MD Anderson IND Sponsor Cover Sheet

Protocol ID	2015-0693/MODCR003
Protocol Title	A Single Arm Study of 6-months Neoadjuvant Apalutamide Prior to Radical Prostatectomy in Intermediate Risk Patients to Reduce the Frequency of Pathologic Features that Drive Post-Operative Radiation Therapy
Protocol Phase	2
Protocol Version	2
Version Date	6/10/2022
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IND Sponsor	MD Anderson Cancer Center
IND #	137461

A Single Arm Study of 6-months Neoadjuvant Apalutamide Prior to Radical Prostatectomy in Intermediate Risk Patients to Reduce the Frequency of Pathologic Features that Drive Post-Operative Radiation Therapy

Version:	2
Study:	Collaborative, Phase 2
Sponsor:	MD Anderson Cancer Center
Supporter:	Janssen Scientific Affairs, LLC Drug and Funding Support
Product Name:	Apalutamide
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1. INTRODUCTION

1.1. Background. Approximately 50% of patients who undergo radical prostatectomy for intermediate risk prostate cancer will have one or more risk features that predict for increased risk of biochemical failure and the need for subsequent radiation and/or hormonal therapy. In 35%, the specific risk features—positive surgical margins, extra-prostatic extension, and seminal vesicle invasion--have been studied in randomized clinical trials as indications for adjuvant radiation therapy. A recent guideline by the American Urological Association states that all men with these risk features should be offered and counseled on the known benefits of adjuvant radiation to prevent disease progression and improve survival. However, there is toxicity associated with adding radiation to a previous surgery patient as well as the risk for over-treatment, i.e. many with these risk features will not fail, or possibly could undergo successful salvage therapy at the time of a known PSA recurrence. Given that traditional endpoints of study for novel systemic agents can take a minimum of 3-5 years of follow-up, it may be reasonable and a significant strategic advantage to examine a much earlier surrogate endpoint found in post-operative histopathology. If the aggregate finding of a positive surgical margin, extraprostatic extension, and/or seminal vesicle invasion should now trigger post-operative radiation, then a novel systemic agent given in the neoadjuvant space could be measured by its ability to reduce this risk, and thereby save cost and morbidity. Although LH/RH agonist and/or abiraterone acetate neoadjuvant could decrease the risk for post-operative XRT, the effects on sexual function would not be practical. Therefore apalutamide monotherapy may be the best candidate agent to test this hypothesis.

1.2. Study Outline: Single center, phase II, open label, 6 months (24 weeks) neoadjuvant apalutamide, intermediate risk prostate cancer selected for extended node dissection, comparison to contemporary (last 4 years) of similar inclusion criteria

2. FULL PROTOCOL BACKGROUND

2.1. The Challenge of Predicting Treatment Failure

In the era of PSA screening, dying of prostate cancer is less common than Incidence [1], and better predicted through recognition of high-grade disease and absence of short to intermediate term other threats to survivorship [2]. Intermediate risk prostate cancer is the most common driver of recurrent disease because it is so common in incidence [3], and more likely to undergo immediate treatment.

On the low risk end of the scale, many patients are now selected for active surveillance, and future treatment may be triggered by increase in volume of low risk, or upgrading to intermediate risk [4]. Higher volume Gleason 6 pattern on

biopsy contributes to the risk of finding higher grades at radical prostatectomy, along with multiple clinical parameters [5] and it is therefore often selected for treatment. Therefore the ratio of Gleason 6 cancer taken for surgery has decreased [6].

A review of a recent MDACC cohort of radical prostatectomy cases, stratified by risk category, demonstrated 15% low risk, 70% intermediate risk, and 15% high risk. If one assumes PSA recurrence rates are 3%, 15%, and 30% [7-8], respectively, then in absolute terms, the number of failures per 1,000 cases would be 5 low risk, **105 intermediate risk**, and 45 high risk (even if high risk failed 50%, then 75 recurrences/1,000 RPs).

Intermediate risk pathology may seem favorable with 15% biochemical recurrences; however, many higher risk features are noted at prostatectomy pathology. Of a typical cohort of 100 intermediate risk cases, 10% will have positive lymph nodes if an extended template is performed [9]. Of the remaining 90% N0, approximately 30-40% will have other higher risk features such as upgrading to Gleason 8-10, tertiary 5 Gleason pattern, upstaging to pT3, or lymphovascular invasion (MDACC—internal data, unpublished). Therefore, only approximately half of intermediate risk patients come out of surgery without an unexpected higher risk factor for recurrence. **Table 1** shows a larger breakdown of these metrics from 2 surgeons over a 4 year period and over 500 cases of confirmed clinically intermediate risk cancer that underwent Robot Assisted Radical Prostatectomy (RARP) with extended pelvic lymphadenectomy (PLND) - a good measure of the pool of patients available at MDACC, as 5 more surgeons are present now.

Table 1: 519 Clinically Intermediate Risk RARP's from 2 surgeons performing extended pelvic lymph node dissection from 1/1/09 to 11/30/12. As many as 48% will have a higher risk feature on final pathology and the remaining having organ confined Gleason 7 with no additional risk findings.

Pathologic Finding	Number	Percent
N1	54	10%
N0 pT3 stage	132	25%
N0 Gleason 8-10	24	5%
N0 Tertiary 5 pattern	50	10%
Lymphovascular Invasion		Estimated 10%
No high risk features	270	52%
Total with higher risk features	249	48%

Nomograms, such as Partin Tables, can be used for prediction of high-risk features. For typical cases with a PSA 2.6-4.0, Gleason 4+3, cT1c, predicted risk features for failure are pT3a 27%, pT3b 4% [10]. In addition, positive surgical

margins may be present in up to 10% of pT2 cases with quality surgeons, up to 25% for pT3a, and higher for pT3b (Table 2—MDACC, internal data). Taken altogether, one could project that as many as 50% of intermediate risk patients may have a pathologic higher risk features, and 35% would trigger radiation therapy consideration in the adjuvant setting.

Table 2: Standard Reporting of Risk for Intermediate Risk Prostate status post RARP and pN0 staging.

Pathologic Stage	Negative Margin	Positive Margin (%)
pT2	303	30 (9%)
pT3a	77	15 (16%)
pT3b	33	7 (18%)

To give another estimate that may be more applicable to a broader population of patients and surgeons, we changed the assumptions of the cohort for multiple surgeons, any lymph node dissection, including Nx cases (thus skews the risk more favorable), and excluding the lymphovascular invasion metric which is not uniformly reported. Of 879 cases, we noted 23% that would clearly meet guidelines for triggering an ART recommendation—Table 3. If we eliminate the Nx cases, under the assumption that they represent the lower tumor volume of the spectrum, then the ART risk rises to 30%. If one includes another 5% of patients with N1 stage, but local features that trigger ART, then the figure is 35%. Therefore, depending upon surgeon selection (i.e. PSA values, volume of biopsies, dominant 4+3), ART risk at baseline may vary from 23-40%, and ***35% may be the best assumption.***

Table 3: Intermediate Risk Prostate Cancer—879 Surgical Pathology Findings that indicate: 1) Small risk of relapse (organ confined, GS 7, N0R0), 2) ART Trigger—R1, +SV, +EPE, 3) early metastatic N1, 4) higher risk of relapse but no obvious adjuvant trigger (upgrading, tertiary 5)

Category	Number	Percent
1: Low risk/No adjuvant	562	64%
2: ART Risk	203	23%
3: Metastatic N1	56	6%
4: High risk/ No adjuvant	58	7%

2.2. Standard Therapy for Intermediate Risk Prostate Cancer

Radical prostatectomy is a standard option [8]. Whether open versus robotic surgery produces better outcomes is discussed in many publications [11-14]. Favorable differences are clear in large datasets that look at objective events captured by billing codes—blood loss, hospital stay, complications, and urinary

strictures [11-14]. However, differences in pathologic results and functional outcomes are either similar or difficult to separate from surgeon experience [15]. Use of hormonal agents is not recommended—no difference in randomized trials [8]. In current practice, robotic technique is the majority utilized at centers with access to the technology and having completed the learning curve [16].

Radiation therapy is a standard option—techniques included external and brachytherapy [8]. Shown by high quality studies, hormonal therapy is standard for 6 months (2 before, 2 during, 2 after) for external beam therapy to reduce PSA recurrences. For brachytherapy, hormonal therapy is not studied/recommended, and noteworthy that the modality is comparatively selective for patients with smaller prostate, no urinary obstructive symptoms, and favorable pelvic bone anatomy [17]. Some practitioners either do not offer brachytherapy for intermediate risk, or would offer it in conjunction with external beam boost—a combination that increases morbidity [17].

