Study Title: A Pre-Operative Study to Assess the Effects of Abiraterone acetate plus LHRH Agonist and Abiraterone acetate plus LHRH Agonist and Enzalutamide for Six Months for Prostate Cancer Patients at High-risk for Recurrence

Study:	Investigator Initiated – Phase 2
Supporters:	Janssen Scientific Affairs, LLC – Drug and Funding Support Medivation Inc. – Drug Support
Product Name(s):	Abiraterone Acetate, Enzalutamide
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1 INTRODUCTION

1.1 PROSTATE CANCER AND PREOPERATIVE TREATMENT

In the United States, prostate cancer is the most common cancer and the second leading cause of male cancer death. Many patients diagnosed with prostate cancer are curable with local therapy as local treatments continue to evolve to minimize morbidity. Notwithstanding the advent of screening, approximately 20% of patients in modern series will initially present with locally advanced or high-grade prostate cancer not likely amenable to a single therapeutic approach i.e. surgery or radiation therapy alone. Experience with preoperative therapy in locally advanced prostate cancer over the past 15 years has been quite different from that anticipated based on observations in other solid tumors i.e. breast or colorectal cancer. Complete pathologic remission is rarely if ever achieved with any of the currently available therapeutic regimens including hormonal ablation with the use of Human luteinizing hormone-releasing (LHRH) analogues or combination of LHRH with docetaxel or other chemotherapeutic regimens. More specifically neo-adjuvant hormonal therapy prior to prostatectomy has not improved overall survival (OR 1.11, 95% CI 0.67 to 1.85, P = 0.69). However, there has been a report of significant reduction in the positive surgical margin rate (OR 0.34, 95% CI 0.27 to 0.42, P < 0.00001) and a significant improvement in other pathological variables such as lymph node involvement, pathological staging and organ confined rates. A borderline significant reduction of disease recurrence rates (OR 0.74, 95% CI 0.55 to 1.0, P = 0.05) in favor of treatment has also been reported.

Androgen deprivation therapy (ADT) remains the mainstay of therapy for patients with advanced prostate cancer and has increased survival in this setting[1]. In fact, earlier introduction of hormonal ablation seems to favor improved survival though androgen deprivation side effects need also be accounted for. With the hope of extending survival time, neoadjuvant androgen deprivation (NAD) has been proposed to treat locally advanced prostate carcinoma.

Introduced in the 1980s, LHRHa and antiandrogens such as flutamide, and cyproterone are considered safe and reversible forms of neoadjuvant androgen deprivation **(**NAD). LHRHa are known to act by stimulating the production of luteinizing hormone (LH) at the pituitary level, followed by suppression of LH and testosterone to castration levels after approximately 2 weeks. Antiandrogens compete with adrenal androgen binding at the receptor level in the target cell. Together, LHRHa and antiandrogens cause significant androgen blockade. The first prospective randomized trial in patients with prostate cancer demonstrated a decreased incidence of positive margins and lymph node metastases in the NAD group compared with the surgery alone group[2]. However, the role of NAD used preoperatively is still debatable[3].

A number of randomized studies that documented long-term follow-up have shown that no significant difference was noted, in recurrence and survival, between the groups that included surgery and those that included NAD[4-6].

The introduction of new targeted therapeutics such as the irreversible CYP 17,20 lyase inhibitor (abiraterone acetate) has enabled a more complete depletion of androgens resulting in striking responses in the castrate resistant metastatic disease[7-9]. Investigators have recently proposed tumor microenvironment production activity for inhibition of 17α-hydroxylase/C17,20 lyase.

More recently two reports detailing the outcome of the pre-operative use of introduction androgen biosynthesis inhibitors suggest a significant increase the efficacy with three and six months of therapy[10-11].

Taken together these are in support of the hypothesis that androgen biosynthesis inhibitors add the efficacy of castration and support the hypothesis that their earlier use will further increase efficacy. Enzalutamide is a novel androgen receptor inhibitor that acts at multiple levels. Recent reports demonstrate that it can meaningfully prolong the survival of patients with castrate resistant prostate cancer[12]. Compelling rationale has been provided to combine the two approaches in an integrated effort to more effectively interrupt androgen signaling-mediated castrate resistant progression, altered steroid metabolome, and alteration in the androgen receptor. We are currently assessing the combination in the setting of advanced castrate resistant prostate cancer progressing in bone.

Study 9785-CL-0011 is an ongoing phase 2 open-label in approximately 60 patients with CRPC. Patients are receiving enzalutamide in combination with abiraterone acetate plus prednisone until disease progression or unacceptable toxicity. The primary endpoint is to assess the safety and tolerability of enzalutamide in combination with abiraterone acetate plus prednisone. Secondary endpoints are to assess the effect on AR signaling and androgen levels and explore the antitumor activity by serum PSA, imaging of soft tissue and bone metastases and markers of bone metabolism. Enzalutamide is dosed at 160 mg/day, abiraterone acetate at 1000 mg/day and prednisone at 5 mg twice daily.

As of 2 May 2013, 43 patients had been treated with at least 1 dose of enzalutamide in combination with abiraterone acetate plus prednisone. The total number of patients who comprise the safety population is 40. Overall, 37 patients (92.5%) have reported at least 1 treatment-emergent adverse event. The following treatment-emergent adverse events have been experienced by 6 or more patients: fatigue (17 patients [42.5%]), blood Alk Phos increase (17 patients [42.5%]), hot flush (16 patients [40%]), hyperglycaemia (13 patients [32.5%]), blood AST increase (9 patients [22.5%]), anemia (9 patients [22.5%]), blood ALT increase (6 patients [15%]), blood glucose increase (6 patients [15%]), arthralgia (6 patients [15%]) and pollakiuria (6 patients [15%]). There were no Grade 4 or 5 toxicities.

Six SAEs occurred in 5 different patients, and all were Grade 3 events with only 2 being treatment-emergent and 2 being unrelated to any given study drug. No patients discontinued the study or interrupted study drug due to the events.

However, we have noted that the responses in earlier disease states may be markedly enhanced and therefore providing compelling rationale for this pre-operative study that will serve as a companion to the advanced metastatic study[10-11].

1.2 LHRHa Leuprolide Acetate (Lupron®) and Goserelin Acetate (Zoladex®)

At the time of diagnosis localized prostate cancers are categorized as low, intermediate or high risk based on clinical stage, prostate specific antigen (PSA) level/velocity and tumor Gleason score[13]. Patients who fall into intermediate and high risk categories have unacceptably high relapse rates (30-80%) after primary local therapy or salvage local approaches[14]. The standard systemic treatment for prostate cancer is androgen deprivation therapy (ADT) most commonly administered with a LHRHa with/without an antiandrogen[15]. Treatment of systemic prostate cancer with ADT is not curative as the patients develop castration resistant prostate cancer (CRPC).

To date, ADT using LHRHa alone has reduced prostate volume by roughly 30% and decreased the rate of positive surgical margins, but has not been shown to improve the biochemical relapse rate for patients who undergo radical prostatectomy. However, because the addition of abiraterone to LHRHa further lowers androgen levels compared to LHRHa alone, there is a strong scientific rationale to now test whether this more potent combination therapy can improve surgical outcomes.

1.3 Abiraterone Acetate

Abiraterone acetate (ZYTIGA) is converted in vivo to abiraterone, an androgen biosynthesis inhibitor that inhibits 17 α hydroxylase/C17, 20-lyase (CYP17). This enzyme is expressed in testicular, adrenal and prostatic tumor tissues and is required for androgen biosynthesis.

CYP17 catalyzes two sequential reactions: 1) the conversion of pregnenolone and progesterone to their 17α-hydroxy derivatives by 17α-hydroxylase activity and 2) the subsequent formation of dehydroepiandrosterone (DHEA) and androstenedione, respectively, by C17, 20 lyase activity. DHEA and androstenedione are androgens and are precursors of testosterone. Inhibition of CYP17 by abiraterone can also result in increased mineralocorticoid production by the adrenals.

Abiraterone acetate has received marketing approval in more than 50 countries for the treatment of men with metastatic castration-resistant prostate cancer (mCRPC) after docetaxel treatment. It is also approved for the treatment of mCRPC in men

who have not previously received chemotherapy. The combination proposed in this protocol is not FDA approved.

For the most comprehensive nonclinical and clinical information regarding the efficacy and safety of abiraterone acetate, refer to the latest version of the Investigator's Brochure/Package Insert for abiraterone acetate.

1.3.1 Summary of Key Safety Information for Study Drugs

1.3.1.1 Warnings and Precautions

Hypertension, Hypokalemia and Fluid Retention Due to Mineralocorticoid Excess

Use abiraterone acetate with caution in patients with a history of cardiovascular disease. Abiraterone acetate may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition. Co-administration of a corticosteroid suppresses adrenocorticotropic hormone (ACTH) drive, resulting in a reduction in the incidence and severity of these adverse reactions. Use caution when treating patients whose underlying medical conditions might be compromised by increases in blood pressure, hypokalemia or fluid retention, e.g., those with heart failure, recent myocardial infarction or ventricular arrhythmia. The safety of abiraterone acetate in patients with left ventricular ejection fraction <50% or NYHA Class III or IV heart failure has not been established because these patients were excluded from the randomized clinical trial. Monitor patients for hypertension, hypokalemia, and fluid retention at least once a month. Control hypertension and correct hypokalemia before and during treatment with abiraterone acetate.

Adrenocortical Insufficiency

Adrenocortical insufficiency has been reported in clinical trials in patients receiving abiraterone acetate in combination with prednisone, following interruption of daily steroids and/or with concurrent infection or stress. Use caution and monitor for symptoms and signs of adrenocortical insufficiency, particularly if patients are withdrawn from prednisone, have prednisone dose reductions, or experience unusual stress. Symptoms and signs of adrenocortical insufficiency may be masked by adverse reactions associated with mineralocorticoid excess seen in patients treated with abiraterone acetate. If clinically indicated, perform appropriate tests to confirm the diagnosis of adrenocortical insufficiency. Increased dosage of corticosteroids may be indicated before, during and after stressful situations.

