 12 core non targeted systematic biopsy. PSA will be

measured at baseline (i.e., within 30 days of initiating treatment per the study) and again within one week of completing apalutamide. PSA progression will be determined based on PCWG2 criteria (i.e., confirmed rising PSA ≥2 ng/mL at least one week apart).[1]

All samples collected as part of this research study will be stored at University of Washington and access to these samples will be limited to the Sponsor-Investigator, Co-Investigators, Janssen Scientific Affairs, LLC or their designees. Only researchers associated with this study will have access to these specimens. Biologic samples will be retained for up to 5 years following the last patient completing the study, and any remaining samples will be destroyed after that time. Likewise, data generated as part of this study will be stored on secure servers at University of Washington and/or Janssen Scientific Affairs, LLC and access will be limited to the Sponsor-Investigator, Co-Investigators, Janssen Scientific Affairs, LLC or their designees. The identity of enrolled subjects will remain confidential, and only the treating physician, research team and/or Sponsor-Investigator will have access to this information. Patient identifiers will not be made available to the Janssen Scientific Affairs, LLC.

4.2. Removal of Patients from Study

A patient may be removed from the study for a variety of reasons, including:

1. Worsening symptoms that can be attributed to prostate cancer
2. Unacceptable adverse event(s)
    - Patients develop urinary outlet obstruction requiring urinary catheterization and/or surgical intervention
    - Patients who develop grade 3 or higher liver function abnormalities:
        - Bilirubin ≥ 2 times institutional upper limit of normal (ULN)
        - AST (SGOT) or ALT (SGPT) ≥ 3 times ULN
    - Patients develop decreased renal function with serum creatinine ≥ 2.5 times baseline level
    - Patients develop hypersensitivity or anaphylactoid reactions to apalutamide.
3. Intercurrent illness that prevents further participation
4. Experiencing a treatment delay of longer than 2 weeks due to drug toxicity; however, if the patient is receiving clinical benefit (at the discretion of the PI and/or

local investigator), treatment may be delayed for longer than 2 weeks and then resumed at the discretion of the Investigator.

5. Patient refuses further treatment through the study and/or withdraws consent to participate
6. Patients is noncompliant with respect to taking drugs, keeping appointments, or having tests required for the evaluation of drug safety and efficacy
7. General or specific changes in the patient's condition that render the patient unacceptable for further treatment in this study in the judgment of the PI or local investigator.
8. Under no circumstance will care of a withdrawn patient be adversely affected by a decision to withdraw or be withdrawn from the study.

5. Treatment Assessment and Evaluation

All required treatment and end of study procedures and assessments must be done within 7 days (+/-) of the specified study visit date unless otherwise noted. With the exception of the surveillance prostate biopsy, screening study procedures and assessments must be done within 30 days prior to enrollment. Long term follow-up procedures and assessments should occur two years following day 1 (+/- 30 days). After two years of follow-up, the medical records for study subjects will be requested and reviewed yearly through year 5 (+/- 90 days) in order to obtain additional follow up data.

Note: If a subject withdraws from the study prior to completing the 90-days of study drug, the "End of Study" procedures will be completed at the time of withdrawal. "Long Term Follow-up" procedures will occur at the specified time regardless of whether the patient received 90-days of study drug.

5.1. Screening Studies (performed within 30 days before enrollment unless otherwise noted; i.e., Day -30 to -1)

1. Comprehensive medical history and physical exam, including height and weight, medications, blood pressure, heart rate and ECOG performance status assessment
2. Systematic 12-core prostate biopsy (within 12-months of enrollment)
3. CBC (Complete blood count) with differential and platelet count
4. CMP (Comprehensive Metabolic Panel - Sodium, Potassium, Chloride, BUN, Serum Creatinine, Calcium, Total Protein, Albumin, Total Bilirubin, AST, ALT, Alkaline Phosphatase, CO2)
5. Thyroid stimulating hormone (TSH)
6. EKG
7. Testosterone
8. PSA

5.2. Treatment Phase

1. Comprehensive medical history and physical exam, including weight, medications, blood pressure, heart rate and ECOG performance status assessment (days 1, 30 and 60)
2. Adverse event assessment (days 1, 30 and 60)
3. Study drug dispensation and collection of unused study drug
4. CBC with differential (days 1, 30 and 60)
5. CMP (days 1, 30 and 60)
6. Serum PSA (day 1)
7. Testosterone (days 1, 30 and 60)
8. LH plasma level (days 1, 30 and 60)
9. TSH (days , 30 and 60)
10. Quality of life questionnaires (FACT-P and SF-36) (day 1)
11. Exploratory biomarkers (see sections 1.4 and 7.3) (performed on tissue, blood and plasma samples) (Days 1 and 30)

5.3. End of Study (i.e., day 91 of treatment)

1. Comprehensive medical history and physical exam, including weight, medications, blood pressure, heart rate and ECOG performance status assessment
2. Adverse event assessment
3. Unused study drug collection
4. Systematic 12-core prostate biopsy AND selective site directed biopsy (3-cores per site)

   Note: In patients with a baseline detectable nodule (PIRADS ≥3 and >5mm), MRI/TRUS fusion guided biopsy will be used to obtain the site directed biopsies

5. CBC with differential
6. CMP
7. Serum PSA
8. Testosterone
9. LH plasma level
10. Exploratory biomarkers (see sections 1.4 and 7.3) (performed on tissue, blood and plasma samples)
11. Quality of life questionnaires (FACT-P and SF-36)

5.4. Long Term Follow-up

1. Adverse event assessment (Days 180, 365, 545 and 730)
2. Minimum 12-core prostate biopsy (Days 365 and 730)
3. Serum PSA (Days 180, 365, 545 and 730)
4. Quality of life questionnaires (FACT-P and SF-36) (Days 180, 365, 545 and 730)

5.5. Long Term Record Review (at Years 3, 4 and 5, +/- 90 days)

1. Most recent PSA
2. Prostate biopsy data (e.g. highest Gleason score, number of involved cores)
3. Local treatment received (e.g. radiation, surgery)

6. **Study Calendar:** All required treatment and end of study procedures and assessments must be done within 7 days (±) of the specified study visit date. With the exception of the screening prostate biopsy, screening study procedures and assessments must be done 30 days prior to enrollment. Long-term follow-up procedures and assessments should occur two years following Day 1 (±30 days). Medical records will be reviewed yearly (+/- 90 days) through year five in years 3, 4 and 5.

