ARN-509 + Abiraterone acetate + Leuprolide with Stereotactic, Ultra-Hypofractionated Radiation (AASUR) in Very High Risk Prostate Cancer: A Single Arm, Phase II Study

Prostate Cancer Clinical Trials Consortium, LLC (PCCTC)

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Principal Investigator
Sean M. McBride, MD, MPH
Memorial Sloan Kettering Cancer Center
1275 York Avenue
New York, NY 10021

McBrides@mskcc.org

Statistician
Zhigang Zhang, PhD
Memorial Sloan Kettering Cancer Center
1275 York Avenue
New York, NY 10021

email: zhangz@mskcc.org

Co-Investigators
Dana Rathkopf, MD
Memorial Sloan Kettering Cancer Center
1275 York Avenue
New York, NY 10021

rathkopd@mskcc.org

Marisa Kollmeier, MD
Memorial Sloan Kettering Cancer Center
1275 York Avenue
New York, NY 10021

Kollmeim@mskcc.org

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APPROVAL OF PROTOCOL

Title: *ARN-509 +Abiraterone acetate +Leuprolide with Stereotactic, Ultra-Hypofractionated Radiation (AASUR) in Very High Risk Prostate Cancer: A Single Arm, Phase II Study*

Sponsor/Principal Investigator Signature: _____

Print: _____

Date: _____

Principal Statistician Signature: _____

Print: _____

Date: _____

PCCTC Signature: _____

Print: _____

Date: _____

PROTOCOL AGREEMENT

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision and providing Memorial Sloan Kettering Cancer Center with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted GCP principles and to abide by the terms of this protocol.

Principal Investigator Signature: _____

Principal Investigator Print: _____

Date: _____

TABLE OF CONTENTS

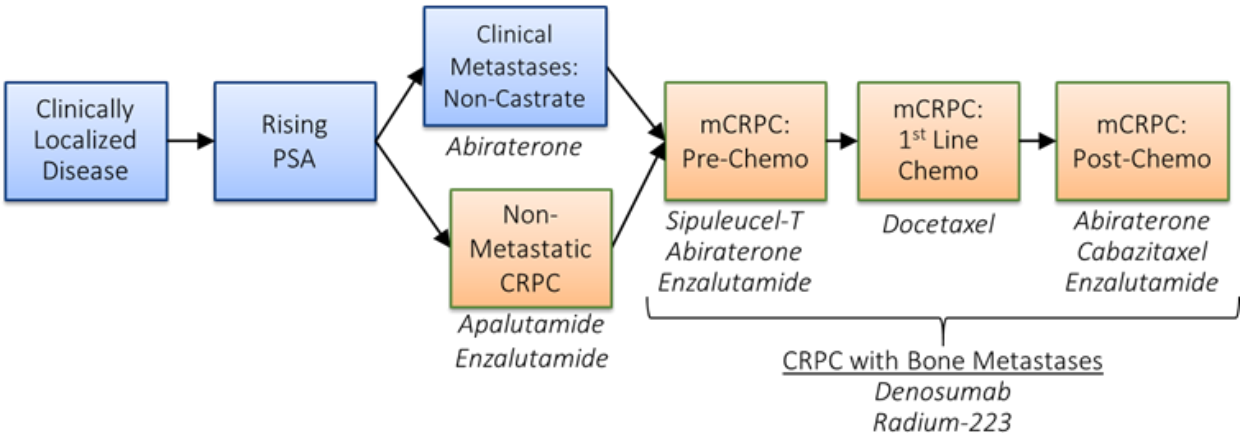
1. INTRODUCTION

1.1 Disease Background

Prostate cancer is the second leading cause of cancer deaths in men. According to American Cancer Society estimates, in 2015 as many as 220,800 American men will be diagnosed with prostate cancer, and nearly 27,540 will die of the disease (1). Yet, localized prostate carcinoma is often curable, and even metastatic disease frequently responds to treatment.

The course of prostate cancer from diagnosis to death is best categorized as a series of clinical states (Figure 1). These clinical states involve the complex interplay of a network of signaling molecules that collectively promote net cell proliferation relative to cell death. Based on the extent of disease, hormonal status, and absence or presence of detectable metastases on an imaging study, the states are localized disease, rising levels of prostate- specific antigen (PSA) after radiation therapy or surgery with no detectable metastases, and clinical metastases in the non-castrate or castrate state.

Figure 1. Clinical states of prostate cancer



1.2 Treatment Background and Rationale

Over the past two decades, the Radiation Therapy Oncology Group (RTOG) has conducted two pivotal phase III trials which have established the combination of radiotherapy and androgen deprivation therapy (ADT) as a standard of care for patients with high-risk prostate cancer. In the 226 high risk patients enrolled on RTOG 94-08, 4 months of neoadjuvant and concurrent combined androgen blockade (Flutamide and Lupron) led to a 19% absolute decrease in biochemical failure and an 8% absolute improvement in overall survival (OS) at 8 years (2). Furthermore, RTOG 92-02 showed that, compared to four months of combined androgen blockade, an additional 28 months of post-radiotherapy treatment with an LHRH agonist further decreased biochemical failures and improved OS in the group of patients with Gleason 8-10 disease (3).

Despite the additional benefit that standard ADT afforded, biochemical failure in the phase III trials remained frequent (5-year biochemical recurrence free survival of only 55% in RTOG 92-02). However, in the aforementioned RTOG trials, dose given to the prostate was less than 70 Gy. Both Kuban, et al and Zelefsky, et al have shown that in high risk patients, dose beyond 70 Gy leads to significant improvements in biochemical control with acceptable toxicities (4, 5). Modern series have confirmed lower rates of biochemical failure using these higher radiation doses in high risk patients (6). But there is a sub-stratum of

high risk patient, variably defined, that continues to have substantial short term risk of PSA recurrence. Shilkrut, et al reported a 5-year biochemical recurrence free survival in this very high risk (defined as patients with >1 high risk feature) group after dose-escalated EBRT and long-term ADT of 60% (7). Narang, et al defined very high risk prostate cancer as patients having >1 high risk feature, or > 4 cores of Gleason 8-10 disease, or primary pattern 5 disease; in this cohort 10-year biochemical recurrence free survival was 38.1% (8). Epstein, et al have reported similarly poor results for Gleason Group 5 patients: defined as those with any Gleason Score 9 or 10 disease.

In order to achieve even these modest results in the very high risk cohort, the length of therapy and extent of toxicity, especially substantial cardiovascular sequelae secondary to ADT, is substantial (9, 10). In the EORTC study of short course versus long course ADT, only 70% of patients completed the prescribed 2 years of adjuvant LHRH agonist therapy (11). And for those who did complete the protracted therapy, it took upwards of two-years for testosterone to return to baseline with all the attendant side effects that came along with such lengthy suppression (12).

The future of definitive radiotherapy trials in the treatment of very high risk prostate cancer should thus focus on two goals: 1) further decreasing the rates of biochemical failure and 2) limiting the length of ADT in order to reduce the negative impact on quality-of-life. These two goals will likely require a combination of further radiation dose escalation and more complete androgen suppression.

One method of dose escalation is the combination of brachytherapy and external beam radiation (13), however widespread utilization of this technique has been limited by the technical complexity required to implement the treatment thus restricting its use to a few high-volume centers. Because of the putative low alpha-beta ratio of prostate cancer, stereotactic, hypofractionated radiation therapy has the advantage of being able to deliver substantial increases of dose to intra-prostatic disease (14). In addition, because the technical requirements are more manageable, it is a treatment that both academic medical centers and community practices can implement safely and effectively. It has the added benefit of a total delivery time (approximately 1.5 weeks) that is greatly decreased compared to the current radiotherapy standard of care that requires 9 weeks or more of daily treatment.

The use of LHRH agonists in the RTOG trials likely failed to completely inhibit androgen responsive gene expression (15), produce levels of testosterone below 20 ng/dL (16), or eradicate prostate cancer clonogens capable of surviving in low-androgen environments (17). It is in overcoming these resistance mechanisms that the second-generation anti-androgens have had their greatest impact: Abiraterone has demonstrated its capacity to dramatically reduce circulating levels of testosterone and thus more effectively suppress the androgen axis (18). Because of its ability to improve OS in the metastatic, castrate- resistant prostate cancer (CRPC) patients, abiraterone is now approved by the FDA for use in that setting (19). Enzalutamide is an oral androgen receptor (AR) antagonist with a binding affinity five to eight times that of bicalutamide. Enzalutamide's binding to the C- terminal portion of the AR inhibits nuclear translocation, DNA binding, and coactivator peptide recruitment (20). This potent antagonism of AR led to a phase III trial demonstrating that enzalutamide conferred an OS benefit on post-docetaxel treated patients (21). The most recently designed AR antagonist, apalutamide, demonstrated *in vitro* potency superior to even enzalutamide, a potential property that can only increase its therapeutic index (22). Indeed, in a recently reported phase I trial, apalutamide

demonstrated maximal AR inhibition at doses well below the maximum tolerated dose (MTD); no patients on trial experienced seizures, a potentially limiting toxicity of enzalutamide (23).

Our central hypothesis is that stereotactic, hypofractionated radiotherapy delivered with a total of 6 months of apalutamide, abiraterone, and leuprolide will result in a superior 3 -year rate of biochemical control compared to the historical control of conventionally fractionated radiation therapy (42-48 treatments) and long term ADT (28-36 months) in patients with very high risk prostate cancer.

1.2.1 Ultra-Hypofractionated, Stereotactic, Image Guided, Intensity Modulated Radiotherapy

Although several randomized controlled trials have demonstrated improvements in biochemical failure-free survival using conventionally fractionated (1.8 Gy- 2.0 Gy per day) regimens, these schedules do not permit further escalation beyond doses currently used because of the unacceptably high rates of acute and late toxicities that could occur. These dose-limiting toxicities with conventional fractionation have led to the investigation of new approaches with hypofractionated regimens that would increase tumor cell killing while maintaining or decreasing normal tissue toxicities. These outcomes are conceivable because of the potentially unique radiobiologic properties of prostate cancer as explained below.

1.2.1.1 Radiobiology of Prostate Cancer

The linear-quadratic (LQ) model of cell survival has long been used to predict and understand the effects of fractionated external beam radiation therapy on tumors and surrounding normal tissue. In addition, the LQ model provides us with a means to compare the biologic effect of different dosing regimens on tumors and the variety of surrounding normal tissues.

In the LQ model, the surviving fraction (S) of a homogenous population of cells is assumed to be proportional to two variables: one variable proportional to the dose administrated (alpha) and one proportional to the square of the administered dose (called beta). The LQ equation for a fractionated regimen of radiation is thusly described $S=exp[-D(\alpha+\beta D/n)]$, wherein S is the proportion of cells surviving in the irradiated volume, D is the total dose, and n is the number of fractions used to deliver D. Alpha purportedly represents the intrinsic radiosensitivity of the cellular population caused by non-repairable injury; it is the initial slope of the cell survival curve and is linearly dependent with dose. Beta represents cell injury that is repairable over time and is responsible for changes in cell survival when the dose-per-fraction or dose-rate is altered. Beta increases with long cell cycle times due to repair processes, is responsible for the curvature of the cell survival cure, and is proportional to the square of the administered dose (24).

The ratio of alpha to beta (alpha-beta ratio) describes a cell population's ratio of intrinsic radiosensitivity to its repair capacity. It also predicts the sensitivity of a cellular population to changes in fraction size. Cells with high alpha/beta ratios are relatively insensitive to changes in fraction size, whereas cells with low alpha/beta ratios are very sensitive to changes in fraction size.

Most tumors have rapidly proliferating cell populations with high alpha/beta ratios of approximately 10, making them relatively insensitive to changes in fraction size. Normal tissues are divided into acutely reacting and late reacting tissues, with the former having alpha/beta ratios of 9-12 and the latter 2-5. Normal tissues with low alpha/beta ratios are more sensitive to dose per fraction.

The LQ model allows for the calculation of a biologically effective dose (BED). The BED provides a quantitative indication of biologic effect that takes into account changes in dose-per-fraction, total dose, and overall treatment time; any two regimens with the same BED will kill the same proportion of cells in a given tissue (tumor or normal). Another value that can be calculated based upon the LQ model is a biologically equivalent dose (EQD); this is the total dose in 1.8 Gy or 2 Gy fractions that would be equivalent to the proposed treatment schedule.

To maximize the therapeutic ratio, a fractionation schedule of radiotherapy should optimize the dose per fraction sensitivity of the tumor relative to that of the nearby critical normal tissues (e.g., bladder, rectum, small bowel, etc.). In most other cancers treated definitively with radiotherapy, adjacent normal late-responding tissues are more sensitive to increase in dose per fraction than the tumor itself; for this reason, small daily doses of radiation typically maximize the long-term therapeutic ratio.

An emerging body of literature suggests that prostate cancer cells are radiobiologically unique compared to most tumors because they have an alpha/beta ratio much lower than 10. A recent comprehensive literature review of 17 such studies found a calculated alpha/beta ratio of 1.5 to 1.8 (25). As such, prostate cancers have a usually high sensitivity to larger doses per fraction. With adjacent normal tissue having a higher alpha/beta ratio (the alpha-beta for late rectal toxicity has been calculated at 4.8, albeit with wide confidence intervals (26)), it should be possible to improve the therapeutic ratio by delivering hypofractionated (more dose per fraction over fewer fractions) regimens of radiation. This should improve biochemical control while maintaining a constant rate of acute and late toxicities (27). The below Table 1 illustrates the associated BED values for prostate cancer, acute responding normal tissue (i.e., tissue with high alpha/beta ratios that express injury during or within 2-3 weeks of radiation), and late responding normal tissue (i.e., tissues with low alpha/beta ratios that express injury several months to years after radiation) comparing the stereotactic, hypofractionated regimen to the Memorial Sloan Kettering Cancer Center (MSK) conventional regimen.

Table 1. Associated BED values for prostate cancer, acute responding normal tissue, and late responding normal tissue

Scheme	Dose/Fraction (Gy)	Fractions	Absolute Dose (Gy)	BED Tumor (α/β=1.5)	BED Acute (α/β=10)	BED Late Rectal (α/β=3)*
Prostate	7.5-8	5	37.5-40	225-253.33	65.6-72.0	131.3-146.7
Pelvis	5	5	25	108.3	37.5	66.7
MSK Standard Prostate	1.8	48	86.4	190.1	101.95	138.2
MSK Standard Pelvis	1.8	25	45	99.00	53.10	72.0

*Marzi, et al *Modeling of alpha/beta for late rectal toxicity from arandomized phase II study: conventional versus hypofractionated scheme for localized prostate cancer*. J Exp Clin Cancer Res. 2009;28:117.

Table 1 demonstrates the theoretical quantitative improvement in the therapeutic ratio using the proposed regimen: an increase in the biologically effective dose to tumor and a relative parity in the biologically effective dose to normal surrounding tissue, be they acute or late responding. The proposed dose to the prostate is equivalent to 115.2 Gy in 1.8 Gy fractions.

1.2.1.2 Clinical Experience with Hypofractionated External Beam Radiation

There are two published randomized controlled trials examining moderate hypofractionated regimens in the treatment of prostate cancer. Arcangeli, et al reported on a prospective phase III trial comparing moderate hypofractionation (62 Gy in 20 fractions) to conventional fractionation (80 Gy in 40 fractions) in the treatment of patients with high risk prostate cancer (28). The equivalent dose in 1.8 Gy fractions for the hypofractionated arm was 86.4 Gy, comparable to our current conventional standard of care at MSK. The authors found no difference in late GI or GU toxicities between the two arms; the 3-year rates of Grade 2 GI toxicity were 17% and 16% comparing the hypofractionated to conventionally fractionated arms, respectively; the rates of GU Grade 2 GU toxicity were 14% and 11% for the hypofractionated and conventionally fractionated arm, respectively. As predicted by the LQ model, these were not significant differences. More compelling, in their "very high risk" sub-group (initial PSA>20 ng/mL or Gleason ≥8, or T stage ≥2c), the 3-year freedom from biochemical failure was 88% for the hypofractionated arm compared to 76% for the conventionally fractionated arm (p=0.014). All patients received 9 months of combined androgen blockade that was initiated 2 months prior to the start of radiotherapy.

Conversely, Pollack, et al reported a phase III trial comparing 70.2 Gy in 26 fractions to 76 Gy in 38 fractions for favorable to high risk prostate cancer patients (29). They found no statistically significant differences in the 5-year rates of biochemical failure: 21.4% for the conventional arm versus 23.3% for the hypofractionated arm (p=0.745). Of note, the equivalent 1.8 Gy per fraction dose of 70.6 Gy in 26 fractions is 89.3 Gy. Again, rates of late toxicity were not significantly different.

The largest and most robust clinical report of ultra-hypofractionation is a pooled analysis from a multi-institutional consortium of prospective phase II trials reported by King, et al (30). This included a cohort of 125 patients with high risk disease by D'Amico classification treated with doses ranging from

35 to 40 Gy in five fractions, 38% of whom received short course (median 4 month) ADT. Although median follow-up for this group was only 23 months, they reported 5-year biochemical recurrence free survival of 82%. Of note, pelvic lymph nodes were not irradiated.

A separate report on health-related quality of life outcomes (HR-QOL) in the larger cohort using the Expanded Prostate Cancer Index Composite (EPIC), with a median follow-up of 3 years, found a transient decline in urinary and bowel domains which returned to baseline by 6 months (31). One-hundred and ninety-four patients were evaluable at 5 years. With such extended follow-up, the probability of substantial late toxicities being under-reported due to inadequate follow-up is slight.