2.3. Management of High Risk Pathology after Radical Prostatectomy

Three randomized clinical trials have compared adjuvant radiation therapy to varying strategies of observation/delayed radiation [18]. In all three studies, adjuvant therapy was superior in preventing various outcomes such as PSA relapse, progression to bone metastases, use of hormonal therapy, and survival. However, in common practice, there is resistance to using adjuvant therapy due to the overtreatment, and potential side effects. Many have argued that the randomized trials did not compare adjuvant therapy to immediate salvage (i.e. PSA 0.2), and such a study is underway [19-20] and it will take several years before the results are available. Although high-risk features are commonly lumped together for study, sub-set analysis show that positive surgical margins are present in the majority of patients who benefited from the radiation. Nevertheless, even if surgery/radiation are not curative, there is increasing interest in achieving maximum local control, now that multiple agents are approved for managing castrate resistant disease, i.e. the oncologic principle of minimizing disease burden for systemic treatments [21].

Although adjuvant radiation is well tolerated compared with salvage prostatectomy, it does result in irritative bowel and urinary side effects and may inhibit recovery of sexual function. The cost is not insignificant in addition to inconvenience to the patient [18].

The AUA and ASTRO 2013 guidelines on post-RP radiotherapy now give a more forceful language to the use of ART for high risk findings [18]. They do not imply that ART must be done, but that it should be offered, and the evidence rationale carefully explained. The cornerstone statement: ***"Physicians should offer adjuvant radiotherapy to patients with adverse pathologic findings at prostatectomy including seminal vesicle invasion, positive surgical margins, or extraprostatic extension because of demonstrated reductions in biochemical recurrence, local recurrence, and clinical progression.***

(Standard; Evidence Strength: Grade A).” The complete list of guidelines statements is in appendix A

2.4. Integration of Neoadjuvant apalutamide into the MDACC Prostate Cancer Progression Model

Morphologic assessment of prostate cancer using the Gleason Score system drives most of our thinking about tumor biology [22], and leaves us with a scale that ranges from insignificant to lethal. Yet the cumulative clinical experience and published high impact trials clearly indicate the need for a better model to explain the heterogeneous behavior of this disease. Illustrative examples include:

- The PCPT trial demonstrated decreased risk of developing prostate cancer, but only in low risk disease [23].
- Androgen ablation, but not chemotherapy works better at early cancer progression [24].
- Chemotherapy is more effective at late stages, i.e. castrate resistant [25-27].
- Metastases to bone versus lymph nodes have different treatment resistance patterns [28-29]
- Although average survival response to abiraterone acetate in CRPC is 4 months, the array of responses ranges from none to > 12 months [30], and some patients also fail to respond to enzalutamide [31]
- Certain late-stage tumors exhibit anaplastic and/or neuroendocrine features, which cause bulky tumor growth and visceral metastases without significant change in PSA [32].

As a construct for piecing together these multiple observations, Logothetis et al have proposed a new biology-based prostate cancer classification [33]. The visual construct is a spiral image, which starts with the early DHT dependent phase, and proceeds through multiple turns towards the cell autonomous stage. The spiral image is also meant to explain the variations observed in progression chronology: some patients have a tightly wound spiral and go through each turn of the spiral at a rapid pace, while others have stretched out spiral that generates much slower progression turns.

The MDACC molecular classification of prostate cancer progression has 3 major categories: endocrine-driven, microenvironment-dependent, and tumor cell autonomous, and androgen signaling plays a key role in each category. The endocrine-driven stage basically represents the PCPT and REDUCE trial findings that DHT depletion inhibits certain low-grade/low-volume tumors. The critical step relevant to this proposal, is the subsequent “escape” into paracrine-driven progression, and the beginning of the proposed “progression spiral” model.

The central observation of the endocrine-to-paracrine transition is that response to androgen ablation (e.g. Lupron) is heterogeneous, ranging from months to years.

Therefore there must be biologically meaningful differences in the role of AR signaling. At this point, the numerous changes observed in oncogenes and tumor suppressor genes enter the model, leading to the acquired resistance to androgen deprivation and disease progression to its preferred sites—bone and lymph nodes. Each turn of the spiral will represent different alterations in the microenvironment, and we hope will be characterized in the future by biomarkers, but for the time being are best represented by response to therapy observations. For example, a tumor responsive to abiraterone acetate, would be its own Cyp17 sensitive turn. But abiraterone acetate is never curative in metastatic disease, indicating that patients will eventually turn out of sensitivity—some immediate, but others after a significant interval. Apalutamide's activity at the AR signaling step make it an attractive area for this study, to ask the biological question as to whether early use of the drug can pull certain tumors out of the progression.

2.5. Current Status of Androgen Receptor Inhibition Therapy in Prostate Cancer

Enzalutamide is a novel, potent inhibitor of the androgen receptor and is approved in the metastatic castration-resistant prostate cancer (CRPC) space. In the multinational PREVAIL study, a phase 3, double-blind, placebo-controlled, randomized trial, 1717 chemotherapy-naïve patients with asymptomatic or mildly symptomatic metastatic prostate cancer that progressed on androgen deprivation therapy were randomly assigned to receive 160 mg/day of enzalutamide or placebo. At the time of interim analysis, enzalutamide was shown to significantly reduce the risk of death by 29% and the risk of radiographic progression by 81% (35). The AFFIRM study [36], a phase 3, double-blind, placebo-controlled trial, 1199 men with CPRC and post chemotherapy were stratified according to performance status and pain, and then randomized 2:1 to enzalutamide at 160 mg daily (n=800) versus placebo (n=399). The study was stopped after 520 deaths, and the median overall survival (primary endpoint) was 18.4 months for enzalutamide versus 13.6 months placebo. Other endpoints were met such as PSA reduction, soft-tissue response, time to PSA progression, radiographic progression-free survival, time to first skeletal-related event, and quality of life.

Enzalutamide 160 mg daily was generally well tolerated in the AFFIRM trial. Adverse events reported by those treated with enzalutamide (160 mg daily) with an incidence of at least 5% and by at least 2% greater than by those who received placebo included fatigue (33.6% v 29.1%), diarrhea (21.4% v 17.5%), hot flush (20.3% v 10.3%), musculoskeletal pain (13.6% v 10.0%), headache (11.6% v 5.5%), insomnia (8.6% v 6.0%), anxiety (6.4% vs. 4.0%), hypertension (6.1% v 2.8%), and nasopharyngitis (5.1% v 3.0%). Other adverse events reported less commonly than 5% but that may be associated with enzalutamide treatment after careful assessment of the adverse events include: falls (4.0% vs. 1.3%), dry skin (3.6% vs. 1.3%), and pruritus (3.5% vs. 1.3%). A greater proportion of patients in the enzalutamide-treated group (4.1% vs. 1.8%) reporting the following adverse event terms: memory impairment, cognitive

disorder, amnesia, disturbance of attention, and dementia. In addition, event terms related to hallucination (visual hallucination, tactile hallucination) were reported more frequently in the enzalutamide-treated group (1.6% vs.0.3%).

Seizure is a known potential toxicity of enzalutamide. In vitro studies have shown that enzalutamide and its metaboliteM2 bind to the GABA-gated chloride channel with IC50 values of 1.2 µg/mL and 3.3 µg/mL, respectively and in a cell-based assay inhibit the channel's activity with IC50 values of 1.4 µg/mL and 1.07 µg/mL, respectively. Some compounds that inhibit the GABA-gated chloride channel are associated with seizures.

In the first clinical study of enzalutamide (S-3100-1-01), a dose-escalation study in men with CRPC with and without prior exposure to chemotherapy, the following doses were evaluated: 30, 60, 150, 240, 360, 480 (as 240 mg twice per day [BID]), and 600 (as 300 mg BID) mg/day. Three patients were reported to have dose-limiting toxicities of seizure, one each at doses of 360, 480, and 600 mg/day. The results of this study led to the selection of the clinical dose of enzalutamide of 160 mg/day. As reviewed in MDACC 2013-0332, 7 patients out of 1100 (0.6%) on clinical trials for castrate resistant disease and exposed to enzalutamide 160 mg/day reported a seizure.

Table 4: Summary of Study Drug Exposure, Adverse Events, and Deaths in Castrate Resistant Prostate Cancer (cited in from Table 3 MDACC 2013-0332, reference AFFIRM trial [31]).

Treated (Safety Population)	Enzalutamide n=800	Placebo n=399
Discontinued treatment	569 (71.1%)	380 (95.2%)
Treatment Duration (median months)	8.3	3.0
Patients with ≥ treatment emergent AE	785 (98.1%)	390 (97.7%)
Patients with ≥ treatment emergent AE (Grade 3 or higher)	362 (45.3%)	212 (53.1%
Patients with ≥ 1 serious treatment emergent AE	23 (2.9%)	14 (3.5%)
Patients with adverse events leading to study drug discontinuation	61 (7.5%)	39 (9.8%)
Deaths	308 (38.5%)	212 (53.1%

Enzalutamide is an FDA-approved option for CRPC in the post-chemotherapy and pre-chemotherapy space The PREVAIL trial [35] has now been completed. At the ASCO GU presentation in 2014, the results were presented that enzalutamide reduced risk of death by 29%, and delayed the time to chemotherapy initiation.