	Screening	Treatment phase			End of Study	Long-term follow-up[h]				Record Review
	Day -30 to -1	Day 1 (±7 days)	Day 30 (±7 days)	Day 60 (±7 days)	Day 91 (±7 days)	Day 180 (±30 days)	Day 365 (±30 days)	Day 545 (±30 days)	Day 730 (±30 days)	Year 3, 4, 5 (±90 days)
Informed Consent	x									
History and Physical[a]	x	x	x	x	x					
Adverse Event Assessment		x	x	x	x	x	x	x	x	
Study drug dispensation		x	x	x						
Unused study drug collection			x	x	x					
CBC[b]	x	x	x	x	x					
CMP[b]	x	x	x	x	x					
EKG	x									
Serum PSA	x	x			x	x	x	x	x	
Testosterone	x	x	x	x	x					
LH plasma level[b]		x	x	x	x					
TSH[c]	x		x	x						
Exploratory biomarkers[d]		x	x		x					
Quality of life questionnaires[e]		x			x	x	x	x	x	
Systematic 12-core biopsy	x[f]				x		x		x	
Site directed biopsy (3-cores per site)[g]					x					
Medical Record Review										x

a. History and physical assessment will include ECOG performance status and toxicity assessments. Visits will also document medications, blood pressure, height (only at screening visit) and weight, and heart rate. Note: nursing assessment will suffice for the physical assessment.
b. CBC = Complete blood count with platelets and differential; CMP = Comprehensive metabolic panel (Sodium, Potassium, Chloride, BUN, Serum Creatinine, Calcium, Total Protein, Albumin, Total Bilirubin, AST, ALT, Alkaline Phosphatase, CO2); LH = Luteinizing hormone; TSH = thyroid stimulating hormone.
c. If TSH is abnormal, Free T3 and T4 levels must be checked.
d. See sections 1.4 and 7.3 for a description of exploratory biomarkers. These will be performed on tissue, blood and plasma sample. Note: Samples obtained at the Day 1 visit will serve as baseline samples.
e. Quality of life questionnaires include the FACT-P and SF-36 questionnaires.
f. Screening 12-core biopsy may be performed up to 12-months prior to enrollment.
g. In patients with a baseline detectable nodule (PIRADS ≥3 and >5mm), MRI/TRUS fusion guided biopsy will be used to obtain the site directed biopsies. Otherwise, this will be done using the saved coordinates of known areas of cancer as determined from the screening systematic 12-core biopsy.
h. Patients will be required to be seen by a provider or research nurse for long-term follow-up appointments on Day 180, Day 365, Day 545 and Day 730. Long-term follow-up on Year 3, Year 4 and Year 5 are conducted by medical record review only to collect data on most recent PSA, highest gleason score on most recent biopsy and local treatment received (e.g. radiation, surgery).
'X' indicates study or exam to be done on the specified day.

7. Study Assessments

7.1. Prostate Biopsy

Systematic 12-core prostate biopsies will be performed using transrectal ultrasound (TRUS) guidance and be performed per the treating physician's discretion. Prostate biopsies will be interpreted through the pathology department at University of Washington. Gleason score, number of involved cores and percent core involvement will all be captured. Coordinates of the biopsy sites must be stored. These coordinates may be stored on either a standard sextant prostate biopsy diagram (Appendix A) or within the MRI/TRUS fusion software. Repeat systematic 12-core prostate biopsies will be performed following treatment with apalutamide. In addition, site directed biopsies will be performed targeting areas of known cancer using the saved coordinates from the screening biopsy. Site directed biopsy may be performed using either: a) TRUS guidance, or b) MRI/TRUS fusion guidance. MRI/TRUS fusion guided biopsy will only occur if an MRI detectable cancer of PIRADS ≥3 and >5mm was pathologically documented at the time of screening biopsy. Note: patients are not required to have baseline MRI/TRUS fusion guided biopsies in order to enroll. A patient will be defined as having a negative biopsy if no cancer is found on systematic 12-core and site directed prostate biopsy as described above. The biopsy (12-core plus site directed) that occurs immediately following 90-days of apalutamide will be used for determining the primary endpoint.

Repeat minimum 12-core TRUS guided prostate biopsy will be performed approximately every year following day 1 of treatment with apalutamide per standard active surveillance guidelines. These biopsies will be used to determine if there has been pathologic progression. Pathologic progression will be defined as: 1) increase in Gleason score, 2) increase in number of involved cores or 3) increase in maximum percentage of any given core's involvement. Only pathologic progression (i.e. not PSA progression) will trigger removal from active surveillance and recommendation for local prostate cancer treatment.

7.2. Prostatic MRI

While not required for study enrollment, we anticipate some patients will have had a baseline MRI and/or MRI/TRUS fusion guided biopsy prior to enrolling on active

surveillance. In addition, select patients will undergo MRI/TRUS fusion guided site directed biopsies following treatment with apalutamide (see Section 7.1: Prostate Biopsy). In these individuals, the following MRI imaging parameters should be used whenever possible.