None of the ultra-hypofractionated (five fractions) trials included the pelvic lymph nodes in the irradiated field. There is no consensus regarding the treatment of pelvic lymph nodes in high risk prostate cancer; as such there is substantial institutional variability with regards to their inclusion (32). Two prospective, randomized controlled trials have demonstrated no benefit to the expansion of the radiotherapy fields to include the nodal basins (33, 34). Furthermore, recent data from a trial of ultra-hypofractionated radiation in high risk, N0 patients revealed unacceptable toxicities with the addition of pelvic lymph nodes. As such, the pelvic lymph nodes will not be treated in this trial. We expect that the total androgen annihilation (lupron+abiraterone+apalutamide) involved in this trial will eliminate any micrometastatic disease in the lymph nodes.

1.2.1.3 Intensity-Modulated and Image-Guided Radiation Therapy

Intensity-modulated radiation therapy (IMRT) in prostate cancer has proven to decrease the acute and late toxicity from definitive external beam radiation therapy by delivering highly conformal dose distributions (35). IMRT techniques have benefited from the addition of image-guided radiation (IGRT) techniques, where sophisticated imaging algorithms allow daily target localization prior to and during treatment. IGRT minimizes interfraction uncertainty, or variability in the target position from fraction to fraction, and intrafraction variability, or variability of the target position during administration of a fraction of radiation. Specifically, placement of localization markers in the prostate gland before a course of external beam radiotherapy allows daily target localization with in-room imaging during administration of a fraction of radiation. For all patients undergoing stereotactic, hypofractionated radiation, we have routinely placed Calypso markers into the prostate prior to treatment. These are radiofrequency transponders placed into the prostate prior to simulation. These are powered by a non-ionizing oscillating electromagnetic field created by an electromagnetic array placed anterior to the supine patient. The location of the transponders in the prostate is then determined by triangulating their position relative to the array.

At the time of the planning CT, the three transponders as well as the treatment isocenter are recorded and input into the Calypso 4D tracking station. Just before treatment, the Calypso system directs lateral, longitudinal, and vertical shifts by comparing the planned and measured

coordinates of the three transponders. After initial localization, the Calypso transponders relay real-time information on any intra-fraction prostate motion while the treatment beam is on. Intra-fraction movement beyond 2mm from initial set-up causes treatment to cease until the target has moved back into position. This level of target precision permits reduced target volumes, less treatment associated toxicities, and safe administration of large daily fractions of radiation. Successful applications of image-guided, hypofractionated radiation therapy have been reported in numerous sites other than prostate, including lung, CNS, pancreas, bones, lymph nodes, and soft tissue.

1.2.2 Abiraterone Acetate

Abiraterone acetate is converted in vivo to abiraterone, an androgen biosynthesis inhibitor, that inhibits 17α-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. Androgen sensitive prostatic carcinoma responds to treatment that decreases androgen levels. Androgen deprivation therapies, such as treatment with GnRH agonists or orchiectomy, decrease androgen production in the testes but do not affect androgen production by the adrenals or in the tumor. Abiraterone acetate decreased serum testosterone and other androgens in patients in the placebo-controlled Phase 3 clinical trial. It is not necessary to monitor the effect of abiraterone acetate on serum testosterone levels. Changes in serum prostate specific antigen (PSA) levels may be observed but have not been shown to correlate with clinical benefit in individual patients.

1.2.2.1 Pharmacokinetics and Metabolism

The pharmacokinetics of abiraterone and abiraterone acetate have been studied in healthy subjects and in patients with metastatic CRPC. *In vivo*, abiraterone acetate is converted to abiraterone. In clinical studies, abiraterone acetate plasma concentrations were below detectable levels in >99% of analyzed samples.

Following oral administration of abiraterone acetate to patients with metastatic CRPC, the median time to reach maximum plasma abiraterone concentrations was two hours. Abiraterone accumulate was observed at steady-state, with a 2-fold higher exposure compared to a single 1000 mg dose of abiraterone acetate.

At the dose of 1000 mg daily in patients with metastatic CRCP, steady-state values of Cmax were 232 ±177 ng/mL and of AUC were 1060 ±681 ng.hr/mL. No major deviation from dose proportionality was observed in the dose range of 250 mg to 1000 mg.

Systemic exposure of abiraterone is increased when abiraterone acetate is administered with food. Abiraterone C_{max} and AUC were approximately 7- and 5-fold higher, respectively, when abiraterone acetate was administered with a low fat meal and approximately 17- and 10-fold higher, respectively, when abiraterone acetate was administered with high-fat meal.

1.2.3 Apalutamide

Apalutamide is an orally available, potent, and selective AR antagonist that acts by inhibiting nuclear translocation of AR and its subsequent binding to DNA androgen response elements (ARE). Unlike bicalutamide, it shows no significant agonist properties in an *in vitro* model of CRPC. Gene transcription of the AR-driven genes, PSA and TMPRSS2, is inhibited by apalutamide and results in concentration-dependent reduction of these protein levels *in vitro*. Apalutamide was also shown to reduce proliferation of CRPC cells as well as increase apoptosis and necrosis *in vivo*. These effects are supported by the anti-tumor activity of apalutamide observed in murine tumor models of CRPC.

In a first-in-human phase I trial of apalutamide in metastatic CRPC patients, 60% of patients had a ≥50% decline in PSA as compared with baseline, and of those, six (20%) had a ≥90% decline. More importantly for our own proposed study, in a phase II trial looking at the sub-group of patients with non-metastatic CRPC (n=47), at 12 weeks, PSA response was 91% and the median time to progression had not yet been reached (36).

In a recently published, randomized phase 3 trial involving men with nonmetastatic castration-resistant prostate cancer, the risk of metastasis or death was 70% lower with apalutamide than with the placebo. The median metastasis-free survival was more than 2 years longer than the placebo group (37).

1.2.3.1 Pharmacokinetics and Metabolism

Apalutamide is a low clearance molecule with moderate volume of distribution in mice, rates, and dogs. High oral bioavailabilitya was obtained with the lipid-based formulation used in exploratory and definitive repeat-dose toxicology studies in rats and dogs. Plasma exposure in rats and dogs increased in a dose-proportional manner over a dose range of 5-300 mg/kg/day and 5-40 mg/kg/day, respectively.

Four metabolites have been identified with different proportions between species. All four were assessed for their on-target effects against AR. Metabolite M1 was found to be essentially inactive as an AR antagonist, while metabolites M2 and M4 were approximately 30-fold less potent against AR than apalutamide. Metabolite M3 was the most potent AR antagonist, but was still 3-fold less potent than apalutamide. M3 is considered the predominant metabolite, with a longer elimination half-life than apalutamide.

In humans, apalutamide was rapidly absorbed, with measurable plasma concentrations within 30 minutes after ingestion of a single oral dose of 1 to 16 soft gelatin capsules (total apalutamide dose, 30mg to 480 mg). On average, peak plasma concentrations occurred 2 to 3 hours after administration in each dose group. The increases in plasma C_{max} values and

in the AUC were linear and dose-proportional. Plasma apalutamide concentrations declined slowly, with a mean half-life value at steady-state of 4 days.

Preliminary pharmacodynamic analysis of 18-fluorodihydrotestosterone positron emitting tomography confirmed substantial inhibition of AR at doses of 120 mg/day. Combining the aforementioned data with pre-clinical studies, 240 mg was selected as the phase II dose (RP2D).

1.2.4 Synergy between Leuprolide, Abiraterone, and Apalutamide

Studies in healthy volunteers have shown that with treatment with LHRH agonists the levels of intraprostatic tissue androgens only decline by 30% (38). This repository of ligand would certainly be sufficient to stimulate the AR pathway in prostate adenocarcinoma. Furthermore, work by the same group revealed that, in hormone-sensitive prostate cancer patients, treatment with LHRH agonists, despite reductions in intraprostatic tissue androgens by 75%, did not suppress key androgen-dependent genes, such as TMPRSS2 and PSA (39). Perhaps more alarming was the finding that the levels of tissue testosterone in metastatic CRPC was even higher than those found in eugonadal prostate controls. The AR-related mechanisms that provide for continued tumor viability in the setting of LHRH agonist therapy (castrate resistance) include AR amplification, mutations leading to promiscuous AR activation by weak androgens, other steroid hormones, and intracrine synthesis of androgens by tumor. Indeed, expression of genes converting adrenal androgens or tissue precursors to testosterone have been seen (40).

Because of abiraterone's success in the metastatic CRPC setting, it is clear that prostate cancer remains reliant on intra-tumoral androgen production for its survival. Until recently, data for this same reliance in high risk, locally-advanced prostate cancer was lacking. However, Taplin, et al recently reported on their outcomes with the use of neoadjuvant abiraterone in combination with leuprolide in the up-front, high risk setting prior to prostatectomy (41). Patients were initially randomized to either leuprolide alone for 12 weeks or leuprolide in combination with abiraterone; all patients then received an additional 12 weeks of combination therapy until radical prostatectomy; biopsies were conducted at week 12 of the study. Compared to leuprolide alone, there were statistically significant decreases at 12 weeks in intra-tumoral levels of DHT and DHEA in the group treated with both leuprolide and abiraterone ($p<0.0001$). Similar decreases were seen with androstenedione and testosterone. A PSA nadir of ≤0.2 ng/mL at 12 weeks was achieved in 90% of the patients in the combination arm versus only 4% in the leuprolide alone arm ($p<0.0001$). At the time of prostatectomy, those who had undergone 24 weeks of combined therapy versus those who had undergone only 12 weeks had a nearly significantly higher rate of near pathological complete response (CR) or total CR, 34% versus 15%, respectively ($p=0.09$). Importantly, toxicity was similar to that seen on the prior phase III trials. Grade 3 adverse events (AEs) included LFT elevation in 9% and hypokalemia in 5%; no Grade 4 AEs were reported (42).

The data from Taplin, et al makes clear that, even in the high-risk, locally advanced setting, there are clonogens capable of escaping chemical castration with LHRH agonists. This cohort of patients may thus benefit from combined ADT.

Although the report by Taplin, et al of near-complete or complete responses in high-risk patients after prostatectomy is encouraging, the data beg the question of whether more complete androgen-axis blockade may improve still further on the rate of tumor cell kill. As mentioned, while intra-tumoral production of androgens via adrenal precursors is present as an acutely activated response to medical castration, and likely suppressed by abiraterone, additional escape mechanisms exist, most notably increases in AR ligand promiscuity, AR copy number alterations and missense mutations in the AR ligand-binding domain (LBD) leading to enhanced ligand binding.

These three strategies represent conceivable mechanisms by which prostate cancer cells could escape death even in the face of the dramatic reductions in intra-tumor androgens seen with abiraterone in combination with leuprolide. And it is the potential presence of these clonogens in higher risk prostate cancers that provides us the principal rationale for the combination of a highly-selective androgen antagonist with leuprolide and abirateroner. Indeed, in phase III clinical trials of metastatic CRPC, enzalutamide has demonstrated an impressive ability to improve OS. Indeed, this strategy is being actively pursued in the Alliance for Clinical Trials in Oncology (Alliance) Trial A031201 in the metastatic CRPC setting (NCT01949337).

A recent phase I/II reported a favorable toxicity profile for bone metastatic CRPC patients treated with a combination of abiraterone and enzalutamide (43). In our own trial, because of the biochemical similarity between enzalutamide and apalutamide, we imagine that a similarly small proportion of patients will experience substantial Grade 2 or Grade 3 toxicities. Indeed, a recently reported Phase Ib trial by Posadas, et al involving 29 patients demonstrated a favorable toxicity profile, with only 14% of patients experiencing a Grade3/4 reaction (44). The majority of patients in the aforementioned trial were continued on an LHRH antagonist/agonist during their therapy.

1.2.5 Synergy between Androgen Deprivation and Radiation

Multiple clinical trials have shown that, for patients with intermediate and high risk prostate cancer, the addition of both short and long course ADT provides significant improvements in biochemical recurrence-free survival, disease-free survival, and OS. One putative mechanism responsible for this achievement may be an increase in local control as evidenced by the reduction in the proportion of patients with positive biopsies two years after radiation; in those patients who received short course neoadjuvant anti-androgen therapy, the rate of positive biopsies at a median of 38 months post-treatment was 16% compared to 42% in those patients who had not (45). Recent *in vitro* data provides a compelling biological explanation for the synergy between anti-androgen therapy and radiation. Polkinghorn, et al found that AR activity up-regulates flux through a host of DNA repair pathways in response to ionizing radiation (46). Inhibition of these pathways with AR antagonists, in their case, apalutamide, decreased tumor cell survival in response to ionizing radiation. These data, in addition to the results of the aforementioned RTOG clinical trials, which have definitively shown that ADT (using LHRH agonists) improves OS when compared with radiation alone, lead us to hypothesize that the combination of ADT, using leuprolide and abiraterone, and AR blockade, using apalutamide, will further improve local and thus biochemical disease control in our cohort of high risk patients.

This is indeed the hypothesis of multiple on-going clinical trials. A phase II trial at Duke University investigating the combination of 6 months of abiraterone and leuprolide in combination with definitive, conventionally dose radiation (75-80Gy) to the prostate and seminal vesicles alone (NCT01717053). In addition, both the Dana-Farber Cancer Center (NCT02028988) and the University of Texas- Southwestern Medical Center (NCT02064582) are conducting phase II trials of enzalutamide (one in combination with leuprolide) with conventionally dosed radiation therapy in intermediate and high risk prostate cancer patients.

Our central hypothesis is the combination of two novel anti-androgens, inhibiting two unique components of the androgen pathway, with leuprolide and stereotactic, hypofractionated radiation therapy will significantly reduce the rate of biochemical recurrence at 3 years in very high risk prostate cancer

While we expect to show a substantial increase in biochemical control compared to historical controls, the benefit of a reduction in treatment duration cannot be underestimated: 1.5 weeks of radiation rather than 8-9 weeks; 6 months of ADT rather than 2 years. Such a regimen, if proven in a phase III setting, would both expand the universe of patients with high risk prostate cancer able to receive curative therapy, especially those in medically underserved communities distant from major centers, and potentially decrease the morbidity associated with extended androgen ablation.

2. OBJECTIVES

2.1 Primary Objective

- To determine the rate of biochemical failure by 36 months post treatment in high risk prostate cancer patients treated with leuprolide, abiraterone acetate, and apalutamide in conjunction with stereotactic, ultra-hypofractionated radiotherapy.

2.2 Secondary Objectives

- To determine the rate of positive prostate biopsies at 24 months (required) after completion of anti-androgen therapy.
- To determine the rate of undetectable PSA at 1, 2 and 3 years post-treatment for men with non-castrate testosterone, (where undetectable PSA is defined as ≤ 0.2 ng/ml).
- To determine overall survival.
- To determine the cumulative incidence of distant metastases and prostate cancer-specific death.
- Evaluate acute and late toxicities, defined as any Grade 3 or greater toxicity based on the NCI CTCAE v 4.0 scoring scale
- Evaluate the effects of treatment on HR-QOL outcomes, comparing baseline to subsequent follow-up using the EPIC-26.
- Correlate MRI imaging with correlative and biopsy results.
- To evaluate the predictive and prognostic capacity of the following biological correlatives:
    - MSK-IMPACT™ (Integrated Mutation Profilingof Actionable Cancer Targets)
    - Circulating tumor cells (CTCs)
    - Circulating tumor DNA (ctDNA)

3. PATIENT SELECTION

3.1 Inclusion Criteria

To be included in this study, patients should meet all of the following criteria:

- Histological or cytologic evidence of adenocarcinoma of the prostate confirmed at local institution.
- At least one of the following:
    - Two or more high risk features OR
        - Gleason score 8-10
        - PSA ≥20 ng/mL within two months prior to registration
        - Clinical Stage ≥T3 disease, as determined by standard digital rectal examination (DRE)
        - Radiographic stage ≥T3 disease as determined by a ≥75% probability of extracapsular extension or seminal vesicle invasion per reading radiologist
    - Any Gleason 9 or 10 disease OR
    - >4 cores of Gleason 8 disease.
- KPS ≥ 70%
- IPSS (International Prostate Symptom Score) ≤ 20
- Patient must be available for follow-up
- Laboratory test findings within 28 days of study registration:
    - Adequate hepatic function:
        - Bilirubin ≤ 1.5 times the upper institutional limits of normal (ULN). Patients with a history of Gilbert's syndrome may be enrolled if the total bilirubin is < 3 mg/dL with a predominance of indirect bilirubin. If the total bilirubin is >1.5 x the institutional ULN, direct and indirect bilirubin will be measured and if direct bilirubin is ≤ 1.5 x the institutional ULN, the patient will be eligible to participate
        - SGPT (ALT) and SGOT (AST) ≤ 2.5 x ULN
    - Adequate renal function with creatinine <2.0 x the institutional ULN
    - Adequate hematologic function:
        - Absolute neutrophil counts ≥ 1500 cell/mm^3
        - Platelets ≥ 100,000 cells/mm^3 (independent of blood transfusion and/or growth factors within 3 months prior to registration)
    - Hemoglobin value ≥9 g/dL at the Screening Visit (independent of blood transfusion and/or growth factors within 3 months prior to registration)
    - Albumin ≥ 3.0 g/dL
    - Potassium ≥ 3.5 mmol/L

- Patients with pelvic and/or retroperitoneal lymph nodes < 1.5 cm in short axis are eligible as they are not considered to have definitive metastases
- Willing and able to provide written informed consent and HIPAA authorization for the release of personal health information

  NOTE: HIPAA authorization may be either included in the informed consent or obtained separately
- Males 18 years of age and above
- The effects of apalutamide, abiraterone, leuprolide and stereotactic, ultra- hypofractionated radiation on the developing human fetus at the recommended therapeutic dose are unknown. Men (including men with vasectomies) must agree to use adequate contraception (a condom and another effective method of birth control) prior to registration, for the duration of study participation, and for at least 3 months thereafter. Men must also agree not to donate sperm for the duration of study participation, and for at least 3 months thereafter.

