Phase II Randomized Placebo-Controlled Double-Blind Study of Salvage Radiation Therapy (SRT) Plus Placebo Versus *SRT Plus Enzalutamide in Men with High-Risk PSA-Recurrent Prostate Cancer after Radical Prostatectomy (SALV-ENZA)*

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The Sidney Kimmel Comprehensive Cancer Center (SKCCC), Johns Hopkins University

Principal Investigator
Daniel Song (Radiation Oncologist)
Emmanuel Antonarakis (Medical Oncologist)
1550 Orleans St
CRB2 Rm 406
Baltimore, MD 21231
410-614-3880
email: dsong2@jhmi.edu & eantona1@jhmi.edu

Statistician
Hao Wang

550 N. Broadway St
550 Building Rm 1101
Baltimore, MD 21231

email: hwang76@jhmi.edu

Co-investigators
Michael Carducci
Mario Eisenberger
Tamara Lotan
Sam Denmeade
Hans Hammers
Channing Paller
Theodore L. DeWeese

The Sidney Kimmel Comprehensive Cancer Center
Johns Hopkins Hospital
401 N. Broadway
Baltimore, MD 21287

Prostate Cancer Clinical Trials Consortium
55 Fifth Avenue, 13th Floor
New York, NY 10003

Participating Site	Lead Investigator	Role

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INVESTIGATOR'S APPROVAL OF PROTOCOL

Title: **Phase II Randomized Placebo-Controlled Double-Blind Study of Salvage Radiation Therapy (SRT) Plus Placebo *Versus* SRT Plus Enzalutamide in Men with High-Risk PSA-Recurrent Prostate Cancer after Radical Prostatectomy (SALV-ENZA)**

Principal Investigator Signature: _____

Principal Investigator Print: **Daniel Song**/Emmanuel Antonarakis_____

Date: _____

SYNOPSIS

Title	Phase II Randomized Placebo-Controlled Double-Blind Study of Salvage Radiation Therapy (SRT) Plus Placebo *Versus* SRT Plus Enzalutamide in Men with High-Risk PSA-Recurrent Prostate Cancer after Radical Prostatectomy
Lead site	The Sidney Kimmel Comprehensive Cancer Center (SKCCC), Johns Hopkins University
Sponsor	Investigator Initiated Johns Hopkins University IND Exempt trial
Investigational agent	Enzalutamide 160 mg PO once daily for 6 months
Phase	II
Target population	Patients with biochemical recurrence after prostatectomy who are considered candidates for salvage radiation therapy (XRT) • Adult male ≥18 years of age • Patients must have histologically confirmed adenocarcinoma of the prostate gland • Patients must have received primary treatment with radical prostatectomy. • Patients must have evidence of biochemical (PSA) relapse after prostatectomy, defined by one rise in PSA above a baseline detectable value (≥0.05 ng/mL) using measurements taken at least 4 weeks apart from each other (all PSA values must be within 12 months of study entry).

- Patients must have pathological Gleason (pG) sum 8-10; or pG sum 7 and either pT3 or R1 disease (*i.e.* positive margins.).
- Patients must have an absolute PSA level between ≥0.05 and <0.7 ng/mL at the time of study entry.
- Patients must have non-metastatic (M0) disease, as defined by a lack of metastases seen on CT scan of the abdomen/pelvis and whole-body radionuclide ^{99}Tc bone scan, (or sodium fluoride PET scan) taken within 3 months of study entry.
- Patients must have had node negative (pN0) disease found at the time of surgery. If a nodal dissection was not performed at the original surgery then patients must be N0, as defined by a lack of radiographic or clinical evidence of local-regional tumor recurrence, including lack of pelvic lymph nodes ≥2 cm in short-axis diameter.
- Patients must have non-castrate levels of serum testosterone (≥ 150 ng/dL), as evidence by any testosterone taken within six (6) months of enrollment
- Patients must not have previously received hormonal therapy (LHRH agonist/antagonist, antiandrogen, or both), with the exception of neoadjuvant or adjuvant hormones given in conjunction with prostatectomy. In such cases, hormone therapy must have been administered for ≤6 months, discontinued ≥6 months ago, and serum testosterone must be ≥150 ng/dL.
- Patients must have ECOG performance status of 0-1, and life expectancy ≥ 3 years.
- Patients must have laboratory test results within the ranges listed below:
  - WBC ≥ 3000/mm^3
  - Granulocytes ≥ 1500/mm^3
  - Hemoglobin ≥ 9 g/dL
  - Platelets ≥ 100,000/mm^3
  - Bilirubin ≤ 1.8 mg/dL
  - ALT and AST ≤ 2.5 times the institutional upper limit of normal
  - Creatinine ≤ 1.8 mg/dL OR a calculated creatinine clearance ≥ 60 mL/hr
- Patients must be disease-free from prior malignancies for ≥3 years, with the exception of non-melanoma skin cancers and superficial urothelial cancers.
- Patients must have the ability to swallow the study drug whole as a tablet or capsule.
- Willingness to use adequate methods of contraception throughout study participation and for at least 3 months after completing therapy
- The patient was informed about the positive survival results of the RTOG 96-01 clinical trial, and has elected to forgo treatment with high-dose bicalutamide

Study centers	Six sites in the United States, including the lead site (SKCCC, Johns Hopkins University)
Start date/Duration	First patients are expected to be enrolled in March 2015. Accrual has been slower than originally estimated but we will end accrual March 2020 with additional 21 months of follow-up after the last patient has been entered.
Expected enrollment	96 patients
Rationale	The primary hypothesis of this study is that outcomes for patients with biochemically recurrent prostate cancer following radical prostatectomy will be improved by the addition of enzalutamide

for 6-months compared to standard-of-care salvage radiation therapy to allow for further study in the definitive phase III setting. This study builds on the prior success of high-dose bicalutamide (for 24 months) when combined with salvage XRT, while using a newer more potent anti-androgen for a shorter duration of time (6 months) in an effort to minimize adverse effects.

Objectives

Primary

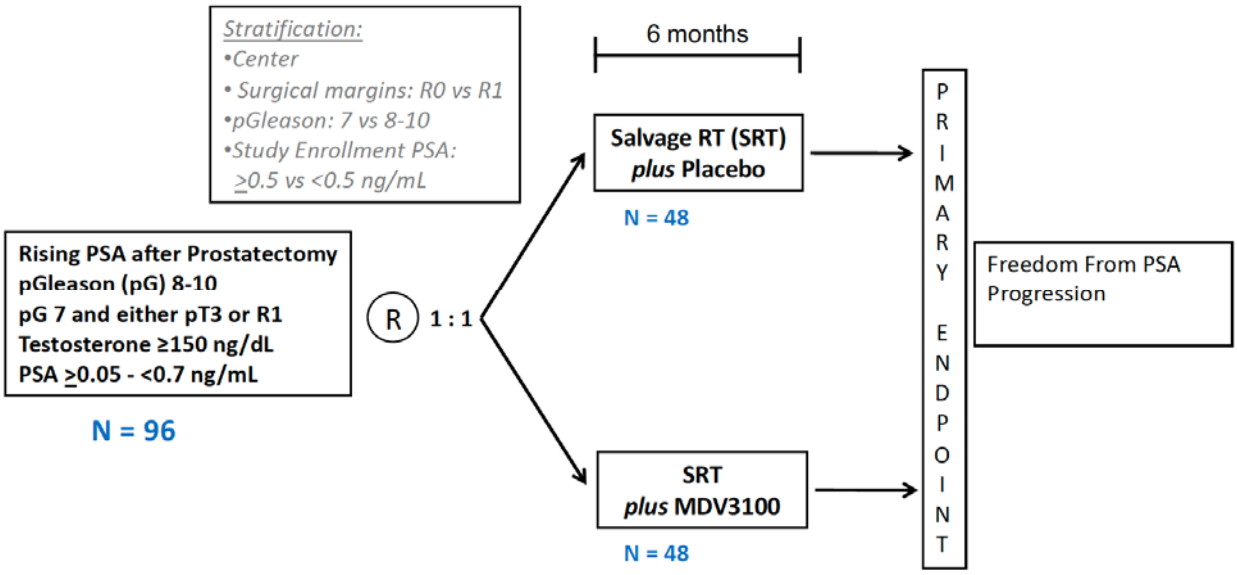
The primary objective of the study is to evaluate the efficacy of the two treatment regimens in terms of freedom-from-PSA-progression (FFPP). FFPP is defined as the time from randomization to the date of PSA progression. In patients who achieve an undetectable PSA value (defined as ≤0.1 ng/mL), PSA progression is defined as a detectable PSA value (≥0.2 ng/mL) that is confirmed by a second consecutive PSA value obtained ≥8 weeks later which is higher (and ≥0.4 ng/mL). In patients who do not achieve an undetectable PSA, PSA progression is defined as a 0.2 ng/mL increase from nadir that is confirmed by a second consecutive PSA value obtained ≥8 weeks later which is higher.

Secondary

- Time to local recurrence within the radiation field (confirmed pathologically).
- Metastasis-free survival (radiographic MFS). Metastasis-free survival will be defined as the time interval from the date of registration to date of evidence of systemic disease on bone scan or cross sectional imaging or death, whichever occurs first.
- Safety as determined by frequency and severity of adverse events (AEs), feasibility, and tolerability.

Study design

This is a randomized, double-blind, phase II, prospective, multicenter study in male adults with biochemically recurrent prostate cancer following radical prostatectomy. Following registration, androgen receptor blockade (ARB) in the form of enzalutamide 160 mg PO once daily (or placebo PO once daily) for 6 months will be administered. Following 2 months of study drug therapy, external beam radiotherapy to 66.6-70.2 Gy will be administered to the prostate bed (no pelvic nodes) over 7-8 weeks. Radiotherapy will be initiated starting on day 61, with allowance up to day 92 for resolution of study drug-related adverse effects.



Treatment Arms and Study Procedures

Patients will be randomized equally (1:1) to one of two arms –

- **Arm A** (control): **Salvage radiation therapy** (3D-CRT/IMRT) 66.6-70.2 Gy given 1.8 Gy M-F for 37 -39 fx

  ***PLUS* Placebo** PO daily for 6 months (2 months prior to SRT, 2 months during SRT and 2 months following SRT)

- **Arm B** (experimental): **Salvage radiation therapy** (3D-CRT/IMRT) 66.6-70.2 Gy given 1.8 Gy M-F for 37-39 fx

  ***PLUS* Enzalutamide** (MDV3100) 160 mg PO once daily for 6 months (2 months prior to SRT, 2 months during SRT and 2 months following SRT)

Criteria for evaluation:

Primary Endpoint:
–Freedom-from-PSA-progression (FFPP).

Secondary Endpoints:
–Local recurrence within the radiation field (confirmed pathologically).
–Metastasis-free survival (MFS).
–Frequency and severity of adverse events (AEs).

Statistical method:

Primary Analysis:

Freedom-from-PSA-progression (FFPP) will be summarized using Kaplan-Meier method by treatment arms. FFPP curves will also be displayed graphically. Differences in FFPP between treatment arms will be compared by the log rank test. The Cox proportional hazards regression model will be fitted, and the estimated hazard ratio (Arm B/Arm A) and corresponding 95% CI will be provided. FFPP probability will be estimated using the Kaplan-Meier method. Additionally, Cox

regression models will be used to explore the potential influences of the other prognostic factors on the primary FFPP endpoints.

Secondary Analysis:

Time-to-event endpoints (time to local recurrence and MFS) will be analyzed similarly as described for the primary endpoint (FFPP).

For safety analysis, overall safety profile and toleration of Arm A and Arm B will be characterized by type, frequency, severity, timing and relationship of study therapy of adverse events and laboratory abnormalities. Adverse events will be summarized by the frequency of patients experiencing treatment emergent adverse events corresponding to body systems and by worst NCI CTCAE (version 4.0) grade.

Safety analysis:	Standard safety summaries will be provided for treatment exposure, patient disposition, adverse events leading to discontinuation, serious adverse events, and all events resulting in death, including those up to 30 days after treatment discontinuation. The incidence of adverse events will be tabulated and reviewed for potential significance and clinical importance.