MR Imaging techniques: Prostate MR imaging will be performed on a 3.0 Tesla magnet (Trio, Siemens Medical Solutions or Ingenia, Philips Healthcare) using a body torso coil. The patient will be imaged in supine position. MRI will be performed at least 8 weeks after biopsy, to minimize the influence of post-biopsy hemorrhage. Patients will receive 1 mg Glucagon IM injection to suppress bowel peristalsis. Imaging will consists of thin-section high-resolution axial, coronal and sagittal T2-weighted fast spin-echo images of the prostate and seminal vesicles (TR/TE = 3500/101 msec, slice thickness 3 mm, interslice gap 0-1mm, FOV 20-28 cm), 3D isotropic T2 weighted image acquisition (TR/TE = 1600/115, slice/space 1/0 mm, FOV 35 cm), diffusion-weighted imaging (2D multislice single-shot echo-planar imaging, TR/TE = 3300/76 msec, b values 50, 500, 800, 1000 section thickness = 3 mm, FOV 20-28 cm), and DCE-MRI imaging sequences, consisting of a precontrast T1 mapping sequences using 3D VIBE (Simens) or 3D THRIVE (Philips) (TR/TE 3.8/1.4, slice/space 3.6/0, FOV 26 cm) with the option to obtain 4 identical measurement parameters except different flip angles (i.e. 2, 5, 8, 15°) and NEX=4. Subsequent dynamic imaging will utilize intravenous power injection (Medrad) of a single-dose (0.1 mmol/kg) of gadopentetate dimeglumine (Gd-DTPA, Magnevist®) at an injection rate 3 mL/second, followed by a 20-mL flush of normal saline. Axial DCE images of the entire prostate gland will be acquired using the TWIST T1 3D GR sequence at high temporal resolution of 4.2 sec (TR/TE 3.8/1.4 msec, flip angle 12, matrix 160x160, FOV 20-28 cm, NEX=1). At total of 70-post contrast phases will be acquired over 5 minutes. The total imaging time is 45 minutes.

Definitions for localizing prostate carcinoma: a) focal area of discrete measurable low signal intensity on T2-weighted images (longest diameter ≥ 0.5 cm); b) apparent diffusion coefficient (ADC) reduction on DWI in reference to normal glandular tissue; d) perfusion abnormality on DCE-MRI in reference to normal glandular tissue. Tumors are detected using a combination of the T2-weighted and diffusion-weighted images. More than one tumor is considered to be present if the tumor noncontiguously involves the left and the right gland, or noncontiguously involves the same ipsilateral side (with two or more noncontiguous slices of "normal appearing" prostate between tumor foci). For the follow-

up post-treatment studies, the baseline pretreatment MR images will be used as a reference to identify tumor regions.

DCE MRI Analysis: Areas suspicious for presence of tumor will be outlined by a radiologist as a region of interest (ROI) on the dynamic images using the T2-weighted and DWI images for guidance. Pharmacokinetic analysis of the DCE MRI images will be carried out using *syngo* Tissue 4D software from Siemens or DynaCAD software from Invivo. The following parameters will be recorded: the volume transfer constant (K^{trans}), the rate constant (k_{ep}), and the fractional leakage space (v_e).

DWI Analysis: Generated apparent diffusion coefficient (ADC) maps will be used to assess areas of low signal intensity reflecting restricted diffusion. Using the T2-weighted images and high b-value DWI images for guidance, the mean ADCs will be calculated for each defined ROI for each separate focus of prostate cancer.

MRI investigational biomarkers that will be assessed at baseline and on a post-treatment mMRI: DCE-MRI: K^{trans} (min^{-1}), k_{ep} (min^{-1}), v_e (%); DWI: ADC ($\times 10^{-3}$ mm^2/s)

7.3. Exploratory biomarkers

This study will incorporate a number of exploratory biomarkers. Given our rapidly evolving understanding of prostate cancer pathobiology, genetics and epigenetics, it is impossible to prospectively define all the relevant biomarkers for the patient population enrolled on this study. So as to not miss an opportunity to assess the utility of yet to be described biomarkers in the context of this active surveillance medical intervention trial, we will plan to store biopsy specimens, plasma and blood samples at -80°C. All samples (i.e., prostate tissue, blood and plasma) will be obtained pre- and post-treatment with apalutamide. Specific biomarkers of interest have been described in section 1.4 of the protocol. Admittedly, given that we may not be able to obtain adequate tissue to assess all of these biomarkers, we will prioritize assessing them in the order that they are described below. All biopsy material will be Formalin-Fixed Paraffin Embedded (FFPE) and IHC and FISH assays will be performed on these FFPE samples. Please refer to the laboratory manual for more detail.

PTEN: Loss of genomic PTEN will be determined using FISH. FISH assays will be conducted using the PTEN-del-TECT™ Four Color Panel FISH Probe (Cymene DX)

according to the manufacturer's directions. A total of 30 cells from each sample will be evaluated and a tumor will be considered to have PTEN loss if the percentage of cells showing 0 or 1 PTEN probe signal is greater than 2 standard deviations (SD) above the mean established from normal tissue and the PTEN probe/centromere 10 probe ratio is more than 2 SD below the mean established in normal tissue. PTEN protein expression will be determined via IHC using a rabbit monoclonal anti-PTEN antibody (clone D4.3, #9188, Cell Signaling Technologies). PTEN IHC and FISH assays will be conducted similar to the methods previously described by Lotan and colleagues.[74]

MYC: Alterations in chromosome 8q24, the region that encompasses the MYC locus, will be assessed via FISH. FISH hybridization will be done with the multicolor probes (ProVysion, Vysis, Inc., Downers Grove, IL) to detect and quantify chromosome 8 centromere probe [chromosome enumeration probe 8 (CEP8)] and with two locus-specific probes, the lipoprotein lipase (LPL; 8p21.3) and the c-MYC8q24 probe. MYC/chromosome 8q24 FISH assays will be conducted similar to the methods previously described by Jenkins and colleagues.[82]

ERG: Given that ERG protein expression has been shown to be an excellent surrogate of TMPRSS2-ERG fusion status, we will plan to assess ERG expression using IHC.[88-90] ERG IHC will be done using an anti-ERG mouse monoclonal antibody (clone 9FY; Biocare, Concord, CA). ERG IHC assays will be conducted similar to the methods described by Chaux and colleagues.[89]

KI-67: Ki67 will be assessed via IHC using an anti-Ki67 mouse monoclonal (clone 7B11; Zymed Laboratories, South San Francisco, Calif). The mouse PowerVisionþ kit (Leica Microsystems, Buffalo Grove, Ill) will be used for these assays. Ki67 IHC assays will be conducted using standard lab practices and in accordance with the mouse PowerVisionþ kit instructions.