3.2 Exclusion Criteria

- Radiographic evidence of metastatic disease
- Patients with one or more positive lymph nodes as determined by radiographic assessment of MRI or CT

  NOTE: lymph nodes noted on MRI or CT to be > 1.5 cm on the short axis will require review by the local reference radiologist per institutional RECIST review practices. If the lymph nodes are considered suspicious on repeat review, they must be confirmed negative for study participation
- Prior treatment for prostate cancer; this includes any prior surgery (including Transurethral resection of the prostate (TURP) prostate cancer treatment), chemotherapy, radiation, or anti-androgen therapy/androgen deprivation therapy with the following exception: patients who will have been on LHRH Agonist/Antagonist Therapy for ≤1 month prior to registration are permitted to enroll with study PI approval
- Prior use of steroidal antiandrogens (megestrol acetate, cyproterone acetate), AR partial agonists, ketoconazole, chemotherapy, immunotherapy, estrogens, radiopharmaceuticals within 3 months before registration
- Prior use of non-steroidal anti-androgens (e.g., bicalutamide, flutamide, nilutamide) within 1 month before registration
- Prior treatment with medications known to lower the seizure threshold within 4 weeks of registration (see section 5.5.2 apalutamide for a list of prohibited medications)
- History of another malignancy within the previous 3 years except for the following: adequately treated basal cell or squamous cell skin cancer, superficial bladder cancer, adequately treated Stage I or Stage II cancer currently in complete remission, or any other cancer that has been in complete remission for at least 3 years
- Severe hepatic impairment (Child-Pugh Class C)
- Concurrent treatment with strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital)
- Major surgery within 4 weeks of registration

- Presence of a pacemaker
- Active infection or other medical condition that would make prednisone use contraindicated
- A known hypersensitivity to abiraterone acetate, apalutamide, and prednisone and/or any of their excipients
- Severe or unstable angina, myocardial infarction, symptomatic congestive heart failure, arterial or venous thromboembolic events (e.g., pulmonary embolism, cerebrovascular accident including transient ischemic attacks), or clinically significant ventricular arrhythmias within 6 months prior to registration.
- Seizure or known condition that may pre-dispose to seizure (including but not limited to prior stroke, transient ischemic attack, loss of consciousness within 1 year prior to randomization, brain arteriovenous malformation; or intracranial masses such as schwannomas and meningiomas that are causing edema or mass effect)
- Any ECG changes that interfere with QT interval interpretation (e.g., left bundle branch block, frequent premature ventricular contractions)
- Prolonged QTc >450ms at the Screening Visit
- Uncontrolled diabetes, heart disease, hypertension
- Gastrointestinal disorder that may affect absorption of study treatment
- Activesymptomatic viral hepatitis or chronic liver disease
- History of pituitary or adrenal dysfunction
- Active Infection (e.g., human immunodeficiency virus [HIV] or viral hepatitis) or other medical condition that would make prednisone/prednisolone corticosteroid) use contraindicated
- Patients with Crohn's disease or ulcerative colitis
- Patients that cannot tolerate MRI
- Inability to have fiducial markers placed
- Any condition that in the opinion of the investigator, would preclude participation in this study
- Enrollment concurrently in another investigational drug study or within 4 weeks of registration
- Concurrent treatment with strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital)

4. ENROLLMENT PLAN AND SUBJECT REGISTRATION

4.1 Enrollment Plan

4.1.1 Participating Study Centers

This study is anticipated to be conducted at 5-6 sites.

4.1.2 Recruitment

Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or research team at participating centers from Medical Oncology, Radiation Oncology and Urology offices. Investigators will screen the patient's medical records for suitable research study subjects and discuss the study and their potential for enrolling in the research study. Any participating sites that require a limited waiver must obtain it from their own site IRB/Privacy Board (PB) via a separate protocol addendum or request. It is the responsibility of the PCCTC to confirm the participating data collection sites have a limited waiver approved by their local IRB(s)/PB(s) if required by the site.

4.2 Registration Procedure

After eligibility screening and confirmation that a patient is eligible, patients who are selected to participate will be registered through Medidata. A record of patients who fail to meet eligibility criteria (i.e., screen failures) will be maintained. Patient registration must be complete before beginning any treatment or study activities. A complete, signed study consent and HIPAA authorization are required for registration.

4.2.1 Registration

- Confirm eligibility as defined in Section 3 Patient Selection.
- Obtain informed consent, by following procedures in Section 11.3 Written Informed Consent.
- Obtain completed or partially completed protocol specific Eligibility Checklist.
- All participants will be registered through Medidata EDC.

Central registration for this study will take place at MSK. To complete registration and enroll a participant, the study staff at that site must contact the designated research staff at the PCCTC to notify him/her of the participant registration. **The following documents must be sent to the PCCTC (PCCTC@mskcc.org) for each enrollment within 24 hours of the informed consent form being signed:**

- The completed or partially completed MSK eligibility checklist
- The signed informed consent and HIPAA Authorization form
- Supporting source documentation for eligibility questions (e.g. laboratory results, pathology report, radiology reports, MD notes, physical exam sheets, medical history, prior treatment records, and EKG report).

Note: Source documentation of eligibility is not required for MSK participants.

Upon receipt, the research staff at the PCCTC will conduct an interim review of all documents for all non-MSK participants. If the eligibility checklist is not complete or source documentation is missing, the participant will be registered PENDING and the participating site is responsible for sending the completed registration documents within 30 days of the consent.

If the external registration is complete, the participating site IRB has granted approval for the protocol, and the participating site is in good standing, the PCCTC will send the completed registration documents to the MSK Protocol Participant Registration Office for participant enrollment as stated in the protocol.

Once the participant is registered, the participant will be assigned a Medidata Subject ID. This Subject ID will be relayed back to study staff at the registering participating site via e-mail and will serve as the registration confirmation. This number is unique to the participant and must be written on all data and correspondence for the participant.

Participating sites will register subjects locally per their Institutional guidelines and the PCCTC will register all non-MSK participants with MSK's Clinical Trials Management System (CTMS) per MSK's guidelines. MSK participants will be fully registered by MSK in the Clinical Trials Management System (CTMS).

5. TREATMENT/INTERVENTION PLAN

This is a single arm, phase II trial designed to determine the efficacy of a novel combination anti-androgen therapy with ultra-hypofractionated radiation therapy (RT) in very high risk prostate cancer. An interim analysis will ensure early termination of the trial should toxicities exceed historical controls. Eligible patients will receive a total of 6 months of leuprolide, abiraterone, and apalutamide to begin three months prior to RT and continuing until approximately 3 months post-RT. Patients will be assessed every 4 weeks (±1 week) (a cycle = 28 days) throughout their treatment with the study drug, and at least once during RT.

On Cycle 1 Day 1, patients will begin abiraterone acetate (four 250 mg tablets per day; 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), apalutamide (four 60 mg tablets taken without food per day), and prednisone 5 mg twice daily (taken with food). On Cycle 1 Day 5 (±3 days) patients will be given a 22.5 mg 3-month depot intramuscular injection of leuprolide. On Cycle 4 Day 1 (+14 days) patients will receive a second and final 22.5 mg intramuscular injection of leuprolide. On Cycle 4 Day 5 (±5 days) patients will start stereotactic, ultra-fractionated radiotherapy to the prostate and seminal vesicles. Abiraterone acetate and apalutamide will continue daily until Cycle 6 Day 28. A physician prescribed taper of prednisone will begin on Cycle 6 Day 28. The nature of the taper will be at the discretion of the treating physicians, but a recommended tapering schedule is as follows:

5mg QD x 7 days, 2.5 mg QD x 7 days, 2.5 mg QOD x 7 days, then discontinue the prednisone.

The following assessments and procedures will occur during the study. A schedule of assessments is provided in Table 2.

Protocol Schema

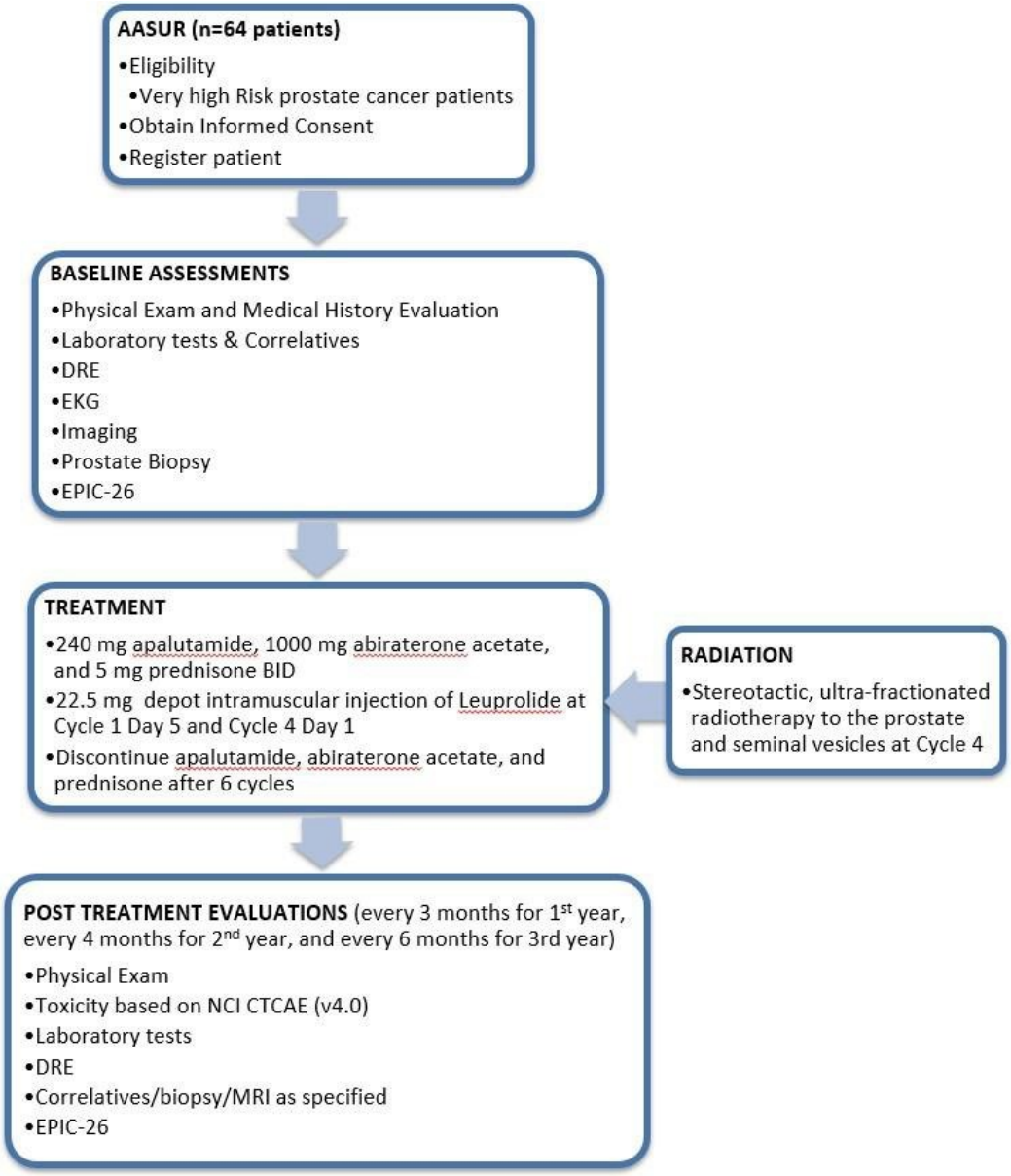


Table 2. Schedule of Assessments

Assessments	Prestudy/ Baseline[1]	Treatment/Intervention Period (Cycle = 4 weeks)									Follow-up*		
		Cycle 1		Cycle 2		Cycle 3		Cycle 4	Cycle 5	Cycle 6	1st Year	2nd Year	3rd Year
		Day 1 (±7 d)	Day 15 (±3 d)	Day 1 (±7 d)	Day 15 (±3 d)	Day 1 (±7 d)	Day 15 (±3 d)	Day 1 (±7 d)	Day 1 (±7 d)	Day 1 (±7 d)	Every 3 months (±2 weeks)	Every 4 months (±2 weeks)	Every 6 months (± 2 weeks)
Informed consent	X												
Demographics	X												
Medical history	X												
Review of comorbidities	X												
Physical exam[2]	X	X		X		X		X	X	X	X	X	X
Performance status	X	X		X		X		X	X	X	X	X	X
Digital Rectal Examination	X										X	X	X
Histologic and radiographic confirmation of disease	X												
Pathology review[3]	X												
Evaluation by Study Doctor	X	X		X		X		X	X	X	X	X	X
EKG	X												
Concomitant meds	X	X		X		X		X	X	X	X[4]	X[4]	X[4]
Toxicity assessment		X	X	X	X	X	X	X	X	X	X[4]	X[4]	X[4]
Pill diary collection		X		X		X		X	X	X			
Imaging													
Bone scan	X												
CT chest/abdomen	X												
MRI prostate/pelvis	X										X[5]	X[5]	
HR-QOL Questionnaires													
EPIC-26	X										X[6]	X[6]	X[6]
IPSS	X												
Laboratory tests													
PSA	X	X		X		X		X	X	X	X	X	X
CBC[7]	X	X	X	X	X	X	X	X	X	X	X	X	X
CMP[8]	X	X	X	X	X	X	X	X	X	X	X	X	X
TSH, T3 & T4[9]	X	X		X		X		X					
Hepatitis B & C Screening	X												

Testosterone	X	X		X		X		X	X	X	X	X	X
Correlatives													
Prostate biopsy	X[10]											X[11]	
MSK-IMPACT™ Testing[12]	X											X	
Circulating Tumor DNA (ctDNA)[13]	X										X	X	
Circulating Tumor Cells (CTCs)[14]	X											X	
Treatment/Intervention													
Leuprolide acetate		X[15]						X[15]					
Apalutamide / abiraterone+pred[16]		X								X			
Fiducial marker placement								X[17]					
Radiation Therapy								X[18]					

1. Within 28 days prior to registration; imaging can be done within 4 months of registration.
2. Physical exam includes vital signs, height/weight. During Treatment/Intervention Period and Follow-up, a targeted physical exam will be completed if deemed necessary by the study doctor.
3. Any time prior to registration.
4. Evaluation of concomitant medications and toxicity will occur until subject begins a new therapy for prostate cancer.
5. In post-treatment follow-up period, recommended MRI will only occur twice: at 6 months post anti-androgen therapy (optional, but encouraged) and 24 months post anti-androgen therapy (mandatory). MRIs should occur within 1 month prior (and not after) biopsy toallow for appropriate targeting.
6. At 6 months, 12 months, 24 months and 36 months (±2 weeks) post anti-androgen therapy.
7. CBC: White blood cells count (WBC), red blood cell count (RBC), hemoglobin (HGB), hematocrit (HCT), platelet count (UNVPLT), neutrophils (NEUTP), lymphocytes (LYMP)
8. Comprehensive Metabolic Panel includes calcium (CA), creatinine (CREAT), alkaline phosphatase (ALK), alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin (TBILI)
9. T3 & T4 should be done only if TSH is abnormal.
10. Baseline prostate biopsy can be done within 4 months of registration. If the biopsywas notperformed at thesite where subject will receive treatment under thisprotocol, a repeat biopsy should be performed when possible. If a repeat biopsy cannot be performed, then a paraffin embedded tumor sample (block or 25 unstained FFPE slides and 1 corresponding hematoxylin and eosin (H&E) slide of 4-5 micron thickness) from the diagnostic biopsy should be obtained and reviewed at the treating institution.
11. A second prostate biopsy will occur at 24 months (±2 months) post anti-androgen therapy (required, if safe and feasible).
12. MSK-IMPACT™ evaluation will be performed on the biopsied tissue sample taken at baseline and 24 months post anti-androgen therapy, if sufficient biopsy material is available. If subject has a metastatic biopsy at metastaticprogression as per standard of care (notmandatoryper protocol), MSK-IMPACT™testing of the biopsied tissue sample will be completed.
13. ctDNA at baseline, 6 months (±2 weeks) and 24 months (±2 weeks) post anti-androgen therapy, and at metastatic progression (See separate Laboratory Manual Appendix C).
14. CTCs will be drawn only for the first 25 subjects enrolled on the study. For these patients, CTCs will be drawn at baseline, 24 months (±2 weeks) post anti-androgen therapy, and at metastatic progression (See separate Laboratory Manual, Appendix C).
15. On Cycle 1 Day 5 (±3 days) and then Cycle 4 Day 1 (+14 days) patients will receive 22.5 mg injection of leuprolide.
16. Taken in the morning, at approximately the same time everyday for 6 cycles, beginning approximately 3 cycles prior to RT start and continuing through Cycle 6 Day 28
17. At least 5 days prior to Radiation Therapy
18. Administered every other day beginning Cycle 4 Day 5 (±5 days) for a total of five treatments

*Note: 1st year begins at conclusion of therapy. The 2nd year begins 12 calendar months after completion of therapy; the 3rd year begins 24 calendar months after completion of therapy.