In both of these pivotal studies, patients had demonstrated CRPC with metastases, and were kept on LHRH agonist therapy per standard of care. In another study

more analogous to this proposal, a phase II cohort of patients with any stage hormone-naïve prostate cancer were treated with enzalutamide monotherapy, i.e. instead of standard LHRH agonist therapy. They enrolled 63 patients (38.8% with metastases at entry), and 94% completed 25 weeks and 81% completed 49 weeks of enzalutamide. As expected, testosterone levels increased 73% from baseline by week 25, and luteinizing hormone 120%. Meanwhile PSA levels decreased from baseline—80%of all patients, and 100%by week 49. The median maximum decline in PSA was 100% and mostly occurred in the first 5 weeks, while maintaining throughout 49 weeks with or without metastases.

In terms of toxicity, 9 patients discontinued treatment between weeks 25 and 49—4 due to AEs including 2 deaths, 1 protocol violation, 2 to progressive disease, and 2 withdrawn. Overall there were 7 SAE's but none drug related, and 3 deaths, none drug related. There were no seizures reported. The most frequent treatment-emergent AEs were gynecomastia (47.8%), fatigue (38.8%), nipple pain (19.4%), and hot flash (17.9%)—grade 1 or 2 severity. Others included diarrhea (11.9%), hypertension (11.9%), nausea (10.4%, and pain in extremity (10.4%). The overall rate of treatment associated AE's was 95.5%. Global health status by EORTC QLQ-C39 was unchanged from baseline to week 49, however fatigue was increased from 11.3 (SD-17.2) to 14.0 (SD-14.3) with a moderate deterioration of sexual activity functional scale of -9.8 (SD-18.0) from 28.6 (SD-24.6) baseline.

The overall conclusions were that: 1) large reductions in PSA were maintained beyond 25 weeks, 2) PSA control maintained in patients continuing to 49 weeks, 3) bone mineral density and other metabolic variables (fat body mass, lipid, glycemic profile) were not impacted, and 4) hormone level changes and common drug related AE's were consistent with potent AR inhibition. In this setting, of course, the risks and benefits would be compared to standard LHRH agonist therapy which carries risks of hot flashes and loss of libido in nearly all patients, and other side effects such as depression, fatigue, decreased bone mineral density, increased fracture risk, obesity, risk of diabetes, and risk of cardiovascular disease.

In the setting of high risk, non-metastatic prostate cancer, ongoing research is being conducted at MDACC in the investigator initiated study 2013-0332: "A Pre-Operative Study to Assess the Effects of Abiraterone acetate plus LHRH Agonist and Abiraterone acetate plus LHRH and Enzalutamide for Six Months for Prostate Cancer Patients at High-risk for Recurrence." The P.I. is Christopher Logothetis, and Co-PIs John Davis and Eleni Efstathiou. The primary objective of this actively enrolling study is to assess the difference in pathologic stage ≤ pT2 at prostatectomy between group A abiraterone acetate plus prednisone and LHRH plus enzalutamide for 6 months versus group B abiraterone acetate plus prednisone and androgen ablation for 6 months. Therefore, the GU center has an ongoing interest and expertise in delivering this drug in the pre-surgical patient, and in this protocol will be the monotherapy variation as more appropriate to the intermediate risk group.

Apalutamide is a novel agent acquired by Janssen Scientific Affairs, LLC. Apalutamide is FDA approved for non-metastatic castration resistant prostate cancer, however, is still considered investigational in this trial setting. It is in the class of enzalutamide, and also causes competitive AR inhibition through antagonistic properties that inhibits nuclear translocation of AR. It is possibly more efficacious than enzalutamide in a mouse xenograft model [37]. It has less penetration of the blood brain barrier with possibly less seizure risk. It also causes grade 1-2 fatigue and nausea. The dose from phase II trials is 240 mg [38].

Apalutamide is a new generation AR antagonist that has been developed to overcome the potential therapeutic deficiencies of first generation AR antagonists (e.g. bicalutamide).

Apalutamide is an orally available, potent and selective AR antagonist that acts by inhibiting the action of androgen, nuclear translocation of the AR and DNA binding to androgen response elements and unlike bicalutamide, it exhibits no significant agonist activity in AR-overexpressing prostate cancer cells.

2.6. Summary of Unmet Needs

Although at face value, a 15% failure rate for curative local treatments may seem too low for integrating systemic strategies, there may be potential contributions for an agent with low impact on perioperative morbidity. Beyond PSA recurrences, 25-50% of intermediate risk cohorts may have a risk feature for recurrence, and a simple method of reducing this rate, may be worthy of study for this purpose as well as long-term disease stability. Given the new AUA/ASTRO guidelines, the endpoint of ART avoidance may be a novel centerpiece of trial design—substituting neoadjuvant systemic therapy for postoperative radiotherapy.

Prostate cancer in advance stages demonstrates significant temporal heterogeneity in terms of optimal timing of events. Therefore if an agent such as apalutamide reduced the risk of needing postoperative radiation, that would be a modest benefit, but if the agent truncates some tumors from shifting into progressive disease biology, then additional benefits may be possible. The ongoing theory is that lethal potential disease will shifts from endocrine regulation to paracrine regulation. In intermediate risk disease, this shift may be pre-destined but not yet engaged, and AR blockade at this early phase may potentially add to the cure fraction of localized disease.

2.7 Biologic Rationale

Neo-adjuvant androgen ablation with radiation has demonstrated complementary response but no equivalent benefit with surgery. Several possibilities may account for these discordant observations: 1) the duration of androgen ablation in the surgical studies was insufficient, 2) the benefit reported with the combination of androgen ablation and radiation is attributed specific synergy between the modalities that do not exist with surgery and androgen ablation. Recent evidence

suggests that paracrine/intracrine androgen signaling is often a driver of resistance to androgen ablation, and not inhibited by androgen ablation. Therefore the absence of specific synergies between androgen ablation and surgery as exists with radiation may account for the apparent paradox. We wish to gain evidence in support of the hypothesis that inhibition of paracrine/intracrine androgen signaling with apalutamide will improve the efficacy of surgery in some men with prostate cancer and reduce the need for postoperative radiation.

3. STUDY OBJECTIVES

3.1. Primary: To determine whether 6 months (24 weeks) of neoadjuvant apalutamide prior to prostatectomy for intermediate risk prostate cancer results in a reduction of aggregate post-operative radiotherapy risk from 35% to 15%.

3.2. Secondary:

3.2.1. To determine the safety and tolerability of 6 months (24 weeks) neoadjuvant apalutamide followed by radical prostatectomy for intermediate risk prostate cancer
3.2.2. To estimate the frequency of clinical complete responses and “near” complete responses (currently defined as <6mm total tumor volume)
3.2.3. To characterize the molecular features of the treated prostate cancers and link them to morphologic characterization
3.2.4. To measure the 3-5 year biochemical recurrence rate and quality of life of treated patients as a baseline to inform a larger phase III trial.

4. INVESTIGATIONAL PLAN

This is a single center, phase II, open label, pre-operative study of apalutamide in patients with intermediate risk prostate cancer. The study period will consist of screening, treatment, and follow-up visits to 12 months post-operative. Additional follow-up onsite or via remote contact will determine disease-free and treatment-free status at yearly intervals 2-5. Surgery will occur within 2 weeks of completing 24 weeks of apalutamide. At the mid-way evaluations (weeks 9 or 12), patients who fail to reach a ≥50% decrease in PSA, or demonstrate suspicious changes in DRE will be considered non-responders and recommended for early surgery. For responders, the plan calls for 5 pre-operative PSA measurements that will be analyzed for rate of decline and nadir. In the post-treatment evaluation, patients will be off formal protocol at 12 months, however the investigating team will track PSA measurements for biochemical failure rates at 2, 3, 4 and 5 years (outside or inside measurements) using >0.2 ng/mL as the failure definition.