Hepatotoxicity

Marked increases in liver enzymes leading to drug discontinuation or dosage modification have occurred. Measure serum transaminases (ALT and AST) and bilirubin levels prior to starting treatment with abiraterone acetate, every two weeks for the first three months of treatment and monthly thereafter. In patients with baseline moderate hepatic impairment receiving a reduced abiraterone acetate dose of 250 mg, measure ALT, AST, and bilirubin prior to the start of treatment, every week for the first month, every two weeks for the following two months of treatment and monthly thereafter. Promptly measure serum total bilirubin, AST, and ALT if clinical symptoms or signs suggestive of hepatotoxicity develop. Elevations of AST, ALT, or bilirubin from the patient's baseline should prompt more frequent monitoring. If at any time AST or ALT rise above five times the ULN, or the bilirubin rises above three times the ULN, interrupt abiraterone acetate treatment and closely monitor liver function.

Re-treatment with abiraterone acetate at a reduced dose level may take place only after return of liver function tests to the patient's baseline or to AST and ALT less than or equal to 2.5X ULN and total bilirubin less than or equal to 1.5X ULN.

The safety of abiraterone acetate re-treatment of patients who develop AST or ALT greater than or equal to 20X ULN and/or bilirubin greater than or equal to 10X ULN is unknown.

Food effect

Abiraterone acetate must be taken on an empty stomach. No food should be consumed for at least two hours before the dose of abiraterone acetate is taken and for at least one hour after the dose of abiraterone acetate is taken. Abiraterone Cmax and AUC0-∞ (exposure) were increased up to 17- and 10-fold higher, respectively, when a single dose of abiraterone acetate was administered with a meal compared to a fasted state. The safety of these increased exposures when multiple doses of abiraterone acetate are taken with food has not been assessed.

1.3.1.2 Drug Interactions

Effects of Abiraterone on Drug Metabolizing Enzymes

Abiraterone acetate is an inhibitor of the hepatic drug-metabolizing enzyme CYP2D6. In a CYP2D6 drug-drug interaction trial, the Cmax and AUC of dextromethorphan (CYP2D6 substrate) were increased 2.8- and 2.9-fold, respectively, when dextromethorphan was given with abiraterone acetate 1000 mg daily and prednisone 5 mg twice daily. Avoid co-administration of abiraterone acetate with substrates of CYP2D6 with a narrow therapeutic index (e.g., thioridazine). If alternative treatments cannot be used, exercise caution and consider a dose reduction of the concomitant CYP2D6 substrate drug.

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

Drugs that Inhibit or Induce CYP3A4 Enzymes

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

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

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

1.3.1.3 Packaging and Labeling

Abiraterone acetate tablets will be provided packaged in individual bottles for patient assignment at the time of randomization.

Information presented on the labels for investigational product will comply with applicable local regulations.

Site pharmacist or medically qualified staff will dispense the study treatment to each patient in accordance with this protocol.

1.3.1.4 Pharmacy Storage Requirements

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 abiraterone acetate Investigator's Brochure.

Handling abiraterone acetate tablets

This medicine may cause harm to the unborn child if taken by women who are pregnant. It should not be taken by women who are breast-feeding. Women who are pregnant or who may be pregnant should wear gloves if they need to touch

abiraterone acetate tablets**.** Study staff and caregivers should be notified of this information, to ensure the appropriate precautions are taken.

1.3.2 Formulation of Study Drug

Abiraterone acetate 250 mg tablets are white to off-white, oval tablets debossed with AA250 on one side. ZYTIGA 250 mg tablets are available in high-density polyethylene bottles of 120 tablets.

NDC Number 57894-150-12

1.4.1 Enzalutamide

The safety and tolerability of enzalutamide have been evaluated in 13 studies, including 2 completed studies (Phase 1), 7 active studies (Phase 1 through 3), and 4 enrolling studies (Phase 2 through 3). It is estimated that a total of 124 healthy volunteers, 16 subjects with hepatic impairment, and approximately 1800 patients with prostate cancer have been exposed to enzalutamide in completed, open-label, and ongoing blinded studies. In the completed interim analysis of the randomized, double-blind, placebo-controlled Phase 3 efficacy and safety study in patients with progressive castration-resistant prostate cancer previously treated with docetaxel-based chemotherapy (CRPC2), 800 patients received enzalutamide (160 mg daily). The duration of enzalutamide exposure in this study ranged from 1 day to 23.3 months (median 8.3 months). No study has been terminated early for safety reasons.

Safety data are presented from the formal interim analysis of data from the CRPC2 study, with a data cut-off date of 25 September 2011. Table 3 provides an overview of exposure to study drug, adverse events, and deaths.

Table 3: Summary of Study Drug Exposure, Adverse Events, and Deaths (CRPC2)

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 ≥ 1 Treatment Emergent Adverse Event	785 (98.1%)	390 (97.7%)
Patients with ≥ 1 Treatment Emergent Adverse Event (Grade 3 or Higher)	362 (45.3%)	212 (53.1%)
Patients with ≥1 Serious Treatment Emergent Adverse Event	268 (33.5%)	154 (38.6%)
Patients with an Adverse Event Leading to Death	23 (2.9%)	14 (3.5%)
Patients with Adverse Events Leading to Study Drug Discontinuation	61 (7.6%)	39 (9.8%)
SUSARs (all in unique patients)	10	6
Deaths	308 (38.5%)	212 (53.1%)

Enzalutamide (160 mg daily) was generally well-tolerated in the placebo-controlled CRPC2 study of 1199 patients with progressive castration-resistant prostate cancer previously treated with docetaxel-based chemotherapy. 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%).

Serious adverse events that occurred at a $\geq$ 0.5% absolute difference in event frequency and more frequently in the enzalutamide arm than the placebo arm included: spinal cord compression (6.0% vs. 3.8%), bone pain (1.5% vs. 1.0%), metastatic pain (1.5% vs. 0.8%), pathological fracture (1.5% vs. 0.5%), urinary tract infection (0.9% vs. 0.3%), and cauda equina syndrome (0.8% vs. 0.0%).

Seizure is a known potential toxicity of enzalutamide. In vitro studies have shown that enzalutamide and its metabolite M2 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[17].

In the first clinical study of enzalutamide (S-3100-1-01), a dose-escalation study in men with castration-resistant prostate cancer 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 of the database cut-off date for the respective unblinded or open-label studies reported in the most current version of the Investigator's Brochure, 7 patients out of a total of 1100 patients (0.6%) exposed to enzalutamide at a dose of 160 mg/day have reported a seizure during the enzalutamide treatment emergent adverse event reporting period. These include one patient each in studies 9785-CL-0007 and 9785-CL-0321, and 5 patients in the CRPC2 study. Two additional patients were identified to have experienced adverse events that may have been seizures, including

one case reported by the Investigator as syncope (CRPC2) and the other reported as a transient ischemic attack with an abnormal electroencephalogram (CRPC-MDA-1). As of the data cut-off date, treatment with enzalutamide at a daily dose of 160 mg is associated with a0.6-0.8% risk of seizure in men with late-stage castration-resistant prostate cancer.

Taking into account information from ongoing blinded studies and events occurring after the database cut-off date, the range for seizure risk is unchanged. No seizures have been reported in the blinded placebo-controlled Phase 3 study enzalutamide-03 (PREVAIL) with over 1300 patients enrolled (randomized 1:1 to enzalutamide 160 mg/day or placebo). One additional patient in the CRPC2 study has been reported to have had a seizure after the safety data cut-off date, and one additional patient in an ongoing blinded study (9785-CL-0222) has also reported a seizure.

Please see the most current version of the Package Insert for additional details.

1.5 Rationale for Study Design

Abiraterone, α 17-lyase inhibitor, has demonstrated activity in patients with metastatic castration resistant prostate cancer (CRPC) who have failed hormonal and currently available chemotherapeutic options; they have few remaining therapeutic alternatives. Enzalutamide is a novel, potent inhibitor of the androgen receptor that prolongs the survival of patients with far-advanced and treatment-refractory prostate cancer. Both alterations in the steroid metabolism and the androgen receptor are implicated in the clinically observed resistance to castration. Taken together, these observations provide compelling rationale to combine optimum medical castration, inhibition of the androgen receptor, and altered androgen biosynthesis in patients at high risk for recurrence.

This knowledge will build on our understanding of the effect of optimum androgen inhibition in the setting of newly diagnosed, high-risk prostate cancer.[10-11, 16] The findings will lead to a framework that will allow us to personalize androgen signaling targeted therapy, by stage of progression, within individual patients and assure the safe use of the drug and the development of a rational combination therapy.

Available evidence indicates that following abiraterone acetate treatment, progression is inevitable in patients with advanced prostate cancer despite the encouraging initial clinical observations. Two mechanisms may be implicated in this progression. The first could be the presence of alternative androgen signaling, which results in further castrate resistant progression. The other possibility could be the existence of alternative stromal-epithelial interacting pathways independent of androgen signaling, which could account for the observed resistance implicated above, resulting in androgen independent progression. In order to develop a foundation for combination therapies, we would like to prioritize candidate pathways, which are implicated in progression of this disease, for further study. We

believe this can be best achieved in the context of the informative pre-operative setting that is proposed in this trial. This study will determine the rate of down staging achieved, and changes in the steroid biosynthesis metabolome, androgen receptor and "driver signaling networks" with abiraterone acetate, prednisone, and LHRH, or abiraterone acetate, enzalutamide, prednisone with LHRH in high risk prostate cancers.

2 STUDY OBJECTIVES

2.1 Primary Objectives

The primary objective of this study is:

- To assess the difference in pathologic stage ≤ pT2 at prostatectomy between Group A (abiraterone acetate plus prednisone and androgen ablation [LHRHa] plus enzalutamide for 6 months) and Group B abiraterone acetate plus prednisone and androgen ablation [LHRHa] for 6 months).