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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 2012, as many as 241,740 American men were diagnosed with prostate cancer, and nearly 28,170 died of the disease[1].

The course of prostate cancer from diagnosis to death is best categorized as a series of clinical states (Fig. 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. Most men that ultimately die of prostate cancer die from metastatic castrate-resistant disease[1]. However, of the approximately 30,000 men that die of prostate cancer per year, the vast majority of these men originally presented with localized prostate carcinoma which failed local therapy such as radical prostatectomy and progress along the pathway as shown in Fig. 1. Importantly, these men at the time of initial PSA relapse following surgery still represent potentially curable patients with salvage radiation (see Fig. 1 – "Rising PSA").

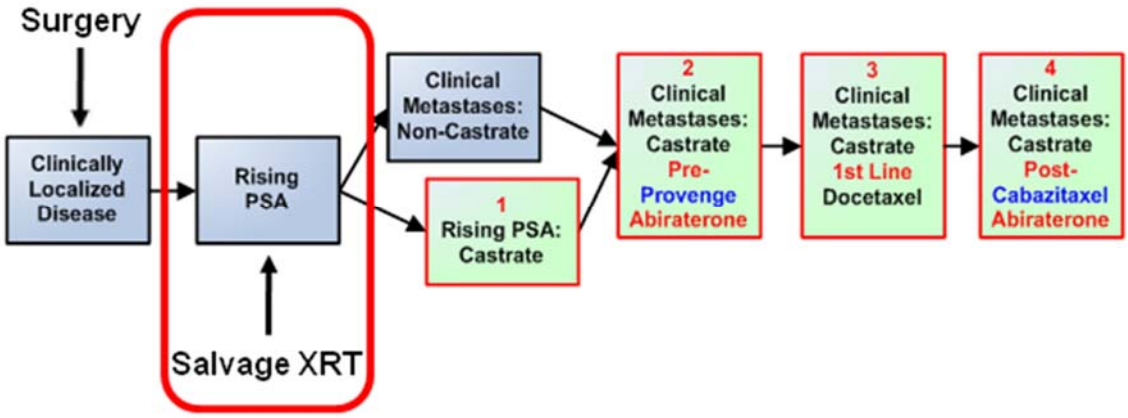

Figure 1 Clinical states of prostate cancer – In red highlights the focus group of this trial.

1.2 Treatment Background

While a significant proportion of patients with clinically localized prostate cancer will be cured with definitive local therapy, those patients with high-risk features such as Gleason grade 8-10, positive lymph nodes, positive surgical margins or positive seminal vesicles have a 50-75% chance of disease recurrence in 10 years [2-7]. Men who undergo prostatectomy and are found to have any of these features have cure rates of less than 25% after long-term follow-up [3,7,8]. As the use of prostatectomy has increased substantially over the last 10 years, so has the application of post-prostatectomy salvage radiotherapy (SRT). SRT is the mainstay of salvage treatment for men with a persistently detectable PSA or a delayed rise in PSA without evidence of metastasis [9-17]. Because there are no published SRT randomized trials, the rationale for this treatment is derived mostly from retrospective series. The largest retrospective analysis was a multi-institutional effort reported by

Stephenson et al.[17] They examined predictors of response to SRT and found that high Gleason score, high pre-SRT PSA, negative prostatectomy surgical margins, short PSA doubling time (PSADT), and seminal vesicle involvement were independently associated with adverse outcome. Similar factors have been reported in many of the other retrospective series as well[18]. Despite gains in understanding how to select patients for salvage treatment, higher level prospective clinical evidence on the outcome of patients receiving well-delineated treatment (e.g., RT technique, use of androgen deprivation/androgen receptor blockade) is still lacking. Regardless, it is clear that SRT alone is not likely to afford high levels of Freedom from PSA progression (FFPP) or cure in high-risk individuals.

1.3 Rationale for Combination SRT and Enzalutamide Treatment Postoperatively

1.3.1 Rationale for improving SRT outcomes with hormonal therapy

Several randomized trials have demonstrated that the addition of hormone therapy improves overall survival in men receiving primary radiotherapy for prostate cancer[8,19-23]. There is no consensus on how to apply hormonal therapy or in what patients in the postoperative setting[24-29] and until recently there were no reported randomized controlled trials addressing the role of hormone therapy in men receiving post-operative radiotherapy.

One study has recently reported, RTOG 96-01 compared SRT alone to SRT plus 2 years of androgen receptor blockade (ARB), accomplished using 150 mg/day of Casodex. RTOG 96-01 has shown significantly improved overall survival by 5% at 12-years and reduced incidence of metastatic prostate cancer and death from prostate cancer by half without adding significantly to radiation toxicity. Post hoc analysis demonstrated that most of the benefit came from patients with PSA $\geq$0.7 and that men with PSA < 0.7 appeared to not benefit and in fact survival was worse in these men placed on high-dose bicalutamide. A few notable criticisms of this trial that was conducted over 15 years ago was the use of a much lower salvage radiation therapy dose of 64.8 Gy, and the study population does not represent the majority of men with rising PSA following surgery seen in the modern era where most men present with PSA <1. In addition, the use of RTOG 96-01 does also not provide information on the use of short-term hormonal therapy in combination with SRT.

Another trial that has reported recently is GETUG-16 that compared SRT alone to SRT plus 6-mos of androgen deprivation therapy using an LHRH analog. GETUG-16 showed an improvement of 5-year any progression-free survival of 62% *vs* 80%. The follow-up was too short to determine overall or prostate cancer specific survival at this time.

Three retrospective non-randomized studies have compared the outcome of SRT alone versus SRT plus short-term (4-6 months) hormone therapy, and have observed improved biochemical control rates with the addition of hormone therapy[24,26,29].

RTOG 05-34 is a Phase III three-arm clinical trial designed to address multiple questions regarding SRT. The most germane question to our proposed trial, attempts to determine whether short-term androgen deprivation (AD) of 4-6 months plus SRT is superior to SRT alone. RTOG 05-03 specifies AD as combined

androgen deprivation in the form of LHRH agonist and first generation ARB such as flutamide or bicalutamide.

RADICALS is an international, multi-center, open-labeled, randomized trial of prostate cancer patients with two separate randomizations for overlapping patient groups. The first randomization is between early post-operative or adjuvant radiotherapy and deferred SRT (for PSA failure). The other randomization is performed shortly before the administration of postoperative radiotherapy and is either no hormone therapy, short-term (6-mos) or long-term (2-years) hormone therapy in combination with SRT.

1.3.2 Rationale for dose and fractionation used with SRT

Our proposal prescribes 66.6-70.2 Gy total given in 1.8 Gy fractions, which is a commonly used dose range although we do acknowledge the use of 2 Gy and higher total doses in the salvage radiation setting. The largest RTOG Phase III salvage radiation trial RTOG 05-34 uses 64.8-70.2 Gy in 1.8 Gy. The RADICALS trial is another Phase III adjuvant/salvage radiation trial which is using 66 Gy in 2 Gy fractions. The biologically equivalent dose (BED) assuming the linear quadratic formalization suggests that 66 Gy in 2 Gy fractions is equivalent/similar to 70.2 Gy in 1.8 Gy fractions over a range of alpha/beta 1.5, 3 and 10 [(BED10 = 2 Gy x 33 = 79.20; BED3 = 2 Gy x 33 = 110; BED1.5 = 2 Gy x 33 = 154) vs. (BED10 = 1.8 Gy x 39 = 82.84; BED3 = 1.8 Gy x 39 = 112.32; BED1.5 = 1.8 Gy x 39 = 154.44. Doses higher than 70.2 Gy such as 74 Gy although used by some in the community and for which there is some retrospective data[31] is not a standard.

1.3.3 Rationale for enzalutamide versus combined androgen deprivation in combination with SRT

Androgen receptor signaling promotes dysregulated growth in the majority of untreated prostate cancers. Androgen deprivation (AD) via medical or surgical castration can induce apoptosis or senescence in prostate cancer cells however those cells that do not die will ultimately become castration-resistant and will grow despite androgen deprivation. Molecular profiling studies have demonstrated progressive changes that occur in the androgen receptor after development of castrate-resistance, most frequently overexpression of the androgen receptor, which can occur via several mechanisms following AD [32]. AD is also associated with long term metabolic adverse effects (adverse changes in fat body mass, lipid and glycemic profiles) and decreases in bone mineral density (BMD). Given this, more potent androgen receptor blockade (ARB) is desirable. First-generation ARB with bicalutamide has been used in combination with SRT as discussed above. Bicalutamide is easy to administer, well tolerated and has a favorable side effect profile, however as with all first-generation androgen receptor antagonists, displays weak agonist properties, particularly in the setting of increased androgen receptor levels. These agents also demonstrate relatively weak binding affinity for the androgen receptor when compared to novel agents in development [33,34].

Enzalutamide is a second-generation androgen receptor signaling inhibitor that significantly prolongs survival in patients with metastatic castration-resistant prostate cancer who have received prior docetaxel chemotherapy [35,36]. Enzalutamide has demonstrated activity in cells that overexpress the androgen receptor. Unlike previous ARB agents, Enzalutamide does not display any agonist properties and blocks translocation of the ligand-receptor complex into the nucleus

preventing DNA binding [33]. Enzalutamide is an oral agent that is generally well tolerated and does not require concurrent steroid administration, which makes it an ideal candidate for combination with SRT.

Finally, provocative preliminary Phase II data presented at the ASCO 2013 by Mathew Smith and colleagues assessed the efficacy and safety of 25-weeks (~6-mos) of enzalutamide alone in prostate cancer of all stages who had never received hormone therapy; presenting with non-castrate testosterone levels (≥230 ng/dL). Enzalutamide alone for 6-mos achieved a high PSA response rate with efficacy similar to castration, but .in contrast to castration, BMD remained stable and metabolic variables were not substantially impacted.

The trial described here differs from RTOG 96-01, GETUG-16, RTOG 05-34 and RADICALS in several ways. First, the eligibility criteria are stricter; less favorable patients have been selected and relative to RTOG 96-01 contemporary patients with modern radiotherapy dose and techniques are being used. Second, short-term ARB is being tested, while in RTOG 96-01 and RADICALS long-term ARB of 2-years was examined. Finally, and most importantly, we are testing the second generation ARB agent, enzalutamide, alone in combination with SRT as opposed to GETUG-16, RTOG 05-34 and RADICALS which use AD.

This trial is not intended to address the efficacy of SRT alone over observation. The complete response rate (a drop in PSA to undetectable levels) after SRT is 70%-80% and durable responses are observed in 30%-40% of patients. For these reasons, it is not feasible or appropriate to randomize men between observation and SRT. The more important issue is whether the proportion of durable responses is increased by altering the therapeutic approach, such as the use of enhanced ARB using enzalutamide. Similarly, as described above, there is considerable controversy regarding the benefit of adding high-dose bicalutamide to men with rising PSA where there PSA is < 0.7 following surgery. Given differences in this old trial consisting of lower SRT dose of 64.8 Gy, and the non-contemporary study population we think it is reasonable to offer SRT alone as a control arm as long as men are informed of the survival results of RTOG 96-01 and the controversy regarding this study in the modern era.

2. OBJECTIVES

2.1 Primary Objective

The primary efficacy endpoint is the rate of Freedom-from-PSA-progression (FFPP). FFPP is defined as the time from randomization to the date of PSA progression. A subject who does not have PSA progression at the time of the analysis will be censored at the last date of PSA measurement.

In patients who achieve an undetectable PSA value (defined as ≤0.1 ng/mL), PSA progression is defined as a detectable PSA value (≥0.2 ng/mL) that is confirmed by a second consecutive PSA value obtained ≥8 weeks later which is higher (and ≥0.4 ng/mL). In patients who do not achieve an undetectable PSA, PSA progression is defined as a 0.2 ng/mL increase from nadir that is confirmed by a second consecutive PSA value obtained ≥8 weeks later which is higher. The date of PSA progression will be defined as the first date of PSA rise from nadir or baseline.

2.2 Secondary Objectives

- Local recurrence within the radiation field (confirmed pathologically)
- Metastasis-free survival (MFS) rates. Metastasis-free survival will be defined as the time from the date of registration to date of evidence of systemic disease on bone scan or cross sectional imaging or death, which occurs first.
- Safety, feasibility, and tolerability as assessed by NCI Common Toxicity Scales (v4.0), quality of life (EPIC survey), and achievement of accrual goals.

