Salvage Therapeutic Radiation with Enzalutamide and ADT in Men with Recurrent Prostate Cancer (STREAM)

Document Date: September 28, 2018

NCT02057939

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DUKE CANCER INSTITUTE

A National Cancer Institute-designated Comprehensive Cancer Center

Sponsor:	PI – Duke Cancer Institute
Funding Source:	Medivation/Astellas
Protocol Source:	PI – Duke Cancer Institute
Duke IRB#:	Pro00049865

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Original version:	November 19, 2013
Amendment 1:	March 12, 2014
Amendment 2:	April 21, 2014
Amendment 3:	June 12, 2014
Amendment 4:	July 7, 2014
Amendment 5:	September 8, 2014
Amendment 6:	February 24, 2015
Amendment 7:	October 5, 2015
Amendment 8:	December 2, 2015
Amendment 9:	May 26, 2016
Amendment 10:	November 28, 2016
Amendment 11:	November 10, 2017
Amendment 12:	September 28, 2018

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2 LIST OF ABBREVIATIONS

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

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

3 PROTOCOL SYNOPSIS AND RESEARCH SUMMARY

3.1 Purpose

Primary Objective:

To describe the 2 year progression-free survival in men with recurrent PSA-only disease after prostatectomy receiving combined enzalutamide and standard androgen-deprivation therapy with salvage radiation therapy **and** who have had testosterone recovery to >100 at 24 months.

Secondary Objectives:

1. To determine the proportion of men at 1, 2, and 3 years with a PSA of <0.1 ng/mL and testosterone recovery to >100
2. To describe the 3 year progression-free survival in men receiving combined enzalutamide and standard androgen-deprivation therapy with salvage radiation therapy **and** who have had testosterone recovery to >100
3. To describe the biochemical (PSA) progression free survival over time
4. To describe the PSA nadir
5. To describe the time to testosterone recovery
6. To describe the safety profile of combination enzalutamide, ADT, and XRT

Exploratory Objectives:

1. To describe the quality of life in patients receiving the combination of enzalutamide, ADT, and XRT
2. Archived prostatectomy specimens will be collected and stored for eventual analysis of the correlation of outcomes with pre-treatment androgen receptor target genes, androgen receptor splice variants, and epithelial-mesenchymal transition (EMT) biomarkers.

Hypothesis:

Based on a model and nomogram for men with recurrent disease after radical prostatectomy, the 2 year rate of progression free survival for men receiving salvage radiation therapy alone is 65% [1]. **We hypothesize that enzalutamide added to standard salvage external beam radiation with androgen deprivation therapy will further prolong progression free survival.**

3.2 Background and Significance

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

for these men are thus needed to improve systemic control and eliminate potential micrometastatic deposits.

Although androgen deprivation therapy (ADT) added to radiation therapy for the primary treatment of prostate cancer has a demonstrated survival benefit [2], the benefit of ADT in the salvage radiation setting remains unclear. A recent retrospective study suggests that ADT concurrent with salvage radiation improves progression-free survival in high risk men [3]. Clinically, high-risk patients with biochemical recurrence after surgery are often managed with the combination of ADT and radiation therapy. Recent data suggests an important role for the androgen receptor in DNA repair during radiation therapy, and that blocking androgen receptor action may improve radiosensitivity [4].

Enzalutamide is an androgen receptor antagonist that not only blocks androgen binding to its receptor but also inhibits nuclear translocation and DNA binding. The phase I/II clinical trial of enzalutamide showed significant anti-tumor response in patients with progressive metastatic CPRC, with median time to progression of 47 weeks [5]. Subsequently, the interim analysis of the phase 3 AFFIRM trial of enzalutamide revealed an improvement in survival of 4.8 months over placebo alone in men with CRPC who had received docetaxel [6]. Therefore, enzalutamide is an effective therapy for patients with progressive, metastatic CRPC after treatment with chemotherapy. Ongoing trials are investigating the earlier use of this agent in the pre-chemotherapy space, and it is anticipated that the pre-docetaxel PREVAIL trial will form the basis for the standard use of enzalutamide prior to chemotherapy. Even earlier treatment with enzalutamide, in pre-metastatic and/or castrate-sensitive disease, may be beneficial and is an active area of investigation. While the safety and tolerability of enzalutamide is very good in the randomized studies published to date, enzalutamide in combination with radiation therapy has not yet been studied.