2.2 Secondary Objectives

The secondary objectives of this study are:

- To assess and compare the changes in levels of androgens (pre, during, and post-treatment) in the serum and primary tumor microenvironment between Group A and Group B.
- To assess changes in biomarkers related to androgen signaling and other cancer-related pathways between Group A and Group B.
- To assess the difference in rate of positive surgical margins between Group A and Group B.
- To assess the safety profile of abiraterone acetate and low dose prednisone in combination with enzalutamide for six months in a preoperative setting.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a study comparing the effect of abiraterone acetate (1,000 mg daily) plus prednisone (5mg once daily) in combination with enzalutamide (160 mg daily) and LHRHa versus LHRHa and abiraterone acetate (1,000 mg daily) plus prednisone (5mg once daily) for six months on pathologic and molecular differences in patients with locally advanced prostate cancer. Patients will be randomized in a 2:1 ratio to Group A (abiraterone acetate plus prednisone and androgen ablation [LHRHa] plus enzalutamide) or Group B (androgen ablation [LHRHa] and abiraterone acetate plus prednisone), respectively. Patients will receive 6 months of LHRHa therapy on trial for a maximum of 7 months before a prostatectomy is performed (patients may

enter the study with no more than one (1) month of LHRHa treatment prior to C1D1).

3.1.1 Endpoints

Primary Endpoint:

- Proportion of patients with pathologic stage ≤pT2 at prostatectomy.

Secondary Endpoints:

- Differences in androgen signaling (e.g., Testosterone, DHT) in the serum and primary tumor microenvironment (pre, during, and post treatment) between Group A and Group B.
- Related androgen metabolites (e.g., Testosterone, DHT) in the serum and primary tumor microenvironment (pre, during, and post treatment) between Group A and Group B.
- Proportion of positive surgical margins rate in Group A and Group B.
- Proportion of patients with PSA ≤ 0.2 ng/mL in Group A and Group B.
- Proportion of patients who achieve pathological CR or near pathological CR (<5% occupancy) at prostatectomy.

Exploratory Endpoints:

Molecular effects of treatment will be assessed in the tumor microenvironment in both Group A and Group B. Effects on the tumor epithelium, angiogenesis, and the broader tumor microenvironment will also be assessed.

- Assessment of androgen signaling components in tumor in the radical prostatectomy specimens (rps), open or robotic, and biopsy specimens in Group A and Group B. This will include, but not be limited to, androgen receptor (AR) expression by immunohistochemistry, AR copy number determination by quantified polymerase chain reaction, and CYP17 expression assessment by immunohistochemistry.
- Assessment of cell proliferation and apoptosis in the tumor epithelium in rps and biopsy specimens in Group A and Group B.
- Assessment of markers of neuroendocrine differentiation in the tumor epithelium in rps and biopsy specimens. These will include but may not be limited to chromogranin synaptophysin and CD56.
- Assessment of other molecular pathways of interest in the tumor microenvironment as follows:
    - Stromal epithelial pathways of interest will be assessed in tumor in the rps and biopsy specimens in Group A and Group B. These will include but not be limited Hh signaling components and Src signaling components.
    - Markers of angiogenesis will include, but not be limited to CD31, VEGF, VEGFR

Biomarkers, including those described above and in Section 12.4, will be assessed by immunohistochemistry in available formalin fixed paraffin embedded tissue.

Tissue microarrays (TMAs) will be constructed from rps while biopsies will be either individually processed or used to construct TMAs depending on the availability of tissue

- Assessment of the steroid hormone metabolome in blood plasma and tissue by liquid chromatography tandem mass spectrometry. These will include, but not be limited to, testosterone, dihydrotestosterone, androstenedione, and pregnenolone.

3.2 Study Duration and Dates

The study period will consist of Screening, Treatment, and Follow-up visit. In this study, patients will be randomized to receive either abiraterone acetate plus prednisone with LHRHa and enzalutamide (Group A) or LHRHa and abiraterone acetate plus prednisone (Group B) for 6 months (24 weeks) followed by a radical prostatectomy (open or Robotic Assisted Laparoscopic). The follow-up visit after the radical prostatectomy will occur 4 to 8 weeks post-surgery.

Treatment following prostatectomy will be determined by the current practice guidelines and individualized to patient needs. Each cycle of treatment will be 28 days with a ± 4 day window.

4 Study Population Selection

Approximately 66 patients with pre-operative locally advanced adenocarcinoma of the prostate will be enrolled at study site(s).

4.1 Inclusion Criteria

Each patient must meet the following criteria to be enrolled in this study.

1. Be willing/able to adhere to the prohibitions and restrictions specified in this protocol.
2. Have signed an informed consent document indicating that the subjects understand the purpose of and procedures required for the study and are willing to participate in the study.
3. Written Authorization for Use and Release of Health and Research Study Information has been obtained.
4. Male age ≥18 years.
5. Histologically or cytologically confirmed adenocarcinoma of the prostate with no histological variants (such as small cell, sarcomatoid, pure ductal cancer, transitional cell carcinoma).
6. Pathology review at treating academic institution or member institution (Note: if patient's prostate biopsy was not read at the treating institution, it must be reviewed at the study site to confirm eligibility).

7. At least three core biopsies involved with cancer (a minimum of 6 core biopsies must be obtained at baseline). A prostate biopsy within 3 months from screening is allowed for entry requirements. Patients must have a Gleason score > 5 (total).
8. At least one of the following features:
   - PSA >10 ng/ml
   - PSA velocity >2 ng/ml/year (defined as a rise in PSA of >2 ng/ml in the preceding 12 month period)
   - Gleason score ≥7
   - Gleason score 6 if either PSA ≥ 10 ng/ml or PSA velocity ≥2 ng/ml/year
9. Serum testosterone >200 ng/dL. For patients treated with up to 1 month of LHRH agonist, a testosterone measurement prior to the LHRH treatment will be used to determine eligibility, and must have been > 200 ng/dL.
10. Urologist must agree that patient is suitable for prostatectomy.
11. No evidence of metastatic disease as determined by imaging procedures.
12. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1.
13. Hemoglobin ≥10.0 g/dL independent of transfusion.
14. Platelet count ≥100,000/μL.
15. Patients should have adequate bone marrow function defined as an absolute peripheral neutrophil count (ANC) >1,500.
16. Creatinine clearance ≥60 mL/min
17. Serum potassium ≥3.5 mmol/L.
18. Serum albumin ≥3.5 g/dL.
19. Liver function test with serum bilirubin ≤ 1.5x ULN and ALT and AST ≤ 1.5x ULN.
20. Able to swallow the study drug whole as a tablet.
21. Patients must have normal coagulation profile and no history of substantial non- iatrogenic bleeding diathesis.
22. Agree to use a double-barrier method of contraception which involves the use of a condom in combination with one of the following: contraceptive sponge, diaphragm, or cervical ring with spermicidal gel or foam, if having sex with a woman of child-bearing potential during the length of the study and for one week after abiraterone is discontinued and for at least three months after enzalutamide is discontinued.
23. Willing to take abiraterone acetate on an empty stomach; no food should be consumed at least two hours before and for at least one hour after the dose of abiraterone acetate is taken.

4.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from the study.

1. Serious or uncontrolled co-existent non-malignant disease, including active and uncontrolled infection.

2. Chronically uncontrolled hypertension, defined conventionally as consistent systolic pressures above 140 or diastolic pressures above 90 despite 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.
3. Requirement for corticosteroids greater than the equivalent of 5 mg of prednisone daily.
4. Poorly controlled diabetes defined by Hemoglobin A1C > 7.0 at screening
5. Active or symptomatic viral hepatitis or chronic liver disease.
6. History of pituitary or adrenal dysfunction.
7. Clinically significant cardiovascular disease including:
    - Myocardial infarction within 6 months of Screening visit;
    - Uncontrolled angina within 3 months of Screening visit;
    - Congestive heart failure New York Heart Association (NYHA) class 3 or 4, or subjects with history of congestive heart failure NYHA class 3 or 4 in the past, or history of anthracycline or anthracenedione (mitoxantrone) treatment, unless a screening echocardiogram or multi-gated acquisition scan (MUGA) performed within three months of the Screening visit results in a left ventricular ejection fraction that is ≥ 50%.
    - History of clinically significant ventricular arrhythmias (e.g., ventricular tachycardia, ventricular fibrillation, torsade de pointes).
    - Prolonged corrected QT interval by the Fridericia correction formula (QTcF) on the screening Electrocardiogram (ECG) > 470 msec.
    - History of Mobitz II second degree or third degree heart block without a permanent pacemaker in place.
    - Hypotension (systolic blood pressure < 86 mmHg or bradycardia with a heart rate of <50 beats per minute on the Screening ECG., unless pharmaceutically induced and thus reversible (i.e. beta blockers).
8. Other malignancy, except non-melanoma skin cancer, that is active or has a ≥ 30% probability of recurrence within 12 months.
9. History of gastrointestinal disorders (medical disorders or extensive surgery) which may interfere with the absorption of the study drug.
10. Prior hormone therapy for prostate cancer including orchiectomy, antiandrogens, ketoconazole, or estrogens (5-α reductase inhibitors allowed), or LHRH agonists/antagonists (*Note: LHRH allowed if begun within 1 month of Day 1). Patients having previous or current antiandrogen treatment of greater than 4 weeks in duration prior to Cycle 1 Day 1 are eligible with appropriate washout.
11. Prior systemic treatment with an azole drug within four weeks of Cycle 1 Day1.
12. Current enrollment in an investigational drug or device study or participation in such a study within 30 days of Cycle 1 Day 1.
13. Allergies, hypersensitivity, or intolerance to prednisone, LHRH analog or excipients of prednisone LHRH analog, abiraterone acetate and enzalutamide.