5. PATIENT POPULATION

5.1. Inclusion Criteria

- Willing and able to provide written informed consent
- Male, age > 18 years
- Histologically confirmed adenocarcinoma of the prostate
- A minimum of 10 core biopsies have been performed at baseline and available. A prostate biopsy within 6 months from screening is allowed for entry requirements. Biopsies performed within 6-12 months from screening are acceptable if the treating physician would allow treatment without further biopsy. Patients must meet intermediate risk criteria from Gleason score, T stage, and PSA value by NCCN criteria: cT2b-T2c or Gleason 7 (3+4 or 4+3) or PSA 10-20 ng/mL. In addition, the Gleason 3+4 or 4+3 must be present.
- Pathology review at MD Anderson Cancer Center. The volume of disease must be high enough for the surgeon to agree to include an extended template pelvic lymph node dissection.
- Serum testosterone > 200 ng/mL
- Patient and urologist must agree that patient is suitable for prostatectomy
- No evidence of metastases on imaging. This risk group does not require metastatic studies, but if performed they must be negative (as determined by urologist or radiologist). Suspicious lymph nodes permissible if < 10 mm.
- Eastern Cooperative Oncology Group (ECOG) Performance Status 0 or 1.
- Hemoglobin ≥ 10.0 g/dL
- Platelet count ≥ 100,000 x 10^9/microliter,
- GFR ≥45 mL/min
- Serum potassium ≥ 3.5 mmol/L
- Serum albumin ≥ 3.0 g/dL
- Able to swallow the study drug whole as a tablet
- Liver function test with serum bilirubin < 1.5x ULN and ALT and AST < 2.5 x ULN Note: In subjects with Gilbert's syndrome, if total bilirubin is >1.5 × ULN, measure direct and indirect bilirubin and if direct bilirubin is ≤1.5 × ULN, subject may be eligible
- Normal coagulation profile and no history of substantial non-iatrogenic bleeding diathesis
- Agrees to use a condom (even men with vasectomies) and another effective method of birth control if he is having sex with a woman of childbearing potential or agrees to use a condom if he is having sex with a woman who is pregnant while on study drug and for 3 months following the last dose of study drug. Must also agree not to donate sperm during the study and for 3 months after receiving the last dose of study drug.

5.2. Exclusion Criteria

- Histological variants in the primary tumor, other than adenocarcinoma; for example: neuroendocrine tumor, small cell or sarcomatoid
- Serious or uncontrolled co-existent non-malignant disease, including active and uncontrolled infection

- PSA is > than 20 ng/mL (NOTE: unless other valid PSAs were ≤ 20 and the treating physician considers a value > 20 related to the biopsy or other non-malignant cause. The treating physician must consider the patient intermediate risk in aggregate.)
- Uncontrolled hypertension. Patients with a history of hypertension are allowed provided blood pressure is controlled by anti-hypertensive therapy. Note that this is NOT a criterion related to particular BP results at the time of assessment for eligibility, nor does it apply to acute BP excursions that are related to iatrogenic causes, acute pain or other transient, reversible causes.
- Active or symptomatic viral hepatitis or chronic liver disease.
- Clinically significant heart disease as evidenced by myocardial infarction, arterial thrombotic events in the past 6 months, severe or unstable angina, or Class III-IV New York Heart Association heart failure.
- Other malignancy, except non-melanoma skin cancer, that is active or has a ≥ 30% probability of recurrence within 12 months
- History of gastrointestinal disorders (medical disorders or extensive surgery) which may interfere with the absorption of the study drug
- Known history of pituitary and/or adrenal disease (or dysfunction)
- Prior hormone therapy for prostate cancer including orchiectomy, antiandrogens, ketoconazole, or estrogens (5-α reductase inhibitors allowed), or LHRH agonists/antagonists
- Severely compromised immunological state, including being positive for the human immunodeficiency virus (HIV)
- Patients who are not appropriate surgical candidates for radical prostatectomy based on the evaluation of co-existent medical diseases and competing potential causes of death (such as but not limited to, unstable angina, myocardial infarction within the previous 6 months, or use of ongoing maintenance therapy for life-threatening ventricular arrhythmia, uncontrolled hypertension)
- History of seizure, seizure disorder, or any condition that may predispose to seizure including, but not limited to underlying brain injury, stroke, primary brain tumors, or brain metastases. Also, history of loss of consciousness or transient ischemic attack within 12 months of enrollment (Day 1 visit). Drugs may not be used which are known to decrease the seizure threshold.

6. STATISTICAL METHODS

The primary objective of the study is to determine whether 6 months of neoadjuvant apalutamide prior to prostatectomy for intermediate risk prostate cancer can result in a reduction of “aggregate pathologic risk features” (APRF) that drive post-operative radiotherapy recommendations. We hypothesize a reduction of 20% (i.e., from 35% to 15%) in terms of the rate of APRF among intermediate risk patients. Using a one-sample exact binomial test and with a two-sided type I error of 0.05, a sample size of 41 patients would provide 84% power to detect this change. We would factor up to

10% additional enrollment for compliance issues, thus the total enrollment from MDACC will be up to 45 patients.

6.1. Endpoints of Study

6.1.1. Primary Endpoint

The primary endpoint, aggregate pathologic risk features, is defined as any of the 3 pathologic staging features on a radical prostatectomy specimen that indicate elevated future risk of a patient needing pelvic radiation therapy. It can be any single or combination of the three. The three drivers per AUA/ASTRO guidelines are positive surgical margins, extraprostatic extension, and/or seminal vesicle invasion. These will be determined by a single expert genitourinary pathologist. The primary objective is to show a 20% decrease in these aggregate pathologic features.

6.1.2. Secondary Endpoints

- To determine safety and tolerability of 6 months neoadjuvant apalutamide followed by radical prostatectomy for intermediate risk prostate cancer
- To estimate the frequency of clinical complete responses (pT0) and “near” complete responses (<6mm total tumor volume)
- To characterize molecular features of treated prostate cancer and link them to morphologic characterization
- To measure 3-5 year biochemical recurrence rate and quality of life of treated patients as a baseline to inform a larger phase III trial.

6.2 Analysis Plan

All patients who receive at least 9 weeks of neoadjuvant therapy of apalutamide and undergo radical prostatectomy will be evaluable for the primary endpoint of APRF. The proportion of patients with APRF will be estimated by the number of patients with APRF divided by the total number of evaluable patients. As a primary analysis, we will estimate this proportion along with the exact 95% confidence interval. All patients who receive any dose of apalutamide will be evaluable for safety. Toxicity data will be summarized by category, grade and attribution. Frequency distributions, graphical techniques and other descriptive measures will form the basis of the analysis of safety data.

The proportion of patients having clinical complete responses and “near” complete responses will be estimated, along with the exact 95% confidence interval. The molecular features of the treated patients will be characterized using descriptive statistics and their association with the primary endpoint, APRR, or

clinical response will be assessed through logistic regression analyses. The Kaplan-Meier method will be used to assess time to biochemical recurrence and to estimate the rate of biochemical recurrence at various time points. The EPIC quality of life data will be summarized by domains and will be compared pre- and post-treatment using paired t-test or Wilcoxon signed rank test as appropriate.

6.3 Interim Analysis

The standard therapy for intermediate risk prostate cancer patients is radical prostatectomy. In the current trial, we are treating patients with apalutamide for 6 months in the neoadjuvant setting followed by the standard radical prostatectomy, thus we do not anticipate the rate of APRF(aggregate pathologic risk features) to be higher than the 35% rate with radical prostatectomy alone. Therefore, no interim analysis for futility is planned.

Monitoring for safety will be implemented in this single arm trial with the benchmark of avoiding extreme toxicities (TOX), defined as any adverse event preventing surgery or treatment-related death before surgery. Patients who voluntarily leave the trial for any reasons, or are successfully treated with dose reductions and proceed with surgery will not be counted as having a TOX. Denote the probability of TOX by θ_T and a beta(0.6, 1.4) distribution was assumed for the prior. Our stopping rule is given by the following probability statement: Pr ($\theta_T > 0.30 \mid$ data) >0.90. That is, we will stop the trial if, at any time during the study, we determine that there is more than a 90% chance that the TOX rate is more than 30%. The corresponding stopping boundaries are shown in Table 1 below and the operating characteristics of the toxicity monitoring are illustrated in Table 2. Multc Lean Desktop (v2.1.0) was used for generating the stopping boundaries and the OC table.

Table 1. Interim toxicity stopping boundaries in cohort size of 5.

Among These Number of Patients	**Stop the trial if these many patients with toxicities**
5	4-5
10	6-10
15	8-15
20	9-20
25	11-25
30	13-30
35	15-35
40	16-40
45	18-45

Table 2. The operating characteristics of toxicity monitoring.

True Toxicity Rate	Prob (stop early)	Average number of patients
0.1	0.0006	44.98
0.2	0.02	44.32
0.3	0.21	39.70
0.4	0.66	28.55
0.5	0.95	17.57

An Efficacy/Toxicity Summary will be submitted after the first five evaluable patients complete 24 weeks of study treatment, and every five patients thereafter. The Investigator is responsible for completing the summary report and submitting it to the IND Office Medical Monitor for review.

