A Salvage Trial of AR Inhibition with ADT and Apalutamide with Radiation therapy followed by Docetaxel in Men with PSA Recurrent Prostate Cancer after Radical Prostatectomy (STARTAR)

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1 LIST OF ABBREVIATIONS

Use this list as a starting point for abbreviations used in this protocol.

ADT	Androgen Deprivation Therapy
AE	Adverse Event
ALT	Alanine Aminotransferase
ALC	Absolute Lymphocyte Count
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DSMB	Data and Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
GnRH	Gonadotropic Releasing Hormone
H&P	History & Physical Exam
HRPP	Human Research Protections Program
IMRT	Intensity-Modulated Radiation Therapy
IV (or iv)	Intravenously
LHRH	Luteinizing Hormone Releasing Hormone
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
ORR	Overall Response Rate
OS	Overall Survival
PBMCs	Peripheral Blood Mononuclear Cells
PD	Progressive Disease
PFS	Progression Free Survival
p.o.	per os/by mouth/orally
PORT	Post-Operative Radiotherapy
PR	Partial Response
SAE	Serious Adverse Event
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SPGT	Serum Glutamic Pyruvic Transaminase
WBC	White Blood Cells

2 PROTOCOL SYNOPSIS AND RESEARCH SUMMARY

2.1 Purpose

Primary Objective:

To describe the rate of 36-month (3-year) progression free survival (composite definition, please see section 5.2) in men with recurrent PSA-only disease after prostatectomy, who receive combined apalutamide (ARN-509 or JNJ-56021927) and standard ADT with salvage radiation therapy followed by docetaxel, ADT, and apalutamide, AND who have had testosterone recovery to >100 ng/dl at 36 months.

Secondary Objectives:

1. To determine the proportion of men at 12, 24, and 36 months with PSA <0.1ng/mL and testosterone recovery to >100 ng/dl
2. To describe the biochemical (PSA) progression free survival over time.
3. To describe the PSA nadir (10%, 50% and 90% PSA decline as maximum response)
4. To describe the time to testosterone recovery
5. To describe the safety profile of combination apalutamide, ADT, and radiation therapy followed by apalutamide, ADT, and docetaxel
6. To describe the percentage of patients completing all treatments including salvage radiation therapy and 6 cycles of docetaxel

Exploratory Objectives:

1. To describe the quality of life in patients receiving the combination of apalutamide , ADT, and salvage radiation therapy, as well as the combination of apalutamide, ADT, and docetaxel
2. Archived prostatectomy specimens will be collected and stored for up to 15 years, for eventual analysis of the correlation of outcomes with pre-treatment genomic risk scores (Decipher assay if available), androgen receptor (AR) target genes, AR splice variants, markers of DNA repair, and epithelial-plasticity (EP) biomarkers.
3. Plasma samples will be collected and stored for eventual analysis of circulating proteins and circulating tumor DNA.

Hypothesis:

Recent data supports an interaction between androgen receptor (AR) activity and DNA repair and radiation sensitivity in prostate cancer. Based on our previous clinical trial experience of treating men with recurrent disease after radical prostatectomy and high risk features, the 3-year rate of progression free survival for men receiving salvage radiation therapy alone is 50% [1]. **We hypothesize that AR inhibition with apalutamide added to standard salvage external beam radiation with androgen deprivation therapy, as well as the addition of 6 cycles of docetaxel, will further prolong progression free survival.**

2.2 Background and Significance

The treatment of men with PSA recurrence following radical prostatectomy has generally been unsatisfying, given the high rates of persistent or recurrent disease despite salvage radiotherapy. In most large series, the rate of development of metastatic disease following salvage radiation therapy for PSA-only disease is approximately 60-70%. This suggests that, in high risk individuals, only 30-40% of PSA-only disease is truly localized and thus curable with radiotherapy. While radiotherapy alone in the salvage setting may reduce the risk of local recurrence in prostate cancer, it has an unclear benefit on reduction of metastatic disease and overall survival. Systemic therapeutic options for these men are thus needed to improve systemic control and eliminate potential micrometastatic deposits.

Androgen deprivation therapy (ADT) added to radiation therapy for the primary treatment of prostate cancer has a demonstrated survival benefit [2], and the benefit of ADT for salvage radiation setting has been shown by two randomized trials, particularly with significant pre-treatment PSA. RTOG 9601 randomized 761 patients with pT3 or pT3R1 with post-resection PSA between 0.2-4 ng/ml to PORT versus PORT with 2 years of bicalutamide 150mg daily. At 12 years of follow up, OS was improved with bicalutamide (76.3% vs. 71.3%, HR 0.77, 95% CI 0.59-0.99, p=0.04) [3]. In addition, the prostate cancer specific incidence of death at 12 years was improved with bicalutamide (5.8% vs. 13.4%, HR 0.49, 95% CI 0.32-0.74, p<0.001). The 12-year incidence of metastatic prostate cancer was also improved with bicalutamide (14.5% vs. 23%, HR 0.63, 95% CI 0.46-0.87, p=0.05). There were no increases in grade 3-4 toxicities [3]. The Phase III GETUG trial randomizing the use of 6 months LHRH agonist with standard salvage PORT provides additional evidence for the currently most common PORT-ADT regimen, finding a biochemical and clinical progression free benefit at 5 years (80 vs 62%, HR 0.5) [4]. Other data also support a multimodal approach - a retrospective case series identified 441 patients who were treated with salvage XRT; of these, 24% also received ADT. Multivariate analysis of concurrent ADT was shown to improve progression-free survival (HR 0.65, p=0.046) in high risk patients [5].

The androgen receptor (AR) has also been shown to control the transcription of key DNA repair genes important in mediating radioresistance in prostate cancer. Indeed, AR inhibition increases DNA damage in tumors, improving radiosensitivity and decreasing survival of prostate cancer cells [6]. This suggests that ADT and potent AR inhibition may act synergistically with radiation. Clinically, high-risk patients with biochemical recurrence after surgery are often managed with the combination of ADT and radiation therapy.

Enzalutamide is an androgen receptor antagonist that not only blocks androgen binding to its receptor but also inhibits nuclear translocation and DNA binding. The Phase I/II clinical trial of enzalutamide showed significant anti-tumor response in patients with progressive metastatic CPRC, with median time to progression of 47 weeks [7]. The phase 3 AFFIRM trial of enzalutamide revealed an improvement in survival of 4.8 months over placebo alone in men with metastatic CRPC who had received docetaxel [8]. Subsequently, the Phase 3 PREVAIL trial of enzalutamide revealed an improvement in both progression free survival and overall survival over placebo alone in men with metastatic CRPC who had not received chemotherapy [9]. Therefore, enzalutamide is an effective therapy for patients with progressive, metastatic CRPC before and after treatment with chemotherapy. Even earlier treatment with enzalutamide, in pre-metastatic and/or castrate-sensitive disease, may be beneficial and is an active area of investigation.

Similar to enzalutamide, apalutamide is a competitive AR inhibitor that is fully antagonistic to AR overexpression, lacking significant agonist activity, or inducing activity for AR nuclear localization or DNA binding [10]. In Phase I testing apalutamide was dosed between 30 mg and 480 mg once daily, resulting at all dose levels and a median 50% decline from baseline PSA at 12 weeks of 47% [11]. The most frequently reported adverse event was grade 1/2 fatigue (47%). A Phase II multicenter study evaluated the clinical efficacy of apalutamide at 240 mg daily in non-metastatic (nm) CRPC patients. In 47 evaluable patients, 89% had ≥50% PSA decline at 12 weeks. Median time to PSA progression was 24.0 mo (95% confidence interval [CI], 16.3 months - not reached [NR]); median metastasis-free survival was NR (95% CI, 33.4 months - NR). The most common AE was fatigue (any grade, n=31 [61%]) [12]. A Phase III Study of apalutamide versus placebo in men with non-metastatic CRPC showed that apalutamide prolonged metastasis-free survival and time to symptomatic progression[13].

The Phase II multicenter study, "Salvage therapeutic radiation with Enzalutamide and ADT in men with recurrent prostate cancer" (STREAM) was recently conducted at Duke and 2 other centers and enrolled 38 patients. The analysis from this trial is pending. Accrual was complete in January 2016 and to date, no patients have progressed with about a 12-month median follow up. Our early data suggest the safety of concurrent ADT/enzalutamide with salvage PORT based on the lack of additive or severe toxicities to date, and based on the high proportion of men with undetectable PSA values early in their treatment course, this regimen appears quite effective at suppressing AR activity and controlling disease. Apalutamide is a second-generation AR antagonist similar to enzalutamide and would likely have similar activity in this patient population.

Docetaxel has been shown to have clinical benefit when used with ADT as first-line for newly-diagnosed metastatic CSPC. The CHAARTED study randomized patients to ADT alone versus ADT and docetaxel 75mg/m2 every 3 weeks for 6 cycles. The combination of ADT and docetaxel increased median overall survival by 13 months (57.6 vs. 44.0 months, HR 0.61, 95% CI 0.47-0.80, p<0.001) [14]. This survival benefit was supported in the STAMPEDE study, which was a multi-arm study including patients with non-metastatic but locally advanced disease, with ADT versus ADT and docetaxel as one of the comparisons. In men with M0 prostate cancer, the addition of docetaxel improved median OS by 10 months (77 versus 67 months, HR 0.76, 95% CI 0.63-0.91, p = 0.003) [15]. There was an increased risk (12%) of febrile neutropenia in patients treated with both docetaxel and ADT. Finally, the RTOG 0521 trial also studied the addition of 6 cycles of docetaxel to ADT and radiation early on for patients with high risk prostate cancer (defined as Gleason 9 or 10 with PSA<150, Gleason 7 or 8 with PSA 20-150, or pT2, Gleason 8 and PSA <20). The 4-year overall survival was 93% with docetaxel and 89% without docetaxel, HR 0.70, 90% CI: 0.51-0.98, with one-sided p=0.04) [16]. Concerns surrounding the RTOG 0521 trial include the one-sided p-value and the deaths from protocol treatment or unknown cause was slightly higher in patients treated with docetaxel (6 out of 43 deaths in docetaxel arm [2 from protocol treatment and 4 from unknown cause] vs. 0 out of 59 in ADT/radiation arm) [16].

Based on these data, there is a role for docetaxel in combination with first-line ADT, and there is evidence to support the early use of docetaxel in men with non-metastatic CSPC who are treated with primary radiotherapy and ADT.

The goal of this study is therefore to determine the feasibility and efficacy of treatment with apalutamide and androgen-deprivation in the setting of standard salvage external beam radiation

therapy, followed by the combination of apalutamide and ADT with 6 cycles of docetaxel, in men with high risk prostate cancer and rising PSA after prostatectomy.

Based on the above data, we hypothesize that potent AR inhibition with ADT will result in radiosensitivity in the PSA recurrent setting and defective DNA repair, as well as effective systemic control. In addition, we hypothesize that the addition of docetaxel will provide greater systemic control over ADT/apalutamide and RT alone. In order to investigate the early use of combination docetaxel and ADT/apalutamide still further, we propose a Phase IB/II clinical trial of ADT, apalutamide, and docetaxel with salvage radiation therapy for biochemical recurrent prostate cancer.

2.3 Design and Procedures

This is a non-blinded single-arm phase II FDA IND multicenter study of approximately 42 subjects to assess feasibility and efficacy of combined apalutamide and androgen-deprivation (ADT) with salvage radiation therapy, followed by apalutamide, ADT, and docetaxel for 6 cycles. Duke is the lead site for this trial, involving 3 additional centers.

Eligible men will have recurrent PSA-only prostate cancer within 4 years of prostatectomy, and a PSA of greater than 0.2 ng/mL and less than 4 ng/mL in the absence of metastatic disease on CT and bone scans.
Week 1 Day 1 of treatment is defined as the first day a subject receives Apalutamide or ADT inclusive of situations where a subject may not receive the second drug until week 2 due to scheduling issues, and treatment would continue for approximately 8 weeks neo-adjuvant to IMRT followed by concurrent with salvage IMRT per standard of care, continue throughout a four-week period between end of radiation and initiation of docetaxel, and continue through approximately 18 weeks with 6 cycles of docetaxel treatment, for a total of approximately 36 weeks of systemic treatment. Apalutamide will be given at a dose of 240 mg by mouth daily for the duration of treatment, and ADT will be administered per institutional standard for approximately 36 weeks (9 months). Standard external beam radiotherapy of 66 to 74 Gy will be administered to the prostate bed according to local standard of care, usually a period of 6-8 weeks. Intensity Modulated RT (IMRT) is allowed for this study. Inclusion of the pelvic nodes as part of the salvage radiation plan for patients with node positive disease will be performed at the discretion of the treating radiation oncologist.

The endpoints are 36-month (3-year) progression free survival and the proportion of men at 12, 24, and 36 months with a PSA of <0.1 ng/mL who also have testosterone recovery to >100 ng/dl.

2.4 Selection of Subjects

2.4.1 Inclusion Criteria

1. Histologically-confirmed diagnosis of prostate adenocarcinoma. Variants of prostate cancer, including predominantly (>50%) neuroendocrine features and small cell carcinoma of the prostate, are not permitted.

2. Gleason sum of 7 (with pT3 disease or positive margins or positive nodes [4 or fewer]), 8, 9, or 10 based on the radical prostatectomy specimen
3. PSA relapse within 4 years of prostatectomy defined by persistently detectable or rising PSA after surgery.
4. Evidence of disease recurrence or progression as evidenced by a PSA > 0.20 ng/ml. This requires 2 consecutive rises in PSA, at least 1 week apart, over the post-prostatectomy nadir **or** one PSA value above 0.20 ng/mL **if** the patient failed to achieve a post-prostatectomy nadir of < 0.2 ng/mL.
5. Age ≥ 18 years
6. Karnofsky performance status ≥ 80%
7. Adequate laboratory parameters
    - Adequate bone marrow function: ANC ≥1.5 x 10^9/L, Platelets ≥100 x 10^9/L, Hb >9g/dL
    - AST/SGOT and ALT/SGPT ≤ 2.5 x Institutional Upper Limit of Normal (ULN)
    - Serum bilirubin ≤ 1.5 x Institutional ULN (In subjects with Gilbert's syndrome, if total bilirubin is > 1.5xULN, measure direct and indirect bilirubin and patient is eligible if direct bilirubin ≤ 1.5xULN).
    - Glomerular filtration rate (either estimated or calculated from 24-hour urine collection) ≥ 45 mL/min
    - Serum potassium ≥3.5 mmol/L
8. A minimum of 4 weeks from any major surgery prior to Cycle 1 Day 1.
9. Ability to swallow, retain, and absorb oral medication.
10. Ability to understand and the willingness to sign a written informed consent document.
11. Must use a condom if having sex with a pregnant woman.
12. Male patient and his female partner who is of childbearing potential must use 2 acceptable methods of birth control (one of which must include a condom as a barrier method of contraception) starting at screening and continuing throughout the study period and for 3 months after final study drug administration.