The goal of this study is therefore to determine the feasibility and efficacy of treatment with enzalutamide and androgen-deprivation for 6 months in the setting of standard salvage external beam radiation therapy in men with a rising PSA after prostatectomy.

Based on a model and nomogram for men with recurrent disease after radical prostatectomy, the 2 year rate of progression free survival for men receiving salvage radiation therapy alone is 65%[1]. **We hypothesize that enzalutamide added to standard salvage external beam radiation with short term androgen deprivation therapy will further prolong progression free survival.**

3.3 Design and Procedures

This is a non-blinded single-arm phase II study of approximately 38 subjects to assess feasibility and efficacy of combined enzalutamide and androgen-deprivation (ADT) for 6 months with salvage radiation therapy.

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

Enzalutamide with ADT would start 2 months prior, continue 2 months concurrent, and be completed 2 months after salvage XRT. Enzalutamide will be given 160mg by mouth daily for 6 months and ADT will be administered per institutional standard for a total of 6 months. Standard external beam radiotherapy to 64.8-68 Gy will be administered to prostate bed over 6-8 weeks. Inclusion of the pelvic nodes as part of the salvage radiation plan for patients with node positive disease will be per the discretion of the treating radiation oncologist.

The endpoints are 2 year progression free survival and the proportion of men at 1, 2, and 3 years with a PSA of <0.2 ng/mL who also have testosterone recovery.

3.4 Selection of Subjects

Inclusion Criteria:

1. Histologically confirmed diagnosis of prostate adenocarcinoma. Variants of prostate cancer, including neuroendocrine features and small cell carcinoma of the prostate, are not permitted.
2. Gleason sum of 7, 8, 9, or 10 at the time of prostatectomy.
3. PSA relapse within 4 years of prostatectomy defined by persistently detectable or rising PSA after surgery.
4. Evidence of disease recurrence or progression as evidenced by a PSA > 0.20. This requires 2 consecutive rises in PSA, at least 1 week apart, over the post-prostatectomy nadir or one PSA value above 0.20 ng/mL if the patient failed to achieve a post-prostatectomy nadir of <0.2 ng/mL.
5. Age ≥ 18 years
6. Karnofsky performance status ≥ 70
7. Adequate laboratory parameters
    - Adequate bone marrow function: ANC ≥1.5 x 10^9/L, Platelets ≥100 x 10^9/L, Hb >9g/dL
    - AST/SGOT and ALT/SGPT ≤ 2.5 x Institutional Upper Limit of Normal (ULN)
    - Serum bilirubin ≤ 1.5 x Institutional ULN
    - Serum creatinine ≤ 1.5 x Institutional ULN or 24-hour clearance ≥ 50 mL/min
8. A minimum of 4 weeks from any major surgery prior to registration.
9. Ability to swallow, retain, and absorb oral medication.
10. Ability to understand and the willingness to sign a written informed consent document.
11. Must use a condom if having sex with a pregnant woman.
12. Male patient and his female partner who is of childbearing potential must use 2 acceptable methods of birth control (one of which must include a condom as a barrier method of contraception) starting at screening and continuing throughout the study period and for 3 months after final study drug administration.