7. OUTLINE OF PATIENT ASSESSMENTS

7.1. Visit Schedule

A. Screening Phase:

1) Screening (day -30 to -1):
- Signed Informed Consent
- Medical history
- Physical exam with Digital Rectal Exam (DRE)
- Vital signs
- ECOG Performance Status
- Laboratories (Serum chemistry and hematology):
  - albumin, calcium, lactate dehydrogenase (LDH), sodium, potassium, chloride, magnesium, carbon dioxide, creatinine, BUN, AST, ALT, alkaline phosphatase, total bilirubin, total protein, glucose. Complete blood count.
- Blood Coagulation profiles:
  - Prothrombin Time (PT)
  - Partial Thromboplastin Time (PTT)
- Thyroid Stimulating Hormone (TSH) (T3 and T4 only to be done if TSH is abnormal)
- Prostate-Specific Antigen (PSA) Test and Testosterone
- Blood collection for Correlative Studies
- EKG
- MRI of the pelvis (as per physician discretion)

- Optional—Repeat prostate biopsy at MDACC if the initial biopsy was performed outside—per treating Urologist discretion, and optional tissue collection.
- Concomitant Medications Review
- Adverse Events
- EPIC Quality of Life (QOL) Questionnaire

B. Treatment Phase:

1) Week 1 Procedures: (If week 1 occurs within 2 weeks after screening visit, these procedures will not need to be repeated)
   - Physical exam with DRE if indicated by the treating physician
   - Vital signs
   - ECOG Performance Status
   - Laboratories (Serum chemistry and hematology)
   - Thyroid Stimulating Hormone (TSH) (T3 and T4 only to be done if TSH is abnormal)
   - Prostate-Specific Antigen (PSA) Test and Testosterone
   - Concomitant Medications Review
   - Adverse Events
   - Medication Dispensing (neoadjuvant apalutamide)

2) Week 5 Procedures (± 3 days):
   - Medication dispensing (neoadjuvant apalutamide)
   - Dosing compliance
   - Physical exam with DRE if indicated by treating physician
   - Vital signs
   - ECOG Performance Status
   - Laboratories (Serum chemistry and hematology)
   - Thyroid Stimulating Hormone (TSH) (T3 and T4 only to be done if TSH is abnormal)
   - Prostate-Specific Antigen (PSA) Test and Testosterone
   - Concomitant Medications Review, Adverse Events
   - Adverse Events

3) Week 9 Procedures (± 3 days):
   - Medication dispensing (neoadjuvant apalutamide)
   - Dosing compliance
   - Physical exam with DRE
   - Vital signs
   - ECOG Performance Status
   - Laboratories (Serum chemistry and hematology)

- Thyroid Stimulating Hormone (TSH) (T3 and T4 only to be done if TSH is abnormal)
- Prostate-Specific Antigen (PSA) Test and Testosterone
- Concomitant Medications Review
- Adverse Events

Note: At the mid-way evaluation (week 9), patients who fail to reach a 50% decrease in PSA, or demonstrate suspicious changes in DRE will be considered non-responders and recommended for early surgery.

4) Week 12 Procedures (± 3 days):

Optional: Repeat prostate biopsy per urologist's discretion. Acceptable to perform at the week 9 or week 17 visit if requested for patient travel needs.

5) Week 17 Procedures (± 3 days):

- Medication dispensing (neoadjuvant apalutamide)
- Dosing compliance
- Physical exam with DRE if indicated by treating physician
- Vital signs
- ECOG Performance Status
- Laboratories (Serum chemistry and hematology)
- Thyroid Stimulating Hormone (TSH) (T3 and T4 only to be done if TSH is abnormal)
- Prostate-Specific Antigen (PSA) Test and Testosterone
- Concomitant Medications Review
- Adverse Events
- EPIC Quality of Life (QOL) Questionnaire
- Blood collection for Correlative Studies

6) Week 24/ Pre-op/ End of Treatment Visit Procedures (± 3 days):

- Dosing compliance
- Physical exam with DRE
- Vital signs
- ECOG Performance Status
- Laboratories (Serum chemistry and hematology)
- Thyroid Stimulating Hormone (TSH) (T3 and T4 only to be done if TSH is abnormal)
- Prostate-Specific Antigen (PSA) Test and Testosterone
- Concomitant Medications Review
- Adverse Events
- EPIC Quality of Life (QOL) Questionnaire

- Blood collection for Correlative Studies

7) Radical Prostatectomy (2 weeks (+/-7 days) after last dose of study drug):
   - Perioperative data collection
   - Pathology Tissue Collection

C. Follow-up Phase:

1) Post Radical Prostatectomy: (within 30 days post-op +/- 3 days)
   - Physical exam and DRE if indicated by treating physician
   - Assess complications from surgery at 30 days using Clavien methodology (Table 5).
   - Adverse Events
   - Epic Quality of Life (QOL) Questionnaire
   - PSA, testosterone

2) Six Months Post-Radical Prostatectomy: **(+/- 4 weeks)**
   a. Update complications to 90 day window
   b. Use of adjuvant/salvage therapies
   c. EPIC Quality Of Life (QOL) Questionnaire
   d. PSA, testosterone

3) Twelve Months Post Radical Prostatectomy—Last on-site Study Visit: **(+/- 4 weeks)**
   a. EPIC Quality Of Life Questionnaire
   b. PSA, testosterone
   c. Use of adjuvant/salvage therapies
   d. Update complications

4) Post Study Follow-up Data Collection (on-site or remote)**:(+/- 4 weeks)**
   a. Intervals 24, 36, 48, 60 months
   b. PSA/biochemical relapse-free status
   c. Use of adjuvant/salvage therapies
   d. Update complications
   e. Epic Quality of Life (QOL) Questionnaire

7.2 Details of Assessment Methods:

7.2.1 QOL assessments per above: may be written or via tablet. Surveys will consist of the Expanded Prostate Cancer Index (EPIC), including the SF-12. As an alternative, the data may be collected using an electronic tablet method. Any post-operative surveys occurring after the incidence of additional post radical prostatectomy radiation or hormonal therapy will continue but be so designated for analysis.

7.2.2 Complications: use Clavien reporting system shown in Table 5.

Table 5: Classification of Surgical Complications [34]

Grades	**Definition**
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Allowed therapeutic regimens are: drugs such as antiemetics, antipyretics, analgesics, diuretics and electrolytes, and physiotherapy. This grade also includes would infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade III	Requiring surgical, endoscopic or radiological intervention
Grade IIIa Grade IIIb	Intervention not under general anesthesia. Intervention under general anesthesia.
Grade IV	Life-threatening complication (including CNS complications)* requiring IC/ ICU management.
Grade IVa Grade IVb	Single organ dysfunction (including dialysis) Multiorgan dysfunction
Grade V	Death of a patient
Suffix “d”	If the patient suffers from a complication at the time of discharge, the suffix “d” (for “disability”) is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.
*Brain hemorrhage, ischemic stroke, subarachnoid bleeding, but excluding transient ischemic attacks, CNS, central nervous system; IC, intermediate care; ICU, intensive care unit.	

Table 6: Study Calendar

Evaluation	Screening[a]	Wk 1	Wk 5	Wk 9	Wk 12	Wk 17	Wk 24/ Preop[h]	Surgery	30 d post op	6 mo	12 mo	2 yr	3 yr	4 yr	5 yr
			+/- 3 days	+/- 3 days	+/- 3 days	+/- 3 days	+/- 3 days		+/- 3 days	+/- 4 wks	+/-4 wks	+/-4 wks	+/-4 wks	+/- 4 wks	+/-4 wks
Medical History	X														
Physical Exam w/DRE	X	X[b]	X[b]	X		X[b]	X		X[b]						
Vital Signs	X	X	X	X		X	X								
ECOG PS	X	X	X	X		X	X								
EKG	X														
MRI Pelvis	X[j]														
Concomitant Medication	X	X	X	X		X	X			X[c]	X[c]	X[c]	X[c]	X[c]	X[c]
AE	X	X	X	X		X	X		X						
Dosing compliance			X	X		X	X								
Serum chemistry/ hematology[d]	X	X	X	X		X	X								
PT/PTT	X														
TSH[e]	X	X	X	X		X	X								
PSA	X	X	X	X		X	X		X	X	X	X	X	X	X
Testosterone	X	X	X	X		X	X		X	X	X				
EPIC QOL	X					X	X		X	X	X	X	X	X	X
Blood Correlative Studies[i]	X					X	X								
Tissue procurement	X[f]				X[f]			X							
Complications, post op therapy[g]									X	X	X	X	X	X	X

a: Within 30 days prior to initiation of study treatment
b: Physical exam and DRE if indicated by treating physician
c: Use of adjuvant/salvage therapies only, such as hormones or radiation
d: albumin, calcium, lactate dehydrogenase (LDH), sodium, potassium, chloride, magnesium, carbon dioxide, creatinine, BUN, AST, ALT, alkaline phosphatase, total bilirubin, total protein, glucose, complete blood count with differential
e: T3/T4 testing to be done if abnormal TSH or clinically indicated
f: Optional collection of tissue for research purposes at time of prostate biopsy at baseline and week 12, if indicated by treating physician. If patient is not available to return to clinic on week 12 for repeat biopsy, this could be done either during week 9 or week 17 visits. Please note that tissue collection at time of radical prostatectomy is mandatory
g: Record post-operative complications using Clavien method within 30 days and 90 days, and any long-term complications related to surgery.

h: Early treatment discontinuation patients will complete all the pre-op assessments within 30 days post treatment discontinuation as their last study visit
i: Including plasma, whole blood and serum samples as indicated in section 9.1
j. As per physician discretion

8. TREATMENT PLANS

8.1. Six-Months Neoadjuvant apalutamide (24 weeks)

8.1.1. Subjects will be instructed to take 240 mg per day orally of apalutamide, 4 tablets (60 mg each). Apalutamide may be taken with or without food and close to the same time each day as possible.