3. PATIENT SELECTION

3.1 Target Population

Prostate adenocarcinoma following radical prostatectomy with evidence of recurrent disease as measured only by rising PSA, without evidence of metastatic disease by bone scan or CT scan within 12 weeks of entry (*i.e.* the salvage radiotherapy population).

3.2 Expected Enrollment

A total of 96 patients will be included in this study. The first patients are expected to be enrolled in March 2015. Accrual was expected to be completed in 18 months once the protocol has been approved by the IRB at each participating institution, but has been slower than expected at about 10 patients per 6 months. We plan to close accrual at March 2020.

3.3 Inclusion Criteria

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

- 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 aged 18 years of age and above
- Patients must have histologically confirmed adenocarcinoma of the prostate gland
- Patients must have received primary treatment with radical prostatectomy.
- Patients must have evidence of biochemical (PSA) relapse after prostatectomy, defined by one rise in PSA above a baseline detectable value (≥0.05 ng/mL) using measurements taken at least 4 weeks apart from each other (all PSA values must be within 12 months of study entry).
- Patients must have pathological Gleason (pG) sum 8-10; or pG sum 7 and either pT3 or R1 disease (*i.e.* positive margins.).
- Patients must have an absolute PSA level between ≥0.05 and <0.7 ng/mL at the time of study entry.
- Patients must have non-metastatic (M0) disease, as defined by a lack of metastases seen on CT scan of the /abdomen/pelvis and whole-body radionuclide ^{99}Tc bone scan, (or sodium fluoride PET scan) taken within 3 months of study entry.
- Patients must have had node negative (pN0) disease found at the time of surgery. If a nodal dissection was not performed at the original surgery then patients must be N0, as defined by a lack of radiographic or clinical evidence of local-regional tumor recurrence, including pelvic lymph nodes ≥2 cm in short-axis diameter.

- Patients must have non-castrate levels of serum testosterone (≥ 150 ng/dL).
- Patients must not have previously received hormonal therapy (LHRH agonist, antiandrogen, or both), with the exception of neoadjuvant or adjuvant hormones given in conjunction with prostatectomy. In such cases, hormone therapy must have been administered for ≤6 months, discontinued ≥6 months ago, and serum testosterone must be ≥150 ng/dL.
- Patients must have ECOG performance status of 0-1, and life expectancy ≥ 3 years.
- Patients must have laboratory test results within the ranges listed below within 4 weeks of enrollment:
    - WBC ≥ 3000/mm^3
    - Granulocytes ≥ 1500/mm^3
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    - Bilirubin ≤1.8 mg/dL
    - ALT and AST ≤ 2.5 times the institutional upper limit of normal
    - Creatinine ≤ 1.8 mg/dL OR a calculated creatinine clearance ≥ 60 mL/hr
- Patients must be disease-free from prior malignancies for ≥3 years, with the exception of non-melanoma skin cancers and superficial urothelial cancers.
- Patients must have the ability to swallow the study drug whole as a tablet or capsule.
- Throughout study, male patient and his female partner who is of childbearing potential must use 2 acceptable methods of birth control (1 of which must include a condom as a barrier method of contraception) starting at screening and continuing throughout the study period and for 3 months after final study drug administration or per local guidelines where these require additional description of contraceptive methods. Two acceptable methods of birth control thus include the following:
    - Condom (barrier method of contraception); AND
    - One of the following is required:
        - Established and ongoing use of oral, injected, or implanted hormonal method of contraception by the female partner.
        - Placement of an intrauterine device or intrauterine system by the female partner.
        - Additional barrier method: Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository by the female partner.
        - Tubal ligation in the female partner.
        - Vasectomy or other procedure resulting in infertility (eg, bilateral orchiectomy), for > 6 months.
- Throughout the study, patients must use a condom if having sex with a pregnant woman.
- The patient was informed about the positive survival results of the RTOG 96-01 clinical trial, and has elected to forgo treatment with high-dose bicalutamide.

3.4 Exclusion Criteria

Patients that meet any of the criteria listed below will not be eligible for study entry:

- Currently active second malignancy
- Primary treatment with radiation therapy.
- Radiographic or clinical evidence of regional tumor nodal recurrence, including pathological pelvic lymph nodes ≥2 cm in short-axis diameter. Radiographic evidence of distant metastases is also an exclusion.
- Concurrent use of other antiandrogens, estrogen-like agents, or 5a-reductase inhibitors.
- Use of systemic corticosteroids equivalent to prednisone 10 mg/day or higher at the time of study entry (inhaled corticosteroids are permitted).
- Concurrent use of other anti-cancer agents or treatments.
- Serious concurrent medical illnesses (including uncontrolled major cardiac, pulmonary, Child-Pugh C liver or psychiatric diseases) or active major infections (including HIV, Hepatitis A-C).
- Clinically significant cardiovascular disease including:
  - Myocardial infarction within 6 months of Screening visit.
  - Uncontrolled angina within 3 months of Screening visit.
  - Congestive heart failure New York Heart Association (NYHA) class 3 or 4, or subjects with history of congestive heart failure NYHA class 3 or 4 in the past, or history of anthracycline or anthracenedione (mitoxantrone) treatment, unless a screening echocardiogram or multi-gated acquisition scan (MUGA) performed within three months of the Screening visit results in a left ventricular ejection fraction that is ≥ 45%.
  - History of clinically significant ventricular arrhythmias (e.g., ventricular tachycardia, ventricular fibrillation, torsade de pointes).
  - Prolonged corrected QT interval by the Fridericia correction formula (QTcF) on the screening electrocardiogram (ECG) > 470 msec.
  - History of Mobitz II second degree or third degree heart block without a permanent pacemaker in place.
  - Hypotension (systolic blood pressure <86 mmHg or bradycardia with a heart rate of <50 beats per minute on the Screening ECG, unless pharmaceutically induced and thus reversible (i.e. beta blockers).
  - Uncontrolled hypertension as indicated by a resting systolic blood pressure >170 mmHg or diastolic blood pressure >105 mmHg at the screening visit.
- Medications which lowers seizure threshold.
- History of seizure or any condition that may predispose to seizure including, but not limited to underlying brain injury, stroke, primary brain tumors, brain metastases, or alcoholism. Also, history of loss of consciousness or transient ischemic attack within 12months of enrollment (Day 1 visit).
- Patients taking medications that may have adverse interactions with enzalutamide (see Appendix B).

3.5 Inclusion of Minorities

Men of all races and ethnic groups are eligible for this trial.

4. PATIENT REGISTRATION AND ENROLLMENT PLAN

4.1 Registration Procedure

Prior to protocol enrollment and initiation of treatment, subjects must sign and date an IRB approved consent form. A centralized, 3-part registration procedure will be used. After eligibility screening and confirmation that a patient is eligible, patients who are selected to participate will be registered centrally at the SKCCC Johns Hopkins Lead Center, at the participating institution, and if applicable, in the online centralized PCCTC database. A record of patients who fail to meet entry criteria (ie, screen failures) will be maintained. The patient must give informed consent before beginning any study-specific procedures. Patient registration must be completed by the lead coordinating center before treatment is initiated. A complete, signed study consent and HIPAA consent are required for registration.

4.1.1 Registration at SKCCC, Johns Hopkins University

Confirm eligibility as defined in ***Section 3. Patient Selection***.

4.1.1.1 Obtain informed consent, by following procedures:

The investigator (or his/her designee) will explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject will be informed that participation in the study is voluntary, that he may withdraw from the study at any time, and that withdrawal of consent will not affect his subsequent medical treatment or relationship with the treating physician(s) or institution. The informed consent will be given by means of a standard written statement, written in non-technical language, which will be IRB approved. The subject should read and consider the statement before signing and dating it, and will be given a copy of the document. No subject will enter the study or have study-specific procedures done before his informed consent has been obtained.

In accordance with the Health Information Portability and Accountability Act (HIPAA), the written informed consent document (or a separate document to be given in conjunction with the consent document) will include a subject authorization to release medical information to the study sponsor and supporting agencies and/or allow these bodies, a regulatory authority, or Institutional Review Board access to subjects' medical information that includes all hospital records relevant to the study, including subjects' medical history.

All subjects considered for enrollment in the study must complete an IRB-approved informed consent prior to any study-specific procedures being performed.

To register a patient, the participating site must contact the Lead Center's Study Coordinator about a potential candidate prior to sending documents. Once acknowledgement is made, the following documents must be completed and faxed to (443-287-8354) or e-mailed to the lead site:

- Signed patient consent form
- Eligibility checklist signed by the participating center PI or Co-I
- Copies of all source documentation verifying eligibility criteria

The Lead Site will review the documents to confirm eligibility. To complete the registration process, the Lead Center will:

- Assign a patient study number
- Randomize the patient onto a treatment arm
- Register the patient on the study with the Sidney Kimmel Comprehensive Cancer Center's Clinical Research Office.
- Fax or e-mail the unique patient study number and assigned study arm to the participating site.

Treatment must not commence until the patient has been registered with the Sidney Kimmel Comprehensive Cancer Center's Clinical Research Office and randomization has been completed by the coordinating center.

4.1.2 Multicenter/Participating site registration

Central registration for this study will take place at *SKCCC, Johns Hopkins University.*

Patient registration at each study site/institution will be conducted according to the institution's established policies. Before registration, patients will be asked to sign and date an Institutional Review Board (IRB)-approved consent form and a research authorization/HIPAA form. Patients must be registered with their local site/institution and also with the sponsor or Lead Site before beginning any treatment.

4.1.3 Randomization

After written informed consent has been obtained and eligibility has been established, the coordinating center will enter demographic and baseline characteristics in an interactive web response system (IWRS). The coordinating center will obtain the patient's randomization assignment from the IWRS and appropriately notify the study site. Randomization to one of the two treatment arms will occur in a 1:1 ratio. The randomization will be stratified by: Center, surgical margin status (R0 vs R1), PSA prior to salvage treatment (PSA ≥0.5 vs <0.5 ng/mL), and pathologic Gleason score (7 vs 8-10). Minimization approach[37] will be applied to ensure balanced assignment to each treatment arm. The investigator and the patient will be blinded to treatment assignment.

5. TREATMENT/INTERVENTION PLAN

This study is a multi-center, double-blind, placebo controlled, randomized Phase II trial in patients with non-castrate PSA-recurrent prostate cancer after radical prostatectomy. Eligible patients will be randomized in a 1:1 ratio to one of two treatment arms: salvage radiation therapy (SRT) *plus* placebo (Arm A) or SRT *plus* enzalutamide (Arm B) (see schema below).

The following assessments and procedures will occur during the study. A schedule of assessments is provided in Table 1.