5.1 Screening Assessment (Within 28 days prior to registration)

Before initiating any screening activities, the scope of the study should be explained to each patient. Patients should be advised of any known risks inherent in the planned procedures, any alternative treatment options, their right to withdraw from the study at any time for any reason, and their right to privacy. After this explanation, patients should be asked to sign and date a Notice of Privacy Practice research authorization/HIPAA form and an IRB-approved statement of informed consent that meets the requirements of the Code of Federal Regulations (Federal Register Vol. 46, No. 17, January 27, 1981, part 50).

During the screening period, subject eligibility will be determined according to the inclusion and exclusion criteria (Sections 3.1 & 3.2). The following assessments will be performed during this time:

- Obtain informed consent and research authorization
- Record demographics (including age) and medical history (including prior treatment forprostate carcinoma)
- Review of comorbidities
- Conduct physical exam (vital signs, height/weight)
- Evaluation by study doctor
- Obtain histologic and radiologic confirmation of disease
- Performlaboratory tests
  - PSA
  - CBC
  - Comprehensive Metabolic Panel
  - Testosterone
  - TSH, T3 & T4 (T3 & T4 should be done only if TSH is abnormal)
  - Hepatitis B & C Screening
- Digital rectal examination (DRE)
- Assess performance status using ECOG or Karnofsky scales (per institutional preference) (Appendix A)
- Determine suitability for protocol directed procedures
- Discuss concurrent medications (see Appendix B for a listing of medications with the potential for drug interactions)
- Pathology review (any time prior to registration)
- EKG
- Imaging (can be completed within 4 months of registration)
  - Chest/Abdomen by Computerized Tomography (CT)
  - Prostate/Pelvis by Magnetic Resonance Imaging (MRI)
  - Radionuclide bone scan
- Biopsy of the prostate within 4 months of registration. If the biopsy was not performed at the site where the patient will receive treatment under this protocol, a repeat biopsy should be performed when possible. If a repeat biopsy cannot be performed, then a paraffin embedded tumor sample (block or 25 unstained FFPE slides and 1 corresponding hematoxylin and eosin (H&E) slide of 4-5

micron thickness) from the diagnostic biopsy should be obtained and reviewed at the treating institution.

- ctDNA and CTC blood draw (See separate Laboratory Manual, Appendix C)
  - Note: CTCs will be drawn only for the first 25 subjects enrolled on the study.
- Administration of EPIC-26 Questionnaire
- Administration of IPSS Questionnaire
- MSK-IMPACT™ evaluation of baseline tumor specimen if sufficient biopsy material available

5.2 Treatment/Intervention Period (Cycle 1 Day 1 – Cycle 6 Day 28)

On Cycle 1 Day 1, patients will begin abiraterone acetate (four 250 mg tablets per day; taken without food and not within two hours of a meal), apalutamide (four 60 mg tablets) taken without food per day), and prednisone 5 mg twice daily (taken with food). On Cycle 1 Day 5 (±3 days) patients will be given a 22.5 mg 3-month depot intramuscular injection of leuprolide. On Cycle 4 Day 1 (+14 days) patients will receive a second and final 22.5 mg intramuscular injection of leuprolide. On Cycle 4 Day 5 (±5 days), patients will start stereotactic, ultra-fractionated radiotherapy to the prostate and seminal vesicles. Abiraterone acetate and apalutamide will continue daily until Cycle 6 Day 28. A physician prescribed taper of prednisone will begin on Cycle 6 Day 28.

The following assessments will be performed during this time:

- Vital signs, height/weight; targeted physical exam if deemed necessary by study doctor
- Toxicity assessment
- Evaluation by study doctor
- Pill diary collection
- Perform laboratory tests
  - PSA
  - CBC (every 2 weeks for the first 3 months)
  - Comprehensive Metabolic Panel (every 2 weeks for the first 3 months)
  - Testosterone
  - TSH, T3 & T4 (T3 & T4 should be done only if TSH is abnormal) (Day 1 of each cycle for the first four cycles)
- Assess performance status using ECOG or Karnofsky scales (per institutional preference) (Appendix A)
- Discuss concurrent medications (see Appendix B for a listing of medications with the potential for drug interactions)
- Administration of leuprolide acetate on Cycle 1 Day 5 (±3 days) and Cycle 4 Day 1 (+14 days)
- Stereotactic, ultra-fractionated radiotherapy will be administered every other day (except weekends and holidays) beginning at Cycle 4 Day 5 for five total treatments using a intensity modulated treatment plan with delivery of 7.5-8.0 Gy to the prostate and seminal vesicles. At least five days prior to CT simulation, 3 fiducial markers will be placed transrectally within the prostate gland to be used for target localization on each treatment day for image-guided therapy.

- Fiducial marker placement (at least 5 days prior to simulation)

5.3 Follow-up (Every 3 months (±2 weeks) for 1st year; every 4 months (±2 weeks) for 2nd year; every 6 months (±2 weeks) for 3rd year)

The following assessments will be performed during follow-up:

- Vital signs, height/weight; targeted physical exam if deemed necessary by study doctor
- Toxicity assessment (will occur until patient begins a new therapy forprostate cancer)
- Discuss concurrent medications (see Appendix B for a listing of medications with the potential for drug interactions) (will occur until patient begins a new therapy for prostate cancer)
- Evaluation by study doctor
- Performlaboratory tests
  - PSA
  - CBC
  - Comprehensive Metabolic Panel
  - Testosterone
- Digital rectal examination (DRE)
- Assess performance status using ECOG or Karnofsky scales (per institutional preference) (Appendix A)
- Imaging
  - Prostate/pelvis by MRI. Should occur at 6 months (optional, but encouraged) and 24 months (mandatory) *post anti-androgen therapy*. Should occur within 1 month prior to (and not after) biopsy to allow for appropriate targeting.
- Biopsy of the prostate at 24 months (±2 months) *post anti-androgen therapy* (required, if safe and feasible). The biopsy should be a standard template 12 core biopsy but include an MRI-fusion component such that any suspicious areas seen on repeat MRI prostate are specifically targeted for additional sampling.
- MSK-IMPACT™ evaluation of 24-month tumor specimen if sufficient biopsy material available.
  - If subject has a metastatic biopsy at metastatic progression as per standard of care (not mandatory per protocol), MSK-IMPACT™ testing of the biopsied tissue sample will be completed.
- ctDNA at 6 months (±2 weeks) and 24 months (±2 weeks) *postanti-androgen therapy*, and at metastatic progression (See separate Laboratory Manual, Appendix C)
- CTCs at 24 months (±2 weeks) *post anti-androgen therapy*, and at metastatic progression (See separate Laboratory Manual, Appendix C)
  - Note: CTCs will be drawn only forthe first 25 subjects enrolled on the study.
- Administration of EPIC-26 Questionnaire (at 6 months, 12 months, 24 months and 36 months post anti-androgen therapy); can be completed ± 2 weeks of times listed.

5.4 Dose Modifications

Table 3. Dose modifications for toxicity attributed to apalutamide

Toxicity	Dose of abiraterone acetate	Dose of apalutamide	Dose of prednisone
Grade 1 or 2	No change	No change	No change
≥ Grade 3	No change	Hold until Grade 1 or baseline, resume at full dose	No change
First Recurrence ≥ Grade 3	No change	Hold until Grade 1 or baseline, resume at 180 mg (3 tablets)	No change
Second Recurrence ≥ Grade 3	No change	Hold until Grade 1 or baseline, resume at 120 mg (2 tablets)	No change
Third Recurrence ≥ Grade 3	No change	Discontinue	No change
First occurrence of seizure of any grade or Grade 4 neurotoxicity	No change	Discontinue	No change

Rash

Dose modifications for rash are allowed only for apalutamide and are summarized in *Table **4***.

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

Table 4. Dose modifications for rash

Severity	Intervention

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

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

Grade ≥3[e]	• Hold apalutamide for up to 28 days
	• Initiate dermatological treatment[a]
	  o Topical steroid cream AND
	  o Oral Antihistamines AND
	  o Consider short course of oral steroids
	• Reassess after 2 weeks (by site staff), and if the rash is the same or has worsened, initiate oral steroids (if not already done) and refer the subject to a dermatologist
	  o Reinitiate apalutamide at a 1 dose level reduction[c, d] when rash is Grade≤1.
	  o If the dose reduction will lead to a dose less than 120mg, the study drug

	must be stopped (discontinued) • If after 28 days, rash has not resolved to Grade≤1, contact Janssen to discuss further management and possible discontinuation of study drug.

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

a. Obtain bacterial/viral cultures if infection is suspected.
b. Subject presents with other rash related symptoms such as pruritus, stinging, or burning.
c. 1 dose level reduction = 60 mg (1 apalutamide tablet)
d. If a subject previously started oral corticosteroids, continue for at least 1 week after resumption of reduced dose of apalutamide. If the proposed total oral steroid use will exceed 28 days, contact Janssen.
e. If there is blistering or mucosal involvement, stop apalutamide dosing immediately and contact Janssen.

Table 5. Dose modifications for liver function test abnormalities attributed to abiraterone acetate

Toxicity	Dose of abiraterone acetate	Dose of apalutamide	Dose of prednisone
Grade 1 or 2	No change	No change	No change
Grade 3	Hold until return to baseline or to AST or ALT ≤2.5 x ULN and total bilirubin ≤1.5 x ULN, resume at 750 mg (3 tablets) only after discussion and agreement with medical monitor	Hold until return to Grade 1	No change
Recurrence Grade 3	Hold until return to baseline or to AST or ALT ≤2.5 x ULN and total bilirubin ≤1.5 x ULN, resume at 500 mg (2 tablets) only after discussion and agreement with medical monitor	Hold until return to baseline	No change
Grade 4	Discontinue AA treatment	Hold until return to baseline	No change or consider tapering if AA is discontinued

Table 6. Dose modifications for hypokalemia attributed to abiraterone acetate

Toxicity	Dose of abiraterone acetate	Dose of apalutamide	Dose of prednisone
Grade 1 or 2	Initiate oral potassium supplementation, titrate to ≥3.5 to ≤5.0 mmol/L, maintenance at ≥4.0 mmol/L recommended	No change	No change

≥Grade 3	Hold and initiate IV potassium and cardiac monitoring, resume only after discussion and approval by the medical monitor	No change	No change or consider tapering if AA is discontinued

Table 7. Dose modifications for hypertension and edema/fluid retention attributed to abiraterone acetate

Toxicity	Dose of abiraterone acetate	Dose of apalutamide	Dose of prednisone
Grade 1 or 2	No change	No change	No change
≥Grade 3	Hold until Grade 1 or baseline, resume at full dose	No change	No change
First Recurrence ≥Grade 3	Hold until Grade 1 or baseline, resume at 750 mg (3 tablets)	No change	No change
Second Recurrence ≥Grade 3	Hold until Grade 1 or baseline, resume at 500 mg (2 tablets)	No change	No change
Third Recurrence ≥Grade 3	Discontinue	No change	No change or consider tapering if AA is discontinued

5.4.1 Abiraterone

Patients enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation. The NCI CTCAEv4.0 will be used to grade AEs.

At each study visit for the duration of their participation, patients will be evaluated for AEs, serious adverse events (SAEs), and AEs that require treatment interruption or discontinuation. Patients discontinued from the treatment phase of the study for any reason will be evaluated approximately 30 days after the last treatment.

The most common adverse reactions (≥10%) are fatigue, joint swelling or discomfort, edema, hot flush, diarrhea, vomiting, cough, hypertension, dyspnea, urinary tract infection and contusion. The most common laboratory abnormalities (>20%) are anemia, elevated alkaline phosphatase, hypertriglyceridemia, lymphopenia, hypercholesterolemia, hyperglycemia, elevated AST, hypophosphatemia, elevated ALT and hypokalemia. (6)

Following prolonged therapy with corticosteroids, subjects may develop Cushing's syndrome characterized by central adiposity, thin skin, easy bruising, and proximal myopathy. Withdrawal of the corticosteroid may result in symptoms that include fever, myalgia, arthralgia, fatigue, and malaise.

<u>Hypokalemia</u>

For patients who develop K+ levels < 2.5 mM, abiraterone acetate must be withheld and oral or IV K+ repletion must be initiated along with cardiac monitoring. These patients will be taken off study. Those with K+ levels between 2.5 and 3.0 will have abiraterone temporarily

withheld and K+ repeated; the abiraterone can then be reinitiated and its dose titrated so that K+ > 3.5 mM.

Hypertension and Fluid Retention

If Grade 3 or Grade 4 AEs occur, hold study medication. Adjust or add medications to mitigate the toxicity or consider specific mineralocorticoid receptor antagonists like eplerenone. If toxicity recurs and resolves, restart abiraterone at 750 mg per day. If toxicity occurs a second time, decrease the dose to 500 mg/day. If it recurs a third time, discontinue.

Hepatic Impairment

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.

Hepatotoxicity

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 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.

5.4.2 Apalutamide

Seizures

Patients experiencing treatment-related seizure of any grade will have study drug permanently discontinued.

Gastrointestinal Discomfort

At any given dose level, if patients experience gastrointestinal discomfort due to the number of tablets, they be allowed to switch to BID regimen as needed (4 in the AM and 4 in the PM).

All other Toxicities

For patients experiencing Grades 1-2 treatment-related AEs, short treatment breaks can be instituted as per the discretion of the investigator until the severity of the toxicity decreases to Grade 1 or returns to baseline. If toxicity recurs, dose reductions to the next lower dose

level will be allowed as per the discretion of the investigator. For patients experiencing Grade ≥3 treatment-related AEs other than seizure, study drug should be held until the severity of the toxicity decreases to Grade 1 or returns to baseline. If toxicity recurs at Grade 3 or higher, the dose of apalutamide should be reduced to the next lower dose level. A maximum of 2 dose level reductions will be allowed. Any patient requiring > 28 day delay in treatment will have met the criteria for study discontinuation.

The two lower dose levels are 180 mg (three 60mg tablets) and 120 mg (two 60 mg tablets).

5.4.3 Treatment Delays on Radiation Timing

Dose reductions or treatment delays in apalutamide and/or abiraterone done prior to initiation of radiation therapy (i.e., within the first 3 cyclesof treatment), will not impact the initiation of radiation therapy at Cycle 4 Day 5 (±5 days).

5.4.4 Dose modifications for abiraterone acetate and apalutamide

1) If both drugs are held simultaneously fora length greater than 1 cycle(28 days in total; do not need to be consecutive days), then patient will be removed from trial and treated per standard of care
2) If any one drug is held forgreater than 56 days (2 cycles), patient will be removed from trial and treated per standard of care

5.5 Concomitant Medications and Supportive Care

5.5.1 Abiraterone acetate

Because of the potential for drug-drug interaction, the concurrent use of all other drugs, over-the-counter medications, and alternative therapies must be documented. The principal investigator (PI) should be alerted if the patient is taking any prohibited agents. Concurrent enrollment in another therapeutic clinical investigation is prohibited.

Supportive Care Medications are permitted with their use following institutional guidelines. The following supportive care medications are permissible during study: conventional multi-vitamins, additional glucocorticoid administration such as a stress dose is permitted if clinically indicated for life-threatening medical conditions, and in such cases, the use of steroids will be documented as concomitant drug.

Prohibited within 30 days prior to administration to study treatment: spironolactone, 5-alpha-reductase inhibitors, , and other investigational drug therapies.

Prohibited 3 months before participant registration and during administration of study treatment: non-steroidal anti-androgens (e.g., bicalutamide, flutamide, nilutamide), steroidal antiandrogens (megestrol acetate, cyproterone acetate), AR partial agonists, ketoconazole, chemotherapy, immunotherapy, estrogens, radiopharmaceuticals,. The following medications are not excluded or prohibited, but are strongly discouraged: digoxin, pomegranate juice, indole-3-carbinol, flaxseed oil.

CYP3A4 Inducers: Avoid concomitant strong CYP3A4 inducers during abiraterone acetate treatment. If a strong CYP3A4 inducer must be co-administered, increase the abiraterone acetate dosing frequency.

CYP2D6 Substrates: Avoidco-administration of abiraterone acetate with CYP2D6 substrates that have a narrow therapeutic index. If an alternative treatment cannot be used, exercise caution and consider a dose reduction of the concomitant CYP2D6 substrate.

CYP2C8: 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 abiraterone acetate.

5.5.2 *Apalutamide*

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

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

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

- Strong CYP3A4 inhibitors: itraconazole, clarithromycin, erythromycin, diltiazem, verapamil, delavirdine, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole, grapefruit juice (or grapefruits); co-administration with any of these agents may increase apalutamide plasma concentrations
- Strong CYP inducers: phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital, efavirenz, tipranavir, St. John'swort; co-administration with any of these agents may decrease apalutamide plasma concentrations.

The potential for drug-drug interaction between apalutamide and warfarin (Coumadin) is unknown at present. If a patient is taking warfarin, reassess PT/INR as clinically indicated and adjust the dose of warfarin accordingly.

See Appendix B. Medications with the Potential for Drug-Drug Interactions for a complete list of medications prohibited while on active treatment with apalutamide.