14. Previous use of abiraterone acetate or other investigational CYP17 inhibitor (e.g., TAK-700).
15. Previous investigational antiandrogens (e.g., Enzalutamide, BMS-641988).
16. Patients receiving anti-coagulant therapy who are unable to stop prior to surgery.
17. Condition or situation which, in the investigator's opinion, may put the patient at significant risk, may confound the study results, or may interfere significantly with patient's participation in the study.
18. Severely compromised immunological state, including being positive for the human immunodeficiency virus (HIV).
19. Patients with 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).
20. Prior chemotherapy, radiation or immune therapy for prostate cancer.
21. Patients unable to tolerate transrectal ultrasound.
22. Concomitant therapy with any of the following
    - Chemotherapeutic, biologic, or other agents with anti-tumor activity against prostate cancer other than assigned study drug.
    - Anti-androgens (steroidal or non-steroidal) such as cyproterone acetate, flutamide, nilutamide, bicalutamide, etc. other than assigned study drug.
    - 5-α reductase inhibitors such as finasteride, dutasteride, anabolic steroids, etc.
    - Estrogens, progestational agents such as megestrol, medroxyprogesterone, DES, cyproterone, spironolactone > 50 mg/kg, etc.
    - Androgens such as testosterone, dehydroepiandrosterone [DHEA], etc.
    - Ketoconazole.
    - Herbal products that may decrease PSA levels (e.g., saw palmetto).
23. Active infection or other medical condition that would make prednisone/ prednisolone (corticosteroid) use contraindicated.
24. Severe hepatic impairment (Child-Pugh Class C).
25. History of seizure or any condition that may predispose to seizure including, but not limited to underlying brain injury, stroke, primary brain tumors, brain metastases, or alcoholism. Also, history of loss of consciousness or transient ischemic attack within 12 months of enrollment (Day 1 visit).
26. History of significant bleeding disorder unrelated to cancer, including:
    - Diagnosed congenital bleeding disorders (e.g., von Willebrand's disease).
    - Diagnosed acquired bleeding disorder within one year (e.g., acquired anti-factor VIII antibodies) of Screening visit.
    - History of GI bleeding within 6 months of Screening visit.

5 Study Treatment(s)

5.1 Description of Treatments(s)

5.1.1 Abiraterone Acetate

Abiraterone acetate is designated chemically as (3β)- 17-(3-pyridinyl)androsta-5,16-dien-3-yl acetate. It is a white to off-white, non-hygroscopic, crystalline powder, its molecular formula is C26H33NO2 and it has a molecular weight of 391.55. Abiraterone acetate is a lipophilic compound with an octanol-water partition coefficient of 5.12 (Log P) and is practically insoluble in water.

Abiraterone acetate 250 mg tablets are white to off-white, oval-shaped tablets debossed with AA250 on one side and provided in bottles with child-resistant induction seal closure.

5.1.2 Enzalutamide

Enzalutamide has the chemical name 4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl}-2-fluoro-N-methylbenzamide. It is a white to off-white solid that is insoluble in water and no salt forms are available at ~pH 2 to 10.

Enzalutamide capsules are white to off-white oblong capsules, printed with "MDV" in black ink. The soft gelatin capsules are filled with a clear, yellowish solution which contains the two antioxidants, butylated hydroxyanisole, and butylated hydroxytoluene , and enzalutamide active ingredient (40 mg), all dissolved in the non-ionic surfactant, Labrasol® (Caprylocaproyl Polyoxylglycerides). Enzalutamide capsules are provided in white, opaque, high-density polyethylene (HDPE) bottles with child-resistant induction seal closure.

5.1.3 Prednisone

Prednisone is a glucocorticoid. Glucocorticoids are adrenocortical steroids, both naturally occurring and synthetic, which are readily absorbed from the gastrointestinal tract. The molecular formula for prednisone is C21H26O5. Chemically, it is 17, 21-dihydroxypregna-1, 4- diene-3, 11, 20-trione. Prednisone is a white to practically white, odorless, crystalline powder and has a molecular weight of 358.44. It melts at about 230°C with some decomposition. Prednisone is very slightly soluble in water, slightly soluble in alcohol, chloroform, dioxane, and methanol.

Prednisone inactive ingredients are: anhydrous lactose, colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, sodium starch glycolate, and talc.

Prednisone 5 mg tablets are white round-shaped tablets and provided in bottles with child- resistant induction seal closure.

5.2 Packaging and Labeling

Abiraterone acetate tablets will be provided packaged in individual bottles for patient assignment at the time of randomization. Patients will be provided with a 60-day supply to allow for visits to occur every 8 weeks.

Information presented on the labels for investigational product will comply with applicable local regulations.

Site pharmacist or medically qualified staff will dispense the study treatment to each patient in accordance with this protocol.

Enzalutamide used in this study will be labeled and supplied to the study subjects through the site designated pharmacy.

Site pharmacist or medically qualified staff will dispense the study treatment to each subject in accordance with this protocol.

5.3 Study Drug Handling

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 is 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.

Enzalutamide will be provided by Medivation and will be stored and handled according to the manufacturer specifications and the pharmacy standards of operation.

Abiraterone Acetate 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.

6 Treatments Administered

6.1 Dosing and Administration of Study Drugs and Other Medications

6.1.1 Dose/Dose Regimen and Administration Period

Abiraterone acetate: Subjects will be instructed to take 4 tablets (250 mg each) orally once daily at least 1 hour before a meal or 2 hours after a meal and should be swallowed whole with water. Tablets may not be crushed or chewed.

Prednisone: Subjects will be instructed to take 5-mg oral prednisone, once daily.

Enzalutamide: Subjects will be instructed to take 4 capsules (40 mg each) per day orally. Enzalutamide may be taken with or without food. Enzalutamide should be taken as close to the same time each day as possible.

6.1.2 Reduction in Dose or Discontinuation of the Study Drugs

In subjects who experience toxicity who cannot be ameliorated by the use of adequate medical intervention, dose reductions can be performed. In these cases dose reductions of abiraterone acetate should be performed first, followed by reduction in enzalutamide doses (if needed).

For abiraterone acetate, 2 dose reductions are allowed, though dosing may be interrupted without a dose reduction. Patients who experience a Grade 3 or greater toxicity considered to be related to abiraterone acetate will be dose reduced per the following schema. At each dose reduction, one tablet of abiraterone acetate will be removed, e.g., 4→3 tablets, and 3→2 tablets. Any return to protocol dose level after dose reduction or after treatment interruption must follow documentation of adverse event resolution and a discussion with the Principal Investigator. Dosing with abiraterone may be held for up to 2 weeks without discontinuation from therapy.

Patients who experience a Grade 3 or greater toxicity considered to be related to enzalutamide that cannot be ameliorated by the use of adequate medical intervention should have their treatment interrupted until the toxicity improves to a Grade 2 or lower severity. Patients may subsequently be re-started on study drug at a reduced dose as per the discretion of the Principal Investigator. Subjects will remain on abiraterone acetate and prednisone during enzalutamide dose interruption.

No dose reductions for prednisone are allowed. Subjects experiencing toxicity considered to be related to the use of prednisone for which a dose reduction is needed will require discontinuation of study drugs.

Subjects should be able to take all three study drugs (abiraterone acetate, enzalutamide, and prednisone) to participate in the study. An interruption of one of these drugs is allowed as per instruction above. Permanent discontinuation of one of the drugs, while continuing the two other drugs, is not allowed.

6.1.3 Previous and Concomitant Medication (Drugs and Therapies)

6.1.3.1 Previous Medication (Drugs and Therapies)

Medication taken within four weeks prior to registration must be captured in the medical record.

At each visit, all concomitant treatments, including blood and blood products, must be reported on the source documentation. Concomitant medications must also be documented at the time of discontinuation and at the 30 day follow-up visit.

The dosage and regimen of the following medications and any chronic permitted concomitant medications should be stabilized for 4 weeks prior to Day 1 and held constant throughout the study:

- Bisphosphonates
- Denosumab
- GnRH agonist/antagonist

No other new systemic therapy or new radiotherapy for treatment of prostate cancer is permitted while subject is on study.

The following medications are prohibited while the subject is on study drug:

- Chemotherapeutic, biologic, or other agents with anti-tumor activity against prostate cancer other than assigned study drug.
- Anti-androgens (steroidal or non-steroidal) such as cyproterone acetate, flutamide, nilutamide, bicalutamide, etc. other than assigned study drug.
- 5-α reductase inhibitors such as finasteride, dutasteride, anabolic steroids, etc.
- Estrogens, progestational agents such as megestrol, medroxyprogesterone, DES, cyproterone, spironolactone > 50 mg/kg, etc.
- Androgens such as testosterone, dehydroepiandrosterone [DHEA], etc.
- Ketoconazole.
- Herbal products that may decrease PSA levels (e.g., saw palmetto).

Medications that inhibit platelet function and anticoagulants should be used with caution while the subject is on study drug:

Src-family kinase inhibitors potentially reduce platelet aggregation. Caution should thus be exercised if subjects are required to take one of the following medications that inhibit platelet function or anticoagulants.

- aspirin or aspirin-containing combinations.
- clopidogrel, dipyridamole, tirofiban, dipyridamole, epoprostenol, eptifibatide, cilostazol.
- abciximab, ticlopidine, cilostazol warfarin.
- heparin/low molecular weight heparin [eg, danaparoid, dalteparin, tinzaparin, enoxaparin].

Use of heparin for flushes of intravenous lines is allowed.

Cytochrome P 450 inhibitors, Inducers, and Substrates

It is currently unknown which CYP enzyme pathways are responsible for clearing enzalutamide. To limit the risk of unpredictable increases or decreases in circulating concentrations of enzalutamide, potent inhibitors or inducers should be taken with caution, and alternative products used when available. In vitro data suggest that enzalutamide may have the potential to induce CYP3A4 and inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5; therefore, concomitant medications that are substrates of any of these enzymes 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. To determine if a particular drug is a potent CYP inhibitor or inducer, the investigator should consult the product label.

Drugs metabolized through the CYP2D6 and CYP1A2 pathways should be used with caution while participating in this study.

In vitro studies showed that enzalutamide is an inhibitor of CYP2C8 and CYP2C19 with lesser inhibitory effects on CYP2B6 and CYP2C9. Substrates of CYP2B6, CYP2C8, CYP2C9, and CYP2C19 that have a narrow therapeutic index (e.g., phenytoin, warfarin) should be used with caution.

In vitro studies showed that enzalutamide may be an inducer of CYP3A4. Co-administration of enzalutamide with CYP3A4/5 substrates may affect oral bioavailability and/or elimination of the CYP3A4/5 substrate. Substrates of CYP3A4/5 that have a narrow therapeutic index should be used with caution. Co-administration of enzalutamide and Abiraterone may lower circulating levels of Abiraterone Acetate.