2.4.2 Exclusion Criteria

1. Radiographic evidence of metastatic disease by standard CT and bone scan. Patients with node-positive disease (≤4 positive nodes) at the time of radical prostatectomy are eligible. Patients with pelvic nodes less than 1.5 cm by short axis at the time of screening are eligible. Patients with any enlarged lymph nodes in the retroperitoneum or above the aortic bifurcation or with pelvic nodes ≥ 1.5 cm must be excluded.
2. PSA ≥ 4.0 ng/mL.
3. Testosterone level ≤ 100 ng/dL.
4. More than 1 month of prior hormone exposure or hormone exposure within 30 days of enrollment (up to 1 month of prior LHRH agonist and/or anti-androgen therapy as neoadjuvant therapy prior to prostatectomy is allowed). Prior enzalutamide, apalutamide, darolutamide, ketoconazole, abiraterone, or TAK700 for prostate cancer are prohibited. Prior first-generation antiandrogen therapy (including but not limited to bicalutamide, flutamide, nilutamide) and prior estrogen therapy (including estrogen patch) are not allowed within 30 days of enrollment. All investigational agents are prohibited within 30 days of enrollment.
5. The following medications are prohibited within 2 weeks of enrollment and while on study drug:

• 5 α-reductase inhibitors (finasteride, dutasteride);
• Biologic or other agents with anti-tumor activity against prostate cancer (excluding herbal supplements);

• Androgens (testosterone, dehydroepiandrosterone [DHEA], etc.)

6. Prior immunotherapy for prostate cancer including sipuleucel-T.
7. Prior systemic chemotherapy (docetaxel, cabazitaxel, estramustine, other cytotoxic agents)
8. History of solid organ or stem cell transplantation.
9. History of seizure or any condition that may predispose to seizure (e.g., prior cortical stroke, prior head or traumatic brain injury with loss of consciousness, prior or current space-occupying lesion in the brain). Also, history of loss of consciousness or transient ischemic attack within 6 months of enrollment.
10. Known or suspected brain metastasis or active leptomeningeal disease.
11. Other concurrent severe and/or uncontrolled concomitant medical conditions (e.g., active or uncontrolled infection) that could cause unacceptable safety risks or compromise compliance with the protocol.
12. Severe or unstable angina, myocardial infarction, symptomatic congestive heart failure, arterial or venous thromboembolic events (eg, pulmonary embolism, cerebrovascular accident including transient ischemic attacks), or clinically significant ventricular arrhythmias within 6 months prior to enrollment
13. Sustained uncontrolled hypertension (>150/90 average over 1 week) despite optimal medical management
14. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of apalutamide or increase the risk of radiation (e.g., uncontrolled nausea, vomiting, diarrhea, malabsorption syndromes, prior small bowel resection, or inflammatory bowel disease).
15. Patients who have received prior prostate or pelvic radiotherapy, including external beam or brachytherapy.
16. Patients who have not recovered from side effects of prior systemic therapy prior to Cycle 1 Day 1.
17. Use of medications known to lower the seizure threshold within 4 weeks prior to study entry.
18. Patients unable or unwilling to abide by the study protocol or cooperate fully with the investigator.

2.5 Subject Recruitment and Compensation

This study will be open to members of all demographic groups who meet the eligibility criteria. A caregiver known to the patient will introduce the study and if the patient is interested, a member of the study team will approach him for enrollment. Patients will not be enrolled without prior approval of their physician (if not a member of the study team).

2.6 Consent Process

The prospective participant will have as much time as he may need to make an informed decision about the study and all treatment related questions will be answered. Prospective participants will be consented in an exam room where it is just the research staff, the patient and his family, if so desired by the patient. Before, during, and after the consent is signed, the research team and

investigators will be available in person and by phone to answer any questions the participants may have. Any and all other available treatment options are offered to the patient in order to avoid undue influence. Participants are not offered compensation for this study in order to avoid any monetary coercion/influence other than the provision of parking passes.

2.7 Subject's Capacity to Give Legally Effective Consent

Subjects who do not have capacity to give legally effective consent will not be enrolled.

2.8 Study Interventions

After consent and enrollment, each subject will receive a GnRH agonist or antagonist depot injection (selection at the discretion of the care provider), and this treatment will be repeated at necessary intervals for a total of about 36 weeks of androgen deprivation therapy. Subjects will receive education about how to take apalutamide, including avoidance of contraindicated concurrent medications, safe handling, and side effects. Subjects will then receive apalutamide 240mg PO daily from the investigational pharmacy and will take apalutamide daily for approximately 36 weeks. On week 9 (+/- 14 days), subjects will begin salvage radiation therapy to the prostate bed. Radiation will be given per institutional standard of care, concurrent with ADT and daily apalutamide. About 4 weeks (+/- 7 days, pending recovery of adverse events from radiation to Grade 2 or less) after completing radiation, patients will start docetaxel 75mg/m^2 intravenously, every 3 weeks for 6 cycles. Patients will continue their ADT and daily apalutamide during chemotherapy with docetaxel. Subjects will return to a clinic for a safety follow-up visit approximately 4 weeks after completion of all therapy. Every 3 months from the SFU visit , subjects will return to clinic for symptoms, laboratory, and prostate cancer monitoring, including PSA and testosterone. Study termination for each subject is 36 months (3 years) after Cycle 1 Day 1. Cycle 1 Day 1 is defined as the first day of treatment (ADT and/or apalutamide)

2.9 Risk/Benefit Assessment

Potential risks of this study include the potential for apalutamide toxicity, including gastrointestinal disorders (abdominal pain, constipation, diarrhea, nausea/vomiting), fatigue, dizziness, taste changes, rashes, decreased appetite, hot flashes, insomnia, hypothyroidism, itching, fractures, increase in falls, increase in blood cholesterol or triglycerides, and very rarely seizure activity. During the chemotherapy portion of the study, patients may develop side effects of docetaxel chemotherapy, including peripheral neuropathy, alopecia, rashes, onycholysis, stomatitis, diarrhea, nausea/vomiting, myelosuppression, anemia, thrombocytopenia, and rare infusion reactions. There is potential that taking apalutamide during radiation therapy and during chemotherapy may make side effects of either one worse; however, there is also the potential benefit that the addition of apalutamide may improve cancer outcomes. Additional risks of study inclusion include potential loss of confidentiality, although all steps will be taken to protect the patient's privacy and confidentiality.

2.10 Costs to the Subject

Patients and their insurers will be expected to pay costs of routine care, including routine clinic visits, radiation therapy and androgen-deprivation therapy with a GnRH agonist/antagonist. Any visit or

procedure solely for research purposes, as well as the cost of both apalutamide and docetaxel, will be covered by research funds.

2.11 Data Analysis and Statistical Considerations

The primary objective of this single arm, open-label, one stage Phase II study is to estimate the 36 month progression-free survival rate of men with recurrent, PSA-only disease after prostatectomy receiving combined apalutamide and standard androgen-deprivation therapy with salvage radiation therapy, followed by apalutamide and ADT with docetaxel. The target sample size is 42. It is primarily hypothesized that the 36-months (3-year) PFS rate will be improved with the combined therapy compared to the historical control data in a similar patient setting. Based on our prior experience conducting a trial of docetaxel and salvage RT in a similar group of men, and based on a model and nomogram by Stephenson et al for men with recurrent disease after radical prostatectomy [1], the PFS rate at 36-months among prostate cancer patients is 40-50%. **This trial is designed to have more than 85% power to reject the null hypothesis of 36-month PFS rate of 40% when the true PFS rate at 36 months is 65%, with a two-sided alpha of 0.05.** The sample size needed will be 38, and factoring in a 10% drop out rate, the final sample size is 42 patients. A one sample one-sided binomial test will be used to test whether the 36-month PFS rate is larger than the hypothesized value from the historical controls.

The Kaplan-Meier product-limit estimator will be used to estimate the distribution of PFS, biochemical progression free survival, time to PSA nadir, and time to testosterone recovery. The median survival times and 95% confidence intervals will be reported. The frequency and proportion (and 95% confidence interval) of men at 12, 24, and 36 months with a PSA of <0.1 ng/ml and testosterone recovery will be reported. In addition, descriptive statistics with 95% confidence intervals will be calculated for secondary endpoints of safety profile and quality-of-life (QOL) endpoints, the continuous safety and QOL endpoints will be summarized as the patient counts, mean, standard deviation, median, $25^{th}$and 75^{th} percentiles, minimum and maximum. The categorical safety and QOL endpoints will be categorized using frequencies and percentages.

2.12 Data and Safety Monitoring

This protocol is being conducted at additional sites external to Duke University. The Sponsor-Investigator is responsible for monitoring these sites to assure the safety and protection of all subjects and to assure that the study is conducted, recorded, and reported in accordance with the protocol and applicable regulations. Data for safety and severe adverse events will be monitored on an ongoing basis through monthly investigator and staff meetings, including data from all centers involved.

To assure that the investigator obligations are fulfilled and all applicable regulations and guidelines are being followed, the Sponsor-Investigator will designate the DCI Monitoring Team to assure that the external site facilities are acceptable, the protocol and investigational plan are being followed, the IRB/IEC has been notified of approved protocol changes as required, complete records are being maintained, appropriate and timely reports have been made to the Sponsor-Investigator and the IRB/IEC, study drug and study drug inventory are controlled and the Investigator is carrying out all agreed activities. Monitoring also includes review regulatory and eligibility, conduct, data quality and adverse event reporting for select cases.

2.13 Privacy, Data Storage, and Confidentiality

The Principal Investigator will ensure that subject privacy and confidentiality of the subject's data will be maintained.

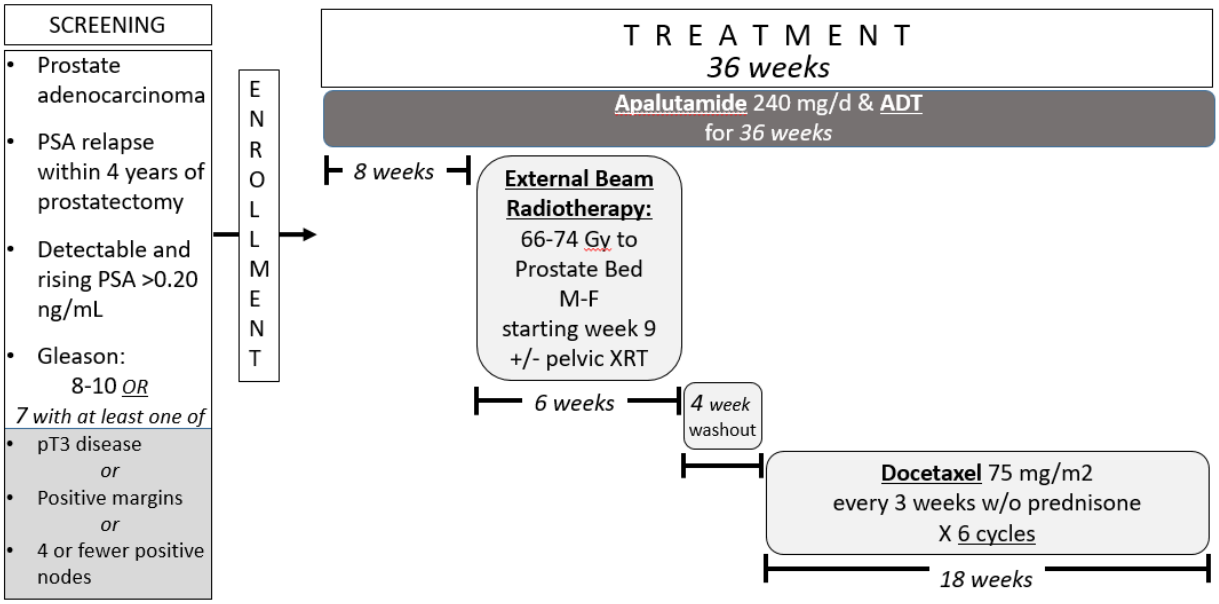
To protect privacy, every reasonable effort will be made to prevent undue access to subjects during the course of the study. All research-related interactions with the participant will be conducted by qualified research staff who are directly involved in the conduct of the research study.

To protect confidentiality, subject files in paper format will be stored in secure cabinets under lock and key accessible only by the research staff. Electronic records of subject data will be maintained using a dedicated web-access secure database, which is housed in an encrypted and password-protected server behind the Duke firewall. Access to electronic databases will be limited to delegated personnel. The security and viability of the IT infrastructure will be managed by the DCI and/or Duke Medicine.

Upon completion of the study, research records will be archived and handled per institutional policy.

Subject names or identifiers will not be used in reports, presentations at scientific meetings, or publications in scientific journals.

3 STUDY SCHEMA



4 BACKGROUND AND SIGNIFICANCE

4.1 Study Disease: Prostate cancer

Worldwide, prostate cancer is the second most common cancer in men. The current lifetime risk of prostate cancer for men in the United States is approximately 1 in 6 [17]. Hormonal therapies include surgical castration or medical therapy with gonadotropin-releasing hormone analogues, AR antagonists, testosterone synthesis inhibitors, ketoconazole and/or estrogenic compounds. Tumors that progress despite castrate levels of testosterone in the blood are considered castration-resistant. Despite the early sensitivity of these tumors to hormonal strategies, castration-resistant progression generally represents a transition to the lethal variant of the illness. The median survival of metastatic castration-resistant disease is approximately 1 to 2 years [18]. Results of clinical investigations and studies on the molecular profiles of these progressing prostate tumors show that the AR remains functional and that the tumors should respond to strategies directed at the AR signaling axis. Overexpression of the AR has been documented in upwards of 50% of CRPC specimens and is believed to contribute to tumor progression [19, 20].

Anti-androgens are most commonly used in combination with gonadotropin-releasing hormone analogues in earlier stage disease resulting in medical castration and the accompanying side effects of fatigue, erectile dysfunction, decreased libido, hot flashes, weight gain, osteoporosis, anemia and acceleration of the metabolic syndrome and potentially cardiovascular disease. Enzalutamide and apalutamide are currently being studied in patients with earlier stage disease.

The treatment of men with PSA recurrence following radical prostatectomy has generally been unsatisfying, given the high rates of persistent or recurrent disease despite salvage radiotherapy. In most large series, the rate of distant or biochemical disease recurrence is approximately 60 to 70% following salvage radiotherapy, indicating that in these high risk individuals, only 30-40% of disease is purely localized and thus curable with salvage radiotherapy [1, 21]. Risk factors for PSA recurrence and progression despite salvage radiation therapy include increasing PSA, fast PSA kinetics, lower dose of radiation used, high Gleason sum, advanced tumor stage, and negative surgical margins [1, 22]. Additional therapeutic options for these men are needed to improve systemic control and eliminate potential micrometastatic deposits.

While radiotherapy alone in the adjuvant or salvage setting may reduce the risk of PSA and local recurrence in prostate cancer, it has an unclear benefit on the reduction of metastatic disease and improvement of overall survival [23, 24]]. However, recent retrospective series suggest that a survival benefit may be seen particularly in those men with rapid PSA doubling times or positive surgical margins, although benefits have been seen across nearly all subgroups [21, 25, 26]. Recent data suggests an important role for the androgen receptor in DNA repair during radiation therapy, and that blocking androgen receptor action may improve radiosensitivity [6].