5.6 Removing Subjects from the Protocol

In the absence of treatment delays because of AEs, treatment will continue for 6 months unless one of the following occurs:

- subject decides to withdraw from the study

- Intercurrent illness that prevents further administration of treatment
- unacceptable AE(s) that may or may not be directly related to treatment but that, in the judgment of the treating physician, makes it dangerous for the subject to be retreated
- general or specific changes in the patient's condition that render the patient unacceptable for further treatment, in the judgment of the investigator
- initiation of non-study therapy forprostate cancer
- unable to swallow study drug

Because an excessive rate of withdrawals can render the study uninterruptable, unnecessary withdrawal of subjects should be avoided. When a subject discontinues treatment early, the investigator should make every effort to contact the subject and to perform a final evaluation. The reason(s) for withdrawal should be recorded. In order to account for an estimated 10% dropout rate during treatment, we will enroll 64 patients upfront to ensure there are 53 evaluable patients.

5.7 Correlative Studies

This trial, prospectively designed to correlate clinical outcomes with molecular analysis of patient samples, presents an ideal platform to identify biomarkers predictive of response.

Eachsubject will have the following specimens obtained at the study site as described below:

a) A paraffin embedded tumor sample (block or 25 unstained FFPE slides and 1 corresponding hematoxylin and eosin (H&E) slide; 4-5 micron thickness) via prostate biopsy at baseline and at 24 months *post anti-androgen therapy*. Baseline and 24-month biopsies will be required if safe and feasible at the discretion of the investigator. Metastatic progression biopsy will be completed per standard of care (not mandatory per protocol). Available archival tumor is acceptable for baseline when new procurement is not possible.
b) Blood for EPIC to interrogate CTC data in this high risk patient population at baseline, 24 months *post anti-androgen therapy*, andat metastatic progression. The first 25 patients will be followed with CTCs by EPIC.
c) Blood forctDNA data at baseline, 6 months and 24 months *post anti-androgen therapy*, and at metastatic progression
d) Targeted tumor sequencing assay, MSK-IMPACT™ (Integrated Mutation Profiling of Actionable Cancer Targets),(47) to detect gene mutations and other critical genetic aberrations in tumor biopsies pre- and post-treatment to better delineate the mechanisms of sensitivity and resistance to therapy; performance of MSK-IMPACT™is dependent on sufficient biopsy material being available.

Specific collection and handling procedures for the correlative studies can be found in the study Laboratory Manual (Appendix C).

Table 8 below describes the planned correlative assays.

Table 8. Schedule of biomarker studies

Assay	**Timepoint & Biospecimen**			
	Baseline	6 Month	24 Month	Met. Progression
CTC (25 patients)	Blood	N/A	Blood	Blood
ctDNA	Blood	Blood	Blood	Blood
MSK-IMPACT™	Biopsy	N/A	Biopsy	Biopsy

6. THERAPEUTIC/DIAGNOSTIC AGENTS/MODALITY

6.1 Description of Treatments

6.1.1 Abiraterone acetate

Abiraterone acetate tablet formulation (ZYTIGA®) in combination with prednisone/prednisolone has been approved for the treatment of men with metastatic castration-resistant prostate cancer (mCRPC). Abiraterone acetate is commercially available in 250 mg tablets that are oval, white to off white and contain abiraterone acetate and compendial grade lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, povidone, sodium lauryl sulfate, magnesium stearate, colloidal silicon dioxide, and purified water, in descending order of concentration. For this study this drug is investigational and will be supplied by Janssen Scientific Affairs, LLC at no cost. Abiraterone acetate must be taken on an empty stomach. No food should be consumed for at least two hours before the dose of ZYTIGA is taken and for at least one hour after the dose of ZYTIGA is taken.

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**.** You should notify any caregivers of this information, to ensure the appropriate precautions are taken.

6.1.2 Prednisone

Prednisone (5 mg tablets) is commercially available and will be prescribed to patients to be taken orally twice daily with food. If a subject has been receiving glucocorticoids other than prednisone or prednisolone, it will be necessary to switch the glucocorticoids to prednisone or prednisolone 5 mg twice daily prior to Day 1.

6.1.3 Apalutamide (also referred to as ARN-509 and JNJ-56021927)

Apalutamide is FDA approved for non-metastatic castration resistant prostate cancer, however, and is considered investigational in this study. The tablet formulation of apalutamide is an immediate release oral tablet containing 60-mg of drug substance, with a non-functional green film coat. Each 60-mg tablet contains the following inactive ingredients: hydroxypropyl methylcellulose acetate succinate (HPMC-AS), colloidal anhydrous silica, croscarmellose sodium, microcrystalline cellulose, silicified microcrystalline cellulose, and magnesium stearate. Commercially available Opadry® coating powder is used for the film coating, which is comprised of polyvinyl alcohol (partially hydrolyzed), titanium dioxide, polyethylene glycol, talc, and colorants iron oxide yellow and iron oxide black (E172).This is an investigational drug and will be supplied by Janssen Scientific Affairs, LLC at no cost.

6.1.4 Leuprolide

This is a commercially available, injectable, long acting analog of the native LHRH peptide available in 7.5 mg (1 month) injections or 22.5 mg (3-month) injections. For this study, only 22.5 mg (3-month) injections will be used. It is administered via intramuscular injection. The manufacturer's instructions should be followed.

6.2 Stereotactic, Ultra-Fractionated Radiotherapy

Intensity-modulated, image-guided, ultra-hypofractionated external beam radiotherapy will begin on Cycle 4 Day 5 (±5 days) after the initiation of treatment with abiraterone acetate. The prostate and seminal vesicles will receive 7.5-8 Gy x 5 fractions.

Image guided, intensity-modulated, ultra-fractionated radiation therapy is considered a reimbursable expense by Medicare.

6.2.1 Prior to Simulation

- Prior to simulation, patientswill be referred for fiducial marker placement.
- Patientsshouldhavefiducial markers at least 5 daysprior to simulation.

6.2.2 Simulation

- Patients will perform a bowel preparation the night before simulation.
- Patientswill be supineand positioned in an appropriateimmobilizationdevice.
- Oralcontrastwill be administered for simulation.
- A Foley catheter can be placed for simulationonly.
- A rectal catheter can be placed for simulationonly.
- CT imageswill be obtained as per existingdepartment protocolsandsent to thetreatment planning system
- If available, MR imageswill be obtained as per existing department protocols, theywill be sent to the treatment planning system as well.
- Patientsshouldhaveacomfortablyandreproduciblyfull bladder.

6.2.3 Treatment Planning

- CTV1 should includetheprostate, seminal vesicles, andany areas at risk of extra-capsular extension.
- PTV1 should include a 0.5 cm expansion on CTV1 inall directions, saveforposterior; the posterior expansion will be 0.3 cm.
- For PTV1, the D95% should be ≥90% of theprescribeddose of 7.5 or 8 Gy per fraction.

6.2.4 Contouring of Normal Tissue Structures

Bowel: should include the small intestines and the large intestines from the duodenum to the peritoneal reflection (distal end of the sigmoid). If the stomach is in close proximity to the target, it should be contoured as part of the bowel.

Rectal Outer: the entire rectum 1cm superior and 1 cm inferior to the PTV will be defined as rectal outer

Rectal Wall: a uniform contraction of 4 mm should be applied to the rectal outer contour. The rind between the outer rectal contour and the contracted volume will be defined as the rectal wall.

Bladder Wall: the entire bladder with urinary contents should be contoured; a uniform contraction of 4mm should then be applied to this contour. The rind between the outer bladder contour and the contracted volume will be defined as the bladder wall.

Kidney: both the right and left kidney, excluding the renal pelvis/collecting system, should be contoured in their entirety (renal cortex).

Femoral Heads: the ball of the head and socket joint should be contoured.

Urethra: should be defined using the contrast filled foley catheter.

Prostate 750x5 = 3750cGy & 800x5 = 4000cGy Prostate ONLY - NO Nodes			**Target Criteria**	
	PTV $D_{95\%} \geq 90\%$			
			Normal Tissue Criter	
	Structures	**Todal Dose* or Volume ≤**	**To:**	
	Rectal Wall	103%	Max Point Dose	
		38.5Gy	D_{1cc}	
		53%	Mean Dose	
		24Gy	$D_{53\%}$	
	Rectum_O	8cc	$V_{30.15Gy}$	
	Urethra	105%	Max Point Dose	
		40Gy	D_{1cc}	
	Bladder Wall	105%	Max Point Dose	
		24Gy	$D_{53\%}$	
	Femoral Heads	31Gy	Max Point Dose	
	Large Bowel	29Gy	Max Point Dose	
	Small Bowel	25Gy	Max Point Dose	

- Beamarrangements, optimizationstructuresandoptimizationparameterswill be defined at the discretion ofthetreatment planner usingroutine departmental procedures.
- Thetreatment planwill be approved andreviewed by theattendingphysician.
- The treatment plan will go through qualityassurance procedures per departmental guidelines.

6.2.5 Treatment Delivery

- Patients should be treated every other day, excluding holidays and weekends. If the participant must miss one or two scheduled treatments due to unexpected events, they will be made up and this will not be considered a deviation/violation per protocol.
- Patients shouldusea Fleet'senemathreehoursprior to each radiationfraction.
- Intra-fraction motion management should be utilized per treating institution protocol.
- Bladder should be comfortably full duringtreatment delivery.

7. SAFETY EVALUATION

7.1 Definitions

7.1.1 Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment (ICH E2A).

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 (investigational ornon-investigational),whether ornot related to themedicinal product.

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

An AE will be recorded and followed from treatment administration to 30 days post treatment or resolution.

7.1.2 Adverse Events of Special Interest

Adverse Events of Special Interest: Adverse events of special interest are events that Janssen Scientific Affairs, LLC, is actively monitoring as a result of a previously identified signal (even if non-serious).

For abiraterone acetate, the adverse events of special interest are:

- Mineralocorticoid excess (Hypertension, Hypokalemia, Fluid retention)
- Hepatotoxicity
- Cardiac disorders
- Osteoporosis including osteoporosis-related fractures
- Increased exposure with food
- Rhabdomyolysis /myopathy
- Acute liver failure/hepatitis which might be fatal
- Drug-drug interaction (CYP2D6)
- Allergic alveolitis

Forapalutamide, theadverseevents of special interest are:

- Seizures/convulsions
- Fractures
- Fall
- Hypothyroidism
- Rashes

Any Adverse Event of Special Interest that is to be reported to the COMPANY should be recorded on a Serious Adverse Event Report Form and be reported to the COMPANY **within24 hours of knowledge of the event**.

7.1.3 Individual Case Safety Report (ICSR)

A valid ICSR must contain the four minimum criteria required to meet regulatory reporting requirements.

- an identifiablesubject(but notdisclosingpersonalinformationsuch as thesubject'sname, initialsor address)
- an identifiable reporter (investigational site)
- a Janssenmedicinal product
- an adverseevent, outcome, or certainspecial

situations The minimum information required is:

- suspected Janssen medicinal product (doses, indication)
- date of therapy (start and end date, if available)

- batch or lot number, if available
- subject details (subject ID and country)
- gender
- ageat AE onset
- reporter ID
- adverse event detail (AE verbatim in English), onset date, relatedness, causality, action taken, outcome, (if available)
- Janssenprotocol ID

7.1.4 Expected Adverse Events

Expected AEs are those that have been previously identified as resulting from administration of the agent. An AE can be considered expected when it appears in the current AE list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.

7.1.5 Unexpected Adverse Events

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational medicinal product) (ICH E2A). For a medicinal product(s) with a marketing authorization, the expectedness of an adverse event will be determined by whether or not it is listed in the applicable product information.

For Abiraterone acetate, the link to the package insert is:

http://www.zytiga.com/sites/default/files/pdf/full_product_information.pdf

For apalutamide, the link to the package insert is:

http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/ERLEADA-pi.pdf

Contact the PI or Sponsor to confirm unexpected AEs when necessary.

7.1.6 Adverse Drug Reaction (ADR)

All noxious and unintended responses to a medicinal product related to any dose should be considered ADRs (ICH E2A).

The phrase *response to a medicinal product* means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out. *Reasonable possibility* means there is evidence to suggest a causal relationship between the drug and the AE.

7.1.7 Serious Adverse Event (SAE)

An SAE/ADR as defined in the Code of Federal Regulations (21CFR312.32) is any event that:

- results in death
- is life-threatening
    - The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
- results in inpatient hospitalization or prolongation of existing hospitalization

- results in persistent or significant disability or incapacity
- results in congenital anomaly or birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- is medically significant in the opinion of the investigator
    - Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

Events that are **not** considered serious adverse events include:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- elective or pre-planned treatment for a pre-existing condition that did not worsen
- emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- respite care

7.1.8 Progression of malignancy

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

7.1.9 Life-threatening

An AE or suspected adverse reaction is considered life-threatening if, in the view of either Investigator or Sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death (FDA 21 CFR 312.32).

7.1.10 Hospitalization (or prolongation of hospitalization)

Hospitalization encompasses any inpatient admission (even for less than 24 hours) resulting from a precipitating, treatment-emergent AE. For chronic or long-term patients, inpatient admission also includes transfer within the hospital to an acute or intensive care inpatient unit. Hospitalizations for administrative reasons or a non-worsening preexisting condition should not be considered AEs (e.g., admission for workup of a persistent pretreatment laboratory abnormality, yearly physical exam, protocol-specified admission, elective surgery). Preplanned treatments or surgical procedures should be noted in the baseline documentation. Hospitalization because of an unplanned event will be deemed an SAE. Signs and symptoms of clinical sequelae resulting from hospitalization or prolongation of hospitalization will be reported if they fulfill the serious adverse event definition.

Prolongation of hospitalization is any extension of an inpatient hospitalization beyond the stay anticipated or required for the original reason for admission.

7.1.11 Persistent or Significant disability/incapacity

Any AE that results in persistent or significant incapacity or substantial disruption of the patient's ability to conduct normal life functions.

7.1.12 Congenital anomaly

If the female partner of a male patient becomes pregnant during the course of the study, the treating physician must be notified immediately. All confirmed pregnancies must be immediately reported to MSK and Janssen Scientific Affairs, LLC. All pregnancies will be followed until resolution (i.e., voluntary or spontaneous termination or birth) and assessed for congenital anomalies and birth defects.

7.1.13 Product Quality Complaint (PQC)

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

Examples of PQC include but not limited to:

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

7.2 Recording and Grading of Adverse Events

7.2.1 Recording

All observed or volunteered AEs, regardless of treatment group, severity, suspected causal relationship, expectedness, or seriousness will be recorded.

A clinically significant change in a physical examination finding or an abnormal test result should be recorded as an AE, if it:

- is associated with accompanying symptoms
- requires additional diagnostic testing or medical or surgical intervention
- leads to a change in study dosing or discontinuation from the study
- requires additional concomitant drug treatment or other therapy, or
- is considered clinically significant by the sponsor investigator

An abnormal test result that is subsequently determined to be in error does not require recording as an AE, even if it originally met one or more of the above criteria.

7.2.2 Grading severity

All AEs will be graded based on the NCI CTCAE version 4.0.

7.2.3 Attributing causality

After assigning a grade to an AE, the investigator must evaluate all AEs for possible causal relationship to the investigational agent/intervention. Causality attribution will be decided using the criteria outlined in Table 9.

Table 9. Relationship of AE to study drug

Relationship	Description
Unrelated	AE is clearly not related
Unlikely	AE is doubtfully related
Possible	AE may be related
Probable	AE is likely related
Definite	AE is clearly related

7.3 Reporting Serious Adverse Events

7.3.1 Reporting serious adverse events

All SAEs, events determined to be medically significant by the treating Investigator, unknown reactions or unexpected events, and any special reporting situations (see 7.3.3) that meet the criteria of a serious adverse event, should be reported to PI, Lead Site/Sponsor, PCCTC, and Janssen Scientific Affairs, LLC, within **24 hours** of knowledge of the event using the contact information below. The initial report should include the following information at a minimum:

- protocol # and title
- study identification number, sex, age at event
- date the event occurred
- description of the SAE
- causal relationship to the study drug

All SAEs that occur any time a patient is on study (i.e., as soon as the informed consent has been signed) or within 30 days of the last dose of study drug or study intervention must be recorded regardless of the suspected relationship to the study drug/intervention. Any SAE occurring more than 30 days after the last dose of study drug/intervention must be recorded if a causal relationship to study drug/intervention is suspected.

The **PCCTC Report Form** will be used for reporting each SAE and should be submitted to the PCCTC within 24 hours of learning of the event. Severity, causality, action taken, concomitant medications, outcome, etc. should be reported to the PCCTC as soon as possible. For MSK subjects, the Clinical Research Database (CRDB) SAE form is acceptable. For outside sites, the "Serious Adverse Event Report Form for Non-MSK Sites" should be used.

In addition, the PCCTC will report all SAE and safety events classified as special reporting situations to Janssen within 24 hours of knowledge of the event using the **Janssen SAE Report Form**.

Sites must submit both the Janssen SAE form along with the MSK SAE form to PCCTC.

All (serious and non-serious) AEs and special situations (which may or may not meet the definition of an adverse event), whether serious or non-serious, related or not related, following exposure to apalutamide and/or abiraterone acetate are to be documented by the Investigator and recorded in the electronic case report form (eCRF) and in the subject's source records. Investigators must record in the eCRF their opinion concerning the relationship of the AE and/or specific situation to apalutamide and/or abiraterone acetate.

Follow-up of AEs should continue until the event and any sequela resolve or stabilize at a level acceptable to the investigator.

The PCCTC will facilitate all SAE reporting to the MSK IRB/PB and Sponsor Investigator within 5 calendar days.