AR-axis liquid biopsy assay: Expression of a panel of RNA markers will be evaluated from whole blood collected in PAXgene RNA tubes. Extracted RNA will come from blood cells as well as circulating tumor cells. RNA extraction and transcriptional profiling will be conducted similar to the methods described by Ross and colleagues.[91]

Prostate Cancer Genomic Classifier: FFPE Prostate tissue samples will be obtained pre- and post-treatment with apalutamide and shipped to a commercial genomic testing

lab (e.g. Decipher [GenomeDX Biosciences, San Diego, CA] and/or Oncotype DX Prostate Cancer Assay [Genomic Health, Inc., Redwood City, CA]).

7.4. Safety

Safety will be evaluated based on the incidence, severity, duration, causality, seriousness, and type of adverse events (AEs), and changes in the patient's physical examination, vital signs, and clinical laboratory results. Investigators will use the NCI CTC version 4.03 (published 14 June 2010) to assess the severity of AEs and toxicities (see Appendix B). For safety considerations specific to apalutamide see section 8.1 of the protocol.

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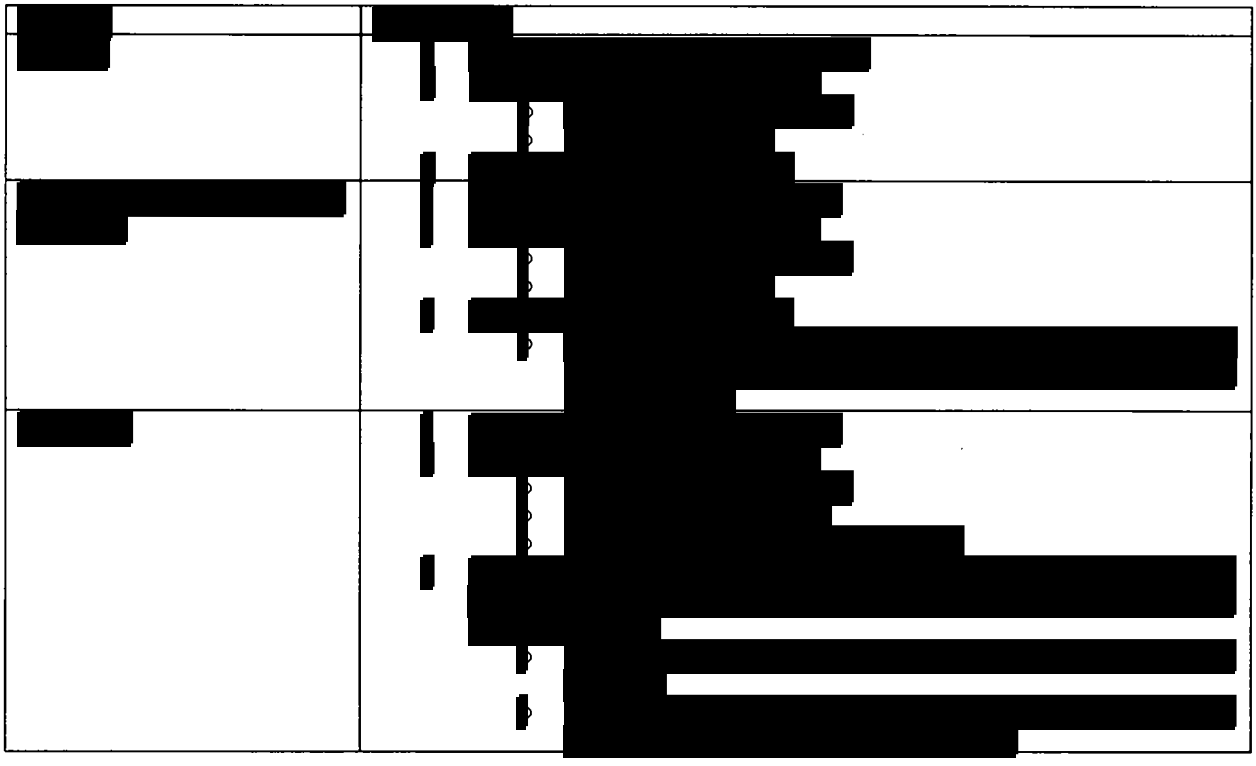

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9. Data Monitoring and Adverse Event Reporting Requirements

Institutional support of trial monitoring at the University of Washington/Seattle Cancer Care Alliance study site will be in accordance with the FHCRC/University of Washington Cancer Consortium Institutional Data and Safety Monitoring Plan. Under the provisions of this plan, FHCRC Clinical Research Support coordinates data and compliance monitoring conducted by consultants, contract research organizations, or FHCRC employees unaffiliated with the conduct of the study. Independent monitoring visits occur at specified intervals determined by the assessed risk level of the study and the findings of previous visits per the institutional DSMP.

In addition, protocols are reviewed at least annually and as needed by the Consortium Data and Safety Monitoring Committee (DSMC), FHCRC Scientific Review Committee (SRC) and the FHCRC/University of Washington Cancer Consortium Institutional Review Board (IRB). The review committees evaluate accrual, adverse events, stopping rules, and adherence to the applicable data and safety monitoring plan for studies actively enrolling or treating patients. The IRB reviews the study progress and safety information to assess continued acceptability of the risk-benefit ratio for human subjects. Approval of committees as applicable is necessary to continue the study.

The trial will comply with the standard guidelines set forth by these regulatory committees and other institutional, state and federal guidelines.

Additionally, scheduled meetings will take place weekly and will include the protocol Principal Investigator (PI) (Michael Schweizer, MD), and when appropriate, the collaborators, sub-investigators, and biostatistician involved with the conduct of the protocol.