In vitro studies showed that enzalutamide is metabolized by CYP2C8 and CYP3A4/5. Use caution when co-administering a strong CYP2C8 inhibitor (e.g., gemfibrozil) or strong CYP3A4/5 inhibitors (e.g., clarithromycin, itraconazole, ketoconazole, grapefruit juice) during enzalutamide treatment.

Use caution when co-administering a CYP2C8 inducer (e.g., rifampin) or strong CYP3A4/5 inducers (e.g., carbamazepine, phenytoin, rifampin, and St. John's wort) during enzalutamide administration.

Please refer to the following link for an up to date list of CYP inhibitors and inducers. http://medicine.iupui.edu/clinpharm/ddis/

Caution is advised when considering the concomitant use of medications known to lower the seizure threshold. These include but are not limited to:

- Aminophylline/theophylline.
- Atypical antipsychotics (e.g., clozapine, olanzapine, risperidone, ziprasidone).
- Bupropion.
- Lithium.
- Pethidine.
- Phenothiazine antipsychotics (e.g., chlorpromazine, mesoridazine, thioridazine).
- Tricyclic and tetracyclic antidepressants (e.g., amitriptyline, desipramine, doxepin, imipramine, maprotiline, mirtazapine).

6.1.3.2 Effects of Abiraterone on Drug Metabolizing Enzymes

Abiraterone acetate is an inhibitor of the hepatic drug-metabolizing enzyme CYP2D6. In a CYP2D6 drug-drug interaction trial, the Cmax and AUC of dextromethorphan (CYP2D6 substrate) were increased 2.8- and 2.9-fold, respectively, when dextromethorphan was given with abiraterone acetate 1000 mg daily and prednisone 5 mg twice daily. Avoid co-administration of abiraterone acetate with substrates of CYP2D6 with a narrow therapeutic index (e.g., thioridazine). If alternative treatments cannot be used, exercise caution and consider a dose reduction of the concomitant CYP2D6 substrate drug.

In vitro, abiraterone acetate was shown to inhibit the hepatic drug-metabolizing enzyme CYP2C8. There are no clinical data on the use of abiraterone acetate with drugs that are substrates of CYP2C8.

Drugs that Inhibit or Induce CYP3A4 Enzymes
Based on in vitro data, abiraterone acetate is a substrate of CYP3A4. The effects of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole) or inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital) on the pharmacokinetics of abiraterone have not been evaluated, in vivo. Avoid or use with caution, strong inhibitors and inducers of CYP3A4 during abiraterone acetate treatment.

6.1.4 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.

6.1.5 Emergency Procedures and Management of Overdose

There is no specific antidote for an overdose of enzalutamide or abiraterone acetate. Patients who develop adverse reactions from a suspected overdose should receive appropriate symptomatic treatment.

7 STUDY PROCEDURES

A signed, Institutional Review Board (IRB) approved, written informed consent must be obtained from patients before any study specific procedures or randomization can occur. Confirmation of the patient's informed consent and the informed consent process must also be documented in the patient's medical record. A copy of the fully signed informed consent should be given to the patient. The study period will consist of screening, treatment, prostatectomy and post-prostatectomy follow up.

7.1 Screening

The following activities/procedures will be conducted during the screening period which may occur within 30 days prior to enrollment on the study:

- Consent prior to study related activities
- Medical history including prior prostate cancer therapies, Stage, and Gleason score at diagnosis
- Demographics
- Physical examination, weight, and height

- 12-lead ECG
- Baseline MUGA scan or cardiac ECHO
- Vital signs including upright blood pressure, heart rate, respiratory rate, and oral or aural body temperature
- Assessment of ECOG Performance Status
- Baseline Symptoms/Adverse Event evaluation
- Laboratory tests:
  - CBC: WBC with differential count, RBC, hemoglobin, hematocrit, platelets.
  - Coagulation studies (PT/PTT, INR). Note: patients receiving anticoagulants during the course of therapy should be monitored closely during the study.
  - Chemistry with electrolytes: albumin, calcium, lactate dehydrogenase (LDH), sodium, potassium, chloride, magnesium, carbon dioxide, creatinine, BUN, AST, ALT, alkaline phosphatase, total bilirubin, total protein, glucose, total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), cholesterol and triglycerides.
  - HgbA1C
  - PSA: All PSAs must be drawn prior to the DRE and within 2 weeks prior to the start of the study.
  - Serum testosterone
  - Urinalysis
  - Optional Blood for Correlative Studies
    A total of 20ml peripheral blood will be drawn for correlative studies (see section 12)

- Baseline tumor assessment:
  - At least three core biopsies positive for prostate cancer (a minimum of 6 core biopsies must be obtained at baseline). Pre-treatment prostate tumor biopsy tissue from within 6 months from screening is allowed for entry requirements from paraffin blocks and will be analyzed for immunohistochemistry (IHC) testing
- Bone Scan
- CXR (PA/lateral) or chest CT
- CT of the abdomen and pelvis or MRI of the pelvis (w/wo endorectal coil)
- Concomitant medications listing: Obtain a listing of all prescription and nonprescription (over-the-counter) medications currently taken including pain medications. This also includes any nutritional supplements and/or herbal preparations.

Patients who are eligible will be randomized and start study treatment within 30 days after eligibility is confirmed.

Randomization may occur on the same day as study registration provided that all screening assessments have been completed and screening results are reviewed prior to randomization.

7.2 Treatment Period

The following procedures should be carried out **prior to study drug administration:**

7.2.1 Both Study Groups (Groups A and B)

Cycle 1 Day 1 (If visit occurs within 7 days of screening visit, Cycle 1 Day 1 procedures will not be repeated).

- Physical Exam (includes monitoring of fluid retention) and weight
- Record current signs and symptoms with associated NCI CTCAE V4.0 grading (0-4) with any event that may have occurred since screening
- Concomitant Medications listing
- Vital signs including upright blood pressure, heart rate, respiratory rate, and oral or aural body temperature. Vital signs will be reviewed to monitor for hypertension.
- Assessment of ECOG Performance Status
- PSA: If patient undergoes a DRE, PSA must be sampled prior to the DRE.
- Laboratory tests
  - CBC: WBC with differential, RBC, hemoglobin, hematocrit, platelets
  - Chemistry with electrolytes: albumin, calcium, lactate dehydrogenase (LDH), sodium, potassium, chloride, magnesium, carbon dioxide, creatinine, BUN, AST, ALT, alkaline phosphatase, total bilirubin, total protein, glucose
  - Optional Blood for Correlative Studies (see section 12)

Cycle 1 Day 15, Cycle 2 Day 15 and Cycle 3 Day 15 Procedures (± 3 days)

- Safety laboratory screening (Liver Function Tests: AST, ALT, LDH, ALKP and Total Bilirubin)

Day 15 lab tests (Cycles 1, 2 and 3) may be done at a local laboratory or physician's office. Results should be faxed to MDACC.

7.2.2 Treatment Period (Both Groups)

Cycles 2-6 Day 1 Procedures (± 3 days)

- Physical Exam (includes monitoring of fluid retention) and weight
- Concomitant Medications listing
- Vital signs including upright blood pressure, heart rate, respiratory rate, and oral or aural body temperature. Vital signs will be reviewed to monitor for hypertension.
- AE evaluation and recording

- Assessment of ECOG Performance Status
- Laboratory tests
  - Chemistry with electrolytes: albumin, calcium, lactate dehydrogenase (LDH), sodium, potassium, chloride, magnesium, carbon dioxide, creatinine, BUN, AST, ALT, alkaline phosphatase, total bilirubin, total protein, and glucose
  - PSA: If patient undergoes a DRE, PSA must be sampled prior to the DRE
  - **Cycle 3 only:** Blood for Correlative Studies (see section 12.1)

Testing on Cycles 2, 4, and 6 may be done at a local physician's office. Results should be faxed to MDACC.

7.2.3 Pre-surgery Visit and End of Treatment Visit (Patients in ALL Study Groups)

The following procedures and evaluations must be performed within 1 to 14 days prior to surgery:

- Complete physical examination (includes monitoring of fluid retention)
- Vital signs including upright blood pressure, heart rate, respiratory rate, and oral or aural body temperature
- Assessment of ECOG performance status
- CXR (PA/lateral) or chest CT
- 12-lead ECG
- Concomitant Medications listing
- AE evaluation and recording
- Laboratory tests
  - CBC: WBC with differential, RBC, hemoglobin, hematocrit, platelets
  - Chemistry with electrolytes: albumin, calcium, lactate dehydrogenase (LDH), sodium, potassium, chloride, magnesium, carbon dioxide, creatinine, BUN, AST, ALT, alkaline phosphatase, total bilirubin, total protein, fasting glucose , total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), cholesterol and triglycerides
  - Urinalysis
  - HgbA1C
  - Coagulation tests (PT/PTT)
  - PSA: If patient undergoes a DRE, PSA must be sampled prior to the DRE.
  - Blood for Correlative Studies (see section 12.1)

7.2.4 Surgery

- Tissue from the prostatectomy will be collected for Correlative Studies (see section 12.2)

7.3. Assessment of Radical Prostatectomy Specimen

7.3.1. Extent of Operation

All patients will have a planned prostatectomy.

7.3.2 Timing of Prostatectomy

The surgery will be planned at the end of Cycle 6. Patients must be off therapy no less than 48 hours prior to surgery. To permit flexibility in surgical scheduling a study window of a maximum of four weeks will be allowed. In the event the surgery is delayed, the patient will be required to return to the clinic for safety assessment.

Surgery will be performed only after recovery from any side effects from abiraterone acetate or enzalutamide to a level considered safe for surgery. In the event of delayed recovery, the patient will be maintained on LHRHa until the clinical condition permits surgery.

7.3.3 Criteria for Completion of Surgery

Grossly enlarged and clinically unresectable appearing lymph node disease will be assessed by frozen section. If under such circumstances viable cancer is detected, or if distant intra-abdominal metastases are encountered, surgery will be abandoned. Routine frozen section analysis will not be performed on patient in whom the visible lymph node enlargement is within the planned operative field or in patients without clinically detectable lymph node enlargement.