The MSK PI is responsible for informing all participating sites about all unexpected SAEs that are either possibly, probably, or definitely related to the study intervention within 15 days of receiving the stamped SAE from the MSK IRB/PB.

The MSK PI is responsible for informing all participating sites about any SAE report pertaining to a Grade 5 event as soon as possible.

SAE contact information for the PCCTC, Lead Site/Sponsor is listed below:

Lead Site/Sponsor: Memorial Sloan Kettering Cancer Center
Name: Sean McBride, MD, MPH
Address: 1275 York Avenue
Email: mcbrides@mskcc.org
Phone: 212-639-5717

PCCTC:
Prostate Cancer Clinical Trials Consortium
Email: pcctc@mskcc.org

Janssen Scientific Affairs, LLC Transmission Methods
The following methods are acceptable for transmission of safetyinformation to Janssen:

- Electronically via Janssen SECURE Email service (preferred)
  - SAE email: IISProgram@OMPUS.jnj.com
- Forbusinesscontinuitypurposes, if SECURE Email is non-functional:
  - Facsimile(fax), receipt of which is evidenced in asuccessful fax transmissionreport
  - Telephone(iffax isnon-functional).
    - SAE fax: 1-866-651-0219

7.3.2 Pregnancy

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

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

7.3.3 Special Reporting Situations

Safety events of interest that require expedited reporting and/or safety evaluation include, but are not limited to:

- Drug exposure to partner during pregnancy
- Overdose of apalutamide and/or abiraterone acetate
- Exposure to apalutamide and/or abiraterone acetate from breastfeeding

- Suspected abuse/misuse of apalutamide and/or abiraterone acetate
- Inadvertent or accidental exposure to apalutamide and/or abiraterone acetate
- For abiraterone acetate only, failure of expected pharmacological action
- Medication error involving apalutamide and/or abiraterone acetate
- Suspected transmission of any infectious agent via administration of a medicinal product
- For abiraterone acetate only, unexpected therapeutic or clinical benefit from use

7.4 Janssen Scientific Affairs, LLC Requirements

7.4.1 Maintenance of Safety Information

All safety data should be maintained in a clinical database in a retrievable format. The INSTITUTION (Memorial Sloan Kettering Cancer Center) and PRINCIPAL INVESTIGATOR (Dr. McBride) shall provide all adverse events, both serious and non-serious, in report format quarterly. However, in certain circumstances more frequent provision of safety data may be necessary, e.g. to fulfill a regulatory request, and as such the data shall be made available within a reasonable timeframe at the COMPANY's (Janssen) request.

7.4.2 Procedures for Reporting Safety Data and Product Quality Complaints (PQCs) for Janssen Medicinal Products to the COMPANY

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

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

7.4.2.1 SAEs and Special Reporting Situations

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

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

The INSTITUTION and the PRINCIPAL INVESTIGATOR) will transmit all SAEs and special situations following exposure to a Janssen product under study in a form provided by the COMPANY in English within24-hours of becoming aware of the event(s).

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

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

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

- The INSTITUTION and/or PRINCIPAL INVESTIGATOR is responsible for ensuring that these cases are complete and if not are promptly followed-up. A safety report is not considered complete until all clinical details needed to interpret the case are received. Reporting of follow-up information should follow the same timeline as initial reports.

- Copies of any and all relevant correspondences with regulatory authorities and ethics committees regarding any and all serious adverse events, irrespective of association with the Janssen Product under study, are to be provided to the COMPANY within 24 hours of such report or correspondence being sent to applicablehealth authorities.

7.4.2.2 Non-Serious AEs

All non-serious adverseevents should be reported to COMPANY according to the timeframeoutlined in the Research Funding Agreement sectionentitled Reporting of Data.

7.4.2.3 PQC Reporting

A PQC may have an impact on the safety and efficacyof the product. Timely, accurate, andcompletereportingandanalysis of PQC informationfromstudies are crucial for theprotection ofpatients, investigators, and the COMPANY, and are mandated by regulatory agencies worldwide. The COMPANY has established procedures inconformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information. Lot and/or Batch #s shall be collected or any reports failure of expected pharmacological action (i.e., lack of effect). The product should be quarantined immediatelyand if possible, take a picture.

All initial PQCs involving a Janssen medicinal product under study must be reported to the COMPANY by the PRINCIPALINVESTIGATOR within 24 hours afterbeingmadeaware of theevent. The Janssencontactwillprovideadditional information/form to be completed.

If thedefect for a Janssenmedicinalproductunderstudyis combinedwitheithera serious adverse event or non-serious adverse event, the PRINCIPAL INVESTIGATOR must report the PQC to the COMPANY according to the serious adverse event reporting timelines. A sample of the suspected product should be maintained for further investigation if requested by the COMPANY.

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

For SAEs, special reporting situationsand PQCs following exposure to anon-Janssen medicinal product understudy, the PRINCIPAL INVESTIGATOR should notifytheappropriate regulatory/competentauthorityor themanufacturer of that medicinalproduct(intheabsence of appropriate local legislation) as soon as possible.

7.5 Safety Reports

MSK must submit outside safety reports to the MSK IRB/PB according to institutional guidelines. All outside safety reports will be made available to the participating sites. Outside safety reports that are

reportable to the MSK IRB/PB will be distributed by the PCCTC to the participating sites immediately upon receiving a stamped copy from the MSK IRB/PB. Participating sites will receive a special alert for any outside safety reports that warrant a significant change to the conduct of the study. Outside safety reports that are not reportable to the MSK IRB/PB, will be sent by the PCCTC to the participating sites monthly.

Participating sites are responsible for submitting safety reports to their site IRB per their local guidelines. All site IRB approvals/acknowledgments of safety reports must be sent to the PCCTC upon receipt.

8. CRITERIA FOR OUTCOME ASSESSMENT/THERAPEUTIC RESPONSE

8.1 Outcome Assessment

8.1.1 Primary endpoint

The primary endpoint used to power this study is the proportion of patients who have had biochemical failure by 36-months post completion of anti-androgen therapy as defined by the Phoenix or surgical progression criteria wherein PSA failure represents an increase in PSA above post-treatment nadir by 2 or more ng/mL or PSA value above or equal to 0.2 ng/mL, respectively. The date the PSA equals or exceeds 0.2 ng/mL will be the date of failure..

Based on historic controls, we assume that the 3-year rate of biochemical failure with conventionally dosed radiation and 2-years of neoadjuvant, concurrent, and adjuvant leuprolide is approximately 25%. With the proposed regimen, we assume a rate of biochemical failure at 3-years of 10%.

Given an unacceptable 3-year rate of biochemical recurrence of 25% and a threshold rate for further study of 10% or below, enrolling 53 patients will give a type-1 error rate of 0.03 (3% probability of declaring the regimen worthy of further study if the true rate of biochemical failure is 25% or higher) and a power of 0.84 (16% probability of declaring the regimen unworthy of further study if the true rate of biochemical failure in the arm is 10% or below). Thus, a sample size of 53 patients will provide us with an alpha of 0.03 and a power of 0.84. With an expected 10% dropout during follow-up, we would aim to enroll 64 patients.

Due to a lower attrition rate than expected, 63 patients are evaluable (among the total 64 enrolled). Therefore, we modified the decision rule by changing the denominator to 63. The current decision rule now adequately specifies that if, at study conclusion, there are more than 9 biochemical failures among 63 evaluable patients, then we shall deem the regimen ineffective. If there are less than or equal to 9 biochemical failures, then we shall declare the experimental regimen effective, i.e., having achieved the proposed improvement to 10%. This decision rule maintains type 1 error rate at 0.03 with a power of 0.90.

Patients who are lost to follow-up prior to 36 months of follow-up but after treatment completion will be counted as biochemical failures. As such, patients who complete the required treatment will be evaluable for the primary end-point of biochemical recurrence.

8.1.2 Secondary endpoints

Additional outcomes on this trial will include acute (defined as within 3 months of treatment completion) and late (toxicities arising more than 3 months after treatment completion), additional tumoral control metrics (negative biopsy rate, rate of undetectable PSA, rate of distant metastases, rate of prostate cancer specific mortality, overall survival, MR imaging correlation with biopsy results, circulating tumor DNA dynamics, circulating tumor cell

enumeration and HR-QOL metrics (EPIC26)). Tumor biopsies pre and post-treatment will be interrogated to better delineate the mechanisms of sensitivity and resistance to therapy. A customized MSK-IMPACT™ sequencing panel will be derived in concert with the MSK computational biology group. Selected genes will be reviewed for expression and reported for correlative analysis with treatment outcomes. The custom panel will be created prior to analysis.

The EPIC 26 is a short form version of the full Expanded Prostate Cancer Index Composite (EPIC). This version contains 26 items and the same 5 domains as the full version of EPIC: urinary incontinence, urinary irritative/obstructive, bowel, sexual, and hormonal. Response options for each EPIC item for a Likert scale, and multi-item scare scores are transported linearly to a 0-100 scale with higher scores representing better HRQOL. The time frame asked in the question relates to symptoms experienced within the prior 4 weeks. The scoring method for EPIC-26 is found at http://medicine.umich.edu/dept/urology/research/epic.

8.2 Therapeutic Response

8.2.1 Criteria for Primary Efficacy End-point

Biochemical failure will be determined using both Phoenix and surgical definitions of PSA progression. PSA Phoenix progression is defined as an increase in PSA by more than 2 ng/mL above the nadir value. The date the PSA rise equals or exceeds 2 ng/mL will be the date of failure. PSA surgical progression is defined as a PSA value above or equal to 0.2 ng/mL. The date the PSA equals or exceeds 0.2 ng/mL will be the date of failure. The proportion of patients with biochemical failure by 36 months after completion of anti- androgen therapy will be determined.

8.2.2 Criteria for Secondary Efficacy End-points

1. Rate of positive biopsies: A prostate biopsy will be required prior to the start of RT—the standard diagnostic biopsy. Additionally, two prostate biopsies post-treatment will be performed—at 24 months post anti-androgen therapy (required, if safe and feasible) and at metastatic disease progression (if collected as per standard of care). Response criteria are defined as complete response or treatment failure based on an either negative or positive biopsy results.
2. Proportion of patients with non-castrate testosterone (>150 ng/dLd) and an undetectable PSA as defined as PSA ≤0.2 ng/mL will be determined at 12 months and 24 months from treatment completion.
3. Cumulative incidence of prostate cancer-specific mortality will be determined at 36 months.
4. Cumulative incidence of distant metastasis will be determined at 36 months.
5. OS will be determined at 36 months.
6. Correlation between MRI and biopsy findings: the absence of restricted diffusion or contrast enhancement, when previously present, will be correlated with the presence of severe treatment effect/negative biopsy results.
7. Incidence of CTCAE v4.0 acute (during and within 3 months of treatment completion) and late (3 months after treatment completion) toxicities will be evaluated
8. The presence of or absence of circulating tumor DNA at baseline, 6 months post completion of anti-androgen therapy, 24 months post completion of anti-androgen therapy and at metastatic progression will be evaluated as a binary variable.
9. The enumeration of circulating tumor cells at baseline, 24 months post completion of anti-androgen therapy, and at metastatic progression will be evaluated for the first 25 patients enrolled. This will be reported as a continuous variable per mL of blood.

Descriptive reports of DNA alterations found in biopsies and correlation with outcome.

9. DATA REPORTING AND REGULATORY REQUIREMENTS

9.1 Data Collection and Management

Data collected during this study will be entered into a secure database.

9.1.1 *Electronic Case Report Forms (eCRFs)*

The participating site(s) will enter data remotely into eCRFs using the internet based system, Medidata Rave. Data entry guidelines have been generated for this study and participating site staff will receive database training prior to enrolling its first participant. The participating site PI is responsible for ensuring these forms are completed accurately and in a timely manner. A Data and Source Documentation Submission Timeline is shown in the table in Section 9.1.5 below.

9.1.2 *Source documentation*

Source documentation refers to original records of observations, clinical findings and evaluations that are subsequently recorded as data. Source documentation should be consistent with data entered into eCRFs. Relevant source documentation to be submitted throughout the study includes:

- Baselinemeasures to assess pre-protocol diseasestatus(e.g., CT, PSA, bonemarrow)
- Treatment records
- Toxicities/AEs of grades that meet study reporting requirements and have not been previously submitted with a SAE Report(s)
- Response designation

Source documentation must include a minimum of two identifiers to allow for data verification. MSK will maintain the confidentiality of any subject-identifiable information it may encounter.

9.1.3 *Record retention*

The investigator will maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. After study closure, the investigator will maintain all source documents and study-related documents. Records are to be retained and securely stored until the later of: (a) two (2) years following the date a New Drug Application is approved for the Study Drug that is the subject of the Clinical Trial; or (b) two (2) years after the Investigational New Drug Application for such Study Drug is terminated or withdrawn, or such longer period of time as may be required by Participant policies, applicable laws, rules or regulations.

9.1.4 *Source Documentation Submission for Registration at Participating Sites*

Participating sites should email any source documentation that corresponds to data entered at registration into the eCRFs to the PCCTC at PCCTC@mskcc.org (see section 4.2.1 for additional details).

9.1.5 *Data Submission Timelines*

All data should be transmitted to the PCCTC within 14 days of visit except for SAE submission (see section 7.3.1).

	Baseline	Visit 1	Visit 2	Visit 3	Visit 4	SAE	Off Study
Submission Schedule							
Source Documentation	**Within 24 hours (see section 15.1.1)**	**Within 14 days of visit**				**Within 24 hours of event (see section 7.3.1); updates to be submitted as**	**Within 14 days of visit**
eCRFs	**Within 7 days of**						

	visit					available	
Required Forms							
Demographics	X						
Medical History	X						
Concomitant Medications	X	X	X	X	X		X
Physical Exam	X	X	X	X	X		X
Treatment		X	X	X	X		X
Laboratory	X	X	X	X	X		X
Lesion/EOD					X		X
Adverse Event*		X	X	X	X	X	X
Serious Adverse Event						X	
Off Study							X

9.1.6 Data Review and Queries

The PCCTC will review data and source documentation as it is submitted. Data will be monitored against source documentation as necessary and discrepancies will be sent as queries to the participating sites. In addition, the PCCTC will review data for logic, consistency, and obvious anomalies. Queries will be sent by the PCCTC to participating sites as needed.

Participatingsitesshouldrespond to dataqueries within14 days of receipt.

9.2 Study Monitoring and Quality Assurance

9.2.1 Data and Safety Monitoring

The Data and Safety Monitoring Plans (DSMP) at MSK[1] were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the

[1] http://inside2/clinresearch/Documents/MSKCC%20Data%20and%20Safety%20Monitoring%20Plans.pdf

document entitled *Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials*.[2] The DSMPs at MSK wereestablished andare monitored by the Office of Clinical Research.

There are several different mechanisms by which clinical trials are monitored for data, safety, and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research quality assurance) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. There are several committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the MSK Research Council and Institutional Review Board. As a moderate risk trial, this study will be monitored by DSMC twiceper year.

Since therapeutic efficacy is a stated primary objective, all participating sites participants' responses are subject to review by MSK's Therapeutic Response Review Committee (TRRC). Radiology and additional lab reports will need to be obtained from the participating sites for MSK TRRC review and confirmation of response assessment. These materials must be sent to MSK promptly upon request

9.2.2 *Data Monitoring and Quality Assurance*

In addition to review by DSMC, PCCTC will conduct regularly scheduled monitoring visits.

Registration reports will be generated by the PCCTC to monitor subject accruals and the completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and the extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period, and potential problems will be brought to the attention of the Principal Investigator for discussion and action.

Each site participating in the accrual of participants to this protocol will be monitored at a minimum of 10% of all subjects, but at least 2 from each site will be 100% source data verified by the PCCTC during interim visits (selected subjects). Monitoring will occur once shortly after initiation of subject recruitment at a site, annually during the study (or more frequently if indicated), and at the end or closeout of the trial, for protocol and regulatory compliance, data verification and source documentation. Monitoring visits may be accomplished in one of two ways: (1) sending source documents and research records for selected patients from participating sites to the PCCTC for review, or (2) on-site monitoring of selected patient records at participating sites.

[2] http://www.cancer.gov/clinicaltrials/conducting/dsm_-guidelines/page1

The monitoring visit will include a review of source documentation to evaluate compliance for:

- Regulatory/IRB compliance (review of current protocol and amendments, Informed consent documents and procedures, annual continuing review reports, AEs/SAEs)
- Protocol defined treatment compliance
- Subject records
    1. Signed and dated informed consent form for each subject
    2. Adherence to eligibility criteria for each subject
    3. Medical history/baseline for selected subjects
    4. On study and follow-up protocol tests forselected subjects
    5. eCRF completion for each subject

Monitoring visit findings will be reviewed by PI, Dr. Sean McBride, and disseminated to the Site PIs and staff.

In addition, each participating site accruing participants to this protocol will be audited by MSK for protocol and regulatory compliance, data verification and source documentation. Audits of selected participant records may be conducted on-site or remotely.

Audits will be summarized and a final report will be sent to the PI at the audited participating site within 30 days of the audit. The report will include a summary of findings, participant-specific case review, recommendations on any performance and/or shortcomings and request for corrective action, when necessary. When corrective action is required, the participating site must reply within 45 days of receipt of the audit report with their corrective action plan.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints

10.1.1 Analysis of the primary endpoints

Data from high-dose, conventional external beam radiation in combination with LHRH agonist treatment in high risk patients suggests a cumulative incidence of biochemical recurrence at 3 years of approximately 25% (conversely, a rate of continued biochemical control of 75% at 3 years). We assume that ultra-hypofractionation in combination with leuprolide, abiraterone, and apalutamide will have a 3-year rate of biochemical failure of 10%.