Table 1 Study Calendar

Procedures	**Baseline**		**Treatment**						**Follow-up***		**Off-Study**
			Day 1‡ (Start of Drug)	Day 61‡ (Start of SRT)	Day 91‡‡	Day 120‡ (End of SRT)	Day 151‡‡	Day 180‡‡ (End of Drug)	**Q3 mos[8] 24-months**	Q3 mos[8,9] Till study ends	PSA progression[10]
Informed Consent	X	**Randomization**									
Demographics	X										
Medical History	X[1]										
Concurrent medications	X[1]			X	X	X	X	X	X		X
Height	X[1]										
Physical Exam, vitals, weight, ECOG	X[1]			X	X	X	X	X	X		X
Adverse event evaluation			X	X	X	X	X	X	X		X
Pill count/diary[12]			X	X	X	X	X	X			
CBC with diff[2]	X[1]			X	X	X	X	X	X		X
Serum Chemistries[3]	X[1]			X	X	X	X	X	X		X
Total serum testosterone	X[1]			X	X	X	X	X	X		X
PSA evaluation[4]	X[1]			X	X	X	X	X	X[4]	X	X
ECG[5]	X[1]										
CT A/P (or MRI)[6]	X[1]										X[6]
Chest X-Ray											X[6]
Radionuclide bone scan	X[1]										X[6]
QoL questionnaires[7]			X	X	X	X	X	X	X		X
Tumor Tissue banking[11]	X										
Decipher Test								X[14]			
Treatments											
SRT[13]				X	X	X					
Placebo PO daily (Arm A)			X	X	X	X	X	X			
Enzalutamide 160mg PO daily (Arm B)			X	X	X	X	X	X			

Abbreviations: CBC, complete blood count; CT, computerized tomography; EKG, electrocardiogram; MRI, magnetic resonance imaging; PSA, prostate-specific antigen; Mos, Month

1. All evaluations should be conducted within 30 days prior to registration/randomization. The exception to this is the radiologic evaluations and informed consent, which can be performed within 90 days prior to day 1.
2. CBC which includes WBC (with differential), platelets, Hgb, and Hct
3. Chemistries include albumin, alkaline phosphatase, total bilirubin, BUN, calcium, chloride, creatinine, glucose, sodium, potassium, total protein, SGOT [AST], and SGPT [ALT].
4. Those patients coming off study prior to PSA progression (i.e. for toxicity, etc.) should be evaluated for PSA levels every 3 months until PSA progression occurs.
5. ECGs may also be performed as clinically indicated throughout the study.
6. Radiologic evaluations (CT/MRI and bone scan) and chest x-ray (if applicable) should be conducted at PSA progression. Scans can also be obtained sooner as clinically indicated.
7. Quality-of-life (QoL) tools will include FACT-P, EORTC QLQ-C30/QLQ-PR25, and SHIM.
8. Patients should remain on study until PSA progression. This is defined as a PSA value ≥0.2 ng/mL above nadir that is confirmed by a second consecutive PSA value ≥8 weeks later which is higher (and ≥0.4 ng/mL). Patients should remain on study until the confirmatory PSA.
9. The total length of the study is 18 months for full enrollment and 24-months of follow-up for the last patient or 42 months. Patients who have 24-months of follow-up following treatment will continue to be followed for PSA determinations only and should remain on study until PSA progression or study end at month 42 whichever comes first.
10. To be conducted 2 months after the patient comes off study.
11. In patients who have consented, a tumor tissue block should be requested for banking, preferably from the prostatectomy specimen. If not available, a tissue block from the prostate biopsy should be submitted. In addition, a normal tissue block from the same patient (preferably from the prostatectomy) should be requested for banking. This only applies to the lead site (JHU).
12. Drug and diary review and dispensing may be done prior to or indicated day.
13. SRT to start 61 days (+/- 3 weeks) after Day 1. SRT will be delivered Monday-Friday
14. Decipher Test can be completed at any time before treatment ends on Day 180.

‡Should occur within 7 days prior (Please note that this window does not apply to the study drug administration. The participant should take the study drug continuously for 180 days)

‡‡ Should occur +/- 14 days (Please note that this window does not apply to the study drug administration. The participant should take the study drug continuously for 180 days)

*Follow-up visits may be performed +/- one month from the scheduled time of visit date. In the event that the participant chooses to undergo follow-up evaluation elsewhere or unexpectedly cannot adhere to the follow-up timeline, QoL assessments may be completed via mail or email and adverse event assessments may be completed by the study team via telephone.

Note that the study calendar is based on the ideal subject. The schedule should be followed as closely and realistically as possible, but may be modified due to problems such as scheduling delays, conflicts such as clinic closure or poor weather conditions, or other unforeseeable events.

5.1 Screening/Baseline Assessment

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).

The screening/baseline procedures will determine patient eligibility according to the inclusion and exclusion criteria (Sections 3.3 Inclusion Criteria & 3.4 Exclusion Criteria).

The following evaluations/assessments will be performed at this visit <u>within 90 days</u> of Day 1:

- Obtain informed consent and research authorization.
- Obtain histologic and radiologic confirmation of disease.
- Collect details and dates of the primary therapy (eg, pathologic stage, dose and type of radiation therapy) and prior hormonal and non-hormonal therapies.
- Record PSA and Gleason score at the time of diagnosis
- Determine suitability for salvage prostate bed radiation therapy
- Assess presence or absence of disease in the primary site
- Imaging: abdomen/pelvis by CT or magnetic resonance imaging (MRI)

radionuclide bone scan. Relevant information should be documented. The institutional registration should be finalized, and appropriate documents (ie, signed informed consent, research authorization/HIPAA form, signed eligibility checklist and supporting source documentation for eligibility questions) faxed or emailed to the lead site/sponsor.

Information for patients who do not meet the eligibility criteria to participate in this study (ie, screening failures) should be captured in consortium database at the pretreatment assessment.

The following assessments must occur **<u>within 30 days</u>** of registration/randomization:

- Physical exam (vital signs, height/weight, EKG, etc)
- Laboratory tests (CBC w/diff, PSA, testosterone, comprehensive chemistry panel, including bilirubin, creatinine, SGOT[AST], SGPT[ALT])
- ECOG performance status (Appendix A)

Review of concurrent medications (see Appendix B for a listing of medications with the potential for drug interactions)

5.2 Treatment Period

The following procedures are to be conducted each study visit on visit on Day 1, 61, 91, 120, 151 and 180 days while on study. Day 1, 61, 120 procedures should be done within seven days prior; day 91,151 and 180 procedures should be done +/- 14 days (see Table 1):

- Review concurrent medications (see Appendix B for a listing of medications with the potential for drug interactions)
- Physical exam (vital signs, weight)
- ECOG performance status (Appendix A)
- Adverse events evaluation
- Review pill diary
- Laboratory tests (CBC w/diff, PSA, testosterone, comprehensive chemistry panel, including bilirubin, creatinine, SGOT[AST], SGPT[ALT]
- QoL questionnaires

The following procedures are to be conducted at each follow-up visit every 3 months ±1 month up to 24 months (see Table 1). If participants are unable to return for follow-up, outside records may be obtained and assessments may be conducted via phone, email, or mail when possible:

- Review concurrent medications (see Appendix B for a listing of medications with the potential for drug interactions)
- Physical exam (vital signs, weight)
- ECOG performance status (Appendix A)
- Adverse events evaluation
- Laboratory tests (CBC w/diff, PSA, testosterone, comprehensive chemistry panel, including bilirubin, creatinine, SGOT[AST], SGPT[ALT]
- QoL questionnaires

The following procedure is to be conducted at each follow-up visit every 3 months ±1 month past the first 24 months and up to 42 months (see Table 1):

- Laboratory test (PSA)

5.2.1 Treatment schema

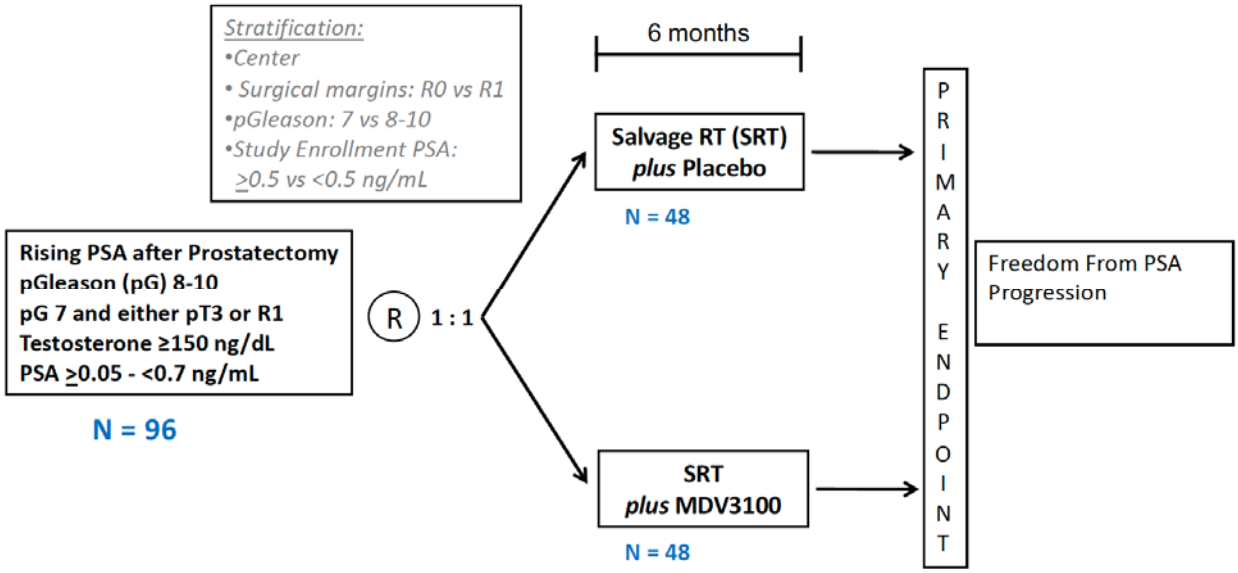

Figure 2 – Treatment Schema.

Treatment Arms and Study Procedures

Patients will be randomized equally (1:1) to one of two arms –

- **Arm A** (control): **Salvage radiation therapy** (3D-CRT/IMRT) 66.6-70.2 Gy given 1.8 Gy M-F for 37 -39 fx

  ***PLUS* Placebo** PO once daily for 6 months (2 months prior to SRT, 2 months during SRT and 2 months following SRT)

- **Arm B** (experimental): **Salvage radiation therapy** (3D-CRT/IMRT) 66.6-70.2 Gy as 1.8 Gy M-F for 37-39 fx

  ***PLUS* Enzalutamide** (MDV3100) 160 mg PO once daily for 6 months (2 months prior to SRT, 2 months during SRT and 2 months following SRT)

Continue treatment until disease progression, unacceptable toxicity, or any criteria in **Section 6.5 - Removing Patients from the Protocol.**

For a maximum period of 6 months.

Placebo: PO once daily for 6 months (2 months prior to SRT, 2 months during SRT and 2 months following SRT) for Arm A.

Enzalutamide: 160 mg PO once daily for 6 months (2 months prior to SRT, 2 months during SRT and 2 months following SRT) for Arm B.

5.2.2 Clinical and laboratory assessments

On day 1, 61, 91, 120, 151 and 180 visits while on study (Day 1, 61, 120 procedures should be done within seven days prior, day 91,151, 180 procedures should be done +/- 14 days, see Table 1) patients will have non-fasting blood drawn for the following values:

- CBC w/diff
- Comprehensive chemistry panel
- PSA
- Testosterone

5.2.3 Safety assessments

Adverse events (AEs) will be monitored at each scheduled visit and throughout the study. Toxicity will be assessed using the most recent National Cancer Institute (NCI) guidance: the most recent version of Common Terminology Criteria for Adverse Events (CTCAE).

All nonserious AEs and SAEs, regardless of relationship to study treatment, will be collected from registration through the post-treatment visit and will be recorded in the subject's medical record and on the CRF. Following the post-treatment visit, only new treatment-related AEs and SAEs will be recorded. Seizures (regardless of causality) will be recorded throughout the study.

5.2.3.1 Seizures

Seizures that occur at any time during the study, regardless of causality, severity, or outcome, will be recorded in the subject's medical record and on the CRF.

5.3 Treatment-Limiting Adverse Event

A treatment-limiting adverse event is any AE related to protocol therapy experienced during the study resulting in treatment termination.

5.4 Dose Modifications

Patients enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study as specified in Section 6. The most recent NCI CTCAE will be used to grade adverse events.

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

If patients either require that the study drug be discontinued because of an adverse event (as described below) or have a treatment interruption of greater than 2 weeks for enzalutamide or placebo, at the investigator's discretion, they may continue on SRT until completion of the SRT.

Dose reduction for enzalutamide or placebo will be allowed. If a patient experiences a ≥ Grade 3 toxicity or an intolerable side effect, withhold dosing for one week or until symptoms improve to ≤ Grade 2, then resume at the same or a reduced dose (120 mg or 80 mg).

Any toxicity requiring enzalutamide discontinuation will be recorded as an AE in the subject's medical record and on the CRF.

5.4.1 Seizures

Seizures that occur at any time during the study, regardless of causality, severity, or outcome, will result in enzalutamide discontinuation and be recorded in the subject's medical record and on the CRF.