7.3.4 Assessment of Surgical Complications

It will be the responsibility of the attending surgeon to accurately tabulate complications and the progress of the surgical procedure. Specifically tabulated will be the duration of anesthesia, blood product requirement, and fluid requirement of the gross description of the operative field (presence for absence of desmoplasia).

7.4 Post-Treatment Follow-up Period

Once a patient has undergone a radical prostatectomy and has completed the study treatment, the 4 to 8 weeks post-surgery follow-up visit will be performed as described below.

7.4.1 Therapy Following Prostatectomy

Treatment following prostatectomy will be determined by the current practice guidelines and individualized to patient's needs.

- If the cancer extends to the surgical margins the patient may be considered for adjuvant radiation therapy with the same criteria and following consent of the patient.
- In the event of detectable metastatic disease, the optimal therapy at recurrence will be recommended.

7.4.2 Post-Radical Prostatectomy Evaluation

Note: These procedures and assessments will be collected at the follow-up visit which will occur 4 to 8 weeks post-surgery.

- Complete physical examination
- Vital signs including upright blood pressure, heart rate, respiratory rate, and oral or aural body temperature
- Assessment of ECOG performance status
- Concomitant Medications listing
- AE evaluation and recording
- Laboratory tests
  - CBC: WBC with differential, RBC, hemoglobin, hematocrit, platelets
  - Chemistry with electrolytes: albumin, calcium, lactate dehydrogenase (LDH), sodium, potassium, chloride, magnesium, carbon dioxide, creatinine, BUN, AST, ALT, alkaline phosphatase, total bilirubin, total protein, glucose
  - HgbA1C
  - PSA
  - Serum testosterone
  - Blood for Correlative Studies (see section 12.1)

7.5 Study Calendar

	Screening	C1D1[c]	C1 Day 15	D1 of C2-C6	C2-3 Day 15	Pre-Surgery Visit/End of Treatment	Surgery[f]	4 to 8 weeks post-surgery
Medical History	x[a]							
Physical Exam	x[a]	x		x		x		x
Vital Signs	x[a]	x		x		x		x
Weight	x[a]	x		x				
Height	x[a]							
ECOG PS	x[a]	x		x		x		x
CBC/ diff. and plt.	x[a]	x				x		x

Serum Chemistry	x[a,b]	x[b]	x[d]	x[b]	x[d]	x[b]		x[b]
PT/PTT	x[a]					x		
PSA	x[a]	x		x		x		x
HGB A1C	x[a]					x		x
Serum Testosterone	x[a]							x
Urinalysis	x[a]					x		
CT Scan Abd/ CT Scan or MRI Pelvis	x[a]							
Chest X-ray or CT Chest	x[a]					x		
MUGA or ECHO	X[a]							
ECG	X[a]					x		
Bone Scan	X[a]							
Monitor Adverse Events		<----------						---------->
Concomitant Medications		<----------						---------->
Blood for Correlative Studies	x[a]	x		x (cycles 3 only)		x		x[e]
Tissue for Correlative Studies							x	
Archived Tissue for Correlative Studies	x							

a. Within 30 days of registration
b. Serum Chemistry with electrolytes: albumin, calcium, lactate dehydrogenase (LDH), sodium, potassium, chloride, magnesium, carbon dioxide, creatinine, BUN, AST, ALT, alkaline phosphatase, total bilirubin, total protein, and glucose. At screening and the pre-surgery visit, the following will also be done: total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), cholesterol and triglycerides.
c. If visit occurs within 7 days of screening visit, C1D1 procedures will not be repeated.
d. Liver Function Tests ONLY: AST, ALT, LDH, ALKP and Total Bilirubin. These LFTs may be done at a local physician's office. Results should be faxed to MDACC.
e. testosterone only
f. study medication will be continued up to 48 hrs prior to surgery

8 Adverse Events and Other Safety Aspects

8.1 Safety Assessments and Reporting Requirements

All patients will be evaluated for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical examination findings, and spontaneous reports of adverse events reported to the investigator by patients. An adverse event is 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. All adverse events encountered after the patient has provided informed consent and until 4 weeks after the patient has stopped treatment

will be evaluated according to the NCI Common Toxicity Criteria (CTCAE) version 4.0. Prior treatment associated toxicities present at the time of informed consent but before study treatment initiation, will be recorded as baseline abnormalities and graded according to CTCAE version 4.0 criteria.

8.1.1 Definitions

Adverse Event (AE)
Any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Adverse Events of Special Interest
Events that Janssen Scientific Affairs, LLC is actively monitoring as a result of a previously identified signal (even if non-serious), and are typically defined in the Protocol.

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.

J&J Medicinal Product
The specific J&J drug under study and any other J&J medicinal product.

Product Quality Complaint (PQC)
Any discrete concern that questions the identity, quality, durability, reliability, safety, efficacy or intended performance of a drug product.
A complaint may allege an injury or malfunction associated with the use of the drug product. It may also involve the design, literature, packaging, advertising, availability, physical appearance or promotion of the drug product.

Serious Adverse Event (SAE)
A serious adverse event is – any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.

- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity – a substantial disruption of a person's ability to conduct normal life functions.
- A congenital anomaly/birth defect.
  - A suspected transmission of infectious agents by a medicinal product

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).

Events *not* considered to be serious adverse events are hospitalizations for the purposes of this protocol and include:

- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- Treatment, which was elective or pre-planned, for a pre-existing condition that did not worsen
- Treatment on an emergency, outpatient basis for an event *not* fulfilling any of the definitions of serious given above and *not* resulting in hospital admission.
- Symptoms related to progressive disease such as bone pain will not be reported as toxicity or serious adverse events

Serious Adverse Events will be reported immediately to the MD Anderson IRB per the IRB policy for reporting adverse events.

<u>Special Reporting Situations</u>
When a report contains a J&J product, an identifiable patient, and identifiable reporter, the following events represent Special Reporting Situations:

- overdose of a Johnson & Johnson medicinal product
- pregnancy exposure (maternal and paternal)
- exposure to a medicinal product from breastfeeding
- suspected abuse/misuse of a medicinal Johnson & Johnson product
- inadvertent or accidental exposure to a medicinal Johnson & Johnson product
- any failure of expected pharmacological action (i.e., lack of effect) of a Johnson & Johnson medicinal product
- unexpected therapeutic or clinical benefit from use of a Johnson & Johnson medicinal product
- medication error involving a Johnson & Johnson 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.

8.2 Site Reporting Obligation to Janssen Scientific Affairs, LLC

All serious adverse events (regardless of relationship or expectedness) will be reported and documented on the Johnson & Johnson SAE form and forwarded directly to Janssen Scientific Affairs, LLC within **24 hours** of becoming aware of the event(s).

All non-serious AEs should be reported according to the timeframe outlined by MD Anderson policies.

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

In general, the INSTITUTION/PRINCIPAL INVESTIGATOR must immediately report to Janssen Scientific Affairs, LLC 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 Scientific Affairs, LLC. The INSTITUTION/PRINCIPAL INVESTIGATOR must record non-serious adverse events and report them to Janssen Scientific Affairs, LLC according to the timetable for reporting as specified either in the protocol 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 serious adverse event or Special Reporting Situations that is ongoing when a subject completes his/her participation in the Study must be followed until any of the following occurs:

- the event resolves or stabilizes;
- the event returns to baseline condition or value (if a baseline value is available);
- the event can be attributed to agents(s) other than the Study Product, or to factors unrelated to Study conduct.

8.2.2 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:

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

8.2.3 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 INSTITUTION/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, LLC's request.

8.2.4 Transmission Methods

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

- Facsimile (fax- 1-866-451-0371), receipt of which is evidences in a successful fax transmission report,
- Electronically subject to strict compliance with the following condition: Reporting may be done electronically only upon written approval by Janssen Scientific Affairs, LLC, which approval must acknowledge that the electronic transmission is in an acceptable encrypted email format. Without such acknowledgement, the approval to use an electronic transmission shall not be valid. The Parties hereby acknowledge the importance of strict precautions with the use of electronic transmission for the security, protection and maintenance of confidentiality of patient health information contained in the reports, or
- Telephone (for business continuity purposes, if fax or authorized electronic system is non-functional).

Please use the contact information and process information provided by Janssen Scientific Affairs, LLC

8.2.5 Procedures for Reporting Adverse Events (AE), Serious Adverse Events (SAE), Special Reporting Situation, and Product Quality Complaints (PQCs) to Janssen Scientific Affairs, LLC

8.2.5.1 Serious Adverse Events (SAE), Adverse Events of Special Interest, and Special Reporting Situations

In clinical trials involving the Study Product regardless of whether causality with the administration of the Study Product is suspected by the PRINCIPAL INVESTIGATOR.

The INSTITUTION/PRINCIPAL INVESTIGATOR will transmit these reports in a form to be provided (or a form substantially similar to the form provided and approved for use by Janssen Scientific Affairs, LLC in writing) in accordance with Section VII Transmission methods, in English within 24 hours of becoming aware of the event(s) along with their determination of whether the event was caused by a J&J product.

All available clinical information relevant to the evaluation of an SAE, Adverse Events of Special Interest, and Special Reporting Situations including pregnancy reports (with or without an AE) including paternal exposure are required.

- The INSTITUTION and/ or PRINCIPAL INVESTIGATOR is responsible for ensuring that these cases from clinical studies are complete and if not are promptly followed-up. This includes ensuring the reports are fully investigated and thoroughly documented by the PRINCIPAL INVESTIAGTOR and that follow-up information is summarized e.g. hospital records, coroner's reports, autopsy results and recorded on the appropriate forms.
- A study case is not considered complete until all clinical details needed to interpret the case are received and the event has resolved, or otherwise explained, or the patient is lost to follow-up. 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 Study Drug in the course of the Study, by facsimile within 24 hours of such report or correspondence being sent to applicable health authorities.

8.2.5.2 Product Quality Complaints

Any PQC, with or without an AE, (including reports of suspicion of counterfeiting, diversion, or tampering, and suspected transmission of pathogens) will be transmitted by the INSTITUTION and the PRINCIPAL INVESTIGATOR in the form provided by Janssen Scientific Affairs, LLC in accordance with Section VII Transmission methods, in English, within 24 hours of becoming aware of the event(s).