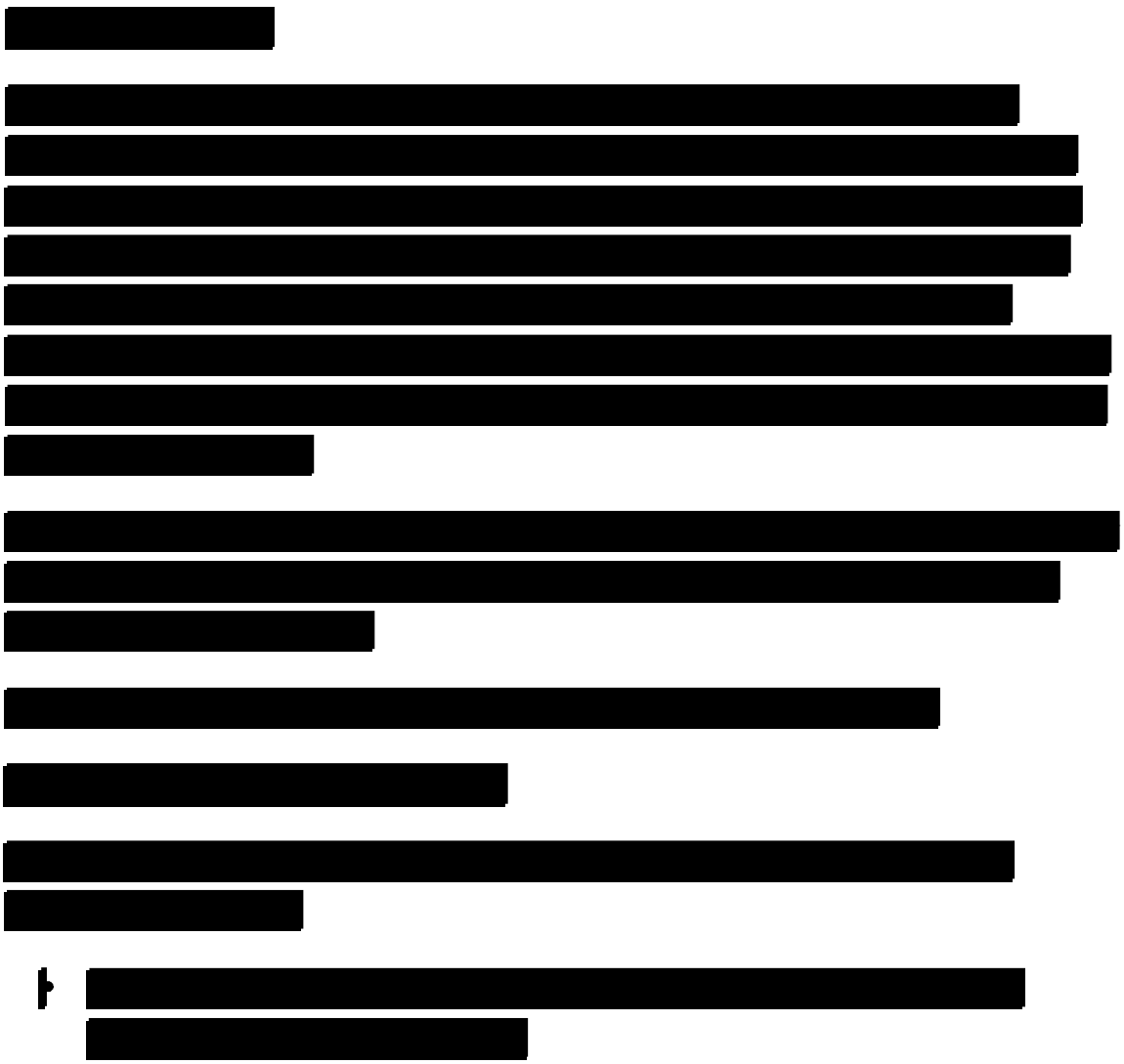
During these meetings the investigators will discuss matters related to: safety of protocol participants, validity and integrity of the data, enrollment rate relative to expectation, characteristics of participants, retention of participants, adherence to protocol (potential or real protocol violations), data completeness, and progress of data for secondary objectives.

External monitoring of participating sites will occur at least once per year, depending on the rate of accrual at these sites.

9.1. Management of Safety Data

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

9.2. Definitions



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9.6. Evaluating Adverse Events

The grade and severity of the event will be determined using the NCI Common Terminology Criteria for Adverse Events, CTCAE version 4.03. A copy of the CTCAE version 4.03 can be downloaded from the CTEP home page (http://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE version 4.03. Adverse events must be defined using CTCAE criteria. Adverse events not included in the CTCAE version 4.03 should be reported and graded under the "Other" adverse event within the appropriate category and grade 1 to 5 according to the general grade definitions, mild, moderate, severe, life-threatening, fatal, as provided in the CTCAE version 4.03.

9.6.1. Determining if the event is expected or unexpected

The determination of whether an AE is expected is based on agent-specific adverse event information provided in Section 7and 8 Pharmaceutical Information. Unexpected AEs are those not listed in the agent-specific adverse event information provided in Section 7and 8 Pharmaceutical Information.

9.6.2. Relationship to the medical treatment or procedure

The Investigator should document his/her opinion of the relationship of the event to study medication as follows:

- *Unrelated*- The adverse event is clearly not related to the investigational agent(s).
- *Unlikely*- The adverse event is doubtfully related to the investigational agent(s).
- *Possible*-The adverse event may be related to the investigational agent(s).

- *Probable*-The adverse event is most likely related to the investigational agent(s).

- *Definite*- The adverse event is clearly related to the investigational agent(s).

Based on this information, a decision will be made whether an adverse event should be reported as an expedited report (Serious Adverse Event, section 3.0) in addition to the routinely reported clinical data. Expedited adverse event reports that meet Institutional reporting criteria should be submitted to the Institutional Review Board (IRB) in accordance with policies of the coordinating center's IRB and local IRB where applicable (for the participating sites), and to the FDA in accordance with regulations under 21 CFR 312.32. Additionally, all SAEs should be submitted to Janssen Scientific Affairs, LLC within 24 hours of becoming aware of event and via secure e-mail.