8.1.2. Study Drug Procedures

8.1.2.1. Apalutamide has the chemical name (4-[7-(6-Cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide)

8.1.2.2. Apalutamide will be provided packaged in individual bottles for patient assignment at corresponding study visits. Information on labels will comply with applicable local regulations. Site pharmacist or medically qualified staff will dispense the study treatment to each patient in accordance with the protocol.

8.1.2.3. The study treatment must be stored in a secure area and administered only to patients entered into the clinical study in accordance with the conditions specified in this protocol. Bottles of study treatment should be stored at 20°C to 25°C (68°F to 77°F); excursions are permitted to 15°C to 30°C (59°F to 86°F) in the original container/closure with the cap on tightly; it should never be refrigerated. Additional information is provided in the apalutamide Investigator's Brochure.

8.1.2.4. Current ICH GCP Guidelines require the investigator to ensure that study drug deliveries are received by a responsible person (e.g. pharmacist), and

- that such deliveries are recorded
- that study drug is handled and stored safely and properly, and should explain the correct use/handling of the investigational product to each subject.
- that study drug is only dispensed to study subjects in accordance with the protocol that any unused study drug is returned or standard procedures for the alternative disposition of unused study drug are followed.

Drug inventory and accountability records for the study drugs will be kept by the investigator/ pharmacist. Study drug accountability throughout the study must be documented. The following guidelines are therefore pertinent:

- The investigator agrees not to supply study drugs to any persons except the subjects in this study.
- The investigator/pharmacist will keep the study drugs in a pharmacy or other locked and secure storage facility under controlled storage conditions, accessible only to those authorized by the investigator to dispense these test drugs.
- A study drug inventory will be maintained by the investigator/pharmacist. The inventory will include details of material received and a clear record of when they were dispensed and to which subject.
- At the conclusion or termination of this study, the investigator/pharmacist agrees to conduct a final drug supply inventory and to record the results of this inventory on the Drug Accountability Record. It must be possible to reconcile delivery records with those of used and returned medication. Any discrepancies must be accounted for. Appropriate forms of deliveries and returns must be signed by the person responsible.
- Returned or expired study drug will be destroyed on site per MDACC Investigational Pharmacy policies.

Apalutamide will be provided by Janssen Scientific Affairs, LLC and will be stored and handled according to the manufacturer specifications and the pharmacy standards of operation.

8.1.3. Study Drug Dose Reductions or Discontinuation of Study Drug

In subjects who experience toxicity who cannot be ameliorated by the use of adequate medical intervention, dose reductions can be performed. Patients who experience a Grade 3 or greater toxicity considered to be related to apalutamide that cannot be ameliorated by the use of adequate medical intervention should have their treatment interrupted until the toxicity improves to a Grade 1or baseline. Patients may subsequently be re-started on study drug at a reduced dose as per the discretion of the Principal Investigator. If study drug needs to be discontinued for more than 30 days due to toxicities, the patient should be discontinued from the study treatment phase, all pre-op visit procedures should be followed, and the patient scheduled to undergo surgery as soon as recommended by medical team.

Apalutamide Dose Levels

Dose Level	Total Daily Dose	Number of 60 mg Tablets (QD)
0	240 mg	4
-1	180 mg	3
-2	120 mg	2

8.1.4. Medications—Drugs and Therapies

8.1.4.1. Medication taken within four weeks prior to treatment initiation must be captured in the medical record. All concomitant medications will be documented at each visit while patient is taking apalutamide, and at the time of early study treatment discontinuation. Only adjuvant/salvage therapies will be documented during the follow-up phase of the study. Standard concomitant medications associated with surgery and post-op care will not need to be captured for the purpose of this study unless it is given to treat a reportable AE.

8.1.4.2. No other new systemic therapy or new radiotherapy for treatment of prostate cancer is permitted while subject is on the active phase of study treatment or prior to surgery. Adjuvant/salvage therapies after surgery could be initiated if necessary at the discretion of the treating physician.

8.1.4.3. As a class effect, AR antagonists have been associated with seizures due to an off-target mechanism of action (gamma amino butyric acid chloride channel [GABAA] inhibition). Drugs known to lower the seizure threshold or cause seizures are prohibited and a representative list is included below. A medication list review must be done by the clinical team if the patient is on medications from the below class list:

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

8.1.4.4. Medications/Supplements, which are NOT RECOMMENDED while on study (monitor for increased toxicity/potential drug interactions):

- Apalutamide (and its main metabolite, ARN000308) are metabolized primarily by human CYP3A4 or CYP2C8, thus co-administration with any of the following agents has the potential to affect the PK of apalutamide and alternative therapies should be used when available:
  - Strong CYP3A4 inhibitors: itraconazole, clarithromycin, erythromycin, diltiazem, verapamil, delavirdine, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole, grapefruit; 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
    - Strong CYP2C8 inducers: rifampin
  - Apalutamide may also induce CYP3A4; therefore, caution should be taken when administered in conjunction with CYP3A4 substrates that have a narrow therapeutic index
  - Apalutamide may also induce other PXR-regulated enzymes and transporters such as CYP2C8, CYP2C9, CYP2C19, UDP glucuronosyl transferase (UGT), and P-glycoprotein. Coadministration of apalutamide withsubstrates of CYP3A4, CYP2B6 (eg, efavirenz, bupropion), CYP2C8 (eg, repaglinide, pioglitazone), CYP2C9 (eg, warfarin, tolbutamide), CYP2C19 (eg, omeprazole, lansoprazole), UGT (eg, levothyroxine, valproic acid) and P-glycoprotein (eg, digoxin, dabigatran etexilate, colchicine) may result in decreased concentrations and loss of efficacy.
  - The potential for drug-drug interaction between apalutamide and warfarin (e.g., Coumadin) is unknown at present. If a patient is taking warfarin, re-assess PT/INR as clinically indicated and adjust the dose of warfarin accordingly.
  - Due to possible resistance mechanisms which may be contributed by glucocorticoid receptor signaling, concurrent use of corticosteroids during the study is not recommended; short term use (≤ 4 weeks) will be allowed if clinically indicated, however, its use must be tapered off as soon as possible.
  - Avoid pomegranate

Reference for a comprehensive list of potential drug to drug interactions:
http://medicine.iupui.edu/clinpharm/ddis/main-table/

8.1.4.5. Treatment Compliance: Study drug accountability will be performed to document compliance with the dosing regimen. Subjects will be asked to bring back all remaining study drug at each study visit for drug accountability.

8.1.4.6. Emergency Procedures and Overdose: There is no specific antidote for an overdose of apalutamide. Patients who develop adverse reactions from a suspected overdose should receive appropriate symptomatic treatment.

8.2. ADVERSE EVENTS

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide.

8.2.1. Adverse Event Definitions and Classifications

Adverse Event

Adverse Event (AE) – Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research in which a subject is administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment.

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.

Expected AE - Any AE with specificity or severity that is consistent with the current Investigator Brochure (IB) or consistent with the risk information described in the Informed Consent Document (ICD) or general investigational plan.

Serious Adverse Event

Serious Adverse Event (SAE) – Any AE associated with the subject's participation in research that:

- results in death;
- is life-threatening, (places the subject at immediate risk of death from the event as it occurred). An adverse event or suspected adverse reaction is considered ''life-threatening'' if, in the view of Principal Investigator, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death;
- results in inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity;
- is a suspected transmission of any infectious agent via a medicinal product

- results in a congenital anomaly/birth defect; or
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, the IND Office.

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

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.

Unexpected (Unanticipated) AE - Any AE, with specificity or severity that is not consistent with the current IB, or the applicable product reference safety information, or not consistent with the risk information described in the informed consent document or general investigational plan.