Given an unacceptable rate of biochemical recurrence by 3 years of 25% (Nguyen et al. Cancer 2013, Page 3265-3271; Shilkrut et al. AJCO 2015, In Press) and a threshold rate for further study of 10% or below, enrolling 53 patients will give a type-1 error rate of 0.03 (3% probability of declaring the regimen worthy of further study if the true rate of biochemical failure is 25% or higher) and a power of 0.84 (16% probability of declaring the regimen unworthy of further study if the true rate of biochemical failure in the arm is 10% or below). The decision rulewas previously noted as follows: If, at study conclusion, among the first 53 evaluable patients, there are more than 7 biochemical failures, then we shall declare the regimen ineffective. If there are less than or equal to 7 biochemical failures, then we shall declare the experimental regimen effective, i.e., having achieved the proposed improvement to 10%. If at any point in the trial, more than 7 patients experience biochemical failure, the study will be stopped for futility.

Patients who die prior to the 36-month end-point due to any cause will be counted as biochemical failures. Patients who complete therapy but who are lost during study mandated follow-up will be regarded as biochemical failures. In order to account for an estimated 17% dropout rate during therapy, we will enroll 64 patients upfront to ensure there are 53 evaluable patients for the above decision rule. We estimate accrual of 2 patients per month onto study (approximately 30 months to accrue). From the time of registration of the last patient, the study will continue for 42 months. The total study duration we thus estimate at 72 months.

Due to a lower attrition rate than expected, 63 patients are evaluable (among the total 64 enrolled). Therefore, we subsequently modified the decision rule upon MSKCC's protocol amendment 15 (i.e., protocol version 9 dated 05JAN2023), by changing the denominator to 63. The current decision rule now adequately specifies that if, at study conclusion, there are more than 9 biochemical failures among 63 evaluable patients, then we shall deem the regimen ineffective. If there are less than or equal to 9 biochemical failures, then we shall declare the experimental regimen effective, i.e., having achieved the proposed improvement to 10%. This decision rule maintains type 1 error rate approximately around 0.025 with a power of at least 0.80.

Due to the uncertainty of the toxicity associated with this novel combination of therapies, the trial will involve a sequential stopping rule. Based on data from Cahlon, et al, an acceptable rate of any acute, treatment-related CTCAE Grade 4 or greater toxicity is approximately 2% (48). We also specify that a 10% CTCAE Grade 4 treatment-related toxicity rate is unacceptable. To this end, the sequential stopping rule is as follows: If ≥2 patients among the first 21, or ≥3 among the first 42, or ≥5 among the total 64 patients developed Grade 4 acute, treatment-related toxicities, then the trial will stop. This ensures a 0.09 probability of stopping the trial if the true toxicity rate is 2% and a 0.88 probability of stopping the trial if the true toxicity is 10%. There will be continuous monitoring of toxicities. At study conclusion, regardless of efficacy, if 5 or more patients experience Grade 4 or greater acute, treatment-related toxicity, we would recommend against use of this regimen in a phase III randomized controlled trial.

Although the primary outcome, as well as the secondary endpoints (see Section 10.1.2 below), is computed from the end of treatment, for future references we will also compute all clinical endpoint measures from the beginning of the treatment.

10.1.2 Analysis of the secondary endpoints

The rates of positive prostate biopsies at 24 months after completion of anti-androgen therapy and at metastatic progression, and the rates of undetectable PSA at 1, 2 and 3 years post-treatment for men with non-castrate testosterone will all be estimated by sample proportions.

Overall Survival will be calculated using the method of Kaplan and Meier. The cumulative incidence of prostate cancer-specific mortality and distance metastasis rate will be calculated using the competing risks cumulative incidence method. Time zero for the calculation of these endpoints will be the completion of all trial-related therapy; patients who die or develop distant metastases during treatment will be regarding as having the respective event at t=0. Acute and Late Toxicities will be defined using the CTCAE version 4.0. The highest grade toxicity experienced by each patient in the first 3 months after treatment will be defined as acute toxicity; the highest grade toxicity attributable to treatment after 3 months will be defined as a late toxicity. Such observed toxicities will be tabulated and summarized.

For the evaluation of EPIC-26, routine summary statistics and pairwise t-tests or Wilcoxon signed-rank tests will be conducted to test potential differences between scores obtained from baseline and during the follow-up period. To incorporate baseline factors, ANCOVA may also be used.

Sensitivities, specificity, positive-predictive value, and negative predictive value will be calculated for MRI versus gold-standard post-treatment biopsy results. The absence of diffusion restriction and contrast enhancement will be categorized as “no residual tumor”; the presence of these factors on multi-parametric imaging will be categorized as “residual tumor”.

Comparisons will then be made to pathological determination of treatment response: complete response/severe treatment effect vs. residual disease.

CtDNA will be reported as a binary variable (present or absent) at baseline, 6 months and 24 months post therapy completion, and at metastatic progression. We will correlate the presence or absence of ctDNA with various established clinical end-points. In addition, ctDNA will be evaluated for the presence or absence of various AR mutations.

The enumeration of circulating tumor cells at baseline, 24 months post completion of anti-androgen therapy, and at metastatic progression will be evaluated for the first 25 patients enrolled. This will be reported as a continuous variable and correlated with tumor control outcomes.

We will describe the various DNA alterations present at the various biopsy end-points (baseline, 24 months post treatment completion, and metastatic progression). We will correlate the presence of certain mutations at baseline (if seen in sufficient number) and outcome.

Additional correlative assessments of tissues collected under the protocol may be performed at the discretion of the study team.

11. REGULATORY AND PROTECTION OF HUMAN SUBJECTS

11.1 Roles and Responsibilities

11.1.1 Sponsor Investigator (Sponsor Principal Investigator)

The Sponsor Investigator is responsible for performing the followingtasks:

- Responsibility for the overall conduct of the study at all participating sites and for monitoring the progress of the study
- Reviewing and ensuring reporting of Serious Adverse Events (SAEs)
- Reviewing data fromall participating sites

11.1.2 PCCTC

The PCCTC is responsible for performing the following tasks:

- Ensuring that IRB approval has been obtained at each participating site prior to the first patient registration at that site, and maintaining copies of IRB approvals and required regulatory documents from each site.
- Managing subject registration
- Developing and maintaining Clinical Data Management documents and procedures
- CRF development, setup of study database, and subsequent design changes
- Participating in review of content of the CRF against the protocol requirements
- EDC system administration (user/site accounts setup, maintenance and revocation)
- Data review, cleaning, query management and resolution
- Establishing procedures fordocumentation, reporting and submitting of AEs and SAEs to the PCCTC.

- Reviewing SAEs
- Training participating sites on EDC
- Collecting and compiling data from each participating site
- Data reviewing from all participating sites
- Facilitating monitoring visits and audits by securing selected source documents and research records from participating sites for monitoring visit and/or audit, or by monitoring at participating sites.

11.1.3 Participating Sites

Participating sites are responsible for performing the followingtasks:

- Following the protocol as written, the guidelines of Good Clinical Practice (GCP), and applicable Standard Operating Procedures (SOPs). Registering all patients with the PCCTC by submitting the eligibility checklist, supporting source documentation, and signed informed consent promptly
- Providing sufficient experienced clinical and administrative staff and adequate facilities and equipment to conduct a collaborative trial according to the protocol
- Maintaining regulatory binders on site and providing copies of all required documents to the PCCTC
- Collecting and submitting data according to the schedule specified by the protocol
- Responding to queries in a timely manner

11.2 Ethical Considerations

This study will be conducted in compliance with the protocol, GCP guidelines established by the International Conference on Harmonisation, and the ethical standards set forth in the Declaration of Helsinki 2004 (available at: www.laakariliitto.fi/e/ethics/helsinki.html).

11.3 Regulatory Documentation

Prior to implementing this protocol at MSK, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the MSK Institutional Review Board/Privacy Board (IRB/PB). There will be one protocol document and each participating site will utilize that document.

The following documents must be provided to the PCCTC before the participating site can be initiated and begin enrolling participants:

- Participating Site IRB approval(s) for the protocol, appendices, informed consent form and HIPAA authorization
- Participating Site IRB approved informed consent form and HIPAA authorization
- Participating Site IRB's Federal Wide Assurance number and OHRP Registration number
- Participating Site 1572
- Conflict of Interest forms forparticipating site Investigators on the 1572
- Curriculum vitae and medical licenses foreach investigator and consenting professional
- Documentation of Human Subject Research Certification training for investigators and key study personnel at the participating site

- Documentation of Good Clinical Practice(GCP) training for the PI and co-PI at the participating site
- Participating site laboratory certifications and reference ranges

Upon receipt of the required documents, the PCCTC will submit a participating site activation request to MSK. Once approved, MSK will formally contact the PCCTC and grant the site permission to proceed with participant registration.

11.4 Protocol Amendments

Each change to the protocol document must be organized and documented by the PCCTC, reviewed and approved by Janssen Scientific Affairs, LLC, and approved by the MSK IRB/PB. Protocol amendments that affect MSK only (e.g. change in MSK Co-Investigator, MSK translation, etc.) do not require IRB review at the participating site(s). All other protocol amendments will be immediately distributed to each participating site upon receipt of MSK IRB/PB approval.

Each participating site must obtain approval for all amendments from their IRB within 45 calendar days of MSK IRB/PB approval. If the amendment is the result of a safety issue or makes eligibility criteria more restrictive, participating sites will not be permitted to continue enrolling new participants until site IRB approval of the revised protocol document is granted and submitted to the PCCTC, who will in turn submit the approval documentation to MSK.

The following documents must be provided to the PCCTC for each amendment within the stated timelines:

- Participating Site IRB approval
- Participating Site IRB approved informed consent form and HIPAA authorization

The PCCTC is responsible for submitting all participating site local IRB approvals and/or acknowledgments to MSK upon receipt.

11.5 Additional IRB Correspondence

Continuing Review Approval

The Continuing Review Approval letter from the participating site's IRB and the most current approved version of the informed consent form should be submitted to the PCCTC within 7 days of expiration. Failure to submit the re-approval in the stated timeline will result in suspension of new participant registration. The PCCTC is responsible for submitting all participating site local IRB approvals and/or acknowledgments to MSK upon receipt.

Deviations

A protocol deviation on this study is defined as any incident involving non-adherence to an IRB approved protocol. Deviations typically do not have a significant effect on the rights, safety, or welfare of research participants or on the integrity of the resultant data. Deviations that represent unanticipated problems involving risks to participants or others, or serious adverse events should be reported according to sections 7.3 and 11.10 of the protocol.

Deviations that do not adversely affect the rights and/or welfare of the participant or the scientific validity of the study and are related to protocol scheduling changes outside of the allowed window due to a holiday (e.g., New Year's, Thanksgiving, etc.) and/or inclement weather or other natural event do not require reporting to the MSK IRB/PB. However, they must be clearly documented in the patient's medical record.

Prospective Deviations

Deviations to the research protocol that involve an informed consent procedure change and/or treatment/pharmacy alterations that are not allowed by the protocol require prospective approval from the MSK IRB/PB prior to the change being carried out. Participating sites should contact the PCCTC who will in turn seek approval from the MSK IRB/PB. Deviations to the research protocol that involve patient eligibility will not be permitted.

Retrospective Deviations

Deviations that include a change or departure from the research protocol without prior approval from the MSK IRB/PB are considered retrospective deviations. Retrospective deviations should be reported to the PCCTC as soon as possible, who will in turn report the deviation to the MSK IRB/PB as per MSK guidelines.

Participating Site IRB Reporting

Participating sites should report all deviations to their institution's IRB per local guidelines. Approvals/acknowledgments from the participating site IRB for protocol deviations should be submitted to the PCCTC upon receipt. The PCCTC is responsible forsubmitting all participating site local IRB approvals and/or acknowledgments to MSK upon receipt.

Other Correspondence

Participating sites should submit all other correspondence to their institution's IRB according to local guidelines, and submit copies of official site IRB correspondences to the PCCTC. The PCCTC is responsible for submitting all participating site local IRB correspondence to MSK upon receipt

11.6 Document Maintenance

The MSK PI and participating site PI will maintain adequate and accurate records to fully document protocol implementation and allow data to be subsequently verified.

The participating sites will ensure that all regulatory documents and participating site IRB correspondence are maintained in an on-site regulatory binder and sent to the PCCTC as outlined within the protocol. The on-site regulatory binder will be reviewed by the designated study monitor at monitoring visits. A regulatory binder for each participating site will also be maintained at the PCCTC; this binder may be paper or electronic.

After study closure, the participating sites must maintain all source documents, study related documents and eCRFs for 7 years.

11.7 Written Informed Consent

The investigators listed on the Consenting Professionals Lists at each participating site may obtain informed consent and care for the participants according to Good Clinical Practice and protocol guidelines.

Before obtaining consent, members of the study team will review the rationale for the treatment program with the patient. The discussion will review the alternatives available (including hormonal therapy, chemotherapy, or supportive care as appropriate), the potential benefits of this program, the risks and the probability of their occurrence, and the procedures to minimize these risks. Should an AE occur, the provisions available to ensure medical intervention will also be reviewed. Why the risks are reasonable in relation to the anticipated benefits, incentives, or costs that will or may be incurred as a result of participating in the study, as well as the efforts to maintain confidentiality, will also be discussed with the patient.

Patients will be required to sign and date an informed consent form that meets the requirements of the Code of Federal Regulations (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the IRB. The medical record will include a statement that written informed consent was obtained (and document the date that it was obtained) before the patient is enrolled in the study. The original signed document will become part of the patient's medical record, a copy will be forwarded to the Lead Site/Sponsor pursuant to sponsor registration and to the PCCTC and a copy will be sent home with each patient. A note will be placed in the participant's medical record documenting that informed consent was obtained for this study, and that the participant acknowledges the risk of participation.

The consent form will include the following:

- the nature and objectives, potential toxicities, and benefits of the intended study
- the length of therapy and likely follow-up required
- alternatives to the proposed therapy (including available standard and investigational therapies)
- the name of the investigator(s) responsible forthe protocol
- the right of the patient to accept or refuse treatment and to withdraw from participation in this study
- text regarding the PCCTC should be added to all institutional informed consent documents and sections in the research authorization/HIPAA forms (e.g., "Prostate Cancer Clinical Trials Consortium")
- the purpose of banking samples for future use, their rights in relation to it, and the safeguards in place to protect the confidentiality of their health information

11.8 Protection of Privacy

Patients will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. After this discussion, they will be asked to sign a Notice of Privacy Practice research authorization/HIPAA form. The original signed documents will become part of the patient's medical records, and each patient will receive a copy of the signed documents. The use and disclosure of protected health information will be limited to the individuals described in the research authorization form. The research authorization form must be completed by the PI and approved by the IRB.

11.9 Terminating or Modifying the Study

Adverse event and laboratory data from this trial will be assessed by the Lead Site or the Sponsor's medical monitor on an ongoing basis. SAEs will be reviewed as they are reported to the Lead Site/Sponsor and the PCCTC, and the medical monitor, Dr. Sean McBride, will make an assessment regarding the safety of continuing or modifying the study. This assessment will be shared with the investigators either in writing or as part of a teleconference. Should the assessment of either the Lead Site/Sponsor or the PI be that the study should be terminated, the study will be closed to further accrual. Patients who are receiving an investigational agent/intervention will be assessed individually by the investigator to see if it is in the patients' best interest to continue, which might be the case for a patient that is responding to the intervention. Follow-up safety assessments will be performed for all patients who are terminated from the study prematurely.

11.10 Unanticipated Problems (UPs)

Unanticipated problems involving risks to participants or others (UPs) are defined as any incident, experience or outcome that meets all of the following criteria:

- Unanticipated (in terms of nature, severity, or frequency) given (a) the research procedures that are describedintheprotocol-related documents, suchasthe IRB-approved researchprotocol and informedconsentdocument; and (b)thecharacteristics of the subject populationbeingstudied; **and**
- Relatedorpossibly related to participatingintheresearch (possibly related meansthereisa reasonableprobabilitythat theincident, experience or outcomemay havebeencaused by procedures involved in the research); **and**
- Suggeststhattheresearchplaceparticipants or others at agreaterrisk ofharm (includingphysical, psychological, economic, or social harm) than was previously known or recognized.

Participating sites are responsible for reporting all UPs to MSK as soon as possible but within 3 calendar days of learning of the event. UPs that are SAEs should be reported to MSK via SAE Report form as per section 7.3 of the protocol. All other UPs should be reported to MSK in a memo signed by the site PI.

MSKis responsible for submitting UPs to the MSKIRB/PB according to institutional guidelines. In addition, the PCCTC is responsible for notifying participating sites of all non-SAEUPs that may affect the sites.

11.11 Noncompliance

If a participating site is noncompliant with the protocol document, accrual privileges may be suspended and/or contract payments may be withheld, until the outstanding issues have been resolved.