9.6.3. Documenting Adverse Events

Each individual sign or symptom must be documented separately. Worksheets must be signed and dated by person conducting evaluation to be used as source documentation. The attribution of all adverse events must be verified by an investigator. Evaluation of laboratory toxicities may be documented directly on a printed laboratory report or CRF provided it is signed by the investigator. However, if an action was conducted due to this abnormality (e.g., RBC transfusion due to low Hgb) this would be recorded on the AE form also.

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 Sponsor Investigator's judgment, a clinically 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).

9.6.4. Maintenance of Safety Information

All safety data should be maintained in a research database in a retrievable format. The 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 Janssen Scientific Affairs' request).

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9.8. Protocol Amendments

Any changes to the study protocol will be made in the form of an amendment and must be approved by the IRB before implementation. These changes may only be made by the Sponsor-Investigator (Dr. Michael Schweizer). Changes to the protocol or informed consent form will be reviewed and approved by Janssen Scientific Affairs, LLC prior to submitting to the IRB for approval.

9.9. Informed consent

Written informed consent will be obtained by a study investigator, or delegated Sub-Investigator working on this study. An explanation of the nature of study, its purpose, procedures involved, expected duration, potential known risks and benefits will be provided to each participant by the investigator or the delegated Sub-Investigator. Each participant will be informed that participation in the study is voluntary and that they may withdraw from the study at any time, and that withdrawal of consent will not affect their subsequent medical treatment. Participants will be allowed time needed to make an informed decision. Participants will be encouraged to ask questions about the study and the consent before signing the consent form. Original signed consent forms will be filed in each patient's research chart, while each patient will receive a copy of the consent document. No patient will enter the study before the informed consent has been obtained.

The Research Coordinator and the Regulatory Coordinator at the coordinating center will be made aware of new participants via email. The Sponsor-Investigator will be responsible for reviewing the informed consent forms from participating sites and verifying eligibility. Once it has been confirmed that a new candidate has provided consent and is eligible to participate in the study, the coordinating center will register the patient and provided him with a unique study identification number. New participants' study checklist and informed consent form should be emailed to:

Zoya Bauer: zbauer@seattlecca.org

and

CC9582@seattlecca.org

10. Statistical Methods

This is an open label, multi-site study to evaluate apalutamide in men with very low-risk to low-intermediate risk prostate cancer (see 'risk' definitions under Inclusion Criteria) enrolled on active surveillance. The primary endpoint for this trial will be the absence of residual carcinoma (i.e., a negative repeat biopsy) as determined by targeted and systematic biopsies following 90-days of apalutamide. The primary objective will be to determine the negative repeat biopsy rate following 90-days of apalutamide for all men enrolled. The negative repeat biopsy rate will be continuously assessed throughout the study. Apalutamide will be dosed at the current recommended Phase II dose of 240 mg daily by mouth.

10.1. Study Design and Sample Size

We will use a Simon minimax 2-stage design, which will allow early stopping for futility after the first stage if the response rate is low. We expect that in the absence of treatment, approximately 20% of patients will have a negative repeat biopsy.[53] We also assume that ≥40% of treated patients must achieve a negative repeat biopsy to warrant further investigation of this treatment approach in active surveillance patients. Thus, our null and alternative hypotheses are H_0: p≤20% vs. H_1: p≥40%. The minimax 2-stage design for these parameters requires a first stage enrolling 18 patients. If ≤4 of 18 have a negative repeat biopsy the trial is stopped and H_0 cannot be rejected. If >4 of 18 patients respond, enrollment in that cohort continues until 33 patients have completed the trial, and the response rate is calculated for all 33 patients. If ≤10 of 33 patients have a negative repeat biopsy the null hypothesis cannot be rejected. This design will provide 80% power to detect a response rate of 40% (one-sided α=0.05). This design also provides a 72% probability of early stopping if H_0 is true, affording protection against treating more patients than necessary if the treatment is not effective.[92]

10.2. Data Analysis

The primary objective is to determine the negative repeat biopsy rate following treatment with apalutamide in men enrolled in active surveillance. This rate will be presented as the percent of subjects with a negative repeat biopsy, and will be calculated as: (Number of patients with a negative biopsy following 90-days of apalutamide) / (Total number of patients enrolled on the study) x 100. For details on the

definition of what constitutes a negative biopsy, refer to section 7.1: Prostate Biopsy. Subjects who drop out of the study due to disease progression, death, or limiting toxicity or individual choice will be considered as failures in estimating the negative repeat biopsy rate. Similarly, patients not undergoing repeat biopsy (for any reason) after treatment with apalutamide will be considered as failures in estimating the negative repeat biopsy rate. Patients who have not received at least one dose of apalutamide will be replaced and not considered in determining the negative repeat biopsy rate. We will use a 1-sample chi-square test to compare the proportion with a negative repeat biopsy to the null hypothesis value of 20% (above). The 95% confidence interval (CI) of the primary endpoint estimate will be computed.

Secondary endpoints will include: exit from active surveillance due to pathologic progression or otherwise at 2 years, the receipt of local treatment for prostate cancer at 2 years, local treatment free survival, PSA progression free survival (PFS) at 2 years, radiographic disappearance of MRI detectable prostate cancer following treatment (only in patients with baseline MRI), quality of life, safety and changes in exploratory biomarkers (see protocol section 1.4) pre- and post-treatment.

For both cohorts, the exit rate (all cause and due to pathologic progression), percent of men undergoing local treatment and PSA progression rate will be computed along with its 95% CI at the two year time point (i.e. Day 730 visit). The local treatment free survival and PSA PFS will be estimated using Kaplan-Meier methods and 95% CI will be estimated using Greenwood's formula.[93] PSA PFS will be censored at the time of local therapy. PSA progression will be defined by the PCWG2 criteria (i.e. confirmed rising PSA ≥2 ng/mL at least one week apart).