8.2.2. Attribution Definitions

The following classification will be used to determine whether an AE is related to the study drug, CT-011:

- Definite - It is clearly related
- Probable - It is likely related
- Possible - It may be related
- Unlikely - It is doubtfully related
- Unrelated - It is clearly NOT related

Definitely related – Events directly or indirectly attributed to study drug, and/or study participation. Events occurring with sufficient frequency to suggest that they are not random. The event follows a temporal sequence from the time of drug administration and follows a known response pattern to the study drug. It occurs immediately following the study drug administration, improves on stopping the drug, or reappears on repeat exposure.

Probably related – The event follows a reasonable temporal sequence from the time of drug administration, and follows a known response pattern to the study drug and cannot be reasonably explained by other factors. There is a reasonable response to withdrawal of the drug. Rechallenge information is not available or advisable.

Possibly related – The event has a reasonable temporal relationship to the study drug administration and follows a known response pattern to the study drug. However, a potential alternate etiology may be responsible for the event. The effect of drug withdrawal is unclear. Rechallenge information is unclear or lacking.

Unlikely – The adverse event is doubtfully related to the investigational agent.

Unrelated – Events that would occur regardless of study participation, including events that are clearly random occurrences. If the frequency of the event suggests a possible connection to the study intervention, then it should be considered related. If the event is clearly related to other factors, such as a patient's clinical

state, therapeutic interventions, or concomitant medications, the event would be considered unrelated to therapy.

8.2.3. Special Reporting Situations

When a report contains a Janssen product, an identifiable patient, and identifiable reporter, the following events represent Special Reporting Situations:

- Drug exposure during pregnancy (maternal and paternal)
- overdose of a Janssen medicinal product
- pregnancy exposure (maternal and paternal)
- exposure to a Janssen medicinal product from breastfeeding
- suspected abuse/misuse of a medicinal Janssen product
- inadvertent or accidental exposure to a medicinal Janssen medicinal product
- any failure of expected pharmacological action (i.e., lack of effect) of a Janssen medicinal product
- unexpected therapeutic or clinical benefit from use of a Janssen medicinal product
- medication error involving a Janssen product (with or without patient exposure to the medicinal Johnson & Johnson product, e.g., name confusion)
- suspected transmission of any infectious agent via a medicinal product.

These safety events may not meet the definition of an adverse event; however, from Janssen Scientific Affairs, LLC perspective, they are treated in the same manner as adverse events. Special situations should be recorded on the Adverse Event page of the Department of Urology database.

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 Scientific Affairs, LLC within 24 hours of becoming aware of the event.

8.2.4. Adverse Events Reporting

All Adverse Events

General guidelines – Toxicity will be scored using CTC AE Version 4.0 for toxicity and adverse event reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP homepage (http://ctep.info.nih.gov). All appropriate treatment areas should have access to a copy of the CTC AE Version 4.0. All adverse clinical experiences must be recorded according to the table “Recommended Adverse Events Recording Guidelines”, after they were documented in the treating

physician's clinic note, utilizing the NCI CTC v 4.0 to determine terminology and grade. Adverse events will be recorded following the first exposure to study drug until 30 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier. For discontinued patients, follow up on serious adverse events will be conducted up to 30 days from last treatment of study drug.

When an adverse event occurs, the following information and assessments should be recorded:

i) The signs, symptoms, or diagnosis of the event.
ii) The date of the event.
iii) The adverse event severity, using the criteria outlined above.
iv) The relationship of the event to the study drug as outlined above.
v) The description of any action taken regarding study drug disposition.
vi) Any required therapy, medication, treatment, or diagnostic procedure.

The Principal Investigator (PI) or physician designee is responsible for the appropriate medical management of all adverse events. The PI or physician designee must evaluate each adverse experience for its seriousness and determine attribution to study drug.

The investigator must appraise all abnormal laboratory results for their clinical significance. If any abnormal laboratory result is considered clinically significant, the investigator must provide details about the action taken with respect to the test drug and about the patient's outcome.

The investigator must appraise all evaluation test results for their clinical significance. If any abnormal evaluation test result is considered clinically significant, the investigator must provide details about the action taken with respect to the test drug and about the patient's outcome. Any evaluation test that is not considered clinically significant will not be captured as an adverse event (AE).

Serious Adverse Events

All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

All life-threatening or fatal events, that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.

Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.

Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event. Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

Reporting to FDA:
Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

Maintenance of Safety Information:

Safety information will be maintained in a clinical database/repository in a retrievable format. At a minimum, at the end of the treatment phase (="last patient off treatment") as well as the end of the follow-up phase (="last patient out") of the Study, the Principal Investigator shall provide all adverse events, both serious and non-serious, in report format. However, in certain circumstances more frequent review of the safety data may be necessary, e/g/ to fulfill a regulatory request, and as such the data shall be made available within a reasonable timeframe at Janssen Scientific Affairs' request.

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

Procedures for Reporting Safety Data and Product Quality Complaints (PQCs) for Janssen Medicinal Products to Janssen Scientific Affairs, LLC

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 Department of Urology database and in the subject's source records. Investigators must record in the

Department of Urology database (REDCap) 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.

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 PRINCIPAL INVESTIGATOR will transmit all SAEs and special situations following exposure to a Janssen product under study in a form provided by Janssen Scientific Affairs, LLC in accordance with an acceptable transmission method, in English **within 24-hours of becoming aware of the event(s).**

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 Scientific Affairs, LLC using the Janssen/MedWatch ’s Serious Adverse Event Form

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

- The 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 Scientific Affairs, LLC using an acceptable transmission

method within **24 hours of such report or correspondence being sent to applicable health authorities.**

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 Scientific Affairs, LLC, and are mandated by regulatory agencies worldwide. Janssen Scientific Affairs, LLC 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 Scientific Affairs, LLC 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 Scientific Affairs, LLC according to the serious adverse event reporting timelines. A sample of the suspected product should be maintained for further investigation if requested by Janssen Scientific Affairs, LLC.

Pregnancy

All initial reports of pregnancy must be reported to Janssen Scientific Affairs by the study-site personnel within 24 hours of their knowledge of the event. Abnormal pregnancy outcomes (eg, spontaneous abortion, stillbirth, and congenital anomaly) are considered serious adverse events and must be reported as a Serious Adverse Event.

Because the effect of the study drug on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported by the study-site personnel within 24 hours of their knowledge of the event.

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

Transmission Methods

The following methods are acceptable for transmission of safety information to Janssen Scientific Affairs, LLC:

- Electronically via Janssen SECURE Email service (preferred) - RA-OMPUS-COBS_Cen_E@its.jnj.com

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

Abnormal Laboratory Results

The criteria for determining whether an abnormal laboratory test result should be reported as an adverse event are as follows:

1. Test result is associated with accompanying symptoms, and/or
2. Test result requires additional diagnostic testing or medical/surgical intervention (merely repeating an abnormal test, in the absence of any of the above conditions, does not meet criteria for reporting and an AE), and/or
3. Test result leads to a change in study dosing or death from the study, significant additional concomitant drug treatment or other therapy, and/or
4. Test result leads to any of the outcomes included in the definition of a serious adverse event, and/or
5. Test result is considered to be an adverse event by the investigator

Any abnormal test result that is determined to be an error does not require reporting as an adverse event, even if it did meet one of the above conditions except for condition #4. Clinically significant laboratory results must be recorded in the Department of Urology database.

Dose Modification/Toxicity Management

Subjects who experience a Grade 3 or greater toxicity considered to be related to apalutamide that cannot be ameliorated by the use of adequate medical intervention should have their treatment interrupted until the toxicity improves to a Grade 1 or baseline. Subjects may subsequently be re-started on study drug at a reduced dose follow a discussion between the Principal Investigator. Dose modifications are provided as guidance and should not replace the investigator's own clinical judgment.

Toxicity	Dose of JNJ-56021927 (assuming 240 mg/day dosing)
Grade 1 or 2	If a Grade 2 Toxicity has not resolved to Grade≤1 after 30 days, study drug will be discontinued. For all other Grade 1 or 2 Toxicities there will be no change.
(First Occurence) ≥Grade 3	Hold until Grade 1 or baseline, resume at full dose
First Recurrence ≥Grade 3	Hold until Grade 1 or baseline, resume at 180 mg (3 tablets)
Second Recurrence ≥Grade 3	Hold until Grade 1 or baseline, resume at 120 mg (2 tablets)
Third Recurrence ≥Grade 3	Discontinue
First occurrence of seizure of any grade or Grade 4 neurotoxicity	Discontinue

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]
	  ○ Topical steroid cream AND
	  ○ Oral Antihistamines
	• Monitor for change in severity[a]

Grade 2 (or symptomatic Grade 1)[b]	• Hold apalutamide for up to 28 days
	• Initiate dermatological treatment[a]
	  ○ Topical steroid cream AND
	  ○ Oral Antihistamines
	• Monitor for change in severity[a]
	  ○ If rash or related symptoms improve, reinitiate apalutamide when rash is Grade≤1. Consider dose reduction at a 1 dose level reduction[c].