4.2 Study Agents – Apalutamide and Docetaxel

4.2.1 APALUTAMIDE

Apalutamide has been approved by the US Food and Drug Administration (FDA) for the treatment of non-metastatic castration resistant prostate cancer and metastatic castration sensitive prostate cancer but not for the treatment of recurrent PSA-only prostate cancer. It is a competitive AR inhibitor developed to optimally antagonize AR transcriptional activity and prostate cancer cell proliferation, pharmacokinetics, and in vivo efficacy [9]. In contrast to bicalutamide, apalutamide lacks significant agonist activity in preclinical models of CRPC. Moreover, apalutamide does not induce AR nuclear localization or DNA binding. In a clinically valid murine xenograft model of human CRPC, apalutamide showed greater efficacy than enzalutamide (an AR antagonist which is FDA

approved for treatment of mCRPC). Maximal therapeutic response in this model was achieved at 30 mg/kg/d of apalutamide, whereas the same response required 100 mg/kg/d of enzalutamide and higher steady-state plasma concentrations. Thus apalutamide exhibits characteristics that predict for a higher therapeutic index with a greater potential to reach maximally efficacious doses in man than current AR antagonists. There is therefore preclinical proof of principle for apalutamide as a promising therapeutic in both castration-sensitive and castration-resistant forms of prostate cancer.

In Phase I testing, apalutamide was dosed between 30 mg and 480 mg once daily, resulting in PSA declines at all dose levels and a median 50% decline from baseline PSA at 12 weeks of 47% [10]. The most frequently reported adverse event was grade 1/2 fatigue (47%). The recommended Phase II dose of apalutamide was found to be 240mg daily.

A Phase II multicenter study evaluated the clinical efficacy of apalutamide at 240 mg daily in non-metastatic (nm) CRPC patients. In 47 evaluable patients, 89% had ≥50% PSA decline at 12 weeks. Median time to PSA progression was 24.0 months (95% confidence interval [CI], 16.3 months - not reached [NR]); median metastasis-free survival was NR (95% CI, 33.4 months - NR). The most common AE was fatigue (any grade, n=31 [61%]) [12]. An ongoing Phase III study comparing apalutamide versus placebo in men with non-metastatic CRPC has showed that apalutamide prolonged metastasis-free survival and time to symptomatic progression [13] .

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

4.2.2 DOCETAXEL

Since 2004, docetaxel has been FDA-approved for treatment of mCRPC, based primarily on the TAX-327 study [24]. More recently, docetaxel has been shown to have clinical benefit when used with ADT as first-line for newly-diagnosed metastatic CSPC in two separate Phase III studies. The CHAARTED study randomized patients to ADT alone versus ADT and docetaxel 75mg/m^2 every 3 weeks for 6 cycles. The combination of ADT and docetaxel increased median overall survival by 13 months (57.6 vs. 44.0 months, HR 0.61, 95% CI 0.47-0.80, p<0.001) [14]. This survival benefit was further supported in the STAMPEDE study, which was a multi-arm study including patients with non-metastatic but locally advanced disease, with ADT versus ADT and docetaxel as one of the comparisons. In men with M0 prostate cancer, the addition of docetaxel improved median OS by 10 months (77 versus 67 months, HR 0.76, 95% CI 0.63-0.91, p = 0.003) [15]. There was an increased risk (12%) of febrile neutropenia in patients treated with both docetaxel and ADT.

Separately, docetaxel was studied in combination with ADT and radiation therapy in the RTOG 0521 trial for patients with high risk, non-metastatic castration sensitive prostate cancer (defined as Gleason 9 or 10 with PSA<150, Gleason 7 or 8 with PSA 20-150, or pT2, Gleason 8 and PSA <20). The 4-year overall survival was 93% with docetaxel and 89% without docetaxel, HR 0.70, 90% CI: 0.51-0.98, with one-sided p=0.04) [15]. Patients treated with ADT, radiation and docetaxel experienced more grade 3 and 4 hematological adverse events (expected anemia, thrombocytopenia, and neutropenia) than patients treated with ADT and radiation without chemotherapy (64% vs. 22%). Concerns surrounding the RTOG 0521 trial include the one-sided p-value and the deaths from protocol treatment or unknown cause was slightly higher in patients treated with docetaxel (6 out of 43 deaths in docetaxel arm vs. 0 out of 59 in ADT/radiation arm) [16].

4.2.3 Androgen Deprivation Therapy

An LHRH agonist concurrent with radiation is standard-of-care for men with intermediate-high risk prostate cancer [27], and is being widely adopted as a new standard of care for those with significantly elevated post-operative PSA. ADT will consist of treatment with a GnRH agonist or antagonist per physician and institutional preference. Either leuprolide acetate (Lupron Depot, 22.5 mg or 45 mg IM), triptorelin pamoate (Trelstar, 11.25 mg or 22.5 mg IM), goserelin acetate (Zoladex, 10.8mg SC) or degarelix (Firmagon 120 mg or 240 mg SC) will be administered monthly, every 3 months, or every 6 months, depending on institutional standards, for 36 weeks total. The addition of apalutamide is hypothesized to improve PFS beyond the use of ADT alone in patients receiving concurrent salvage external beam radiation therapy. ADT will be administered for the duration of the treatment, spanning approximately 36 weeks.

4.2.4 Radiation Therapy

Radiation is a proven adjuvant therapy for high risk prostate cancer [28, 29]. In the salvage setting, radiation has improved prostate-specific survival for men with short doubling times [21]. The radiation dose in this study is based on benefit seen with dose escalation while recognizing limitations of nearby critical organs. Dose constraints are provided in Section 7 to ensure protection of nearby normal tissues.

4.3 Purpose/Rationale

For patients with rising PSA after prostatectomy without evidence of metastatic disease, salvage radiation therapy to the prostate bed is the standard of care, and the progression-free survival at 2 years for men receiving salvage radiation therapy is around 65% [1]. Clinically, high-risk patients with biochemical recurrence after surgery are often managed with the combination of ADT and radiation therapy. Only approximately 15% of men in the salvage radiation study mentioned above also received some treatment with ADT, although a recent retrospective study suggests that ADT concurrent with salvage radiation improves progression-free survival in high risk men [5]. There is also evidence that treatment with the anti-androgen bicalutamide during radiation therapy improves outcomes. At 12 years of follow up, OS was improved with bicalutamide (76.3% vs. 71.3%, HR 0.77, 95% CI 0.59-0.99, p=0.04) [3]. In addition, the prostate cancer specific incidence of death at 12 years was improved with bicalutamide (5.8% vs. 13.4%, HR 0.49, 95% CI 0.32-0.74, p<0.001). The 12-year incidence of metastatic prostate cancer was also improved with bicalutamide (14.5% vs. 23%, HR 0.63, 95% CI 0.46-0.87, p=0.05). There were no increases in grade 3-4 toxicities [3]. The Phase III GETUG trial randomizing the use of 6 months LHRH agonist with standard PORT for early salvage provides evidence for the currently most common PORT-ADT regimen, finding a biochemical and clinical progression free benefit at 5 years (80 vs 62%, HR 0.5) [4]. There are 2 large prospective studies that will likely be reported in the next few years to help further address whether giving ADT with salvage radiation therapy is beneficial. The RADICALS trial is designed to address the question of adjuvant versus delayed radiation therapy, and one arm of the RADICALS trial will look at RT alone and with 6 and 24 months of hormones in the salvage setting. RTOG 0534 is a Phase III trial of ADT with prostate bed only versus pelvic lymph node radiation therapy in the salvage setting. While awaiting the results of these studies, the use and duration of ADT or other therapies concurrent with

salvage radiation therapy for biochemical recurrence is clinician-dependent. However, the available data indicates that a substantial number of patients are not cured with radiation therapy alone and that therefore additional options are necessary.

The Phase II multicenter study, "Salvage therapeutic radiation with Enzalutamide and ADT in men with recurrent prostate cancer" (STREAM) was recently conducted at Duke and 2 other centers and enrolled 38 patients. The analysis from this trial is pending. Accrual was complete in January 2016 and to date, no patients have progressed with about 12 month median follow up. Our early data suggest the safety of concurrent ADT/enzalutamide with salvage PORT based on the lack of additive or severe toxicities to date, and based on the high proportion of men with undetectable PSA values early in their treatment course, this regimen appears quite effective at suppressing AR activity and controlling disease. Apalutamide is a next-generation AR antagonist similar to enzalutamide and would likely have similar activity in this patient population.

Docetaxel, as discussed above, has been shown to provide survival advantage when given early with ADT in metastatic castration sensitive prostate cancer. There is therefore a role for docetaxel in combination with first-line ADT, and there is evidence to support the early use of docetaxel in men with non-metastatic CSPC who are treated with primary radiotherapy and ADT. We propose to study the combination of ADT and apalutamide first with radiation therapy, followed by ADT and apalutamide with 6 cycles of docetaxel.

This is a non-blinded single-arm Phase II study of approximately 42 subjects for feasibility of combined apalutamide and ADT with salvage radiation followed by apalutamide and ADT with 6 cycles of docetaxel. Standard external beam radiotherapy will be administered to the prostate bed according to local standard of care, usually a period of6-8 weeks. The endpoints are 36-month (3-year) progression free survival and the proportion of men at 12, 24, and 36 months with a PSA of <0.1 ng/mL who also have testosterone recovery.

5 OBJECTIVES AND ENDPOINTS

5.1 Objectives

Primary objective: To describe the rate of 36-month (3-year) progression free survival (composite definition, please see section 5.2) in men with recurrent PSA-only disease after prostatectomy, who receive combined apalutamide and standard ADT with salvage radiation therapy followed by docetaxel, ADT, and apalutamide, AND who have had testosterone recovery to >100 ng/dl at 36 months.

Secondary objectives:

1. To determine the proportion of men at 12, 24, and 36 months with PSA <0.1ng/mL and testosterone recovery to >100 ng/dl
2. To describe the biochemical (PSA) progression free survival over time.
3. To describe the PSA nadir (10%, 50% and 90% PSA decline as maximum response)
4. To describe the time to testosterone recovery

5. To describe the safety profile of combination apalutamide, ADT, and radiation therapy followed by apalutamide, ADT, and docetaxel
6. To describe the percentage of patients completing all treatments including salvage radiation therapy and 6 cycles of docetaxel

Exploratory objectives:

1. To describe the quality of life of patients receiving the combination of apalutamide, ADT, and radiation therapy.
2. Archived prostatectomy specimens will be collected and stored for eventual analysis of the correlation of outcomes with pre-treatment androgen receptor target genes, androgen receptor splice variants, and epithelial-mesenchymal transition (EMT) biomarkers.
3. Plasma samples will be collected and stored for eventual analysis of circulating proteins and circulating tumor DNA.

5.2 Endpoints

Primary endpoint: The rate of progression free survival (PFS) at 36 months, with PFS defined as the proportion of subjects with testosterone >100 ng/dl at 36 months post-Cycle 1 Day 1 without one or more of the following:

- Serum PSA value of 0.2 ng/mL or more above the post-radiotherapy PSA nadir and confirmed (at least) 4 weeks later by a second PSA measurement higher than the first by any amount
- Continued rise in the PSA level following study treatment if no nadir is experienced, defined as 2 rising values greater than the baseline PSA and separated by at least 4 weeks
- Evidence of clinical progression or initiation of systemic therapy for progressive disease
- Death

Secondary endpoints:

1. To determine the proportion of men at 12, 24, and 36 months with a PSA of <0.1 ng/mL and testosterone recovery (defined as testosterone >100 ng/dl)
2. To describe the biochemical (PSA) progression free survival over time. bPFS is similar to PFS but includes only PSA-based endpoints or death.
3. To describe the median PSA nadir
4. To describe the time to testosterone recovery
5. To describe the safety, feasibility and tolerability profile of combination apalutamide, ADT, and radiation therapy followed by apalutamide, ADT, and docetaxel as assessed by NCI common toxicity scales
6. To describe the percentage of patients completing all treatments including salvage radiation therapy and 6 cycles of docetaxel

Exploratory endpoints:

1. To determine the quality of life of patients receiving the combination of apalutamide, ADT, and radiation therapy using the Expanded Prostate Cancer Index Composite (EPIC) short form,

a validated scale of prostate-cancer specific quality of life. Surveys will be performed at baseline, week 13, and at 12, 24 and 36 months post C1D1 follow-up.

6 INVESTIGATIONAL PLAN

6.1 Study Design

This is a non-blinded single-arm Phase II study of approximately 42 subjects to assess feasibility and efficacy of combined apalutamide and androgen-deprivation (ADT) for 36 weeks concurrent with salvage radiation therapy and then with docetaxel. This study will be conducted at 4centers: Duke Cancer Institute and three outside study centers.

Eligible men will have recurrent PSA-only prostate cancer within 4 years of prostatectomy, and a PSA of >0.2 ng/mL to <4 ng/mL in the absence of metastatic disease on CT and bone scans. **APPENDIX D** provides a list of lymph node locations for determining eligibility of patients with node-positive disease.

Apalutamide and/or ADT would start at week 1, continued during radiation therapy, continued during docetaxel therapy, and completed at the end of 18 weeks on docetaxel (approximately 36 weeks total). ADT will be administered as standard of care GnRH agonist or antagonist at the treating physician's discretion. Apalutamide will be given at 240mg by mouth daily for the duration of treatment (approximately 36 weeks) and ADT will be administered per institutional standard. Standard external beam radiotherapy to 66-74 Gy will be administered to the prostate bed per institutional standard of care. Inclusion of the pelvic nodes as part of the salvage radiation plan will be per the discretion of the treating radiation oncologist. The treating physician will assess for risk of osteoporosis on a case-by-case basis. Subjects will be encouraged to take calcium and vitamin D, and an additional appropriate regimen (e.g. bisphosphonate, denosumab or others) will be prescribed at the discretion of the treating physician. Docetaxel therapy will begin at least 4 weeks post-radiotherapy.

The endpoints are 36-month (3-year) progression free survival and the proportion of men at 12, 24, and 36 months with a PSA of <0.1 ng/mL who also have testosterone recovery.

6.1.1 Definition of Dose-Limiting Toxicity (DLT)

Not applicable.

6.1.2 Dose Modification

Patients should be carefully monitored for toxicity related to treatment. Toxicity due to apalutamide administration may be managed by symptomatic treatment, dose interruptions and adjustment of the apalutamide dose. All toxicity will be reported using CTCAE v4.03. Dosage modifications are not recommended for grade 1 or 2 events. Therapy with apalutamide should be interrupted upon the occurrence of a grade 3 adverse event related to study drug. Once the adverse event has resolved or decreased in intensity to grade 1 or less, then apalutamide can be restarted at one dose level lower OR as adjusted according to the table below. Once the dose has been reduced it should not be increased at a later time. If a grade 4 toxicity related to apalutamide occurs, therapy should be discontinued. Patients may remain on study for radiation and docetaxel/ADT if they have an

apalutamide related grade 3 or 4 AE leading to discontinuation of apalutamide. Patients who discontinue treatment for adverse events will be followed for progression outcomes.