5.5 End of Treatment/Treatment Discontinuation Visit (+/- 30 days from last dose)

The following procedures are to be conducted every 3 months ±1 month up to 24 months (see Table 1):

- Review concurrent medications (see Appendix B for a listing of medications with the potential for drug interactions)
- Physical exam (vital signs, weight)
- ECOG performance status (Appendix A)
- Adverse events evaluation
- Laboratory tests (CBC w/diff, PSA, testosterone, comprehensive chemistry panel, including bilirubin, creatinine, SGOT[AST], SGPT[ALT]
- QoL questionnaires
- Decipher Test (Will only be completed once before treatment ends on Day 180. This test will not be repeated.)

5.6 Follow-up (Every 3 months for ≥24 months or until death)

Patients will be followed for ≥2 years (and up to 42 months total) after removal from treatment or until death. Patients withdrawn from the study because of AEs will be followed until the adverse event has either resolved or stabilized. Reasons for premature withdrawal should be determined and noted.

Freedom-from-PSA-progression (FFPP) is the primary objective and is defined as the time from randomization to the date of PSA progression. A subject who does not have PSA progression at the time of the analysis will be censored at the last date of PSA measurement. In patients who achieve an undetectable PSA value (defined as ≤0.1 ng/mL), PSA progression is defined as a detectable PSA value (≥0.2 ng/mL) that is confirmed by a second consecutive PSA value obtained ≥8 weeks later which is higher (and ≥0.4 ng/mL). In patients who do not achieve an undetectable PSA, PSA progression is defined as a 0.2 ng/mL increase from nadir that is confirmed by a second consecutive PSA value obtained ≥8 weeks later which is higher.

5.7 Concomitant Medications

Because of the potential for drug-drug interaction, the concurrent use of all other drugs, over-the-counter medications, or alternative therapies must be documented on the case report form (CRF). The principal investigator should be alerted if the patient is taking any agent found in Appendix B (a listing of medications with the potential for drug-drug interactions).

5.7.1 Supportive Care Medications

Subjects should receive full supportive care, including transfusions of blood and blood products, antibiotics, antiemetics, or other therapies, in accordance with standard practice at the clinical trial site.

All concomitant medications administered from screening through the post-treatment visit, including indication, dose, route, frequency and treatment dates, will be recorded in the subject's medical record and on the CRF. After the post-treatment visit, only anticancer therapies will be recorded.

5.7.2. Prohibited before enrollment and during administration of study treatment

- Any therapy for prostate cancer except for that radical prostatectomy and those administered in this protocol.
- Strong inducers or inhibitors of CYP2C8 (gemfibrozil, rifampin [see examples in Appendix B]).
- Medications that are metabolized by CYP3A4, CYP2C9, or CYP2C19 that have a narrow therapeutic index (see examples in Appendix B).
- Strong inducers or inhibitors of CYP3A4 (including but not limited to phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, and phenobarbital [see examples in Appendix B]).
- Medications that may lower seizure threshold as determined by the investigator.

5.7.3 Drugs that may affect exposure to Enzalutamide

The principal investigator should be alerted if the patient is taking any agent found in Appendix B (a listing of medications with the potential for drug-drug interactions).

Refer to the following links for updated lists of CYP inhibitors, inducers, and substrates:
•http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DruglnteractionslabeIing/ucm093664.htm#potency
• http://medicine.iupui.edu/clinpharm/ddis/table.aspx

Drugs That Inhibit or Induce CYP2C8

Co-administration of a strong CYP2C8 inhibitor (e.g., gemfibrozil) increased the composite AUC_0-∞ of enzalutamide plus its active metabolite in healthy volunteers (Section 7.2.2); therefore, co-administration of enzalutamide with strong CYP2C8 inhibitors should be avoided if possible. If co-administration of enzalutamide with strong CYP2C8 inhibitors cannot be avoided, reduce the enzalutamide dose to 80 mg once daily. If co-administration of the strong inhibitor is discontinued, the enzalutamide dose should be returned to the dose used prior to initiation of the strong CYP2C8 inhibitor.

The effects of CYP2C8 inducers on the PK of enzalutamide have not been evaluated in vivo. Co-administration of enzalutamide with strong or moderate CYP2C8 inducers (e.g., rifampin) may alter the plasma exposure of enzalutamide and should be avoided if possible. Selection of a concomitant medication with no or minimal CYP2C8 induction potential is recommended.

Drugs That Induce CYPJA4
The effects of CYP3A4 inducers on the PK of enzalutamide have not been evaluated in vivo. Co-administration of enzalutamide with strong CYP3A4 inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine) may decrease the plasma exposure of enzalutamide and should be avoided if possible. Selection of a concomitant medication with no or minimal CYP3A4 induction potential is recommended. Moderate CYP3A4 inducers (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin) and St. John's Wort may also reduce the plasma exposure of enzalutamide and should be avoided if possible.

6. THERAPEUTIC AGENTS

6.1 Enzalutamide

Compound Number: MDV3100

Proposed International

Nonproprietary Name: enzalutamide

Molecular Formula: C21H16F4N4O2S

Chemical Name: 4-{3-[4-Cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-2-fluoro-N-methylbenzamide

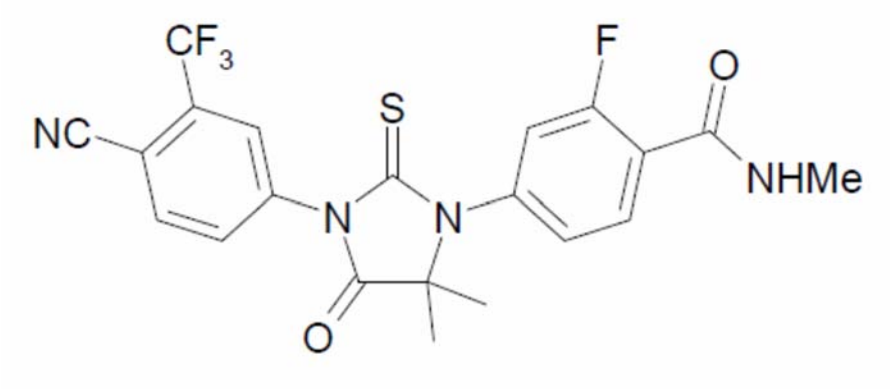

Figure 3 Chemical Structure of Enzalutamide

Molecular Weight: 464.44

Appearance: White crystals

Solubility: Practically insoluble in water

Hygroscopicity: Not hygroscopic

Enzalutamide (MDV3100) is an orally-available synthetic small molecule being developed as a potential treatment for prostate, breast and potentially other cancers. Enzalutamide is presented in a soft gelatin capsule filled with a formulation containing 40 mg of the active pharmaceutical ingredient. The therapeutic dose under phase 3 clinical investigation is 160 mg once daily (4 capsules, each 40 mg).

Table 2 Agents Studied in this Protocol

Study Drug	Lot #	Batch #	Source of Supply
Enzalutamide			Astellas/Medivation
Salvage Radiation Therapy	NA	NA	Radiation Oncology Department

6.1.1 Pharmacokinetics

Following oral administration in animals, enzalutamide is eliminated slowly from plasma with a long half-life (t1/2) across species. The t1/2 does not appear to be affected by the dose size; but, the bioavailability in animals appears to decrease with increasing dose size. The 2 major human metabolites (N-desmethyl enzalutamide and an inactive carboxylic acid metabolite) are also produced in animals. In vitro studies show that enzalutamide is metabolized by human recombinant cytochrome P450 (CYP) isoenzymes CYP2C8 and CYP3A4/5. Enzalutamide and/or its major human metabolites caused direct in vitro inhibition of multiple CYP enzymes including CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5; however, subsequent clinical data showed that enzalutamide is an inducer of CYP2C9, CYP2C19 and CYP3A4/5 and has no clinically meaningful effect on CYP2C8 in vivo. In vitro data show that enzalutamide and N-desmethyl enzalutamide are potential inhibitors, but not substrates, of the efflux transporter P-glycoprotein (P-gp). The protein binding of enzalutamide in human plasma is 97% to 98% and is similar in mice, rats, rabbits and dogs. The protein binding of the carboxylic acid derivative and N-desmethyl enzalutamide in human plasma are 98% and 95%, respectively, and are comparable across species. The extent of binding for enzalutamide, the carboxylic acid derivative and N-desmethyl enzalutamide is constant over a wide range of concentrations.

6.1.2. Dosage Selected

6.1.2.1 Preparation, and Schedule of Administration

Enzalutamide or placebo: 160 mg PO once daily for 6 months (2 months prior to SRT, 2 months during SRT and 2 months following SRT). This consists of taking four 40-mg capsules all at one time. Enzalutamide or placebo is to taken at the same time daily Enzalutamide or placebo can be administered with/without food and needs no premedication. Treatment will be administered on an outpatient basis and agent dispensed at the time of pill diary review (see Table 1 – Study Calendar).

6.1.2.2 Supply, storage requirements, and special handling

Supply and packaging:
Enzalutamide: Fill solution: enzalutamide, caprylocaproyl macrogolglycerides, butylhydroxyanisole, butylhydroxytoluene.
Capsule: gel mass (gelatin, purified water, sorbitol sorbitan solution and glycerol, titanium dioxide), ink (iron oxide black). The appearance is an opaque white to off-

white oblong liquid filled soft gelatin capsule. Capsules are packaged in polyvinyl chloride laminated with polychloro-trifluoroethylene/aluminum foil blisters or packaged in high-density polyethylene bottles with child-resistant induction seal closure. Each capsule is 40 mg. Patients must take four capsules all at one time, for a total daily dose of 160 mg.

Placebo: Fill solution: Caprylocaproyl Polyoxylglycerides, NF or Caprylocaproyl Macrogolglycerides, EP (Labrasol®)[a], Butylated Hydroxyanisole, NF or Butylhydroxyanisole, EP (BHA), Butylated Hydroxytoluene, NF or Butylhydroxytoluene, EP (BHT).
Capsule: Soft gelatin capsule (Gelatin, NF, EP[b]), plasticizer (Sorbitol Special-Glycerin Blend[b, c]), colorant (Titanium Dioxide USP), capsule print ink (Opacode® WB Black Ink [d]).

Enzalutamide and placebo will be provided by Astellas Scientific and Medical Affairs, Inc.

Storage requirements for enzalutamide or placebo:
Store at room temperature (≤ 25C).

Special handling:
For more information please follow the storage instructions provided on the drug product label.

6.1.3. Dosing Delays and Treatment Modifications for Toxicity
Toxicity will be assessed using the most recent NCI CTCAE.

Dose reduction for enzalutamide or placebo will be permitted. If a patient experiences a ≥ Grade 3 toxicity or an intolerable side effect, withhold dosing for one week or until symptoms improve to ≤ Grade 2, then resume at the same or a reduced dose (120 mg or 80 mg).

If patients either require that the study drug be discontinued because of an adverse event (as described below) or have a treatment interruption of greater than 2 weeks for enzalutamide, at the investigator's discretion, they may continue on SRT until completion of the SRT.

6.1.3.1 Dose-limiting toxicity (DLT)
A DLT for this study will be defined as a ≥ Grade 3 toxicity or an intolerable side effect. In addition, enzalutamide should be permanently discontinued in patients who have a seizure while on treatment.

6.2 Salvage Radiation Therapy (SRT)
Note: Intensity Modulated RT (IMRT) is allowed for this study.

Patients will undergo salvage radiation therapy (SRT) to start 60 days (31 day window allowed) after Day 1 (Day 61). Research visits during radiotherapy will occur during the first week of SRT and within 1 week of completion of radiotherapy according to the above schedule of events. Weekly visits during radiotherapy may be performed locally by the treating radiation oncologist according to standard of care practice and should include a

review of systems, vital signs, and examination. Radiation therapy may be performed locally as standard-of-care provided it conforms to protocol-specified treatment and dosing specifications. Receipt of protocol specified salvage radiation will be documented including dose, field, and timing.

6.2.1 Dose specifications

SRT will start 60 days after Day 1 (31 day window). Radiotherapy dose will be specified to the Planning Target Volume (PTV), as described in section 5.3.3.4. The total dose to the prostate bed is 66.6-70.2 Gy in 37-39 fractions.≥ 95% of the PTV should receive the prescribed dose.