We will characterize toxicity as percentage by type and grade. Changes in quality of life (as assessed by the FACT-P and SF-36 instrument scores) and changes in exploratory biomarkers pre- and post-treatment will be assessed using paired t-test or signed-rank test for continuous variables, or McNemar chi-square tests for categorical variables. Baseline exploratory biomarker levels/values and change in exploratory biomarkers pre-/post-treatment will be correlated with the primary endpoint using chi-square tests and logistic regression, and with secondary endpoints using proportional hazards models, Kaplan-Meier methods and log-rank tests.

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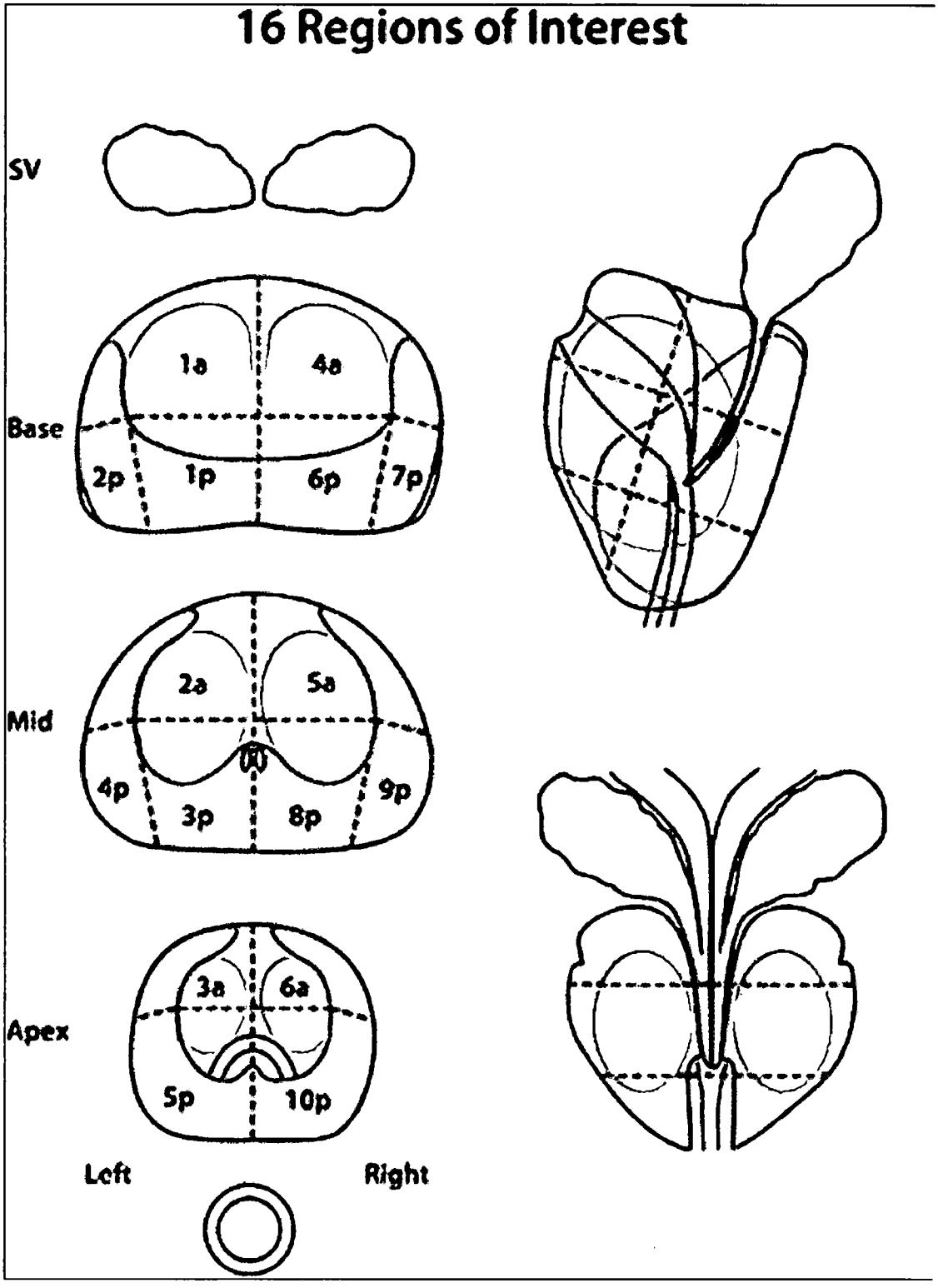
Appendix A

Sextant Prostate Biopsy Diagram



Appendix B
NCI COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS, VERSION 4.03

Version 4.03 of the NCI CTCAE, dated 14 June 2010, may be viewed and/or downloaded by accessing the following website:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Appendix C
Prohibited Concomitant Medications

Generic Name	Brand Name*
aminophylline	Aminocont; Aminomal; Diaphyllin; Filotempo; Neophyllin; Norphyl; Phyllocontin; Syntophyllin; Tefamin; Truphylline; Xing You Shan;
aminophylline in combination	Asmeton; Cha Xin Na Min; Emergent-Ez; Fufang Dan An Pian; Ke Zhi
amitriptyline	Amirol; Amitrip; Amixide; Deprelio; Diapatol; Elatrol; cElatrolet; Elavil; Endep; Enovil; Emitrip; Klotriptyl; Laroxyl; Levate; Limbitrol; Limbitryl; Mutabase; Mutabon; Nobritol; Novo-Triptyn; Pertriptyl; Redomex; Saroten; Sarotex; Sedans; Syneudon; Teperin; Triptizol; Triptyl; Tryptizol
amitriptyline in combination	PMS-Levazine
bupropion	Aplenzin; Buproban; Contrave; Elontril; Forfivo; Fortivo XL; Le Fu Ting; Prexaton; Quomem; Voxra; Wellbutrin; Wellbutrin XL; Wellbutrin SR; Yue Ting; Zyban
chlorpromazine	Aminazin; Chlorazin; Hibernal; Klorproman; Largactil; Megaphen; Ormazine; Plegomazin; Solidon; Taroctyl;Thorazine; Vegetamin; Wintermin; Zuledin Note: in Ireland also called "Clonazine" – very easy to confuse with clozapine.
clozapine	Azaleptin; Clopine; Closastene; Clozaril; CloZAPine; Denzapine; Elcrit; Fazacio ODT; Klozapol; Lanolept; Leponex; Lozapine; Nemea; Ozapim; Synthon, Versacloz; Zaponex
desipramine	Deprexan; Norpramin; Nortimil; Pertofrane
doxepin	Adapin; Anten; Aponal; Deptran; Gilex; Li Ke Ning; Quitaxon; Silenor; Sinepin; Sinequan; Zonalon
imipramine	Impril; Melipramin; Mipralin; Norfranil,; Novo-Pramine; Persamine; Pertofram; Pryleugan; Talendep; Tofranil; Tolerade