Two dose reductions of apalutamide are allowed. Doses below 120 mg daily are not permitted and require removal of the patient from the treatment phase of the study. If apalutamide must be held for any reason, it must be restarted **within 28 days** or the subject should discontinue treatment with apalutamide but remain on study for study treatments (radiation, ADT, and docetaxel as planned).

Dose reductions or cycle delays of docetaxel can be made at the treating physician's discretion based on docetaxel-related AEs during period of treatment. Although the intention to treat is with 6 cycles of docetaxel, docetaxel can be stopped early in case of severe (>grade 3 related) toxicity, at the discretion of the treating physician.

If one subject is unable to tolerate the combination of radiation therapy with apalutamide and requires a ≥5 day delay in radiation therapy due to toxicity, this would trigger a temporary hold in accrual, until a meeting of the data and safety monitoring committee at the lead site is held to review the AEs and to determine if the study may proceed and if changes to the protocol are required.

Dose Level Reduction	APALUTAMIDE Dose
-2	120 mg daily (2 tablets)
-1	180mg daily (3 tablets)
0	240 mg daily (4 tablets)

Rash

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

Severity	Intervention

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

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

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

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

a Obtain bacterial/viral cultures if infection is suspected

b Subject presents with other rash related symptoms such as pruritus, stinging, or burning

c One dose level reduction = 60mg (1 apalutamide tablet)

d If there is blistering or mucosal involvement, stop apalutamide dosing immediately and contact Janssen

e If a subject previously started oral corticosteroids, continue for at least 1 week after resumption of reduced dose of apalutamide. If the proposed total oral steroid use will exceed 28 days, contact sponsor-investigator.

6.1.2.1 Non-hematologic:

Apalutamide is generally well-tolerated. Because apalutamide and ADT block the effects of the male sex hormones, both drugs can cause infertility and impotence and may contribute to loss of muscle and bone and lead to hot flashes. Fatigue is the most common side effect of apalutamide. Other possible side effects include nausea with or without vomiting, constipation or diarrhea, joint or muscle pains, shortness of breath, dizziness, headache, flushing, leg swelling, and trouble sleeping.

Docetaxel is a commonly used chemotherapeutic agent. Side effects of docetaxel include fatigue, alopecia, nausea, vomiting, diarrhea, nail changes, sensory neuropathy, stomatitis, changes in taste, peripheral edema, myalgia, and dyspnea.

Radiation AEs: Acute radiation toxicity typically presents several weeks into treatment, and can persist for 1-2 months after completion of RT. Side effects include fatigue, increased urinary bother (frequency, dysuria, urgency), increased bowel irritation (frequency, tenesmus, diarrhea, cramping), hematuria and hematochezia. Late effects present 6 months or more after completion of treatment and include urinary bother (frequency, urgency, incomplete emptying/stricture, dysuria), hematuria,

pelvic pain, rectal pain or bleeding ("radiation proctitis"), urinary or bowel incontinence, erectile dysfunction, osteoradionecrosis, and secondary malignancies.

Symptoms will be monitored regularly and abnormalities will be managed per CTCAE v4.03 grading as above.

6.1.2.2 Hematologic:

Low blood counts are rarely reported with apalutamide. Counts will be monitored regularly and abnormalities will be managed per CTCAE v4.03 grading as above.

Neutropenia, anemia, and thrombocytopenia are expected side effects with docetaxel therapy. Patients will have a CBC check on day 11 (+/- 4 days) for a nadir draw per standard of care during docetaxel therapy and this check may be performed locally. If ANC < 500 at the time of a nadir draw, patients should be treated with granulocyte colony-stimulating factor (G-CSF) per local standard of care. Patients will be transfused at the discretion of the treating physician for anemia and thrombocytopenia at standard of care thresholds.

Radiation hematologic AEs: Radiation can infrequently cause a pan-lineage decrease in blood counts, which are rarely symptomatic when occurring without concomitant therapies. As long as total bone marrow is not irradiated, counts recover spontaneously.

Blood counts will be monitored regularly and abnormalities will be managed per CTCAE v4.03 grading.

6.1.3 Safety Considerations

As a class effect, AR antagonists have been associated with seizures due to an off-target mechanism of action (gamma amino butyric acid chloride channel [$GABA_A$] inhibition). Drugs known to lower the seizure threshold or cause seizures are prohibited and a representative list is included below:

- Atypical antipsychotics (e.g. clozapine, olanzapine, risperidone, ziprasidone)
- Bupropion
- Lithium
- Meperidine and pethidine
- Phenothiazine antipsychotics (eg, chlorpromazine, mesoridazine, thioridazine)
- Tricyclic antidepressants (eg, amitriptyline, desipramine, doxepin, imipramine, maprotiline, mirtazapine

Any seizure activity while on this study will result in immediate discontinuation of apalutamide. Patients may remain on study to complete radiation and docetaxel, at the discretion of the treating physician.

6.1.4 Missed Doses

If 1 or 2 consecutive doses of apalutamide are missed, the patient will be instructed to take the dose as scheduled the following day. However, if more than two doses are missed, the patient should contact their study physician. Missed doses should not be added to the end of treatment.

6.1.5 Concomitant Medications

Concomitant medication will be evaluated at each study visit during apalutamide therapy. Concomitant medications include all vitamins, herbal remedies, over the counter, and prescription medications. ADT in the form of GnRH agonists or antagonists for 36 weeks is permitted as part of the study as per standard of care practice.

The following medications are prohibited within 2 weeks of enrollment and while on study drug, unless otherwise indicated below:

- 5 α-reductase inhibitors (finasteride, dutasteride);
- Biologic or other agents with anti-tumor activity against prostate cancer;
- Systemic glucocorticoids greater than the equivalent of 10 mg per day of prednisone;
- Androgens (testosterone, dihydroepiandrosterone [DHEA], etc.);
- All investigational agents are prohibited within 4 weeks of enrollment;

The following treatments do not require study discontinuation:

- Blood transfusions and growth factor support per standard of care and institutional guidelines;
- Steroids given at a maximum equivalent daily dose of 10 mg of prednisone;
    - Except premedication with systemic glucocorticoids greater than the equivalent of 10 mg per day of prednisone is permitted prior to docetaxel infusions.
    - Short term use of systemic corticosteroids are allowed for side effect management or non-treatment related, emergent comorbidities that arise during the course of treatment.
- Pain therapy per standard of care and institutional guidelines;

APPENDIX C provides a partial list of potent CYP enzyme inhibitors and inducers that have a theoretical concern for drug-drug interactions with apalutamide. Concomitant medications that are substrates of CYP3A4 should be used with caution, and relevant monitoring should be considered, especially for substrates known to cause seizure, because the possibility of drug-drug interactions cannot be fully excluded.

6.1.5.1 Drugs that Inhibit or Induce CYP3A4

Apalutamide is metabolized primarily by human CYP3A4, thus co-administration with strong inhibitors or inducers of CYP3A4 (changing plasma levels of apalutamide) should be avoided as much as possible. Apalutamide may also induce CYP3A4; therefore, caution should be taken when administered in conjunction with CYP3A4 substrates that have a narrow therapeutic index. Examples of the strong CYP3A4 inhibitors and inducers include the following:

- Strong CYP3A4 inhibitors: itraconazole, clarithromycin, erythromycin, diltiazem, verapamil, delavirdine, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole, grapefruit juice (or grapefruits); co-administration with any of these agents may increase apalutamide plasma concentrations

- Strong CYP3A4 inducers: phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, efavirenz, tipranivir, St. John's wort; co-administration with any of these agents may decrease apalutamide plasma concentrations

6.1.5.2 Effect of apalutamide with warfarin

The potential for drug-drug interaction between apalutamide and warfarin (eg, Coumadin, metabolized by CYP2C9) is unknown at present. If a subject is taking warfarin, re-assess PT (prothrombin time)/international normalized ratio (INR) as clinically indicated and adjust the dose of warfarin accordingly.

6.1.6 Study Drug Blinding

Not applicable, this is an open-label study.

6.1.7 Randomization

Not applicable, this is a non-randomized study.

6.2 Rationale for Selection of Dose, Regimen, and Treatment Duration

The dosing used for the ADT is the standard-of-care dosing. Apalutamide 240mg daily has been studied for efficacy in a Phase II trial as well as in a Phase III trial of men with non-metastatic CRPC. Docetaxel 75mg/m^2 for 6 cycles was studied in the CHAARTED, STAMPEDE, and RTOG 0521 trials. Clinically, high-risk patients with biochemical recurrence after surgery are often managed with the combination of ADT and radiation therapy, although the optimal duration and benefit of ADT in the salvage radiation setting remains unclear. The treatment duration of 36 weeks was chosen in hopes of providing maximal efficacy while minimizing toxicity.

6.3 Rationale for Correlative Studies

Archived prostatectomy specimens and plasma samples will be collected and stored for eventual analysis of androgen receptor target genes, androgen receptor splice variants, and epithelial-mesenchymal transition (EMT) biomarkers. If available, the pre-treatment genomic risk score (for example by the Decipher assay) will be used to correlate with outcomes. The current protocol and funding allows only for archival prostatectomy specimens and plasma samples to be obtained and banked. Please see laboratory manual for further details.

6.4 Definition of Evaluable Subjects, On Study, and End of Study

Patients who consent but do not receive a dose of study drug will be replaced and will not be considered evaluable.

All subjects enrolled onto the study who receive at least one dose of apalutamide will be included in the intention-to-treat analysis for the primary endpoint.

The primary endpoint is the rate of PFS at 36 months, with PFS defined as the proportion of subjects with testosterone >100 at 36 months post Cycle 1 Day 1, without progression as defined above. We

hypothesize that ~20% of patients will not have testosterone recovery at this point and therefore will not be evaluable for the primary endpoint.

All subjects enrolled onto the study who receive at least one dose of apalutamide will be evaluable for the secondary and exploratory endpoints.

6.5 Early Study Termination

This study can be terminated at any time for any reason by the PI-sponsor. If this occurs, all subjects on study should be notified as soon as possible. Additional procedures and/or follow up should occur in accordance with Section 10.8, which describes procedures and process for prematurely withdrawn patients.

7 RADIATION THERAPY

Note: Intensity Modulated RT (IMRT) is allowed for this study.
Radiotherapy will start on week 9 +/- 14 days after Cycle 1 Day 1.

Radiation therapy may be performed locally per standard-of-care, provided it conforms to protocol-specified treatment and dosing specifications. Weekly visits during radiotherapy may be performed locally by the treating radiation oncologist according to standard of care practice. Research visits during radiotherapy will occur at the treating institution at week 9 and week 13, according to the schedule of events.

All study activities occurring after the completion of radiation therapy, (excluding apalutamide, ADT administration, EPIC questionnaires, and correlative sample collection) will have timing based on the end of radiation treatment. The first day of docetaxel treatment should occur at least 4 weeks, but no more than eight weeks, after the last radiation treatment.

7.1 Dose Specifications

Radiotherapy will start on week 9 (+/-14) days. Radiotherapy dose will be specified to the Planning Target Volume (PTV), as described in section 7.4. The total dose to the prostate bed must be 66-74 Gy in 1.8-2 Gy daily fractions. A simultaneous integrated boost to any prostate bed residual mass is allowed as long as DVH constraints can still be met. ≥ 95% of the PTV should receive the prescribed dose. Pelvic nodal coverage for pN1 patients is allowed at the discretion of the treating provider.

7.2 Technical Factors

Megavoltage equipment is required with effective photon energies ≥ 6 MV.

7.3 Localization, Simulation, and Immobilization

Simulation should be with a moderately full bladder (the patient should not be uncomfortable at simulation). Moderate bowel prep is recommended to prevent an overly distended rectum, which can introduce a systematic positioning error that may increase the probability of missing the CTV.

A treatment planning CT scan will be required to define the clinical and planning target volumes, and the critical normal structures. The treatment planning CT will be acquired with the patient set

up in the same position as for daily treatments. Each patient will be positioned in the supine position. The CT scan of the pelvis should start at or above the iliac crest down to below the perineum (below the ischial tuberosities). All tissues to be irradiated must be included in the CT scan. CT scan thickness should be ≤ 0.5 cm through the region that contains the target volumes (i.e., from the bottom of the sacroiliac joints down to the penile urethra). The regions above and below the target volume region may be scanned with slice thickness ≤ 1.0 cm. A urethrogram or MRI is recommended, but not required, to establish the most inferior portion of the prostate bed. Use of contrast, other than for the urethrogram, is discouraged.

Immobilization may be performed per institutional preference and image guidance is highly recommended.

7.4 Treatment Planning/Target Volumes

The definition of volumes (CTV, PTV) will be in accordance with ICRU Report #50: Prescribing, Recording, and Reporting Photon Beam Therapy.

7.4.1 CTV (Prostate Bed)

Contrast may be used for simulation but can distort the anatomy slightly and so is not recommended. The bladder should be reasonably full for simulation, keeping in mind that patients may not be able to maintain as full a bladder during radiotherapy. The seminal vesicles or remnants thereof, if identified on CT or MRI as being present, must be included in entirety within the CTV. The immediate periprostatic bed surgical clips must also be included within the CTV. Superior nodal clips do not need to be targeted. The CTV will include the urogenital diaphragm inferiorly, or 1.5 cm below the urethrogram peak if done, and extend superiorly to include the inferior bladder neck (typically just at the superior pubic symphysis) and to SV remnants. Laterally, the CTV will extend from the medial edge of one obturator internus muscle to the other. Anteriorly the CTV will include the entire bladder neck until the superior pubic symphysis, where a gradual reduction off of the anterior bladder is made. Posteriorly, the CTV is defined by the anterior rectal border. The CTV may be increased (but not decreased) beyond these limits based on pre-prostatectomy imaging information.

The pelvic lymph nodes are not to be included in the CTV except in the setting of node positive disease, where it may be done by physician preference. If included, the pelvic nodal CTV should include external iliac nodes to the level of the superior femoral heads, internal iliac nodes to the superior contours of the prostate/seminal vesicle CTV, and the common iliac nodes to the L5-S1 junction. Inclusion of presacral nodes is recommended but may be omitted at physician discretion to improve organ-sparing. If nodal irradiation is performed, a cone-down to the prostate bed must occur no later than 50.4 Gy. Alternatively, simultaneous integrated boost is allowed with maximum pelvic dose of 52 Gy.

7.4.2 PTV

The PTV margins should be a 0.5-1.5 cm in all dimensions. 95% of the PTV must receive the prescribed dose. Care should be taken to conform the prescribed dose as closely to the PTV as possible, so as to avoid including the entire width of the rectum in the posterior blocked margin at the bladder neck-rectum interface. The maximum dose heterogeneity allowable in the PTV will be 10%; a variation will be > 10% and a violation > 15%.