6.2.2 Radiation technical factors

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

6.2.3 Localization, simulation and immobilization

A urethrogram or MRI is recommended, but not required, to establish the most inferior portion of the prostate bed. Use of contrast, other than for the urethrogram, is discouraged. Simulation should be with a moderately full bladder (the patient should not be uncomfortable at simulation and probably will have more difficulty maintaining a full bladder during treatment). An overly distended rectum can introduce a systematic positioning error that may increase the probability of missing the CTV.

A treatment planning CT scan will be required to define the clinical and planning target volumes, and the critical normal structures. The treatment planning CT will be acquired with the patient set up in the same position as for daily treatments. Each patient will be positioned in the supine position. The CT scan of the pelvis should start at or above the iliac crest down to below the perineum (below the ischial tuberosities). All tissues to be irradiated must be included in the CT scan. CT scan thickness should be ≤ 0.5 cm through the region that contains the target volumes (i.e., from the bottom of the sacroiliac joints down to the penile urethra). The regions above and below the target volume region may be scanned with slice thickness ≤ 1.0 cm

6.2.4 SRT target volumes

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

<u>CTV (Prostate Bed)</u>

Contrast may be used for simulation but can distort the anatomy slightly and so is not recommended. The bladder should be reasonably full for simulation, keeping in mind that patients may not be able to maintain as full a bladder during radiotherapy. Having a full bladder at simulation ensures that the CTV will be of maximal dimensions. The seminal vesicles or remnants thereof, if identified on CT or MRI as being present, will receive the full dose. The immediate periprostatic bed surgical clips should receive the full dose. The CTV will extend from the top of the penile bulb inferiorly, or 1.5 cm below the urethrogram peak if done, to just above the pubic symphysis superiorly (at least for the anterior-most portion of the bladder). Laterally, the CTV will extend from the medial edge of one obturator

internus muscle to the other. Anteriorly the CTV will include the entire bladder neck until the mid-pubic symphysis, where a gradual reduction off of the anterior bladder is made. Posteriorly, the CTV is defined by the anterior-most aspects of the anus-rectum. The CTV may be increased (not decreased) beyond these limits based on pre-prostatectomy imaging information. The pelvic lymph nodes are not to be included in the CTV on this protocol.

PTV

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

Normal Tissues

Normal tissues will be outlined as solid structures, including the rectum, bladder and femoral heads. The penile bulb may be outlined as a reference structure. No constraints will be placed on the penile bulb. The rectum will be outlined from the anterior flexion of the rectosigmoid superiorly to the ischial tuberosities inferiorly. The planning parameters outlined below for IMRT should be used as a guide; formal 3D-CRT normal tissue prostate bed constraints have not been the standard in the past and are not specified here. It should be possible to come close to achieving the constraints outlined for IMRT, at least within the variation range.

6.2.5 Prostate bed planning for IMRT

Planning Parameters

The plan will be deemed acceptable under the following conditions.

PTV: The dose marker levels for bladder and rectum have been modeled after prior studies in men treated definitively with IMRT for prostate cancer. At least 95% of the PTV should receive the prescribed dose (66 Gy); a variation will be noted if < 95% to 90% of the PTV receives the prescribed dose, and a protocol violation will be noted if < 90% of the PTV receives the prescribed dose. The maximum dose heterogeneity allowable in the PTV will be 10%; a variation will be > 10% and a violation > 15%. Since the dose is prescribed to the minimum isodose line of the PTV, the dose variability is seen in portions of the target volume receiving higher than the specified dose.

Rectum: Less than or equal to 25% and 45% of the rectum should receive ≥ 65 Gy and ≥ 40 Gy, respectively. A variation will be noted if up to an additional 7.5% of the rectal volume receives above the target doses specified. The inclusion of rectal volumes beyond these constraints will be considered a protocol violation.

Bladder: Less than or equal to 40% and 60% of the bladder (minus prostate bed CTV) should receive ≥ 65 Gy and ≥ 40 Gy, respectively. The criteria for the bladder have been relaxed because the dosimetric relationship of volume exposed to the specified marker doses is much less clear and the bladder neck is included in the CTV. A primary variation will be noted if up to an additional 7.5% of the bladder

volume receives above the target doses specified. The inclusion of bladder volumes beyond these constraints will be considered a secondary protocol variation; it will not be considered a protocol violation.

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

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

6.2.6 Critical structures

The critical normal structures are the bladder, rectum, and femoral heads. The normal tissues will be contoured and considered as solid organs.

- The bladder should be contoured from its base to the dome, excluding the CTV1 (the CTV1 includes the bladder neck).
- The rectum should be contoured from the anus (at the level of the ischial tuberosities) to the rectosigmoid flexure (this is roughly at about 10 cm) or for a maximum length of 15 cm if the sigmoid flexure if felt to be higher.
- Each femoral head should be outlined down to the interface between the greater and lesser trochanters.

6.2.7 SRT documentation requirements

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

6.2.8 Potential SRT adverse events

All patients will be seen weekly by their radiation oncologist during radiation therapy. Any observations regarding radiation reactions will be recorded and should include attention toward the following potential side effects:

- Small bowel or rectal irritation manifesting as abdominal cramping, diarrhea, rectal urgency, proctitis, or hematochezia;
- Bladder complications including urinary frequency/urgency, dysuria, hematuria, urinary tract infection, and incontinence;
- Radiation dermatitis.

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

may be managed with phenazopyridine. Erectile dysfunction is often treated with medical management or mechanical devices. SRT adverse event reporting.

6.2.9 Laboratory tests during SRT

Standard of care practice during IMRT will be performed and includes the following assessments:

- Medical history, adverse event assessment, and medication review
- CBC with differential, Serum chemistries (see above)
- Physical examination and performance status with vital signs

Research visits during treatment will occur at day 1, 61, 92, 120, 151 and 180 +/-14 days according to the above schedule of events. Subjects will be referred back to registering institution if during the 6 weeks an AE is suspected.

6.3 Removing Patients from the Protocol

In the absence of treatment delays because of adverse events, treatment will continue for 6 months or until one of the following criteria applies:

- Patient decides to withdraw from the study
- Disease progression
- Symptomatic disease progression at any time
- Objective clinical disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(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 patient 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

Because an excessive rate of withdrawals can render the study uninterpretable, unnecessary withdrawal of patients should be avoided. When a patient discontinues treatment early, the investigator should make every effort to contact the patient and to perform a final evaluation. The reason(s) for withdrawal should be recorded.

6.4 Concomitant Medications and Supportive Care

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 on the CRF. The principal investigator should be alerted if the patient is taking any agent found in Appendix B (a listing of medications with the potential for drug-drug interactions). Refer to Section 5.7 for concomitant medication guidelines.

7. ADVERSE EVENTS

7.1 Definitions

7.1.1 Adverse Event (AE)

An adverse event is any untoward medical occurrence in a research patient during a clinical study or within 30 days post-treatment, regardless of causality. This includes adverse clinical or laboratory findings, any adverse drug reaction (ADR), an illness with onset during the study, or an exacerbation of preexisting illness or condition.

7.1.2 Serious Adverse Event (SAE)

The investigator must assess each event to determine if it meets the criteria for classification as an SAE or serious adverse drug reaction.

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

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

- results in death
- is life-threatening
- 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 medically significant in the opinion of the investigator

7.1.3 Progression of malignancy

Progression of a patient's malignancy should not be considered an AE, unless in the investigator's opinion, study treatment resulted in an exacerbation of the patient's condition. If disease progression results in death or hospitalization while on study or within 30 days of the last dose of enzalutamide, progressive disease will be considered an SAE.

7.1.4 Life-threatening events

A life-threatening event is any AE that places the patient at immediate risk of death from the reaction as it occurs. It is not a reaction that, had it occurred in a more severe form, might have caused death.

7.1.5 Hospitalization or prolongation of hospitalization

Hospitalization encompasses any inpatient admission (even for less than 24 hours) resulting from a precipitating, treatment-emergent adverse event. 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 nonworsening preexisting condition should not be considered AEs (eg, 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.

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

7.1.6 Significant disability
Disability is a substantial disruption of the patient's ability to conduct normal life functions.

7.1.7 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 the SKCCC< Johns Hopkins and recorded in the consortium database. If the female partner partner becomes pregnant, we will seek permission to follow the pregnany until resolution and assess for any effects related to the study drug. This will require the partner to sign a separate consent form.

7.1.8 Medical significance
An event that is not fatal or life-threatening and that does not necessitate hospitalization may be considered serious if, in the opinion of the investigator, it jeopardizes the patient's status and might lead to medical or surgical intervention to prevent any of the above outcomes. Such medically significant events could include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias that do not result in inpatient hospitalization, or the development of drug dependency or abuse.

The most recent version of the NCI CTCAE handbook will be used for adverse event descriptions and grading.

Follow-up of adverse events should continue until the event and any sequela resolve or stabilize at a level acceptable to the investigator and the study site/sponsor or medical monitor.

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

7.2 Expectedness

Adverse events can be considered, "expected," or, "unexpected."

7.2.1 Expected Adverse Events

Expected adverse events are those that have been previously identified as resulting from administration of the agent. An adverse event can be considered expected

when it appears in the current adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.

7.2.2 Unexpected Adverse Events

An adverse event can be considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list, the Investigator's Brochure, the package insert or when it is not included in the informed consent document as a potential risk. Contact the lead site, principal Investigator or sponsor to confirm unexpected adverse events when necessary.

7.3 Recording and Grading

7.3.1 Recording

All observed or volunteered adverse events, regardless of treatment group, severity, suspected causal relationship, expectedness, or seriousness will be documented.

A clinically significant change in a physical examination finding or an abnormal test result (ie, laboratory, x-ray, EKG) 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 investigator or ASMA

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

7.3.2 Grading severity

All adverse events will be graded for intensity on a scale of 0 to 5. Severity grades will be recorded and based on the most recent version of the NCI CTCAE handbook.

7.3.3 Attributing causality

After grading for severity, the investigator must evaluate all clinical AEs and abnormal laboratory values for possible causal relationship to enzalutamide. Causality attribution will be decided using the criteria outlined in Table 6.

Table 3 Relationship of Adverse Event to Study Drug

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

Abnormal laboratory values of clinical significance that were present at baseline and did not change in severity or frequency during experimental therapy or intervention and those that can obviously be attributed to underlying disease will be recorded as unrelated and will not be considered when evaluating the AEs.

7.4 Reporting Adverse Events

7.4.1 Reporting serious adverse events

Sponsor-Institution and Sponsor-Investigator shall be responsible for reporting any and all serious adverse events associated with the use of the Study Drug to the FDA via MedWatch (FDA Form 3500A), with a copy to Astellas via e-mail to safety-us@us.astellas.com, or fax to 847-317-1421 and, when necessary, to the applicable IRB.

Life-threatening (grade 4 or 5) SAEs, events determined to be medically significant by the treating Investigator, and unknown reactions or unexpected events should be reported to the principal investigator, site IRB and the lead site/sponsor within 24 hours and be reported according to institutional and the following guidelines.

SAEs that are fatal and possibly protocol related and any treatment emergent seizure events should be reported by phone to the Protocol Chair immediately upon knowledge of the event.

The Lead Center's Study Coordinator should be contacted when reporting an SAE or death. If this person cannot be reached within 24 hours, the Protocol Chair (Lead Center's PI) should be contacted: Daniel Song, MD, 410-614-3880.

The initial report for each SAE or death should include the following information:

- Protocol # and title
- Patient initials, study identification number, age
- Date the event occurred
- Description of the SAE
- Dose level and treatment month at the time the SAE occurred
- Description of the patient's condition
- Relationship of SAE to study drug/treatment (see Table 6)
- Indication whether the patient remains on study

Follow-up information including severity, causality, action taken, concomitant medications, and outcome should be communicated to the lead site/sponsor as soon as possible with an indication whether an amendment will need to be made to the protocol, the consent form, or both, as a result of this event.

7.4.2 Reporting SAEs at multi-site/participating institutions

A subject's AEs and SAEs will be recorded and reported from the signing of the ICF up to at least 30 days after completing salvage radiotherapy. The investigator must instruct the subject to report AEs and SAEs during this time period.