Grade ≥3[d]	• Hold apalutamide for up to 28 days
	• Initiate dermatological treatment[a]
	  ○ Topical steroid cream AND
	  ○ Oral Antihistamines AND
	  ○ Consider short course of oral steroids
	• Reassess after 2 weeks (by site staff), and if the rash is the same or has worsened, initiate oral steroids (if not already done) and refer the subject to a dermatologist
	  ○ Reinitiate apalutamide at a 1 dose level reduction[e] when rash is Grade≤1.

	○ If the dose reduction will lead to a dose less than 120mg, the study drug must be stopped (discontinued) • If after 28 days, rash has not resolved to Grade≤1, contact Janssen to discuss further management and possible discontinuation of study drug.

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

a Obtain bacterial/viral cultures if infection is suspected
b Subject presents with other rash related symptoms such as pruritus, stinging, or burning
c 1 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 Janssen.

Criteria for Discontinuation of Study Treatment

To discontinue Study Treatment, either of the criteria below must be met:

- The patient completed 24 weeks of study treatment;
- Patients who fail to reach a 50% decrease in PSA or demonstrate suspicious changes in DRE at mid-way evaluation (week 9);
- Sustained side effects: patients who have sustained toxicities, such as hyperglycemia or hypertension that do not return to NCI CTCAE (version 4.0) grade 1 or less within 30 days despite appropriate medical management, should be discontinued from the study treatment phase. All end-of-study treatment procedures should be conducted. The patient will be followed to the pre-op visit;
- Dosing noncompliance: study treatment administration and dosing compliance will be assessed on Day 1 of all cycles, and at Pre-surgery/End of Treatment Visit. A count of study treatment will be conducted during this visit and patient dosing compliance will be assessed. If dosing compliance is not >75% in the absence of toxicity, patient should be re-instructed regarding proper dosing procedures and continue in the protocol. Subsequent dosing compliance procedure will be conducted at each study visit. If a patient misses 14 or more doses within 4 weeks, the patient should be discontinued from the study treatment phase. All end-of-study treatment procedures should be followed. The patient will be followed to the pre-op visit
- Initiation of new anticancer treatment: patients will be discontinued from the study treatment when investigator, in his or her judgment, determines new treatment for prostate cancer is warranted. All end-of-study treatment procedures should be conducted and the patient will be followed to the preo-op visit
- Administration of prohibited medications: the patient will be discontinued from the protocol treatment when prohibited drug is administered (Section 8.1.4.3). All end-of-study treatment procedures should be conducted and the patient

will be followed to the pre-op visit. Supportive care medications are permitted with their use following institutional guidelines. The concurrent administration of other anticancer therapy, including cytotoxic, hormonal (except LHRHa), or immunotherapy is prohibited during study treatment phase. Use of other investigational drug therapy for any reason is prohibited

- Patient met Grade 4 criteria for elevated Liver Function Tests or the criteria for dose discontinuation of non-mineralocorticoid based side effects.
- Subjects experiencing toxicity considered to be related to the use of for which more than two dose reductions areneeded will require discontinuation of study drugs.

Withdrawal from Study

An investigator may withdraw a patient from the study at any time based on clinical judgment or if a patient withdraws consent. In this event, the reason(s) for withdrawal must be documented and clarification if withdrawal of consent includes Post-Radical Prostatectomy Evaluation data collection. A patient's decision to take part in the study is voluntary and he may choose not to take part in the study or to stop taking part at any time. If he chooses not to take part or to stop at any time, it will not affect his future medical care or medical benefits. A patient may withdraw from study treatment phase for any reason. In general, subjects who withdraw will not be replaced unless the number of completed subjects falls below the estimated sample size required to provide the desired precision.

Radical Prostatectomy

Within 2 weeks of stopping apalutamide, patients will undergo planned radical prostatectomy. The surgical access is per the attending surgeon discretion such as open or robot-assisted. The extent of primary surgery such as inclusion/exclusion of the neurovascular bundles and bladder neck is per attending surgeon discretion. The seminal vesicles should be completely removed if possible. The lymph node dissection should attempt to consist of an extended template, specifically: a) obturator fossa, b) external iliac from the medial aspect of the external iliac artery and clearing the triangular space at the junction of the external and internal arteries, c) hypogastric artery to include a continuation of the obturator fossa beneath the obturator nerve. The protocol does not require the surgeon to deviate from his/her common practice and judgment in the event unexpected grossly enlarged lymph nodes are encountered.

9. CORRELATIVE STUDIES

The specimens collected in the context of this protocol are blood and tissue. These will be stored in a manner that will allow us to address the secondary aims in this protocol.

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

All specimens will be prospectively encoded with de-linked numbers such that the receiving lab will not have access to patient identifiers. Investigators involved in this project will ensure confidentiality of patients by restricting access to the GU Research Laboratory database in which the unique identification numbers cross-referenced to the MDACC patient medical record number will be kept. Clinical information will be accessed by investigators using the institutional electronic medical record, which stores clinical information and care reports of patients who are being treated at MDACC. Access to the MDACC electronic medical record is restricted with a security password. Any individual patient's information will not be reused or disclosed to any other person or entity, or for other research. All requests for use of this material must be in the context of IRB approved protocols.

Caveolin-1 (Cav-1), a major structural component of caveolae, is secreted by prostate cancer cells and associated with malignant progression through multiple mechanisms and signaling pathways (Thompson TC et al. Prostate Cancer Prostatic Dis 13:6, 2010). We have shown that Cav-1 is implicated in the transition from high-grade prostatic epithelial neoplasia to prostate cancer through c-Myc regulation and Akt signaling induction (Yang G et al. Mol Cancer Res 10:218, 2012). Other studies show that Cav-1 levels rise during prostate cancer progression and mediate resistance to hormone therapy (Nasu et al. Nat Med 4:1062, 1998, Karantanos T et al. Oncotarget 7: No. 29, 2016) by inducing glycolytic activities in prostate cancer cells and promoting hormone resistance under androgen deprivation through upregulation of acetyl-CoA carboxylase 1 and fatty acid synthase (Karantanos T et al. Oncotarget 7: No. 29, 2016, Tahir SA et al. Cancer Res 73:1900, 2013). Finally, investigations show serum Cav-1 associated with high-risk prostate cancer (Gumulec J et al. Oncol Rep 27:831, 2012); biochemical recurrence after prostatectomy (Tahir SA et al. Clin Cancer Res 12:4872, 2006); and, when levels are high, with castration-resistant prostate cancer rather than with hormone-naive disease (Sugie S et al. Anticancer Res 33, 1893, 2013).

Sample Logistics

Prostatectomy tissue from surgery follows standard pathology procedures including room temperature transportation to pathology (attached to MDACC OR) for fresh cut by GU pathologist. Serum samples drawn in the clinic will be transported by MDACC clinical research staff to the Eckstein lab—Mays Clinic, 7th floor, MDACC inside GU medical oncology clinic. Blood will be stored in the Eckstein lab; and tissue in Alexander lab, Tan zone on MDACC main campus. Samples will be stored approximately for 10 years after following protocol completion.

9.1 Biomarker Plan

A. Blood and Derivatives

1. Blood (PAXgene) will be collected from all subjects at time points indicated in the T&E schedule to assess mRNA for ARv7 and other high risk molecular markers such as SRD5A1, FOXA1, HOXB13, KLK3 (Labcorp)

2. Blood will be collected for assessment of germline DNA repair gene mutations (Futreal Lab – MDACC)

3. Plasma will be collected for CAV-1 assessment at pretreatment and prespecified timepoints (Thompson Lab- MDACC)

B. Formalin-fixed paraffin-embedded (FFPE) tumor blocks or tumor slides from biopsy and radical prostectomy specimens will be collected from all subjects in this study to evaluate expression of markers using prespecified methods: Radical Prostatectomy specimens will be also employed.

1. A custom mRNA panel includes markers previously identified as markers predictive of response to abiraterone acetate in AA-302 study (Ricci D. 2014 ASCO). This will be conducted on pretreatment specimens (biopsies) (Labcorp)

2. Protein assessment of markers of interest by immunohistochemistry (IHC) These markers include but will not be limited to the following: AR-N, AR (C19), AR-V7, PSA-GR, Ki67, p-cMET, pSrc, CD56, Chromogranin A, NKX3.1, Rb p53, ATM, PTEN, and immune markers. Additional markers assessment will be assessed based on available data and findings at the time of analysis and will be dependent on tissue availability. Protein assessment will be performed both on biopsy and radical prostatectomy specimens based on availability (Alexander Lab – MDACC)

3. DNA sequencing will be performed for assessment of somatic DNA repair gene alterations. This will be conducted on pretreatment specimens unless unavailable in which case radical prostatectomy specimens will be used (Alexander /Futreal Labs-MDACC).

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