7.4.3 Normal Tissues

The critical normal structures are the bladder, rectum, and femoral heads. The normal tissues will be contoured and considered as solid organs. The bladder should be contoured from its base to the dome, excluding the CTV (the CTV includes the bladder neck). The rectum should be contoured from the anus (at the level of the ischial tuberosities) to the rectosigmoid flexure (this is roughly at about 10 cm) or for a maximum length of 15 cm if the sigmoid flexure if felt to be higher. Each femoral head should be outlined down to the interface between the greater and lesser trochanters. The penile bulb may be outlined as a reference structure. No constraints will be placed on the penile bulb.

The planning parameters outlined below should be used as a guide. Both 3D-CRT and IMRT are acceptable planning and delivery methods. If 3D-CRT planning is unable to achieve normal dose constraints described below, IMRT is recommended.

7.4.4 Prostate Bed Planning for IMRT

The plan will be deemed acceptable under the following conditions.

PTV: The dose marker levels for bladder and rectum have been modeled after prior studies in men treated definitively with IMRT for prostate cancer. At least 95% of the PTV should receive the prescribed dose; a variation will be noted if < 95% to 90% of the PTV receives the prescribed dose, and a protocol violation will be noted if < 90% of the PTV receives the prescribed dose. The maximum dose heterogeneity allowable in the PTV will be 10%; a variation will be > 10% and a violation > 15%. Since the dose is prescribed to the minimum isodose line of the PTV, the dose variability is seen in portions of the target volume receiving higher than the specified dose.

Rectum: Less than or equal to 35% and 55% of the rectum should receive ≥ 65 Gy and ≥ 40 Gy, respectively. Less than 10 cc should receive 70 Gy. A variation will be noted if up to an additional 7.5% of the rectal volume receives above the target doses specified. The inclusion of rectal volumes beyond these constraints will be considered a protocol violation.

Bladder: Less than or equal to 50% and 70% of the bladder (minus prostate bed CTV) should receive ≥ 65 Gy and ≥ 40 Gy, respectively. Less than 10 cc should receive 70 Gy. The criteria for the bladder have been relaxed because the dosimetric relationship of volume exposed to the specified marker doses is much less clear and the bladder neck is included in the CTV. A primary variation will be noted if up to an additional 7.5% of the bladder volume receives above the target doses specified. The inclusion of bladder volumes beyond these constraints will be considered a secondary protocol variation; it will not be considered a protocol violation.

Femoral Heads: Less than or equal to 10% of each femoral head should receive ≥ 50 Gy. A variation will be noted if up to an additional 5.0% of either femoral head receives > 50 Gy.

Penile Bulb: The penile bulb may be outlined as a reference structure. No constraints will be placed on the penile bulb.

Sigmoid colon (in setting of nodal irradiation): The sigmoid colon should be contoured from the recto-sigmoid junction until it transitions to descending colon (or L4 level, whichever is inferior). No more than 10 cc of the sigmoid colon should receive more than 60 Gy, with less than 5% receiving ≥ 54 Gy.

Bowel (in setting of nodal irradiation): The entire intraperitoneal cavity from the recto-sigmoid junction to 1.5 cm above the PTV volume should be contoured. No more than 1% of the small bowel volume outside of the PTV should receive more than 50.4 Gy.

7.5 Treatment Localization

Patients must have portal imaging performed at a minimum of once weekly for 3D-CRT and daily for IMRT. Image guidance is not required but recommended and can take the form of KV matching to surgical clips or pelvic bones, or cone beam CT to the prostate bed. Other forms of treatment localization are accepted with approval by the lead site (Duke) Radiation Oncology. Treatment with a full bladder is required.

7.6 Documentation Requirements

The institution will archive treatment prescription and verification images for later review if requested. For conformal RT, at least one port film or pretreatment alignment film per field along with the digital reconstructed radiographs (DRRs) from the treatment planning program or, alternatively, a simulation verification radiograph shall be acquired and kept for evaluation if requested except where geometrically impractical. For IMRT, at least pretreatment alignment orthogonal set along with the digital reconstructed radiographs (DRRs) from the treatment planning program shall be acquired and kept for evaluation.
Note: Images are required to be taken but not submitted.

Dosimetric details will be submitted after planning approval via [the AbiRT or Stream data intake sheet with DVH criteria].

7.7 Radiation Adverse Events

All patients will be seen weekly by their radiation oncologist during radiation therapy. Any observations with respect to the following symptoms/side effects will be recorded using CTCAE v4.03 grading including but not limited to:

- Bowel/rectal irritation manifesting as cramping, diarrhea, urgency, proctitis, or hematochezia
- Urinary frequency, urgency, dysuria, hematuria, urinary tract infection, or incontinence
- Radiation dermatitis

Clinical discretion may be exercised to treat side effects from radiation therapy. Examples of typical medications used in the management of rectal side effects, such as diarrhea, include diphenoxylate or loperamide. Bladder or rectal spasms are usually treated with anticholinergic agents or tolterodine. Bladder irritation may be managed with phenazopyridine. Erectile dysfunction can be treated with medical management or mechanical devices.

See Section 11 for Adverse Events and Adverse Event Reporting Guidelines.

8 STUDY DRUG

8.1 Names, Classification, and Mechanism of Action

Apalutamide

Apalutamide is being developed for the treatment of prostate cancer at a dose of 240 mg per day. Apalutamide is currently approved by the FDA for non-metastatic castration resistant prostate cancer and metastatic castration sensitive prostate cancer .

Tablets: The apalutamide drug substance is an almost white to slightly brown powder that is formulated in tablets at a strength of 60 mg.

Apalutamide is administered orally on a continuous once daily dosing schedule. Each cycle of drug administration consists of 28 days. Doses from 30 to 480 mg were tested in the Phase 1 portion of the first clinical study [9]. The therapeutic dose is 240 mg once daily. Apalutamide can be taken with or without food.

Docetaxel

Docetaxel is an antineoplastic agent belonging to the taxane family that acts by disrupting the microtubular network in cells that is essential for mitotic and interphase cellular functions. Docetaxel is FDA-approved for the treatment of metastatic castration resistant prostate cancer. For our current study, docetaxel is investigational in the high risk biochemical relapse setting. Docetaxel is administered intravenously every 3 weeks, at a dose of 75mg/m^2. To prevent fluid retention and hypersensitivity, patients should be pre-medicated with oral corticosteroids such as oral dexamethasone 8 mg twice the day before and 12 mg 1 hour prior to docetaxel infusion or per institutional guidelines.

Pharmacology

The mechanism of action of apalutamide is through antagonism of the androgen receptor andinhibition of AR nuclear translocation and DNA binding to AREs. Unlike bicalutamide, apalutamide shows no significant agonist properties in a model of CRPC (e.g., AR-over-expressing prostate cancer cells; LNCaP/AR cells). Gene transcription of PSA and TMPRSS2 is inhibited by apalutamide and results in concentration-dependent reduction of these protein levels *in vitro*. Apalutamide was also shown to reduce proliferation of CRPC cells as well as increase apoptosis and necrosis *in vivo*. These effects are supported by the anti-tumor activity observed in murine tumor CRPC models, where apalutamide showed dose-dependent tumor growth inhibition and tumor regression over a dose range of 0.1 to 10 mg/kg/day, with effects that were superior to bicalutamide.

Docetaxel binds free tubulin, promoting the assembly of tubulin into stable microtubules and inhibiting the disassembly of microtubules, thus inhibiting cell proliferation. Docetaxel's maximum stoichiometry is one mole docetaxel per mole tubulin in microtubules.

8.2 Packaging and Labeling

How Supplied:
Apalutamide
Apalutamide tablets (60 mg) are packaged in 120-count bottles, and should at all times be kept in the original packaging.

Docetaxel
Docetaxel concentrate solution will be obtained from a commercial supplier, but will likely be Teva Pharmaceuticals, Pfizer/Hospira, or Sagent Pharmaceuticals. Specifications for Docetaxel will be provided in the pharmacy manual.

Detailed information on handling and storage conditions will accompany the clinical drug supplies to the clinical study site(s). The storage conditions and expiry will be indicated on the label of the drug product.

8.3 Supply, Receipt, and Storage

Treatment will be administered on an outpatient basis. Apalutamide will be given to the patient from clinic and patients will receive 240 mg/day (four 60 mg tablets) in an unblinded fashion. Apalutamide will be supplied by Janssen. The product is provided as a tablet with a non-functional green film coat, in high density polyethylene (HDPE) bottles with child-resistant caps. Apalutamide can be taken with or without food.

Commercially available docetaxel (Taxotere®) will be used. Docetaxel will be given intravenously at a dose of 75mg/m^2 in an infusion treatment room every 3 weeks, and patients will be supervised during treatment. Docetaxel will be prepared as described in the product package insert. Docetaxel will be supplied through this study given its investigational nature. Prior to receiving any dose of docetaxel, patients must have an absolute neutrophil count of >1500 cells/mm^3 and a platelet count of >100,000 cells/mm^3. In addition, the body surface area (BSA) should be capped at 2.2 m^2 using the patient's actual weight.

Pre-medication with oral corticosteroids
Docetaxel treatment has been associated with severe fluid retention and hypersensitivity reactions in a minority of patients. For this reason, all patients should be pre-medicated with oral corticosteroids such as oral dexamethasone 8 mg twice the day before and 12 mg 1 hour prior to docetaxel infusion or per institutional guidelines. In the event that dexamethasone is not taken according to the above schedule, it can be given as an infusion prior to docetaxel infusion, but should be documented as a deviation to the protocol.

Storage and Handling:

Apalutamide will be stored in a secure location with limited access within the following temperature range: 59°F to 86°F (15°C to 30°C). Bottles will be labeled with the study protocol number, medication or kit number, contents, directions for use, storage directions, clinical trial statement, and sponsor. Patients will be instructed to store study drug at room temperature out of the reach of children.

Docetaxel should be protected from light and stored between 36^{o}F to 77^{o}F. Docetaxel should be diluted and prepared per each institutional standards.

8.4 Dispensing and Preparation

After receipt of prescription by the site Investigational Pharmacy Services, a secondary label will be applied with patient's name, date, prescription, expiration, contact information, and indication. Apalutamide 240 mg daily will be dispensed by the site investigational pharmacy services on an as need basis to maintain adequate supply between study visits. Apalutamide will be given for approximately 36 weeks x7 days = 252 days total. Docetaxel will be prepared as described in the product package insert.

8.5 Compliance and Accountability

Drug accounting on receipt, shipment, and dispensing will be carried out per site Investigational Pharmacy Services SOP. Patient compliance with prescription will be monitored by a study drug diary which will be reviewed with the research nurse staff monthly.

8.6 Disposal and Destruction

Any apalutamide tablets returned unused by patients will be documented by the site Investigational Pharmacy Services and then incinerated according to SOP.

9 SUBJECT ELIGIBILITY

Eligibility Criteria can be found in protocol section 2.4.

10 SCHEDULE OF EVENTS

		Timing anchored on Apalutamide start (Week #)						Timing anchored on end of radiation treatment (Weeks After Radiation = WAR)								
	Screening[a] Within 60 days	Week 1	Week 5	Week 9[c]	Week 13	Week 17	After this bar event timing is anchored to end of radiation not start of Apalutamide	4 WAR[,n]	5 WAR	7 WAR[n]	8 WAR	10, 13,16, 19 WAR[n]	11, 14, 17,20 WAR[n]	22 WAR End of treatment[d,]	Safety follow up (approx. 4 weeks after EOT)[m,n]	Follow up every 3 months after SFU[e,o,p]
window (+/-)	n/a	+/- 7 days		+/- 2 weeks	+/- 7 days			+/- 4 weeks						+/- 7 days		see footnotes,[e,o]
Informed consent	X															
Inclusion/exclusion criteria	X	X														
Medical history & AE assessment[l, b]	X	X	X	X	X	X		X		X		X		X	X	
Prior & concomitant medications[m, b]	X	X	X	X	X	X		X		X		X		X	X	
Physical examination[b]	X	X	X	X	X	X		X		X		X		X	X	
Karnofsky performance status[b]	X	X	X	X	X	X		X		X		X		X	X	
Vital signs, height & weight[b]	X	X	X	X	X	X		X		X		X		X	X	
CT chest, abd, pelvis[f]	X															
Bone scan[f]	X															
CBC with differential[g,m]	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X[m,o]
Serum chemistries[g,m]	X	X	X	X	X	X		X		X		X		X	X	X [m,o]
Serum PSA[g]	X	X	X	X	X	X		X		X		X		X	X	X[o]
Testosterone [g]	X	X	X	X										X	X	X[o]
TSH[g]	X		X	X	X	X				X				X		
Apalutamide dispensing[h]		X	X	X	X	X		X[n]		X[n]		X[n]				
ADT administration[i]		X			X							X[n]				
Radiation therapy and weekly treatment checks[c]				X	X											
Docetaxel								X		X		X				
EPIC quality of life questionnaire[k]	X				X											X[p]
Archival tumor blocks[j]		X														
Correlative sample-Plasma[g]	X[g]															X[p]

Footnotes to Study Flow Chart:

a. Screening/baseline evaluations must be completed within 60 days prior to the first dose of study agent.
b. Visits will occur every 4 weeks (+/- 7 days, except week 9 which is +/- 14 days), through week 17. Starting at 4 weeks after radiation (4 WAR), the visits will occur every 3 weeks while receiving docetaxel. If possible, VAS pain and fatigue score will be collected with the physical exam. Blood pressure CTCAE grading will be done based on the blood pressure reading, not the number of blood pressure medications the subject is taking.
c. Radiation therapy will begin on week 9 (+/- 14 days). Radiation therapy may be performed locally as standard-of-care, provided it conforms to protocol-specified treatment and dosing specifications. Receipt of protocol-specified salvage radiation will be documented including dose, field, and timing. Weekly visits during radiotherapy may be performed locally by the treating radiation oncologist according to standard of care practice. Research visits during radiotherapy will occur at week 9 and week 13, according to the schedule of events.
d. End-of-treatment visit will occur at 22 Weeks after radiation (22 WAR) (+/- 7 days), at which point all therapeutic intervention will be complete.
e. Long-term follow-up visits will occur every 3 months from the safety follow-up visit and will have a +/- 28 day allowance window. Follow up will continue until 36 months post-Cycle 1 Day 1 or until early withdrawal. If the full 36 weeks (9 months) of treatment is completed then the subject will continue to be followed for up to 27 months from end of treatment.
f. CT scan of chest, abdomen, and pelvis (without IV contrast is permitted, but CT of abdomen and pelvis with contrast is preferred for patients with sufficient renal clearance as determined by the treating physician) and whole body Tc-99 bone scan will be performed within 60 days of initial study drug administration, as per standard-of-care to evaluate for metastatic disease. Chest CT may be omitted per current NCCN guidelines. PET CT and MRI modalities are acceptable if used instead of CT or bone scan but must cover skull base to mid-thigh. Subsequent imaging studies will be performed at the discretion of the treating physician.
g. Standard-of-care laboratory assessments at the times indicated include:
    - Complete blood count (CBC) with differential: WBC count with differential, platelet count, hemoglobin, and hematocrit. During docetaxel therapy, a CBC w/diff will be drawn on day 11 from the docetaxel infusion (+/- 4 days) and may be performed locally.
    - Serum chemistries: Sodium, potassium, chloride, blood urea nitrogen (BUN) or urea, creatinine, glucose, carbon dioxide (CO_2) or bicarbonate, calcium, total protein, aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, total bilirubin, and alkaline phosphatase.
    - Testosterone and PSA levels
    - TSH: TSH will be measured per discretion of treating oncologist at screening and at the following visits: weeks 5, 9, 13, 17, 7 weeks after radiation (7 WAR), and 22 weeks after radiation (WAR 22)/End of treatment. If TSH is abnormal, obtain a T3/T4.
    - Correlative plasma sample: Drawn once at baseline (draw will be performed during screening; if draw cannot be performed at screening it may also be drawn on Day 1 prior to dosing) and also for follow up at 24 & 36 months post Cycle 1 Day 1.