8.2.5.3 Reconciliation of SAEs

At a minimum, on a quarterly basis and at the end of the Study, Janssen Scientific Affairs, LLC will provide to the INSTITUTION and/or PRINCIPAL INVESTIGATOR, a listing of all SAEs reported to Janssen Scientific Affairs, LLC. PRINCIPAL INVESTIGATOR will review this listing and provide any discrepancies to the Janssen Scientific Affairs, LLC.

Upon request, INSTITUTION and PRINCIPAL INVESTIGATOR shall provide Janssen Scientific Affairs, LLC with a summary list of all SAEs, and AEs of Special Interest and Special Reporting Situation reports to date, for reconciliation purposes.

8.2.5.4 Dissemination of Safety Information from Janssen Scientific Affairs, LLC to INSTITUTION/PRINCIPAL INVESTIGATORS

Janssen Scientific Affairs, LLC will provide to the INSTITUTION/PRINCIPAL INVESTIGATOR IND safety reports/SUSAR (Serious Unexpected Suspect Adverse Reaction) reports generated by the Janssen Scientific Affairs, LLC 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).

8.3 Site Reporting Obligation to Medivation

In the case of a serious adverse event (SAE) for a patient receiving enzalutamide, the investigator must contact the delegated CRO by telephone or fax immediately (within 24 hours of awareness).The investigator should complete and submit an SAE Worksheet containing all information that is required by the Regulatory Authorities to the delegated CRO by fax immediately (within 24 hours of awareness). Please fax the SAE form to:

[redacted]

Full details of the SAE should also be recorded on the medical records.

The following minimum information is required:

- ISN/Study number
- Subject number, sex and age
- The date of report
- A description of the SAE (event, seriousness of the event)
- Causal relationship to the study drug

Collection of all SAEs must continue for 30 days after the last administration of the investigational product.

8.4 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 patient's CRF.

9 Dose Modification/Toxicity Management

9.1 Abiraterone Acetate

If a patient experiences **≥ Grade 3** adverse events (AE) that are, in the opinion of the investigator, possibly related to the study drug, treatment will be withheld until the toxicity resolves to within NCI CTCAE grade 1 criteria or normal limits. After resolution of a grade 3 adverse event, the patient may be retreated at full dose of therapy. Recurrence of the same toxicity (grade 3) will require dose reduction as outlined below.

If dose-reduction is used for AE management, 2 dose reductions are allowed. At each dose reduction, one tablet of abiraterone acetate will be removed, i.e., 4→3 tablets, and 3→2 tablets. If abiraterone acetate is held, prednisone therapy should continue uninterrupted. Any return to protocol dose level must follow documentation of AE resolution.

Management of Study Drug-Related Events

The most common adverse drug reactions (≥ 10%) reported in the two randomized clinical trials that occurred more commonly (> 2%) in the abiraterone acetate arm were fatigue, joint swelling or discomfort, edema, hot flush, diarrhea, vomiting, cough, hypertension, dyspnea, urinary tract infection and contusion.

The most common laboratory abnormalities (> 20%) reported in the two randomized clinical trials that occurred more commonly (≥ 2%) in the abiraterone acetate arm were anemia, elevated alkaline phosphatase, hypertriglyceridemia, lymphopenia, hypercholesterolemia, hyperglycemia, elevated AST, hypophosphatemia, elevated ALT and hypokalemia.

If abiraterone acetate is held, prednisone should be continued if the patient is expected to resume abiraterone acetate after resolution of the precipitating cause of the interruption in therapy.

Fluid Retention

Monitor for symptoms of fluid retention at least monthly.

Hypertension

Control hypertension before and during treatment with abiraterone acetate. Monitor blood pressure at least monthly.

Adrenocortical insufficiency

Use caution and monitor for symptoms and signs of adrenocortical insufficiency, particularly if patients are withdrawn from prednisone, have prednisone dose reductions, or experience unusual stress. Symptoms and signs of adrenocortical insufficiency may be masked by adverse reactions associated with mineralocorticoid excess seen in patients treated with abiraterone acetate. If clinically indicated, perform appropriate tests to confirm the diagnosis of adrenocortical insufficiency. Increased dosage of corticosteroids may be indicated before, during and after stressful situations.

Management of Hypokalemia

Correct hypokalemia before and during treatment with abiraterone acetate. Monitor serum potassium at least monthly.

At the initial observation of Grade 1 hypokalemia (serum potassium < 3.5 mM or below lower limit of normal range, but ≥ 3.0 mM), oral potassium supplement will be initiated. The dose of potassium supplement must be carefully titrated to maintain serum potassium at ≥ 3.5 mM but ≤ 5.0 mM. Any patient with low potassium while on study or a history of hypokalemia from a pre-existing or concurrent medical condition will undergo weekly or more frequent laboratory electrolyte evaluation. The investigator should consider maintaining the patient's potassium level at ≥ 4.0 mM in these patients.

If any patient experiences Grade 3 hypokalemia (serum potassium levels < 3.0 mM – 2.5mM, NCI CTCAE v4.0) or life-threatening hypokalemia with potassium levels < 2.5 mM (NCI CTCAE v4.0 hypokalemia Grade 4), abiraterone acetate treatment will be withheld, and the patient hospitalized for intravenous potassium replacement and cardiac monitoring.

Re-initiation of abiraterone acetate treatment after normalization of potassium levels must be discussed with the PI. No dose reduction is required when abiraterone acetate is resumed after hypokalemia.

Management of Hepatic Impairment

For subjects with baseline hepatic impairment or those that develop hepatoxicity, please refer to mandatory dose modification guidelines below.

In patients with baseline moderate hepatic impairment (Child-Pugh Class B), reduce the recommended dose of abiraterone acetate to 250 mg once daily. A once daily dose of 250 mg in patients with moderate hepatic impairment is predicted to result in an area under the concentration curve (AUC) similar to the AUC seen in patients with normal hepatic function receiving 1,000 mg once daily. However, there are no clinical data at the dose of 250 mg once daily in patients with moderate hepatic impairment and caution is advised. In patients with moderate hepatic impairment monitor ALT, AST, and bilirubin prior to the start of treatment, every week for the first month, every two weeks for the following two months of treatment and monthly thereafter. If elevations in ALT and/or AST greater than 5X upper limit of normal (ULN) or total bilirubin greater than 3X ULN occur in patients with baseline moderate hepatic impairment, discontinue abiraterone acetate and do not re-treat patients with abiraterone acetate.

Avoid abiraterone acetate in patients with baseline severe hepatic impairment (Child-Pugh Class C), as abiraterone acetate has not been studied in this population, and no dose adjustment can be predicted.

Hepatotoxicity

Serum transaminases (ALT and AST) and bilirubin levels should be measured prior to starting treatment with abiraterone acetate, every two weeks for the first three months of treatment and monthly thereafter. Promptly measure serum total bilirubin, AST, and ALT, if clinical symptoms or signs suggestive of hepatotoxicity develop. Elevations of AST, ALT, or bilirubin from the patient's baseline should prompt more frequent monitoring.

For patients who develop hepatotoxicity during treatment with abiraterone acetate (ALT and/or AST greater than 5X ULN or total bilirubin greater than 3X ULN), interrupt treatment with abiraterone acetate. Treatment may be restarted at a reduced dose of 750 mg once daily following return of liver function tests to the patient's baseline or to AST and ALT less than or equal to 2.5X ULN and total bilirubin less than or equal to 1.5X ULN. For patients who resume treatment, monitor serum transaminases and bilirubin at a minimum of every two weeks for three months and monthly thereafter.

If hepatotoxicity recurs at the dose of 750 mg once daily, re-treatment may be restarted at a reduced dose of 500 mg once daily following return of liver function tests to the patient's baseline or to AST and ALT less than or equal to 2.5X ULN and total bilirubin less than or equal to 1.5X ULN.

If hepatotoxicity recurs at the reduced dose of 500 mg once daily, discontinue treatment with abiraterone acetate. The safety of abiraterone acetate re-treatment of patients who develop AST or ALT greater than or equal to 20X ULN and/or bilirubin greater than or equal to 10X ULN is unknown.

Drug/Drug Interaction

Per Section 1.3.1.2: Drug Interactions, Strong inducers of CYP3A4 (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital) during treatment with ZYTIGA are to be avoided, or used with careful evaluation of clinical efficacy. Closely monitor clinical efficacy in patients taking strong inducers of CYP3A4.

9.2 Enzalutamide

Subjects who experience a Grade 3 or greater toxicity considered to be related to enzalutamide that cannot be ameliorated by the use of adequate medical intervention should have their treatment interrupted until the toxicity improves to a Grade 2 or lower severity. Subjects may subsequently be re-started on study drug at a reduced dose follow a discussion between the Principal Investigator. Subjects will remain on abiraterone acetate and prednisone during enzalutamide dose interruption.

No dose reductions for prednisone are allowed. Subjects experiencing toxicity considered to be related to the use of prednisone for which a dose reduction is needed cannot participate in the study any longer.

9.3 General

Subjects should be able to take all three study drugs (abiraterone acetate, enzalutamide, and prednisone) to participate in the study. An interruption of one of these drugs is allowed as per instruction above. Permanent discontinuation of one of the drugs, while continuing the two other drugs, is not allowed.

10 Criteria for Discontinuation of Study Treatment

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

- The patient completed 6 months of study treatment;
- 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 with 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 EOS visit;
- Dosing noncompliance: study treatment administration and dosing compliance will be assessed on Day 1 of all cycles, and at Pre-surgery/End of Study Visit. A count of study treatment will be conducted during this visit and patient dosing compliance will be assessed. If dosing compliance is not $\geq$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 EOS 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 EOS Visit;
- Administration of prohibited medications: the patient will be discontinued from the protocol treatment when prohibited drug is administered (Section 6.1.3.1). All end-of-study treatment procedures should be conducted and the patient will be followed to the EOS 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 prednisone for which a dose reduction is needed will require discontinuation of study drugs.

10.1 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.