Subjects with evidence of enzalutamide related toxicity at the post-treatment follow-up visit will be followed via telephone contact or weekly visits until the drug-related toxicity has resolved. Adverse events should be based on the signs or symptoms detected during the physical examination and on clinical evaluation of the subject. In addition to the information obtained from those sources, the subject should be asked the following nonspecific question: "How have you been feeling since your last visit?" Signs and symptoms should be recorded using standard medical terminology. Any unanticipated risks to the subjects must be reported promptly to the IRB/IEC. In the event of an adverse event the first concern will be for the safety of the subject.

All AEs and SAEs must be recorded on source documents. All AEs and SAEs for subjects who meet inclusion and exclusion criteria will be recorded in the CRFs and submitted to the lead site. The investigator must follow up on all AEs and SAEs until the events have subsided, returned to baseline or, in case of permanent impairment, until the condition stabilizes.

Additional reporting is required for SAEs as follows:

- SAEs that are fatal and possibly protocol related should be reported by phone to the Protocol Chair immediately upon knowledge of the event.

Each participating site is responsible for evaluating and completing any additional reporting to their local IRB according to local IRB guidelines.

8. CRITERIA FOR OUTCOME ASSESSMENT

8.1 Outcome Assessment

All baseline evaluations will be performed as closely as possible to the beginning of treatment. For subsequent evaluations, the method of assessment and techniques will be the same as those used at baseline.

- Measurement of clinical lesions
- Chest x-ray

  Should be conducted at PSA progression. Scans can also be obtained sooner as clinically indicated.

- Conventional CT, MRI

  Should be conducted at PSA progression. Scans can also be obtained sooner as clinically indicated.

- Ultrasound
- Endoscopy/laparoscopy
- Tumor markers

  FFPP is defined as the time from randomization to the date of PSA progression. A subject who does not have PSA progression at the time of the analysis will be censored at the last date of PSA measurement. In patients who achieve an

undetectable PSA value (defined as ≤0.1 ng/mL), PSA progression is defined as a detectable PSA value (≥0.2 ng/mL) that is confirmed by a second consecutive PSA value obtained ≥8 weeks later which is higher (and ≥0.4 ng/mL). In patients who do not achieve an undetectable PSA, PSA progression is defined as a 0.2 ng/mL increase from nadir that is confirmed by a second consecutive PSA value obtained ≥8 weeks later which is higher.

- Cytology/histology

8.1.1 Primary endpoint

The primary objective of the study is to evaluate the efficacy of the two treatment regimens based on freedom-from-PSA-progression (FFPP). Overall survival has been the preferred primary endpoint for most phase III trials in metastatic prostate cancer, as well as for most registration trials for other metastatic malignancies. Many of the practice-changing adjuvant trials, however, have used disease-free or progression-free survival as the primary endpoint [38,39]. Probably the most analogous adjuvant therapy is the use of endocrine therapy for early stage breast cancer. The primary endpoint for many of the trials evaluating tamoxifen and the aromatase inhibitors has been disease-free survival [40-43]. Several of the described prostate cancer adjuvant trials reported a lower-than-expected event rate requiring re-assessment of sample size and follow-up time. Even men with the highest risk prostate cancers are likely to survive beyond 12 years after prostatectomy [44]. This data originated in the pre-docetaxel era and does not reflect the arsenal of new therapeutic agents that have become available to patients with advanced prostate cancer. We do not yet have reported data for survival after prostatectomy that accounts for these new treatments, which makes estimating survival a challenge. Furthermore, cabazitaxel, abiraterone acetate, enzalutamide, and alpharadin were all tested in advanced metatstatic disease patient populations, so although we know the benefits of these drugs individually, the impact on survival when administered sequentially has not been established. We estimate that with the approval of cabazitaxel, sipuleucel-T, abiraterone acetate, enzalutamide, and radium-223, men may live as long as 15-20 years after prostatectomy. The size, duration, and cost of a trial powered to detect an overall survival benefit in the this setting for prostate cancer is substantial and such trials must be carefully designed to ensure responsible utilization of resources. Despite these challenges, it is important to move novel therapies earlier in the treatment of prostate cancer with the hope that these agents improve cure rates such that the long-term cost-benefit ratio is favorable. The ultimate goal of adjuvant systemic therapy is to increase the number of patients cured of their cancer. The earliest indication of prostate cancer relapse is a rising PSA after definitive local therapy. For these reasons, we will use 2-year FFPP defined as our primary endpoint. FFPP reflects a clinically meaningful endpoint for high-risk patients, yet minimizes the patients and resources necessary to answer this question.

FFPP is defined as the time from randomization to the date of PSA progression. A subject who does not have PSA progression at the time of the analysis will be censored at the last date of PSA measurement. In patients who achieve an undetectable PSA value (defined as ≤0.1 ng/mL), PSA progression is defined as a detectable PSA value (≥0.2 ng/mL) that is confirmed by a second consecutive PSA

value obtained ≥8 weeks later which is higher (and ≥0.4 ng/mL). In patients who do not achieve an undetectable PSA, PSA progression is defined as a 0.2 ng/mL increase from nadir that is confirmed by a second consecutive PSA value obtained ≥8 weeks later which is higher.

8.1.2 Secondary endpoints

The first secondary endpoint is time to local recurrence within the radiation field, defined as the time from randomization to the date of local recurrence of disease. Subjects who do not have local recurrence will be censored on the date of their last evaluable tumor assessment for local recurrence. Subjects who start any subsequent anti-cancer therapy without a prior reported local recurrence will be censored at the last evaluable tumor assessment prior to initiation of the subsequent anti-cancer therapy.

The second secondary endpoint is radiographic metastasis free survival (rMFS), defined as the time from randomization to the date of metastasis or death from any cause, whichever occurs first. A subject who does not have metastasis and is alive will be censored at the last date of tumor assessment. We will pay particular attention to the 2-year MFS rate.

Safety and tolerability will also be evaluated as secondary objectives.

9. DATA REPORTING AND REGULATORY REQUIREMENTS

The SKCCC Lead Coordinating Center will monitor the conduct and progress of the clinical trial at all participating sites. It will provide administrative, data management, regulatory, and organizational support in the conduct of this multi-center trial. The Coordinating Center will also function as the central location for multi-center trial documents and patient registration. For more information regarding reporting, regulatory requirements and guidelines, see Appendix D.

9.1 Multicenter Guidelines

9.1.1. The Protocol Chair

The Protocol Chair, Daniel Song, is responsible for performing the following tasks:

- Taking responsibility for the overall conduct of the study at all participating institutions and for monitoring the progress of the study.
- Coordinating, developing, submitting, and obtaining approval for the protocol as well as its subsequent amendments.
- Assuring that all participating institutions are using the correct version of the protocol.
- Reviewing and ensuring reporting of Serious Adverse Events (SAEs).
- Reviewing data from all sites

9.1.2. Lead Coordinating Center

The Lead Center SKCCC, Johns Hopkins University is responsible for performing the following tasks:

- Verifying that each participating institution has a Federal Wide Assurance (FWA) number.
- Ensuring that IRB approval has been obtained at each participating site prior to the first patient registration at that site.
- Maintaining copies of IRB approvals from each site.
- Implementing central patient registration
- Prepare appropriate data as required for review by the Protocol Chair.
- Establishing procedures for documentation, reporting and submitting of AE's and SAE's to the Protocol Chair and all other applicable parties.
- Facilitating audits by securing selected source documents and research records from participating sites for audit, or by auditing at participating sites.

9.1.3. Participating PCCTC Sites

Participating sites are responsible for performing the following tasks:

- Following the protocol as written, and the guidelines of Good Clinical Practice (GCP).

- Submitting data to the Lead Center. Please follow the submission schedule in section 9.2.1.
- Registering all patients with the Lead Center by submitting patient registration form, 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 Lead Center
- Collecting and submitting data according to the schedule specified by the protocol

9.2 Data Entry

Data collected during this study will be entered into a secure database. Staff at the PCCTC coordinating center will be responsible for the initial study configuration and setup in the consortium database and for any future changes.

9.2.1 Case report forms

Case report forms will be generated by the coordinating center for the collection of all study data. Investigators will be responsible for ensuring that the CRFs are kept up-to-date.

The schedule for completion and submission of Case Report Forms and **all** supporting documents to the Lead Coordinating Center is as follows:

Form	**Submission Timeline**
Eligibility Checklist	Complete prior to registration
Baseline Assessment Form	Within 14 days of registration
On-Treatment Forms (including drug diary)	Within 10 days of course completion
Adverse Event Report Form	Within 14 days of each visit date
Follow-up Form	Within 14 days of visit date
Off Study Form	Within 14 days of being taken off study for any reason

Data should also be submitted within the Johns Hopkins Oncospace Portal.

9.2.2 Source documents

Study personnel will record clinical data in each patient's source documents (ie, the patient's medical record). Source documentation will be made available to support the patient research record. Study monitors will review entries on the CRFs at regular intervals, comparing the content with source documents.

9.2.3 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, study-related documents, and the CRFs. Because the length of time required for retaining records depends upon a number of regulatory and legal factors, documents should

be stored until the investigator is notified that the documents may be destroyed. In this study, records are to be retained and securely stored for a minimum of 3 years after the completion of all study activities.

9.3 Data Management

9.3.1 Lead research program coordinators

A Lead Research Program Coordinator at the Coordinating Center will be assigned to the study. A Lead Research Program Coordinator will manage the study activities at each of the participating sites. The responsibilities of the Lead Research Program Coordinator include project compliance, data collection, data entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordination of the activities of the protocol team.

9.4 Study Monitoring and Quality Assurance

All clinical trials at SKCCC, Johns Hopkins are required to have Data and Safety Monitoring Plan (DSMP). The Clinical Research Review Committee (CRC) is charged with ensuring that protocols meets the Center's standards for Scientific Merit, Scientific Priority, and Adequate Scientific Progress. The CRC in concurrence with the PI determines the risk level, then reviews and approves the study specific DSMP.

Regularly scheduled registration reports will be generated to monitor patient 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.

Random-sample data quality and protocol compliance audits will be conducted by the study team at least once a year, more frequently if indicated. Audits by the coordinating center may entail (1) shipping source documents and research records for selected patients from participating sites to the coordinating center for audit, or (2) on-site auditing of selected patient records at participating sites.

All clinical work conducted under this protocol is subject to Good Clinical Practice (GCP) guidelines. This includes inspection of study-related records by the lead site, sponsor, its designee, or health authority representatives at any time.

9.4.1 Data and Safety Monitoring

The SKCCC Compliance Monitoring Program will provide external monitoring for JHU-affiliated sites in accordance with SKCCC DSMP (Version 6.0, 02/21/2019). The SMC Subcommittee will determine the level of patient safety risk and level/frequency of monitoring.

The PI is responsible for internally monitoring the study. Data must be reviewed to assure the validity of data, as well as, the safety of the subjects. The PI will also monitor the progress of the trial, review safety reports, and clinical trial efficacy endpoints and to confirm that the safety outcomes favor continuation of the study

9.5 Clinical Trial Agreement

This trial is being conducted under one or more clinical trial agreements that contain, among other terms, the publication policy, indemnity agreements, and financial arrangements for the study.

9.6 End of Study

This study will end and study database locked when 24 months of follow up is reached from the last patient being enrolled. A final study report will be provided within 3 months of the end of the study.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints

10.1.1 Analysis of the primary endpoint

The study is a multi-center, double-blind, placebo controlled, randomized Phase II trial in patients with non-castrate PSA-recurrent prostate cancer after radical prostatectomy. Eligible patients will be randomized in a 1:1 ratio to one of two treatment arms: SRT *plus* placebo (Arm A) or SRT *plus* enzalutamide (Arm B). Randomization will be stratified by center, and surgical margin status (R0 *vs* R1), PSA prior to salvage treatment (PSA ≥0.5 *vs* <0.5 ng/mL), and pathologic Gleason score (7 *vs* 8-10).

The primary objective of the study is to evaluate the efficacy of the two treatment regimens based on freedom-from-PSA-progression (FFPP). FFPP is defined as the time from randomization to the date of PSA progression. A subject who does not have PSA progression at the time of the analysis will be censored at the last date of PSA measurement. In patients who achieve an undetectable PSA value (defined as ≤0.1 ng/mL), PSA progression is defined as a detectable PSA value (≥0.2 ng/mL) that is confirmed by a second consecutive PSA value obtained ≥8 weeks later which is higher (and ≥0.4 ng/mL). In patients who do not achieve an undetectable PSA, PSA progression is defined as a 0.2 ng/mL increase from nadir that is confirmed by a second consecutive PSA value obtained ≥8 weeks later which is higher.