    NOTE: Week 1 lab tests do not need to be repeated if the baseline labs were obtained within 7 days of initial study drug administration.
h. Apalutamide will be dispensed on an as need basis to maintain adequate supply between study visits. and should be taken daily for a total of 36 weeks. Cycle 1 Day 1 is defined as the first day of treatment (apalutamide and/or ADT). Apalutamide treatment will stop at 36 weeks regardless of scheduling of other treatments.

i. ADT (3-month dose) will be given in clinic on day 1 and during clinic visits on week 13 and 10 weeks after radiation (10 WAR) for a total of 36 weeks of therapy. Alternative SOC schedules including (but not limited to) 6-month dose are permitted provided total treatment duration of ADT is unchanged at 36 weeks.
j. Archival specimen: Previously archived formalin-fixed or frozen primary prostate tumor blocks or cores will be collected on this study through the Duke Cancer Institute or participating site biorepository and linked to subject outcomes if available. Slides are also acceptable in lieu of blocks. This is an optional component of the study as detailed in the ICF. At least 250 mg of tumor tissue is needed for the genomic correlative component of this study. Frozen primary tumor samples will be collected if available. See section 10.9.3 for details.
k. Quality-of-life questionnaire (EPIC Short Form) will be administered at screening, at week 13, then during the 12, 24, and 36-month post C1D1 follow-up visits (5 per subject).
l. All AEs are collected for the duration of study treatments as well as for 30 days following the last administration of any study treatment including chemotherapy, radiation or apalutamide. During follow-up, AEs definitely, probably or possibly attributed to study drug occurring during treatment are tracked until resolution to grade 1 or baseline, but new AEs not related to the study drug are not collected.
m. During follow-up, treatments for prostate cancer will be collected (eg. ADT). PSA and testosterone should be measured every 3 months. CMP and CBC to be drawn only if there are abnormalities due to chemo and these can be followed until resolution to grade 1. SOC laboratory assessments may be performed locally during long term follow-up.

n. ADT and apalutamide treatment should occur as scheduled for 36 weeks no matter the length of radiation treatment.
o. In follow up, EPIC questionnaires and correlative plasma draws have a window of +/- 3 months

10.1 Screening Examination

The screening examination will take place within 60 days of initiation of therapy. An informed consent form must be signed by the subject before any study-specific screening procedure takes place.

Subject data to be collected at the Screening Examination includes:

- Informed consent process utilizing a signed and dated IRB-approved ICF
- Confirmation of inclusion/exclusion criteria
- Medical history including concomitant illnesses and oncologic history. Oncologic history must include specific documentation of prostate cancer histologic diagnosis.
- Prior and concomitant medications and non-pharmacologic treatments taken within 4 weeks of screening will be recorded. In addition, all prior treatments including surgery and radiotherapy for prostate cancer will be recorded, regardless of when administered.
- CT of the chest, abdomen, and pelvis or PET scan for tumor assessment, standard-of-care
- Whole body bone scan (99-Technetium), standard-of-care
- Sample collection for the following laboratory evaluations (all standard-of-care):
    - Complete blood count (CBC) with differential: WBC count with differential, platelet count, hemoglobin, and hematocrit.

- Serum chemistries: Sodium, potassium, chloride, blood urea nitrogen (BUN) or urea, creatinine, glucose, carbon dioxide (CO_2) or bicarbonate, calcium, total protein, aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, total bilirubin, alkaline phosphatase, and thyroid stimulating hormone (TSH).
- Testosterone and PSA levels.

- Correlative plasma samples will be drawn at screening or prior to day 1 dosing
- Physical examination to be conducted and height (cm), weight (kg), and vital signs (including temperature [°C], blood pressure [mmHg], heart rate [beats per minute], respiratory rate [breaths per minute]. Height will be collected at screening only.
- Karnofsky performance status
- Quality-of-life questionnaire (EPIC Short Form) will be administered at screening.

Upon study registration, tumor pathology will be collected as below:

Previously archived formalin-fixed or frozen primary prostate tumor blocks or cores will be collected on this study through the Duke Prostate Center or participating site biorepository and linked to subject outcomes if available. Slides are also acceptable in lieu of blocks. This is an optional component of the study as detailed in the ICF. At least one frozen biopsy (250 mg) of tumor tissue is needed. Frozen primary tumor samples will be collected if available. See section 10.9.3 for details.

10.2 Subject Registration and Enrollment

10.2.1 Informed Consent

Authorized study personnel should fully explain the scope of the study to each subject before obtaining informed consent. Subjects should be advised of any known risks inherent in the planned procedures, of any alternative treatment options, of their right to withdraw from the study at any time for any reason, and of their right to privacy.

When obtaining informed consent, study personnel should:

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

Next: Obtain dated and signed informed consent.

Finally: Confirm that the subject is eligible as defined in Section 2.4 (Inclusion/Exclusion Criteria). A record of subjects who fail to meet entry criteria (i.e., screening failures) will be maintained.

Subjects will be entered into the Duke clinical trial subject registry per institutional policy.

10.2.2 Registration

Subject registration at each study site/institution will be conducted according to the institution's established policies and all sites will be overseen by the Duke University Medical Center Genitourinary Oncology Group. Prior to registration, subjects will be asked to sign and date an Institutional Review Board (IRB)-approved consent form. After obtaining informed consent, the consent document and any registration documents will be submitted for review and registration of

the subject by the lead site (Duke). All consented subjects will be registered and assigned a unique study ID. A record of subjects who fail to meet entry criteria (i.e., screen failures) will be maintained.

Refer to Subject Registration Instructions in the Coordinator Manual for details.

10.2.3 Enrollment

Subjects will be enrolled only after all pre-treatment screening evaluations are completed and all eligibility criteria are met. Once the subject has been registered and found to meet all eligibility criteria, the subject will be approved for enrollment. Study treatment must not commence until the subject has received his/her identification number and enrollment approval from the lead site. The date of enrollment is the date the subject takes the first dose of study drug.

10.3 Run-In Period

Not applicable.

10.4 Treatment Period

Treatment will be administered on an outpatient basis. Apalutamide and/or ADT treatment will start on week 1 and continue throughout the study. Cycle 1 Day 1 is defined as the first day of treatment with apalutamide and/or ADT. On week 9 (+/-14 days), salvage radiation therapy will be started according to local standard of care, which is usually 6-8 weeks. There will be a radiation washout of at least 4 weeks, prior to starting docetaxel. Docetaxel will then be given for 6 cycles, per the schedule of events. Prednisone will not be given with docetaxel, per treatment in the CHAARTED protocol. Treatment period will last approximately 36 weeks.

10.5 Chemotherapy administration will begin at the 4 WAR visit, at least 4 weeks, but no more than 8 weeks after the completion of radiation treatment. Scheduling of all post-radiation events will be based on the end of radiation treatment, with the exceptions of ADT administration, apalutamide discontinuation, EPIC questionnaires, and correlative plasma samples, which are based on the start of apalutamide treatment. End of Treatment

At approximately WAR 22, in the event of disease progression, unacceptable toxicity, or withdrawal of consent, study treatment is to be stopped and an end-of-treatment visit is to be conducted within 7 days.

The following procedures are to be conducted at the end-of-treatment visit:

- Concomitant medications and non-pharmacologic treatments to be reviewed and recorded.
- Sample collection for the following laboratory evaluations (all standard-of-care):
  - CBC: WBC with differential, platelet count, hemoglobin, and hematocrit.

  - Chemistries: sodium, potassium, chloride, blood urea nitrogen (BUN) or urea, creatinine, glucose, carbon dioxide (CO_2) or bicarbonate, calcium, total protein, aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, total bilirubin, alkaline phosphatase, and TSH.
  - PSA and testosterone.
- Physical examination to be conducted, including weight (kg) and vital signs (including temperature [°C], blood pressure [mmHg], heart rate [beats per minute], respiratory rate [breaths per minute] and if possible, VAS pain and fatigue score [scale of 1-10, subject reported]).
- Karnofsky performance status
- Adverse Events

10.6 Follow-up Period

The safety follow-up visit will occur approximately 4 weeks after last administration of study treatment including chemotherapy, radiation, or apalutamide. All AEs are collected for the duration of study treatments as well as for 30 days following the last administration of any study treatment including chemotherapy, radiation or apalutamide. During follow-up, AEs definitely, probably or possibly attributed to study drug occurring during treatment are tracked until resolution to grade 1 or baseline, but new AEs not related to the study drug are not collected.

Regular follow up visits will occur every 3 months from safety follow-up and continue for 36 months from Cycle 1 Day 1. Follow-up visits will be scheduled every three months from the safety follow-up visit (with a 28-day window period allowance). Correlatative plasma samples and EPIC Quality of life questionnaires will be collected per the Schedule of Events with a +/-3 month collection window.Imaging studies will be performed as per standard-of-care for those men with evidence of PSA recurrence or symptomatic disease or based on concerns of disease recurrence in the absence of PSA progression.

Every three months laboratory assessments will be performed for PSA and testosterone outcomes. Other laboratory studies will be performed at the discretion of the treating physician. CMP and CBC to be drawn only if there are abnormalities due to chemo (Docetaxel only) and these can be followed until resolution to grade 1. If a subject is unable to travel to the research site during long term follow-up, the standard of care laboratory assessments may be performed locally. Correlative plasma samples will be drawn at 24 & 36 months post Cycle 1 Day 1.

Regular follow up visits will include medical history and review of any treatments for prostate cancer (eg. ADT) taken since the prior visit. Quality-of-life questionnaire (EPIC Short Form) will be administered at baseline, at week 13, then during the 12, 24, and 36 month post C1D1 follow-up visits (5 per subject). These questionnaires and review of prostate cancer treatments may also be administered by mail or over the phone.

10.7 End of Study

Each subject will be followed every 3 months following their safety follow-up visit for a total of 36 months (3 years) from Cycle 1 Day 1 or until early withdrawal. The overall end of study will occur when the last enrolled subject has completed his last follow up visit. If the full 36 weeks (9 months)

of treatment is completed then the subject will continue to be followed for up to 27 months from end of treatment.

10.8 Early Withdrawal of Subject(s)

10.8.1 Criteria for Early Withdrawal

Subjects may voluntarily withdraw from the study at any time. The PI may also withdraw a subject from the study at any time based on his/her discretion.

Reasons for PI-initiated withdrawal may include the following:

- Progression of disease defined as PSA rise 0.2 ng/ml above nadir or imaging consistent with metastatic disease;
- Unacceptable toxicity (at the discretion of the treating physician) — Reason(s) for removal must be clearly documented in the physician progress note
- Noncompliance with oral medication
- A delay in radiotherapy > 2 weeks;
- The patient may withdraw from study treatment at any time for any reason and still be followed per protocol**.**

If one subject is unable to tolerate the combination of apalutamide with radiation and requires a ≥5 day delay in radiation therapy due to toxicity, this would trigger a temporary hold in accrual, until a meeting of the data and safety monitoring committee at the lead site is held to review the AEs and to determine if the study may proceed and if changes to the protocol are required.

10.8.2 Follow-up Requirements for Early Withdrawal

Upon early withdrawal from study treatment, an end of treatment visit will be conducted within 7 days as described above. At withdrawal, all on-going study-related toxicities and SAEs should be followed until resolution, unless in the investigator's opinion, the condition is unlikely to resolve due to the subject's underlying disease. Subjects should be followed up for new AEs for 30 calendar days after the last administration of study therapy including chemotherapy, radiation or apalutamide. All new AEs possibly related to study treatment occurring during the follow up period should be collected.

10.8.3 Replacement of Early Withdrawal(s)

Patients who consent but do not receive a dose of study drug will be replaced and will not be considered evaluable. Subjects who prematurely withdraw will not be replaced.

10.9 Study Assessments

10.9.1 Medical History

At the initial visit, the detailed medical history will include concomitant illnesses and oncologic history. All prior treatments including surgery and radiotherapy for prostate cancer will be recorded,

regardless of when administered. This medical history will be updated at subsequent visits. Concomitant medications and non-pharmacologic treatments taken will be recorded at each visit.

10.9.2 Physical Exam

Physical examination should include: height (cm – screening visit only), weight (kg), and vital signs. Vital signs include temperature [°C], blood pressure [mmHg], heart rate [beats per minute], respiratory rate [breaths per minute] and, if possible, VAS pain and fatigue score [scale of 1-10, subject reported]. Karnofsky performance status will be assessed and recorded at each visit. All additional elements of the physical exam will be documented per the provider's discretion.

Please see **APPENDIX A** for ECOG and Karnofsky Performance Status Criteria and **APPENDIX B** for VAS Pain and Fatigue Score Criteria.

10.9.3 Correlative Assessments

Previously archived formalin-fixed or frozen primary prostate tumor blocks or core biopsies will be collected on this study through the Duke Cancer Institute or participating site biorepository and linked to subject outcomes if available. This is an optional component of the study as detailed in the ICF. At least 250 mg of tumor tissue is needed for the genomic correlative component of this study. Frozen primary tumor samples will be collected if available. Slides are an acceptable alternative; twenty (20) slides, 5 microns thick (unstained and unbaked) will be collected.

These archived specimens will be collected and stored for analysis of the correlation of outcomes with pre-treatment androgen receptor target genes, androgen receptor splice variants, and epithelial-mesenchymal transition (EMT) biomarkers for mechanisms of resistance to apalutamide, ADT, and radiation. If available, a pre-treatment genomic risk score (for example by the Decipher assay) will be used to correlate with outcomes. Prior to storage, all specimens will be labeled with the study ID and date that specimen was obtained from patient. To maintain patient confidentiality, specimens will not be labeled with any patient identifier except the subject ID and date of collection. Specimens will be stored until either they are used according to established SOPs in the Duke Biospecimen Repository and Processing Core (BRPC) for up to 15 years after collection, whichever is shorter.

A single EDTA tube will be drawn at baseline and upon follow up (24 and 36 months after Cycle 1 Day 1), for storage of plasma and future work in evaluation of circulating proteins and cell free DNA analysis. Please refer to the lab manual for details.

11 SAFETY MONITORING AND REPORTING

The PI is responsible for the identification and documentation of adverse events and serious adverse events, as defined below. At each study visit, the PI or designee must assess, through non-suggestive inquiries of the subject or evaluation of study assessments, whether an AE or SAE has occurred.