lithium	Arthriselect; Camcolit; Carbolith; Carbolithium; Eskolith; Hypnorex; Li-Liquid; Licarbium; Limas; Liskonum; Litarex; Lithane; Lithicarb; Lithioderm; Lithionit; Lithobid; Liticarb; Litiomal; Lito; Maniprex; Neurolepsin; Plenur; Priadel; Quilonorm; Quilonum; Saniquiet; Sedalit; Teralithe
lithium in combination	Boripharm No 23; Emser Salz; Girheulit HOM; Helidonium-Plus; Heweurat N; rheuma-loges; Rhus Toxicodendron Compose; Rhus-Plus; Ricinus Compose
maprotiline	Cronmolin; Deprilept; Ludiomil; Mapromil; Melodil; Neuomil; Psymion
meperidine/pethidine	Alodan ; Atropine and Demerol; Centralgine ; Demerol ; Dolantin ; Dolantina,; Dolantine ; Dolargan,; Dolcontral,; Dolestine ; Dolosal ; Dolsin; Fada; Hospira; Liba; Mepergan ; Meprozine,; Mialgin,; Opystan; Pethidine ; Petigan Miro ; Psyquil compositum
meperidine/pethidine in combination	Pamergan P100
mesoridazine	Serentil, Mesorin
mirtazapine	Arintapin; Avanza; Axit; Combar; Esprital; Mi Er Ning; Miro; Mirta TAD; Mirtabene; Mirtachem; Mirtadepi; Mirtagamma; Mirtalan; MirtaLich; Mirtamylan; Mirtaron; Mirtaz; Mirtazelon; Mirtazon; Mirtazonal; Mirtel; Mirtin; Mirtor; Mirzaten; Norset; Noxibel; Paidisheng; Psidep; Remergil; Remergon; Remeron; Remirta; Rexer; Yarocen; Zispin
olanzapine	Anzorin, Arenbil; Arkolamyl; Atyzyo; Bloonis; Clingozan; Egolanza; Lansyn; Lanzek; Lazapix; Nolian; Nykob; Olafid; Olanzaran; Olanzep; Olanzin; Olanzine; Olapin; Olasyn; Olazax; Olpinat; Olzapin; Olzin; Ou Lan Ning; Ozilormar; Parnassan; Ranofren; Sanza; Stygapon; Synza; Ximin; Zalasta; Zamil; Zappa; Zapris; Zerpi; Zolafren; Zolaxa; Zonapir; Zopridoxin; Zylap; Zypadhera; Zypine; Zyprexa; Zyprexa Relprew; Zydis
olanzapine in combination	Symbyax
risperidone	Aleptan; Apo-Risperid; Arketin; Calmapride; Diaforin; Doresol; Hunperdal; Jing Ping; Ke Tong; Leptinorm; Lergitec; Orizon; Ozidal; Perdox; Ranperidon; Resdone; Ridal; Ridonex; Rileptid;

	Ripedon; Risepro; Rispa; Rispaksole; Rispefar; Rispemylan; Rispen; Rispera; Risperanne; Risperdal; Risperdalconsta; Risperdaloro; Risperigamma; Risperon; Rispolept; Rispolux; Rispond; Rispons; Risset; Rixadone; Rorendo; Ryspolit; Si Li Shu; Sizodon; Speridan; Suo Le; Torendo; Zhuo Fei; Zhuo Fu; Ziperid; Zoridal
theophylline	Aerolate; Afonilum; Aminomal; An Fei Lin; Apnecut; Apo-Theo; Asmalix; Asmalon; Bi Chuan; Bronchoparat; Bronchoretard; Cylmin; Diffumal; Elixifilin; Elixophyllin; Etipramid; Euphyllin; Euphyllina; Euphylline; Euphylong; Frivent; Gan Fei Lin; Nuelin; Protheo; Pulmophylline; Quelesu; ratio-Theo-Bronc; Respicur; Retafyllin; Shi Er Ping; Slo-Bid; Slo-Phyllin; Telbans; Teotard; Terdan; Teromol; Theo-24; Theo-Dur; Theo; Theochron; Theodur; Theofol; Theolair; Theoplus; Theospirex; Theostat ; Theotard; Theotrim; Theovent; Tromphyllin; Unicon; Unicontin; Unifyl; Uniphyl; Uniphyllin Continus; Uniphyllin; UniXan; Xanthium; Xi Fu Li; Yan Er
theophylline in combination	Antong; Baladex; Bi Chuan; Binfolipase; Broncho-Euphyllin; Broncomar; Do-Do ChestEze; Elixophyllin-GG; Elixophyllin-KI; Insanovin; Marax ; Neoasma; Theofol Comp; Theophedrinum-N; Xu Hong; Yi Xi Qing
thioridazine	Detril; Elperil; Melleril; Ridazin; Ridazine; Thiodazine; Thioril; Sonapa
ziprasidone	Geodon; Li Fu Jun An; Pramaxima; Si Bei Ge; Ypsila; Zeldox; Zipwell; Zypsila; Zypsilan

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