It is very unlikely deaths in the time frame of this trial will be from prostate cancer. Censoring the subjects that have died at the date of the last PSA measurement before death will be performed (as we will not know if PSA changes in the interval) unless there is clear evidence of death from prostate cancer per the treating physician and/or by autopsy.

FFPP will be summarized using Kaplan-Meier method by treatment arms. FFPP probability will be estimated using the Kaplan-Meier method. FFPP curves will also be displayed graphically. Differences in FFPP between treatment arms will be compared by the log rank test. The Cox proportional hazards regression model will be fitted, and the estimated hazard ratio (Arm B/Arm A) and corresponding 95% CI will be provided. Additionally, Cox regression models will be used to explore the potential influences of the other prognostic factors on the primary FFPP endpoints.

10.1.2 Analysis of secondary endpoints

The first secondary endpoint is time to local recurrence within the radiation field, defined as the time from randomization to the date of local recurrence of disease. Subjects who do not have local recurrence will be censored on the date of their last evaluable tumor assessment for local recurrence. Subjects who start any subsequent anti-cancer therapy without a prior reported local recurrence will be censored at the last evaluable tumor assessment prior to initiation of the subsequent anti-cancer therapy.

The second secondary endpoint is metastasis free survival (MFS), defined as the time from randomization to the date of metastasis or death from any cause up to 90 days following the last response assessment, whichever occurs first. A subject who does not have metastasis and is alive will be censored at the last date of tumor assessment.

Time-to-event endpoints (time to local recurrence and MFS) will be analyzed similarly as described for the primary endpoint (FFPP).

Safety and tolerability will also be evaluated as secondary objectives. For safety analysis, overall safety profile and toleration of Arm A and Arm B will be characterized by type, frequency, severity, timing and relationship of study therapy of adverse events and laboratory abnormalities. Adverse events will be summarized by the frequency of patients experiencing treatment emergent adverse events corresponding to body systems and by worst NCI CTCAE (version 4.0) grade.

10.2 Analysis Populations

10.2.1 Intent-to-treat/Response-to-treatment/Evaluable population

The Intent-to-Treat (ITT) Population includes all subjects who are randomized with study treatment assignment designated according to initial randomization. The ITT population will be the primary population for evaluating time-to-event efficacy endpoints (i.e. FFPP, time to local recurrence, MFS, and time to reinitiation of hormonal therapy) and patient characteristics.

Per Protocol Population will include all patients who are randomized and received at least one dose of study medication, and do not have any major protocol violations (for example, incorrect treatment group allocation according to randomization, not meeting the major inclusion/exclusion criteria for disease status and prior therapies, noncompliance to treatment plan or assessment schedule; additional concurrent prohibited therapies). The per-protocol analysis will serve as supportive.

10.2.2 Safety population

Safety Population will include all patients who receive at least one dose of study medication, with treatment assignments designated according to actual study treatment received. The safety analyses population will be the primary population for evaluating treatment administration/compliance and safety.

10.2.3 Special populations

10.2.3.1 Severe liver disease

Patients with baseline severe hepatic impairment (Child-Pugh C) are excluded from this clinical trial.

10.2.3.2 Lowered seizure threshold

In clinical studies, seizure was identified as a risk associated with enzalutamide treatment. In the controlled clinical Study CRPC2, seizures occurred in 0.9% (7/800) of patients receiving enzalutamide 160 mg daily, whereas no seizures occurred in patients treated with placebo. Confounding factors may have contributed to the occurrence of seizures in several of these cases. Dose appears to be an important predictor of seizure, with a greater risk of seizure at daily doses higher than 160 mg. In a dose escalation study involving 140 patients, no patients experienced seizures at or below daily doses of 240 mg, whereas 3 seizures were reported, 1 each at 360, 480 and 600 mg/day. Caution should be used in administering enzalutamide to patients with a history of seizures or other predisposing factors including, but not limited to, underlying brain injury, stroke, primary brain tumors or brain metastases or alcoholism. In addition, the risk of seizure may be increased in patients receiving concomitant medications that may lower the seizure threshold. Enzalutamide should be permanently discontinued in patients who have a seizure while on treatment.

10.3 Safety Analysis

10.3.1 Evaluation of adverse events

Treatment-emergent adverse events will be translated from investigator terms to MedDRA v6.0 terminology and summarized (number and percentage of patients) for all patients who receive at least 1 dose of enzalutamide. Adverse event summaries will be organized by body system, frequency of occurrence, intensity (ie, severity grade), and causality or attribution. Patients who experience an adverse event more than once will be counted only once. The occurrence with the maximum severity will be used to calculate intensity.

10.3.2 Evaluation of serious adverse events and premature withdrawals

Adverse events deemed serious and those resulting in treatment withdrawal or death will be summarized separately. Narrative paragraphs will be generated to describe the circumstances surrounding each SAE and death.

10.3.3 Evaluation of laboratory parameters and assays

Selected clinical laboratory parameters will be summarized and clinically significant changes from baseline will be discussed.

10.3.4 Extent of exposure

Treatment exposure will be summarized for all patients, including dose administration, number of cycles, dose modifications or delays, and duration of therapy.

10.4 Statistical Procedures

Summary statistics include the number of observations, mean, standard deviation, median, minimum, and maximum values.

10.4.1 Sample size calculation

Based on the largest multi-institutional SRT series published (n=1,540) in which patients received SRT followed by observation until the PSA reached ≥0.2 ng/mL above the post-SRT nadir, the 2-year FFPP was approximately 60% with SRT. For our primary endpoint of 2-year FFPP we expect an absolute 20% improvement with the treatment of SRT+ enzalutamide (2-year FFPP 80%) over SRT alone (2-year FFPP 60%).

We originally assumed an accrual time of 18 months, with ≥24 months of additional follow-up time. FFPP at 2 year from 60% to 80%, a 20% increase (corresponding to a hazard ratio of 0.44 under the assumption of exponential distribution of event times) corresponds to 39 events total of PSA progression (for example 26 in Arm A, and 13 in Arm B) with a 90% power to detect an improvement of, using a one-sided log-rank test at significance level 0.1. Adjusting for 15% non-evaluable or dropout patients, we will randomize a total of 122 patients (61 patients in each arm).

The power of the study is driven by the number of PFS progression events. The design requires 39 events when the analysis of the primary endpoint is conducted. Under the assumption that there are not non-evaluable patients or no dropout, a total of 102 patients needs to be enrolled over 18 months with ≥24 months of additional follow-up to reach 39 events. Because the study duration is as long as 3.5 years, a fair number of patients may be lost to follow-up before that and their time to PSA progression will be censored at the last date of PSA measurement. So we assume a e non-evaluable and loss-to-follow-up rate of 15% when we estimate the total number of participants.

The trial started enrolling patients in April 2015, and has enrolled 80 patients by April 2019. The rate of accrual is about 10 patients every 6 months. Due to slower than expected enrollment, we propose to extend the accrual time to the end of March 2020. We plan to conduct the primary analysis when 39 events occur.

Our new efficacy assumption stays the same as to detect the difference of Freedom From PSA Progression (FFPP) at 2 year from 60% in SRT+placebo arm to 80% in SRT+enzalutamide arm, a 20% increase (corresponding to a hazard ratio of 0.44 under the assumption of exponential distribution of event times.) The study power remains at 90% with one-sided type I error 0.1 using log-rank test.

The sample size is 96 total (48 per arm) accounting for 15% loss-to-follow up before PSA progression events. Below represents the new enrollment target for patients given this revised power calculation based on number of events thus far, follow-up and drop out to date.

Total number of PSA progression events	Sample size	Planned accrual time (mons)	Additional follow-up time (mons)	End of accrual	End of follow-up (start the analysis)	Power
Original design						
39	122 (61 per arm)	18	24			90%
New design						
39	96 (48 per arm)	60	21	March 2020	Dec. 2021	90%

10.4.2 Stratification factors

Randomization will be stratified by center, and surgical margin status (R0 *vs* R1), PSA prior to salvage treatment (PSA ≥0.5 *vs* <0.5 ng/mL), and pathologic Gleason score (7 *vs* 8-10).

10.4.3 Derived variables

- FFPP will be summarized using Kaplan-Meier method by treatment arms. FFPP curves will also be displayed graphically. Differences in FFPP between treatment arms will be compared by the log rank test. The Cox regression model will be fitted, and the estimated hazard ratio (Arm B/Arm A) and corresponding 95% CI will be provided.
- FFPP probability will be estimated using the Kaplan-Meier method
- Additionally, Cox regression models will be used to explore the potential influences of the other factors on the primary FFPP endpoints.
- Time-to-event endpoints time to local recurrence and radiographic MFS will be analyzed similarly as described for the FFPP.
- For safety analysis, overall safety profile and toleration of Arm A and Arm B will be characterized by type, frequency, severity, timing and relationship of study therapy of adverse events and laboratory abnormalities. Adverse events will be summarized by the frequency of patients experiencing treatment emergent adverse events corresponding to body systems and by worst NCI CTCAE (version 4.0) grade.

11. PROTECTION OF HUMAN SUBJECTS

11.1 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).

11.2 Protocol Amendments

Before starting the study, the protocol must be approved by each institution's IRB or Independent Ethics Committee (IEC). Amendments to the protocol may be made only with consent of the lead site/sponsor and principal investigator and are subject to IRB approval before instituting.

11.3 Written Informed Consent

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 adverse event 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 (in triplicate) a 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) 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 coordinating center at MSKCC, and a copy will be sent home with each patient.

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 for the protocol
- the right of the patient to accept or refuse treatment and to withdraw from participation in this study
- Text regarding the consortium and the coordinating center should be added to all institutional informed consent documents and sections in the research authorization/HIPAA forms (eg, "Prostate Cancer Clinical Trial Consortium, Coordinating Center at Memorial Sloan-Kettering Cancer Center, New York, NY")

11.4 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 principal investigator and approved by the IRB.

11.5 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. At least quarterly, data from the clinical database will be reviewed. The results of this review will be shared with all investigators either in writing or as part of a teleconference. SAEs will be reviewed as they are reported to the lead site/sponsor, and the medical monitor 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 principal investigator be that the study should be terminated, the study will be closed to further accrual. Patients who are receiving enzalutamide 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.

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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 (eg, 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

Class	Agents	Class	Agent
Drugs that Inhibit CYP2C8	gemfibrozil	Drugs that are metabolized by CYP3A4	alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus and tacrolimus
Drugs that Induce CYP2C8	rifampin	Drugs that are metabolized by CYP2C19	S-mephenytoin
Drugs that Inhibit CYP3A4	itraconazole)	Drugs that are metabolized by CYP2C9	phenytoin, warfarin
Drugs that Induce CYP3A4	carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine, bosentan, efavirenz, etravirine, modafinil, nafcillin	Substrates for efflux transporter P-gp	colchicine, dabigatran etexilate, digoxin
Substrates for BCRP, MRP2 or OAT3	methotrexat		

APPENDIX C: GLOSSARY OF ABBREVIATIONS AND ACRONYMS

17-AAG	17-allylamino-17-demethoxygeldanamycin
17-DMAG	17-dimethylaminoethylamino-17-demethoxygeldanamycin
2-MPPA	2-(3-mercaptopropyl) Pentanedioic acid
AdEERS	Adverse Event Expedited Reporting System
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 Monitoring Service
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 Organisation 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 Harmonisation
IEC	Independent Ethics Committee
IHC	immunochemical
IM	intramuscular
IMSL	International Mathematical Statistical Library
IND	investigational new drug
INR	international normalized ratio
IP	intraperitoneal
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
MSKCC	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 MSKCC
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 D: SKCCC DATA AND SAFETY MONITORING PLAN

SIDNEY KIMMEL COMPREHENSIVE CANCER CENTER AT JOHNS HOPKINS

DATA AND SAFETY MONITORING PLAN

Version 5.0: 12/6/2012
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