11.1 Definitions

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non- investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonization [ICH])
This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Adverse Events of Special Interest
There are no adverse events of special interest for apalutamide.

Definition of Adverse Drug Reaction (ADR)

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

Individual Case Safety Report (ICSR)
A valid ICSR must contain the four minimum criteria required to meet regulatory reporting requirements.

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

The minimum information required is:

- suspected Janssen medicinal product (doses, indication)
- date of therapy (start and end date, if available)
- batch or lot number, if available
- subject details (subject ID and country)
- gender
- age at AE onset
- reporter ID

- adverse event detail (AE verbatim in English), onset date, relatedness, causality, action taken, outcome, (if available)
- Janssen protocol ID

Product Quality Complaint (PQC)

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

Examples of PQC include but not limited to:

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

Serious Adverse Event (SAE)

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

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

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

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

Hospitalization

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

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

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

Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.]

Life-Threatening Conditions

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

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

11.2 Unlisted (Unexpected) Adverse Event/Reference Safety Information

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

For apalutamide, the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure.

11.3 Special Reporting Situations

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

- Drug exposure during pregnancy (maternal and paternal)
- Overdose of a Janssen medicinal product
- Exposure to a Janssen medicinal product from breastfeeding
- Suspected abuse/misuse of a Janssen medicinal product
- Inadvertent or accidental exposure to a Janssen medicinal product
- Medication error involving a Janssen medicinal product (with or without patient exposure to the Janssen medicinal product, e.g., name confusion)

- Suspected transmission of any infectious agent via administration of a medicinal product

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

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

11.3.1 Pregnancy

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

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

11.4 Maintenance of Safety Information

All safety data should be maintained in a clinical database in a retrievable format. The INSTITUTION and PRINCIPAL INVESTIGATOR shall provide all adverse events, both serious and non-serious, in report format. However, in certain circumstances more frequent provision of safety data may be necessary, e.g. to fulfill a regulatory request, and as such the data shall be made available within a reasonable timeframe at the request of JANSSEN Scientific Affairs, LLC.

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

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

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

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

The sequence and timing of reporting requirements is described in section 11.9 Reporting Timelines.

11.5.1 SAEs and Special Reporting Situations

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

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

The INSTITUTION and the PRINCIPAL INVESTIGATOR will transmit all SAEs and special situations following exposure to a Janssen product under study in a form provided by JANSSEN in English **within 24-hours of becoming aware of the event(s).**

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

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

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

- The INSTITUTION and/or PRINCIPAL INVESTIGATOR is responsible for ensuring that these cases are complete and if not are promptly followed-up. A safety report is not considered complete until all clinical details needed to interpret the case are received. Reporting of follow-up information should follow the same timeline as initial reports.
- Copies of any and all relevant correspondences with regulatory authorities and ethics committees regarding any and all serious adverse events, irrespective of

association with the Janssen Product under study, are to be provided to JANSSEN within **24 hours of such report or correspondence being sent to applicable health authorities.**

11.5.2 Non-Serious AEs

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

11.5.3 PQC Reporting

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

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

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

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

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

Transmission Methods

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

- Electronically via Janssen SECURE Email service (preferred)
- For business continuity purposes, if SECURE Email is non-functional:

  - Facsimile (fax), receipt of which is evidenced in a successful fax transmission report
- Telephone (if fax is non-functional).

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

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

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

For each subject, AEs SAEs, and Special Reporting Situations should be recorded after informed consent is obtained until the subject has completed participation in the study as follows:

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

Any theft, loss, or misplacement of any Janssen supplied study drug from either Duke or the subject's supply must be reported to Janssen starting with initial distribution of the study drug until the end of the study. This applies even if there is no suspicion of misuse or overdose on the part of the subject.

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

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

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

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

Further, a procedure or surgery is not an adverse event; rather, the event leading to the procedure or surgery is considered an adverse event. Any event requiring in-patient hospitalization that occurs during the course of a subject's participation in a trial must be reported as an SAE. Hospitalizations that do not meet the criteria for SAE reporting are:
A: Reasons described in the Protocol, e.g. drug administration, Protocol-required testing
B. Surgery or procedure planned prior to entry into the Study.

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

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

11.9 Reporting Timelines

Serious safety information (SAEs, Special Reporting Situations, and PQCs), whether or not considered drug related, should be reported to the DCI Safety Desk within **24 hours** of becoming aware of the event(s), using the provided Janssen SAE Report Form and the DCI SAE Review Form (Site Assessment). These documents should be sent via the REDCap survey system using the web link provided by the Duke multisite coordinators. For more information on and access to the REDCap system, please contact the GU multisite team: phone (919) 668-3018, e-mail:GU-Multisite@dm.duke.edu

If Duke staff cannot be reached within 24 hours, the Sponsor/Investigator should be contacted: Dr. Andrew Armstrong (phone: (919) 668-4667 before 3:30pm on weekdays, for after 3:30, weekends, and holidays call the paging operator at (919) 684-8111 and ask to have Dr. Armstrong paged; fax: 919-660-0178; email: andrew.armstrong@duke.edu).

The initial report for each SAE or death should include at minimum the following information:
- protocol # and title
- patient initials, study identification number, sex, age

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

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

Upon receipt of the Serious Adverse Event Reporting form by DCI Safety Desk, the PI will be notified and be required to complete the PI assessment of the DCI Safety SAE Report Review Form. Within 24 hours of notification from the site, the DCI safety desk will, in turn, send the Janssen SAE Report Form to Janssen. Safety information will be sent to Janssen by encrypted email using Cisco Registered Envelope Service to <IIS-BIO-VIRO-GCO@its.jnj.com>. Delivery and read receipt of the secure email will serve as evidence of successful communication.

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

11.10 FDA Reporting Requirements

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

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

JANSSEN will provide to the INSTITUTION/PRINCIPAL INVESTIGATOR IND safety reports/SUSAR (Serious Unexpected Suspect Adverse Reaction) reports generated by the JANSSEN for the Study Product as they become available until all subjects in the Protocol have completed their last Study visit according to the Protocol (i.e. Last Subject Last Visit has occurred).

11.12 Safety Oversight Committee (SOC)

The Duke Cancer Institute SOC is responsible for annual data and safety monitoring of DUHS sponsor-investigator Phase I and II, therapeutic interventional studies that do not have an independent Data Safety Monitoring Board (DSMB). The primary focus of the SOC is review of safety data, toxicities and new information that may affect subject safety or efficacy. Annual safety reviews includes but may not be limited to review of safety data, enrollment status, stopping rules if applicable, accrual,

toxicities, reference literature, and interim analyses as provided by the sponsor-investigator. The SOC in concert with the DCI Monitoring Team oversees the conduct of DUHS cancer-related, sponsor-investigator therapeutic intervention and prevention intervention studies that do not have an external monitoring plan, ensuring subject safety and that the protocol is conducted, recorded and reported in accordance with the protocol, standing operating procedures (SOPs), Good Clinical Practice (GCP), and applicable regulatory requirements.

12 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Monitoring

This clinical research study will be monitored both internally by the PI and institutionally by the Duke Cancer Institute (DCI). In terms of internal review the PI will continuously monitor and tabulate adverse events. Appropriate reporting to the Duke University Medical Center IRB will be made. If an unexpected frequency of Grade III or IV events occur, depending on their nature, action appropriate to the nature and frequency of these adverse events will be taken. This may require a protocol amendment, dose de-escalation, or potentially closure of the study. The PI of this study will also continuously monitor the conduct, data, and safety of this study to ensure that:

- Interim analyses occur as scheduled;
- Stopping rules for toxicity and/or response are met;
- Risk/benefit ratio is not altered to the detriment of the subjects;
- Appropriate internal monitoring of AEs and outcomes is done;
- Over-accrual does not occur;
- Under-accrual is addressed with appropriate amendments or actions;
- Data are being appropriately collected in a reasonably timely manner.

DCI review and monitoring of this protocol occurs in accordance with the NCI-approved Data and Safety Monitoring Plan. Briefly, protocol review begins with an initial review by the Cancer Protocol Committee (CPC), which assesses the ethics and safety of the protocol. Documentation of these assessments will be maintained. Formal, independent monitoring will be conducted by the DCI Monitoring Team after the first 3 subjects are enrolled, followed by annual monitoring of 1-3 subjects until the study is closed to enrollment and subjects are no longer receiving study interventions that are more than minimal risk. DCI Monitoring Team reports and additional data/safety/toxicity reports submitted by the PI will be reviewed by the Safety Oversight Committee (SOC) on an annual basis. Additional monitoring may be prompted by findings from monitoring visits, unexpected frequency of serious and/or unexpected toxicities, or other concerns. Monitoring visits may also be initiated upon request by DUHS and DCI Leadership, CPC, SOC, the Duke Office of Audit, Risk and Compliance, a sponsor, an investigator, or the IRB. All study documents must be made available upon request to the DCI Monitoring Team and other authorized regulatory authorities, including but not limited to the National Institute of Health, National Cancer Institute, and the FDA. Every reasonable effort will be made to maintain confidentiality during study monitoring

12.2 Safety Oversight Committee

The Duke Cancer Institute SOC is responsible for annual data and safety monitoring of DUHS sponsor-investigator Phase I and II, therapeutic interventional studies that do not have an independent Data Safety Monitoring Board (DSMB). The primary focus of the SOC is review of safety data, toxicities and new information that may affect subject safety or efficacy. Annual safety reviews includes but may not be limited to review of safety data, enrollment status, stopping rules if applicable, accrual, toxicities, reference literature, and interim analyses as provided by the sponsor-investigator. The SOC in concert with the DCI Monitoring Team oversees the conduct of DUHS cancer-related, sponsor-investigator therapeutic intervention and prevention intervention studies that do not have an external monitoring plan, ensuring subject safety and that the protocol is conducted, recorded and reported in accordance with the protocol, standing operating procedures (SOPs), Good Clinical Practice (GCP), and applicable regulatory requirements.

12.3 Data Management and Processing

12.3.1 Study Documentation

Study documentation includes but is not limited to source documents, case report forms, monitoring logs, appointment schedules, study team correspondence with sponsors or regulatory bodies/committees, and regulatory documents that can be found in the DCI-mandated "Regulatory Binder", which includes but is not limited to signed protocol and amendments, approved and signed informed consent forms, FDA Form 1572, CAP and CLIA laboratory certifications, and clinical supplies receipts and distribution records.

Source documents are original records that contain source data, which is all information in original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source documents include but are not limited to hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial. When possible, the original record should be retained as the source document. However, a photocopy is acceptable provided that it is a clear, legible, and an exact duplication of the original document.

12.3.2 Case Report Forms (CRFs)

The electronic CRF will be the primary data collection document for the study. The CRFs will be updated in a timely manner following acquisition of new source data. Only the key personnel delegated on the delegation of authority log are permitted to make entries, changes, or corrections in the CRF.

An audit trail will be maintained automatically by the electronic CRF management system. All users of this system will complete user training, as required or appropriate per regulations.

12.3.3 Data Management Procedures and Data Verification

Users of the electronic CRF will have access based on their specific roles in the protocol.

Completeness of entered data will be checked automatically by the eCRF system, and users will be alerted to the presence of data inconsistencies. Additionally, the data manager and project manager will cross-reference the data to verify accuracy. Missing or implausible data will be highlighted for the PI requiring appropriate responses (i.e. confirmation of data, correction of data, completion or confirmation that data is not available, etc.).

The database will be reviewed and discussed prior to database closure, and will be closed only after resolution of all remaining queries. An audit trail will be kept of all subsequent changes to the data.

12.3.4 Study Closure

Following completion of the studies, the PI will be responsible for ensuring the following activities:

- Data clarification and/or resolution
- Accounting, reconciliation, and destruction/return of used and unused study drugs
- Review of site study records for completeness
- Shipment of all remaining laboratory samples to the designated laboratories

13 STATISTICAL METHODS AND DATA ANALYSIS

All statistical analysis will be performed under the direction of the statistician designated in key personnel. Any data analysis carried out independently by the investigator must be approved by the statistician before publication or presentation.

The primary objective of this single arm, open-label, one stage Phase II study is to estimate the 36 month progression-free survival rate of men with recurrent, PSA-only disease after prostatectomy receiving combined apalutamide and standard androgen-deprivation therapy with salvage radiation therapy, followed by apalutamide and ADT with docetaxel. The target sample size is 42. It is primarily hypothesized that the 3-year PFS rate will be improved with the combined therapy compared to the historical control data in a similar patients setting. Based on a model and nomogram by Stephenson et al for men with recurrent disease after radical prostatectomy [1], the PFS rate at 36-months among prostate cancer patients is 50%. The historical sample studied in the publication by Stephenson et al has fewer high risk features than the population that the current trial is studying. Therefore, this trial assumes a null hypothesis of 36-month PFS rate of 40%. **This trial is designed to have more than 85% power to reject the null hypothesis of 36-month PFS rate of 40% when the true PFS rate at 36 months is 65%, with a two-sided alpha of 0.05.** The sample size needed will be 38, and factoring in a 10% drop out rate, the final sample size is 42 patients. A one sample one-sided binomial test will be used to test whether the 36-month PFS rate is larger than the hypothesized value from the historical controls.

The Kaplan-Meier product-limit estimator will be used to estimate the distribution of PFS, biochemical progression free survival, time to PSA nadir, and time to testosterone recovery. The median survival times and 95% confidence intervals will be reported. The frequency and proportion (and 95% confidence interval) of men at 12, 24 and 36 months (1, 2, and 3 years) with a PSA of <0.1 ng/ml and testosterone recovery will be reported. In addition, descriptive statistics with 95%

confidence intervals will be calculated for secondary endpoints of safety profile and quality-of-life (QOL) endpoints, the continuous safety and QOL endpoints will be summarized as the patient counts, mean, standard deviation, median, $25^{th}$and 75^{th} percentiles, minimum and maximum. The categorical safety and QOL endpoints will be categorized using frequencies and percentages.

13.1 Analysis Sets

This is a non-blinded single-arm Phase II study of approximately 42 subjects to assess feasibility and efficacy of combined apalutamide and androgen-deprivation (ADT) first with salvage radiation therapy, followed by apalutamide and ADT with 6 cycles of docetaxel. Patients who receive at least one dose of apalutamide and ADT will be included in the analysis.

13.2 Patient Demographics and Other Baseline Characteristics

Eligible men will have recurrent PSA-only prostate cancer within 4 years of prostatectomy, and a PSA of 0.2 - 4 ng/mL in the absence of metastatic disease on CT and bone scans.

13.3 Treatments

Apalutamide and/or ADT treatment will be started on week 1. Cycle 1 Day 1 is defined as the first day of treatment with apalutamide and ADT. Apalutamide will be given 240mg by mouth daily for 36 weeks, and ADT will be administered per institutional standard. Standard external beam radiotherapy to 66-74 Gy will be administered to the prostate bed per local standard of care, which is usually a period of 6-8 weeks. Inclusion of the pelvic nodes as part of the salvage radiation plan for patients with node positive disease will be per the discretion of the treating radiation oncologist. Docetaxel 75mg/m^2 will be given every 3 weeks intravenously for 6 cycles. The entire treatment period is estimated to be 36 weeks.