11.12 Return of Genomic Data

In regards to the return of genomic data, the protocol consent form asks participants for permission for re-contact to discuss research findings that may occur during the course of next generation sequencing (i.e. MSK-IMPACT™ assay). These incidental findings may be critical to the patient and/or family's preventative care. If an MSK participant agrees to be re-contacted, he or she will not be told the specific results of the research test, but will be informed that his or her samples were analyzed and a potential risk was uncovered. If the participant is interested in further discussion of the research findings, he or she will be asked to come into the MSK Clinical Genetics Service for counseling and specific genetic testing. If a participating site participant agrees to have tissue sent to MSK for our secondary objective with MSK-IMPACT™ testing and s/he wished to be re-contacted in the consent form, then any significant incidental findings uncovered during MSK-IMPACT™ testing will be relayed to the treating physician at the treating institution so they may carry out their institution's policy with regard to offering the patient confirmatory testing and genetic counseling.

In the course of the research, a research finding may be obtained that, in the opinion of the MSK PI, may be critical to the preventive care of the participant or their family. When this occurs, the MSK PI will communicate this to the MSK IRB Genomic Advisory Panel (GAP). The finding will be reviewed by the GAP to determine whether the incidental finding should be discussed with the participant. In the event that the GAP determines that the finding should be discussed with the participant, results will be returned to the Site Principal Investigator via the PCCTC. If the participant has agreed to be re-contacted, site policies on returning these research findings to the patient should be followed.

For MSK patients, after appropriate counseling and consent, the Clinical Genetics Service will request permission to confirmthe result in a New York DOH-approved laboratory prior to communication of the specific result. If the patient is not available (e.g. deceased) then the surrogate designated on the consent will be contacted and the above should occur.

If the subject is not an MSK patient and is being treated at one of the participating institutions, the findings will be returned to the outside Principal Investigator and local policies on returning these research findings to the patient should be followed.

Lastly, patients will be asked to consent to tumor banking such that both frozen and fixed tumor cores can be utilized for future investigations.

When samples are to be analyzed, the individual investigator needs to write an IRB biospecimen protocol. This protocol is fast-tracked through Research Council review and is reviewed at IRB by the expedited review process. This protocol is only for research that will be done on biospecimens obtained under identified protocols and their informed consent and research authorization that include the institutional future use questions. The consent and research authorization for the use of the biospecimens will be waived as per 45 CFR 46.116(d) and 45 CFR 164.512(i)(2)(ii).

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APPENDIX A: PERFORMANCE STATUS CRITERIA

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

APPENDIX B: MEDICATIONS WITH THE POTENTIAL FOR DRUG-DRUG INTERACTIONS

Table 9. Medications Prohibited while on active treatment with apalutamide

Generic Name	Brand Name*
aminophylline	Aminocont; Aminomal; Diaphyllin; Filotempo; Neophyllin; Norphyl; Phyllocontin; Syntophyllin; Tefamin; Truphylline; Xing You Shan;
aminophylline in combination	Asmeton; Cha Xin Na Min; Emergent-Ez; Fufang Dan An Pian; Ke Zhi
amitriptyline	Amirol; Amitrip; Amixide; Deprelio; Diapatol; Elatrol; cElatrolet; Elavil; Endep; Enovil; Emitrip; Klotriptyl; Laroxyl; Levate; Limbitrol; Limbitryl; Mutabase; Mutabon; Nobritol; Novo-Triptyn; Pertriptyl; Redomex; Saroten; Sarotex; Sedans; Syneudon; Teperin; Triptizol; Triptyl; Tryptizol
amitriptyline in combination	PMS-Levazine
bupropion	Aplenzin; Buproban; Contrave; Elontril; Forfivo; Fortivo XL; Le Fu Ting; Prexaton; Quomem; Voxra; Wellbutrin; Wellbutrin XL; Wellbutrin SR; Yue Ting; Zyban
chlorpromazine	Aminazin; Chlorazin; Hibernal; Klorproman; Largactil; Megaphen; Ormazine; Plegomazin; Solidon; Taroctyl;Thorazine; Vegetamin; Wintermin; Zuledin Note: in Ireland also called "Clonazine" – very easy to confusewith clozapine.
clozapine	Azaleptin; Clopine; Closastene; Clozaril; CloZAPine; Denzapine; Elcrit; Fazacio ODT; Klozapol; Lanolept; Leponex; Lozapine; Nemea; Ozapim; Synthon, Versacloz; Zaponex
desipramine	Deprexan; Norpramin; Nortimil; Pertofrane
doxepin	Adapin; Anten; Aponal; Deptran; Gilex; Li Ke Ning; Quitaxon; Silenor; Sinepin; Sinequan; Zonalon
imipramine	Impril; Melipramin; Mipralin; Norfranil,; Novo-Pramine; Persamine; Pertofram; Pryleugan; Talendep; Tofranil; Tolerade
lithium	Arthriselect; Camcolit; Carbolith; Carbolithium; Eskolith; Hypnorex; Li-Liquid; Licarbium; Limas; Liskonum; Litarex; Lithane; Lithicarb; Lithioderm; Lithionit; Lithobid; Liticarb; Litiomal; Lito; Maniprex; Neurolepsin; Plenur; Priadel; Quilonorm; Quilonum; Saniquiet; Sedalit; Teralithe
lithium in combination	Boripharm No 23; Emser Salz; Girheulit HOM; Helidonium-Plus; Heweurat N; rheuma-loges; Rhus Toxicodendron Compose; Rhus-Plus; Ricinus Compose
maprotiline	Cronmolin; Deprilept; Ludiomil; Mapromil; Melodil; Neuomil; Psymion
meperidine/pethidine	Alodan ; Atropine and Demerol; Centralgine ; Demerol ; Dolantin ; Dolantina,; Dolantine ; Dolargan,; Dolcontral,; Dolestine ; Dolosal ; Dolsin; Fada; Hospira; Liba; Mepergan ; Meprozine,; Mialgin,; Opystan; Pethidine ; Petigan Miro ; Psyquil compositum
meperidine/pethidine in combination	Pamergan P100

mesoridazine	Serentil, Mesorin
mirtazapine	Arintapin; Avanza; Axit; Combar; Esprital; Mi Er Ning; Miro; Mirta TAD; Mirtabene; Mirtachem; Mirtadepi; Mirtagamma; Mirtalan; MirtaLich; Mirtamylan; Mirtaron; Mirtaz; Mirtazelon; Mirtazon; Mirtazonal; Mirtel; Mirtin; Mirtor; Mirzaten; Norset; Noxibel; Paidisheng; Psidep; Remergil; Remergon; Remeron; Remirta; Rexer; Yarocen; Zispin
olanzapine	Anzorin, Arenbil; Arkolamyl; Atyzyo; Bloonis; Clingozan; Egolanza; Lansyn; Lanzek; Lazapix; Nolian; Nykob; Olafid; Olanzaran; Olanzep; Olanzin; Olanzine; Olapin; Olasyn; Olazax; Olpinat; Olzapin; Olzin; Ou Lan Ning; Ozilormar; Parnassan; Ranofren; Sanza; Stygapon; Synza; Ximin; Zalasta; Zamil; Zappa; Zapris; Zerpi; Zolafren; Zolaxa; Zonapir; Zopridoxin; Zylap; Zypadhera; Zypine; Zyprexa; Zyprexa Relprew; Zydis
olanzapine in combination	Symbyax
risperidone	Aleptan; Apo-Risperid; Arketin; Calmapride; Diaforin; Doresol; Hunperdal; Jing Ping; Ke Tong; Leptinorm; Lergitec; Orizon; Ozidal; Perdox; Ranperidon; Resdone; Ridal; Ridonex; Rileptid; Ripedon; Risepro; Rispa; Rispaksole; Rispefar; Rispemylan; Rispen; Rispera; Risperanne; Risperdal; Risperdalconsta; Risperdaloro; Risperigamma; Risperon; Rispolept; Rispolux; Rispond; Rispons; Risset; Rixadone; Rorendo; Ryspolit; Si Li Shu; Sizodon; Speridan; Suo Le; Torendo; Zhuo Fei; Zhuo Fu; Ziperid; Zoridal
theophylline	Aerolate; Afonilum; Aminomal; An Fei Lin; Apnecut; Apo-Theo; Asmalix; Asmalon; Bi Chuan; Bronchoparat; Bronchoretard; Cylmin; Diffumal; Elixifilin; Elixophyllin; Etipramid; Euphyllin; Euphyllina; Euphylline; Euphylong; Frivent; Gan Fei Lin; Nuelin; Protheo; Pulmophylline; Quelesu; ratio-Theo-Bronc; Respicur; Retafyllin; Shi Er Ping; Slo-Bid; Slo-Phyllin; Telbans; Teotard; Terdan; Teromol; Theo-24; Theo-Dur; Theo; Theochron; Theodur; Theofol; Theolair; Theoplus; Theospirex; Theostat ; Theotard; Theotrim; Theovent; Tromphyllin; Unicon; Unicontin; Unifyl; Uniphyl; Uniphyllin Continus; Uniphyllin; UniXan; Xanthium; Xi Fu Li; Yan Er
theophylline in combination	Antong; Baladex; Bi Chuan; Binfolipase; Broncho-Euphyllin; Broncomar; Do-Do ChestEze; Elixophyllin-GG; Elixophyllin-KI; Insanovin; Marax ; Neoasma; Theofol Comp; Theophedrinum-N; Xu Hong; Yi Xi Qing
thioridazine	Detril; Elperil; Melleril; Ridazin; Ridazine; Thiodazine; Thioril; Sonapa
ziprasidone	Geodon; Li Fu Jun An; Pramaxima; Si Bei Ge; Ypsila; Zeldox; Zipwell; Zypsila; Zypsilan

APPENDIX C: LABORATORY MANUAL

PLEASE SEE SEPARATELY ATTACHED APPENDIX C – LABORATORY MANUAL INCLUDING REQUISITION FORMS.

APPENDIX D: EPIC-26

PLEASE SEE SEPARATELY ATTACHED APPENDIX D – EPIC-26

APPENDIX E: IPSS

PLEASE SEE SEPARATELY ATTACHED APPENDIX E – IPSS

APPENDIX F: GLOSSARY OF ABBREVIATIONS AND ACRONYMS

17-AAG	17-allylamino-17-demethoxygeldanamycin
17-DMAG	17-dimethylaminoethylamino-17-demethoxygeldanamycin
2-MPPA	2-(3-mercaptopropyl) Pentanedioic acid
ADR	adverse drug reaction
ADT	androgen-deprivation therapy
AE	adverse event
AGA	androgenetic alopecia
AI	accumulation index
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
ANOVA	analysis of variance
APTT	activated partial thromboplastin time
AR	androgen receptor
ASAEL	Agent Specific Adverse Event List
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC(INF)	area under the concentration-time curve from time zero extrapolated to infinite time
AUC(0-T)	area under the concentration-time curve from time zero to the time of the last quantifiable concentration
AUC(TAU)	area under the concentration-time curve in one dosing interval
AUMC(INF)	area under the moment concentration time curve extrapolated to infinity
A-V	atrioventricular
β-HCG	beta-human chorionic gonadotrophin
%BE	percent biliary excretion
bid	bis in die (twice a day)
BLQ	below limit of quantification
BMI	body mass index
BP	blood pressure
BSA	Body Surface Area
BUN	blood urea nitrogen
C	Celsius
Ca++	calcium
caBIG	Cancer Biomedical Informatics Grid
CAEPR	Comprehensive Adverse Event and Potential Risks
CALGB	Cancer and Leukemia Group B
CBC	complete blood count
CCC	Clinical Consortium Committee
CCD	Central Consortium Database

CDE	common data element
CDUS	Clinical Data Update System
CFR	Code of Federal Regulations
CI	confidence interval
Cl-	chloride
Clcr	creatinine clearance
CLNR	nonrenal clearance
CLR	renal clearance
CLT	total body clearance
CLT/F	apparent total body clearance
Cm	centimeter
Cmax	maximum plasma concentration
Cmin	trough observed concentration
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CNS	central nervous system
CR	complete response
CRC	Clinical Research Center
CRDB	Clinical Research Database
CRF	case report form
CRMIS	Clinical Research Management Information System
CRPC	castration resistant prostate cancer
CT	computerized tomography
CTC	circulating tumor cell
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTMS	Clinical Trials Management System
CTO	Clinical Trials Office
CV	coefficient of variation
CYP	cytochrome p-450
DCTD	Division of Cancer Treatment and Diagnosis
DEV	deviation from the nominal value
%DEV	percent deviation
dL	deciliter
DHEA	dehydroepiandrosterone
DHEA-S	dehydroepiandrosterone sulfate
DHT	dihydrotestosterone
DLT	dose-limiting toxicity
DSM	data and safety monitoring
EA	extent of absorption

ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
EEG	electroencephalogram
EKG	electrocardiogram
EORTC	European Organization for Research and Treatment of Cancer
ESF	eligibility screening form
ESR	expedited safety report
F	bioavailability
FDA	Food and Drug Administration
FDG-PET	2-[18F]fluoro-2-deoxyglucose positron emitting tomography
FDHT	18-fluoro-dehydrotestosterone
%FE	percent fecal excretion
FISH	fluorescence in situ hybridization
FSH	follicle stimulating hormone
GAPDH	glyseraldehayde-3-phophate dehydrogenase
GC	gas chromatography
GCP	good clinical practice
GCPII	glutamate carboxypeptidase II enzyme
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
GnRH	gonadotropin-releasing hormone
HAT	histone acetyltransferases
HCO3-	bicarbonate
HDAC	histone deacetylase
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HL7	American National Standards Institute's Health Level Seven
HPF	high power field
HPLC	high-performance liquid chromatography
HR	heart rate
HRPC	hormone-refractory prostate cancer
HRT	hormone replacement therapy
HSP90	heat-shock protein 90
ICD	International Classification of Diseases
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IHC	immunochemical
IM	intramuscular

IMSL	International Mathematical Statistical Library
IND	investigational new drug
INR	international normalized ratio
IP	Intraperitoneal
IPSS	International Prostate Symptom Score
IRB	Institutional Review Board
ITT	intent-to-treat population
IV	intravenous
K	slope of the terminal phase of the log concentration-time curve
K+	potassium
K3EDTA	potassium ethylenediaminetetraacetic acid
KLK1	kallikrein 1
LBD	ligand-binding domain
LC	liquid chromatography
LCM	laser capture microdissection
LC-MS	liquid chromatography/mass spectrometry
LD	longest diameter
LDH	lactate dehydrogenase
LLQ	lower limit of quantitation
ln	natural logarithm
LOCF	last observation carried forward
LOI	letter of intent
LPF	low power field
MAD	maximum administered dose
MDS	myelodysplasia
MedDRA	Medical Dictionary for Regulatory Activities
MIC	minimum inhibitory concentration
MMP	matrix metalloproteinase
MRI	magnetic resonance imaging
MRT	mean residence time
MRT(INF)	mean residence time adjusted for infusion time
MRT(PO)	mean residence time following oral administration
MRT(SS)	mean residence time at steady-state
MSK	Memorial Sloan Kettering Cancer Center
MS	mass spectrometry
MTD	maximum tolerated dose
N	number of subjects or observations
NA	not applicable
N/A	not available
NBN	National Biospecimen Network

NCI	National Cancer Institute
NIH	National Institutes of Health
NOAEL	no observed adverse effect level
NOS	not otherwise specified
NSAID	nonsteroidal anti-inflammatory drug
NTX	N-telopeptide cross-link
NVB	neurovascular bundle
OCR	Office of Clinical Research at MSK
PCCTC	Prostate Cancer Clinical Trials Consortium
PCRP	Department of Defense Prostate Cancer Research Program
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PI	principal investigator
PIN	prostatic intraepithelial neoplasia
PK	pharmacokinetics
PMB	Pharmaceutical Management Branch
PO	per os (by mouth)
PR	partial response
PSA	prostate-specific antigen
PSA-DT	prostate-specific antigen doubling time
PSMA	prostate specific membrane antigen
PT	prothrombin time
PTT	partial thromboplastin time
QC	quality control
qd	quaque die (every day)
qRT-PCR	quantitative reverse transcription-polymerase chain reaction
QOL	quality of life
RBC	red blood cell
RC	Research Council
RDBMS	Relational Database Management System
RDRC	Radioactive Drug Research Committee
RECIST	Response Evaluation Criteria in Solid Tumors
RP	radical prostatectomy
RPC	eResearch Program Coordinator
RSA	Research Study Assistant
RSD	relative standard deviation
%RSD	percent relative standard deviation
SAE	serious adverse event

SAHA	suberoylanilide hydroxamic acid
SC	subcutaneous
SD	standard deviation
SD	stable disease
Seq	sequence
SHBG	sex hormone binding globulin
SKI	Sloan-Kettering Institute for Cancer Research
SMD	stable metabolic disease
SOP	Standard Operating Procedures
SPORE	Specialized Programs of Research Excellence
STAR	Symptom Tracking and Reporting
SUV	standardized uptake value
t	temperature
t1/2	terminal half-life
T	time
TAUC(TAU)	trapezoidal area under the concentration-time curve in one dosing interval
TAUC(0-T)	trapezoidal area under the concentration-time curve from time zero to the time of the last quantifiable concentration
TDP	time to disease progression
TGP	prostate-specific transglutaminase
tid	ter in die (3 times a day)
TMA	tissue microarray
Tmax	time of maximum observed concentration
TMPRSS2	transmembrane protease, serine 2
TNM	tissue, lymph node, metastases
TX	treatment
ULN	upper limit of normal
ULQ	upper limit of quantitation
UR	urinary recovery
VEGF	vascular endothelial growth factor
Vss	volume of distribution at steady-state
WBC	white blood cell
WHO	World Health Organization

APPENDIX G. PILL DIARY

Please see separately attached Appendix G – Pill Diary