11 Planned Statistical Methods

11.1 General Considerations

All statistical analyses will be performed using SAS®. Unless otherwise specified, all continuous endpoints will be summarized using descriptive statistics, which will include the number of patients (n), mean, standard deviation, median, minimum, and maximum. All categorical endpoints will be summarized using frequencies and percentages. The baseline measurement will be the last value on or before the date of first study treatment.

11.2 Determination of Sample Size

A total of approximately 66 patients will be randomized in a ratio of 2:1 to Group A (approximately 44 patients) and Group B (approximately 22 patients), respectively. This sample size will have 80% power to detect the difference of proportions of ≤pT2 disease between Group A (proportion of 0.8) versus Group B (proportion of 0.5), using a two-sided Chi-squared test at a significance level of 0.1. All patients randomized to the study will be considered for the summary of baseline characteristics. Patients who have undergone prostatectomy will be evaluable for the primary endpoint, pT2. 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. Patients who drop out of the study or are withdrawn prior to the evaluation of the primary endpoint will be counted as failures in the primary efficacy analysis.

11.3 Analysis Population

All patients randomized into the study will be included in the analysis of efficacy/biochemical related endpoints. Patients who received any part of a study drug will be included in the analysis of safety (Safety Population).

11.4 Demographics and Baseline Characteristics

Demographic variables will include age, race, ethnicity, height, and weight. Baseline disease characteristics include time from diagnosis and other clinical characteristics (as documented in the CRF) will be provided in summary tables.

11.5 Study Endpoints

11.5.1 Primary Efficacy Endpoint

The proportion of patients with ≤pT2 will be descriptively summarized and compared using Chi-squared test. Other tests may be used if appropriate.

11.5.2 Secondary Efficacy Endpoints

The proportion of patients expressing differences in androgen signaling and related genes markers, the difference in the rate of positive surgical margins between the two groups, and proportion of patients with PSA≤0.2 ng/mL will be descriptively summarized.

No interim analysis is planned.

11.6 Safety Evaluations

11.6.1 Summary of Safety Monitoring

The safety monitoring will be based on a beta-binomial distribution [18]. With prostatectomy alone, the historical probabilities of death and rectal injury in this patient group (based on about 60 patients) are 0.15 and 0.30, respectively. Denote the probabilities of death and rectal injury within a given treatment group by pH,D and pH,R for historical data, and pE,D and pE,R for the experimental data. Group A will be terminated early if either Pr[pH, D<pE, D | data] > 0.95 or Pr[pH, R < pE, R | data] > 0.95. The prior of pH, D is beta (9, 51) and theprior of pH, R is beta (18, 42); the prior of pE, D and pE, R is beta(1,1). Applying these rules and starting from the 4th patient, Group A will be terminated if [# deaths]/[# patients evaluated]≥ 2/4, 3/5-8, 4/9-12, 5/13-15, 6/16-19, 7/20-23, 8/24-27, 9/28-32 or 10/33-36, 11/37-40, or 12/41-43; or [#patients with a rectal injury]/[# patients evaluated] ≥ 3/4, 4/5-6, 5/7-8, 6/9-10, 7/11-13, 8/14-15, 9/16-17, 10/18-20, 11/21-22, 12/23-24, 13/25-27, 14/28-29, 15/30-32, 16/33-34, 17/35-36, 18/37-39, 19/40-41, or 20/42-43. Tables 1 and 2 below demonstrate the operating characteristics for the Bayesian monitoring rules for death and rectal injury, respectively. If complications from LHRH agonist, abiraterone acetate, or enzalutamide delay prostatectomy by greater than 3 months, the study enrollment will be temporarily held for safety analysis.

Table 1. Operating characteristics of the Bayesian monitoring rule for death.

True death rate	Early stopping probability	Average sample size
0.10	0.083	40.9
0.15	0.218	36.4
0.20	0.431	29.9
0.30	0.851	16.4
0.40	0.988	8.7

Table 2. Operating characteristics of the Bayesian monitoring rule for rectal injury.

True death rate	Early stopping probability	Average sample size
0.20	0.041	42.4
0.30	0.184	37.7
0.40	0.528	27.7
0.50	0.878	16.1
0.60	0.991	9.0

MultcLeanDestop: Version 2.0 was used to generate the above design output, including the safety stopping boundaries and the operating characteristic tables.

The theoretical definition for rectal injury is surgically induced perforation requiring a temporary colostomy.

11.6.2 Safety Analysis

Safety analysis will be summarized using the Safety Population. AEs will be graded and summarized according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

Extent of exposure to study drug will be summarized and details will be provided.

Treatment emergent adverse events (AEs) are those events that occur or worsen on or after first dose of study drug up through 30 days post last dose.

Incidence of adverse events will be summarized by system organ class (SOC) and preferred term (PT), and will be presented for overall and by treatment period, as appropriate. Adverse events will be summarized by grade. In addition, most frequently observed adverse events will be summarized by treatment groups. In the summary of AE, an AE occurs more than once within a SOC and PT will be counted only once using the worst grade experienced.

Serious adverse events and deaths will be provided in a listing. All adverse events resulting in discontinuation, dose modification, dosing interruption, and/or treatment delay of study drug will also be listed and tabulated by preferred term.

Clinical laboratory test results will be collected pretreatment and through 30 days post last dose of study treatment. All laboratory test results will be classified according to the NCI CTCAE 4.0 criteria. Standard reference ranges will be used for missing or discrepant normal ranges. Baseline laboratory test values are the results from the last blood samples drawn on or prior to the first day of study treatment. On-study laboratory test values are those results from blood samples drawn after the first study treatment up until 30 days after the last dose of study treatment.

Mean change from baseline in laboratory test values at each visit will be provided. On-study clinical laboratory test abnormalities will be summarized. Shifts in laboratory test values will also be provided.

12 Correlative Procedures (for exploratory endpoints)

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 analyses will be performed after IRB approval for patients who have consented to the testing.

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 Web-based custom application Clinic Station, which stores clinical information and care reports of patients who are being treated at MDACC. Access to Clinic Station 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. Unused samples will be destroyed 5 years after the last study visit.

12.1 Steroid Metabolome and Proteonomics

Steroid Metabolome and Proteonomics will be assayed in the Laboratory of Dr Mark Titus at MD Anderson using Agilent 6490 mass spectrometer. Peripheral Blood will be obtained at baseline (screening), on day one of cycles 1, 2 plus 3, pre-prostatectomy and at post-prostatectomy visit. A total of twenty (20) ml of blood will be collected in Serum No Additive (2 red top no additive tubes) for study hormone levels Peripheral blood will be collected into the vacutainer and allowed to clot (upright) at room temperature for 20 minutes prior to centrifugations. Samples are centrifuged at 4^{o}C for 20 minutes at 1200xg. The serum is removed and aliquoted into multiple cryovials (minimum of three). All samples are processed and frozen within 2 hours of collection. The serum will stored frozen at -80^{O}C in the GU biorepository located at MDACC until they are transported to the laboratory for analysis. Serum will be assayed for total testosterone, DHT, androstenedione, DHEA, DHEA-S, estradiol, progesterone, 3α-diol-G, steroid biosynthesis metabolome, and applied markers of minimal residual disease. Post prostatectomy only serum testosterone, DHT, steroid biosynthesis metabolome, and applied markers of minimal residual disease will be measured.

12.2 Prostate Tissue Handling

12.2.1 Archival prostate biopsies

An archival tumor tissue block (or at least 10 unstained slides from the tumor tissue block; archived or recent) or fresh frozen tissue in liquid nitrogen will be required from the patient's initial prostate biopsy. These will be reviewed by the pathologist for confirmation of cancer and Gleason scoring. The patient will not be required to undergo a second biopsy procedure prior to starting study therapy (screening) if archival biopsies are available.

12.2.2 Prostatectomy specimen

In order to preserve androgen levels in tissues, open intraoperative cores biopsies will be obtained prior to prostatectomy. The biopsies must be obtained prior to ligation of the vascular supply to the prostate. A minimum of 6 biopsies will be obtained attempting to focus on known regions of cancer. Each biopsy core should be placed in a separate 2 ml screwtop cryotube and immediately snap frozen in liquid nitrogen or dry ice/ethanol bath and stored at -80°C. If there is palpable tumor, it is recommended that at least 3 cores be obtained from the area of suspected tumor.

To process the radical prostatectomy specimen post-operatively, the following procedures must be followed.

- The prostate will be inked in four colors depicting left, right, superior and inferior sections and serially sectioned.
- Alternate coronal sections will be numbered sequentially from apex to base, divided into 4 quadrants (also labeled clockwise from the superoposterior quadrant as A, B, C, D) and immediately frozen in OCT (liquid nitrogen or dry ice/ethanol bath) for subsequent evaluation. The alternate sections will be placed in formalin, then processed and imbedded in paraffin using the tissue-tek®vip® 6 system (for histology analysis) and stored in the Prostate Tissue Bank at MDACC for future analysis. The coronal sections embedded in OCT will be stored, in the GU biorepository located at MDACC, for future analysis. Any future additional analyses not specified in this protocol will be agreed upon by prior approval from Janssen Scientific Affairs, LLC.

12.3 Tissue Androgen Measurements

Prostate tumor and normal prostate tissue will be obtained by macrodissection when possible. Testosterone and DHT will be analyzed by a research laboratory at MD Anderson.

12.4 Immunohistochemistry

Standard methods will be used to assess prostate tumor for AR, CYP17, CD31, VEGF, VEGFR, and other relevant biomarkers plus proteins associated with steroid metabolism and prostate cancer.

Comprehensive characterization of the process of known and candidate pathways implicated in PCa progression and resistance to therapy: cellular PTEN,P53, Rb : stromal epithelial pathways : Src, Phos CMet ,Hedgehog, VEEGFR2

12.5 RNA Analysis

Transcriptomic characterization of the tumor will be conducted in the Laboratory of Dr Mark Titus at MD Anderson. Where available, analysis will be carried out on the pre-prostatectomy specimens and prostatectomy specimens using fresh frozen tissue (section 12.3) for primary tumor, normal tissue and metastatic tissue. RNA Analysis will include long non coding RNA (lnRNA) examples as per www.lncrnadb.org ; oncomir RNA; and micro RNA (miRNA) such as #205, 146, 1256 and let7.

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