Chemotherapy administration will begin at 4 WAR, at least 4 weeks, but no more than 8 weeks after the completion of radiation treatment. Scheduling of all post-radiation events, except for, ADT administration, apalutamide discontinuation, EPIC Questionnaires, and correlative plasma samples, will be based on the last day of radiation treatment.

13.4 Primary Endpoint

To describe the 36 month (3-year) progression-free survival in men with recurrent PSA only disease after prostatectomy receiving combined apalutamide and standard androgen-deprivation therapy with salvage radiation therapy **and** who have had testosterone recovery to >100 ng/dl.

13.4.1 Variable

36-month (3-year) progression-free survival time.

13.4.2 Statistical Hypothesis, Model, and Method of Analysis

The null hypothesis is that the PFS rate at 36-months among prostate cancer patients is equal to 40%. This rate was assumed to be 40% in our higher risk population, compared to the historical

control population with 36-month PFS rate of 50% [1]. One sample binomial test will be used to test whether the 36 month PFS rate is higher than the hypothesized value from the historical controls.

13.4.3 Handling of missing values, censoring, and discontinuations

Ineligible patients and patients who cancel registration before receiving any therapy will not be included in the analyses. We will follow each patient long enough to avoid censoring due to end of study, until 36 months (3 years) after last patient first visit. The binomial test assumes that other censoring than due to end of study is rare. However, we are comparing historical control with our data, which makes the study already limited and other assumptions for comparability of two data sets are necessary. The study results are just important reference and more studies will be necessary for medical decision making.

13.5 Secondary Objectives

1. To determine the proportion of men at 12, 24, and 36 months with PSA <0.1ng/mL and testosterone recovery to >100 ng/dl
2. To describe the biochemical (PSA) progression free survival over time.
3. To describe the PSA nadir (10%, 50% and 90% PSA decline as maximum response)
4. To describe the time to testosterone recovery
5. To describe the safety profile of combination apalutamide, ADT, and radiation therapy followed by apalutamide, ADT, and docetaxel
6. To describe the percentage of patients completing all treatments including salvage radiation therapy and 6 cycles of docetaxel

13.5.1 Key Secondary Objective – analysis plan

To determine the proportion of men at 12, 24, and 36 months with a PSA of <0.1 ng/mL and testosterone recovery. The frequency and proportion (and 95% confidence interval) of men at 12, 24, and 36 months with a PSA of <0.1 ng/ml and testosterone recovery will be reported.

13.5.2 Other Secondary Objectives – analysis plan

The Kaplan-Meier product-limit estimator will be used to estimate the distribution of PFS, biochemical progression free survival, time to PSA nadir, and time to testosterone recovery. The median survival times and 95% confidence intervals will be reported. In addition, descriptive statistics will be calculated for secondary endpoints of safety profile and quality-of-life (QOL) endpoints, the continuous safety and QOL endpoints will be summarized as the patient counts, mean, standard deviation, median, $25^{th}$and 75^{th} percentiles, minimum and maximum. The categorical safety and QOL endpoints will be categorized using frequencies and percentages.

13.6 Exploratory Objectives

1. To describe the quality of life of patients receiving the combination of apalutamide, ADT, and radiation therapy.

2. Archived prostatectomy specimens will be collected and stored for eventual analysis of androgen receptor target genes, androgen receptor splice variants, and epithelial-mesenchymal transition (EMT) biomarkers.

3. Plasma samples will be collected and stored for eventual analysis of circulating proteins and circulating tumor DNA.

13.6.1 Key Exploratory Objective

Descriptive statistics will be calculated for quality-of-life (QOL) endpoints, and the continuous QOL endpoints will be summarized as the patient counts, mean, standard deviation, median, 25thand 75th percentiles, minimum and maximum. The categorical QOL endpoints will be categorized using frequencies and percentages.

13.6.2 Other Exploratory Objectives

Archived prostatectomy specimens will be collected and stored for eventual analysis of androgen receptor target genes, androgen receptor splice variants, and epithelial-mesenchymal transition (EMT) biomarkers. Plasma samples will be collected and stored for eventual analysis of circulating proteins and circulating tumor DNA. The specific methodology and analysis plan has not been determined, as this will require additional funding.

13.7 Interim Analysis

Not applicable.

13.8 Sample Size Calculation

The target sample size is 42. It is primarily hypothesized that the 3-year PFS rate will be improved with the combined therapy compared to the historical control data in a similar patients setting. Based on a model and nomogram by Stephenson et al for men with recurrent disease after radical prostatectomy [1], the PFS rate at 36-months among prostate cancer patients is 50%. **This trial is designed to have more than 85% power to reject the null hypothesis of 36-month PFS rate of 40% when the true PFS rate at 36 months is 65%, with a two-sided alpha of 0.05.** The sample size needed will be 38, and factoring in a 10% drop out rate, the final sample size is 42 patients. A one sample one-sided binomial test will be used to test whether the 36-month PFS rate is larger than the hypothesized value from the historical controls.

14 ADMINISTRATIVE AND ETHICAL CONSIDERATIONS

14.1 Regulatory and Ethical Compliance

This protocol was designed and will be conducted and reported in accordance with the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice, the Declaration of Helsinki, and applicable federal, state, and local regulations.

14.2 DUHS Institutional Review Board and DCI Cancer Protocol Committee

The protocol, informed consent form, advertising material, and additional protocol-related documents must be submitted to the DUHS Institutional Review Board (IRB) and DCI Cancer Protocol

Committee (CPC) for review. The study may be initiated only after the Principal Investigator has received written and dated approval from the CPC and IRB.

The Principal Investigator must submit and obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent form. The CPC should be informed about any protocol amendments that potentially affect research design or data analysis (i.e. amendments affecting subject population, inclusion/exclusion criteria, agent administration, statistical analysis, etc.).

The Principal Investigator must obtain protocol re-approval from the IRB within 1 year of the most recent IRB approval. The Principal Investigator must also obtain protocol re-approval from the CPC within 1 year of the most recent IRB approval, for as long as the protocol remains open to subject enrollment.

14.3 Informed Consent

The informed consent form must be written in a manner that is understandable to the subject population. Prior to its use, the informed consent form must be approved by the IRB.

The Principal Investigator or authorized key personnel will discuss with the potential subject the purpose of the research, methods, potential risks and benefits, subject concerns, and other study-related matters. This discussion will occur in a location that ensures subject privacy and in a manner that minimizes the possibility of coercion. Appropriate accommodations will be made available for potential subjects who cannot read or understand English or are visually impaired. Potential subjects will have the opportunity to contact the Principal investigator or authorized key personnel with questions, and will be given as much time as needed to make an informed decision about participation in the study.

Before conducting any study-specific procedures, the Principal Investigator or designee must obtain written informed consent from the subject or a legally acceptable representative. The original informed consent form will be stored with the subject's study records, and a copy of the informed consent form will be provided to the subject.

14.4 Study Documentation

Study documentation includes but is not limited to source documents, case report forms (CRFs), monitoring logs, appointment schedules, study team correspondence with sponsors or regulatory bodies/committees, and regulatory documents that can be found in the DCI-mandated "Regulatory Binder", which includes but is not limited to signed protocol and amendments, approved and signed informed consent forms, FDA Form 1572, CAP and CLIA laboratory certifications, and clinical supplies receipts and distribution records.

Source documents are original records that contain source data, which is all information in original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source documents include but are not limited to hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic

negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial. When possible, the original record should be retained as the source document. However, a photocopy is acceptable provided that it is a clear, legible, and an exact duplication of the original document.

An electronic case report form (CRF) will be the primary data collection document for the study. Only the key personnel delegated on the delegation of authority log are permitted to make entries, changes, or corrections in the CRF. For electronic CRFs, an audit trail will be maintained by the electronic CRF management system.

14.5 Privacy, Confidentiality, and Data Storage

The Principal Investigator will ensure that subject privacy and confidentiality of the subject's data will be maintained.

To protect privacy, every reasonable effort will be made to prevent undue access to subjects during the course of the study. All research related interactions with the participant will be conducted by qualified research staff who are directly involved in the conduct of the research study.

To protect confidentiality, subject files in paper format will be stored in secure cabinets under lock and key accessible only by the research staff. Electronic records of subject data will be maintained using a dedicated web-access secure database, which is housed in an encrypted and password-protected server behind the Duke firewall. Access to electronic databases will be limited to delegated personnel. The security and viability of the IT infrastructure will be managed by the DCI and/or Duke Medicine.

Upon completion of the study, research records will be archived and handled per institutional policy.

Subject names or identifiers will not be used in reports, presentations at scientific meetings, or publications in scientific journals.

14.6 Data and Safety Monitoring

Data and Safety Monitoring will be performed in accordance with the external site Data and Safety Monitoring Plan, provided under separate cover.

14.7 Protocol Amendments

All protocol amendments must be initiated by the Principal Investigator and approved by the IRB prior to implementation. IRB approval is not required for protocol changes that occur to protect the safety of a subject from an immediate hazard. However, the Principal Investigator must inform the IRB and all other applicable regulatory agencies of such action immediately.

Though not yet required, the CPC should be informed about any protocol amendments that potentially affect research design or data analysis (i.e. amendments affecting subject population, inclusion/exclusion criteria, agent administration, etc.).

14.8 Records Retention

The Principal Investigator will maintain study-related records for a period of at least six years after study completion per Duke policy.

14.9 Conflict of Interest

The Principal Investigator and Sub-Investigators must comply with applicable federal, state, and local regulations regarding reporting and disclosure of conflict of interest. Conflicts of interest may arise from situations in which financial or other personal considerations have the potential to compromise or bias professional judgment and objectivity. Conflicts of interest include but are not limited to royalty or consulting fees, speaking honoraria, advisory board appointments, publicly-traded or privately-held equities, stock options, intellectual property, and gifts.

The Duke University School of Medicine's Research Integrity Office (RIO) reviews and manages research-related conflicts of interest. The Principal Investigator and Sub-Investigators must report conflicts of interest annually and within 10 days of a change in status, and when applicable, must have a documented management plan that is developed in conjunction with the Duke RIO and approved by the IRB/IEC.

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APPENDICES

APPENDIX A: ECOG and Karnofsky Performance Status Criteria

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

APPENDIX B: VAS Pain and Fatigue Score Criteria

15.1.1 VAS Pain Score Criteria

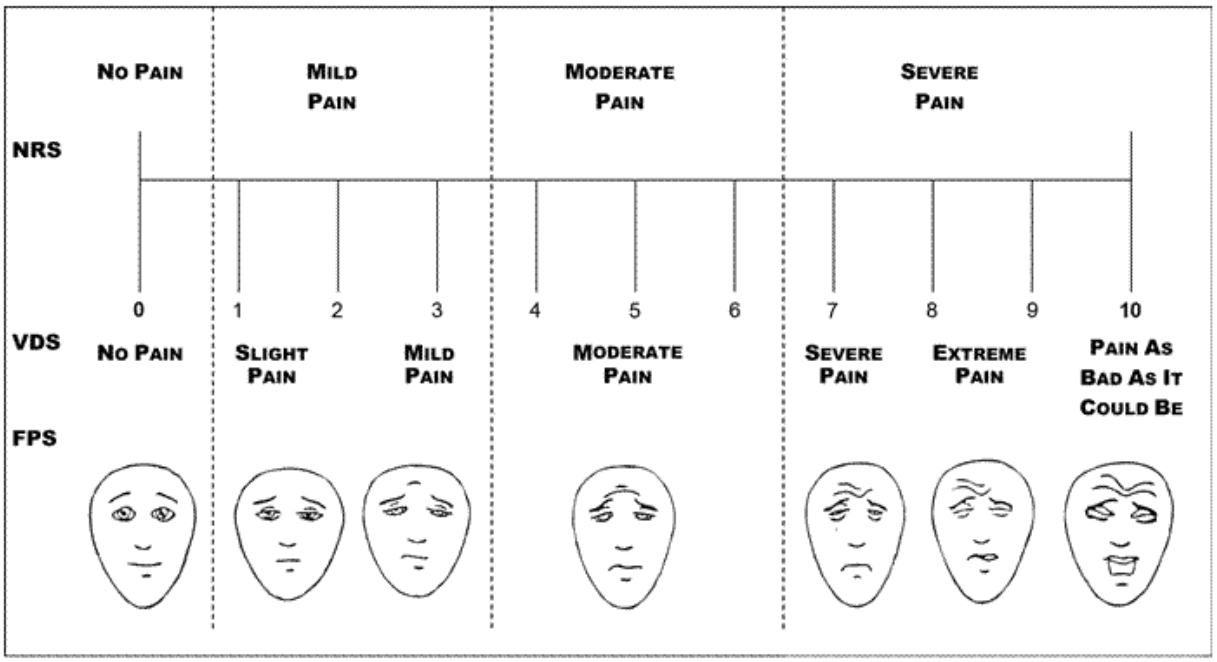

Figure.

15.1.2 Fatigue Score Criteria

Fatigue Scale	
Current Level of Fatigue	**Description**
0	No Fatigue – PI has received information regarding fatigue management
1	Mild Fatigue – Initiate Fatigue Management
2	Mild Fatigue – Initiate Fatigue Management
3	Mild Fatigue – Initiate Fatigue Management
4	Moderate Fatigue – Initiate Fatigue Management
5	Moderate Fatigue – Initiate Fatigue Management
6	Moderate Fatigue – Initiate Fatigue Management
7	Severe Fatigue – Initiate Fatigue Management
8	Severe Fatigue – Initiate Fatigue Management
9	Severe Fatigue – Initiate Fatigue Management
10	Severe Fatigue – Initiate Fatigue Management

APPENDIX C: Concomitant medications to be avoided

Strong inhibitors or inducers of CYP2C8

- Gemfibrozil
- Rifampin

Strong inhibitors or inducers of CYP3A4

- Bosentan
- Carbamazepine
- Efavirenz
- Etravirine
- Itraconazole
- Modafinil
- Nafcillin
- Phenobarbital
- Rifabutin
- Rifampin
- Rifapentine
- St. John's Wort

Substrates of CYP3A4, CYP2C9, CYP2C19

- Alfentanil
- Apixaban
- Cyclosporine
- Dihydroergotamine and ergotamine
- Fentanyl
- Midazolam
- Phenytoin and S-mephenytoin
- Pimozide
- Quinidine
- Sirolimus
- Tacrolimus
- Warfarin (If coadministration with warfarin cannot be avoided, must monitor INR as clinically indicated while on apalutamide)

APPENDIX D: Lymph node locations

Regional Lymph Nodes:

- Pelvic
- Hypogastric
- Obturator
- Iliac (external and internal)
- Sacral

Distant lymph nodes:

- Aortic
- Common iliac
- Inguinal (deep)
- Inguinal (superficial, femoral)
- Supraclavicular
- Cervical
- Scalene
- Retroperitoneal