Exclusion Criteria:

1. Radiographic evidence of metastatic disease. Patients with node-positive disease (≤2 positive nodes) at the time of radical prostatectomy are eligible. Patients with pelvic nodes up to 2 cm by short axis at the time of screening are eligible. Patients with any enlarged lymph nodes in the retroperitoneum or above the aortic bifurcation or with pelvic nodes ≥ 2 cm must be excluded.
2. PSA > 4.0 ng/mL.
3. Testosterone level ≤ 100 ng/dL.
4. More than 1 month of prior hormone exposure or hormone exposure within 30 days of registration. Prior enzalutamide, ketoconazole, abiraterone, or TAK700 prohibited. Prior 5α-reductase inhibitors are allowed.
5. Prior immunotherapy including sipuleucel-T.
6. Prior systemic chemotherapy (docetaxel, cabazitaxel, estramustine, other cytotoxic agents)

7. History of solid organ or stem cell transplantation.
8. History of seizure or any condition that may predispose to seizure (e.g., prior cortical stroke, prior head or traumatic brain injury with loss of consciousness, prior or current space-occupying lesion in the brain). Also, history of loss of consciousness or transient ischemic attack within 12 months of Day 1 visit.
9. Known or suspected brain metastasis or active leptomeningeal disease.
10. Other concurrent severe and/or uncontrolled concomitant medical conditions (e.g., active or uncontrolled infection) that could cause unacceptable safety risks or compromise compliance with the protocol.
11. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of enzalutamide or increase the risk of radiation (e.g., uncontrolled nausea, vomiting, diarrhea, malabsorption syndromes, prior small bowel resection, or inflammatory bowel disease).
12. Patients who have received prior prostate or pelvic radiotherapy, including external beam or brachytherapy.
13. Patients who have undergone major surgery ≤ 4 weeks prior to starting study drug or who have not recovered from side effects of such therapy prior to registration.
14. Patients unable or unwilling to abide by the study protocol or cooperate fully with the investigator.

3.5 Subject Recruitment and Compensation

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

3.6 Consent Process

The prospective participant will have as much time as he may need to make an informed decision about the study and all treatment related questions will be answered. Prospective participants will be consented in an exam room where it is just the research staff, the patient and his family, if so desired by the patient. Before, during, and after the consent is signed, the research team and investigators will be available in person and by phone to answer any questions the participants may have. Any and all other available treatment options are offered to the patient in order to avoid undue influence. Participants are not offered compensation for this study in order to avoid any monetary coercion/influence.

3.7 Subject's Capacity to Give Legally Effective Consent

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

3.8 Study Interventions

After consent and enrollment, each subject will receive a GnRH agonist 3 month depot injection, and this treatment will be repeated in 3 months for a total of 6 months of androgen deprivation therapy.

Subjects will receive education about how to take enzalutamide, including avoidance of contraindicated concurrent medications, safe handling, and side effects. Subjects will then receive enzalutamide 160mg PO daily from the investigational pharmacy and will take enzalutamide daily for 6 months. On week 9 (+/- 14 days), subjects will begin salvage radiation therapy to the prostate bed. This will continue for 6-8 weeks, concurrent with ADT and daily enzalutamide. After 6 months upon completion of all therapy, subjects will return to clinic every three months for symptom, laboratory, and prostate cancer monitoring, including PSA and testosterone. Study termination for each subject is three years post-registration.

3.9 Risk/Benefit Assessment

Potential risks of this study include the potential for enzalutamide toxicity, including fatigue, nausea, muscle/joint aches, and very rarely seizure activity. There is potential that taking enzalutamide during radiation therapy may make these side effects worse; however, there is also the potential benefit that the addition of enzalutamide may improve cancer outcomes. Additional risks of study inclusion include potential loss of confidentiality, although all steps will be taken to protect the patient's privacy and confidentiality.

3.10 Costs to the Subject

Patients and their insurers will be expected to pay costs of routine care, including radiation therapy and androgen-deprivation therapy with a GnRH-agonist. Research visits and procedures as well as the cost of enzalutamide will be covered by research funds.

3.11 Data Analysis and Statistical Considerations

The primary objective of this single arm, open-label, one stage phase II study is to estimate the 24 month progression-free survival rate of men with recurrent, PSA-only disease after prostatectomy receiving combined enzalutamide and standard androgen-deprivation therapy with salvage radiation therapy. The target sample size is 38. It is primarily hypothesized the 2 year PFS rate will be improved with the combined therapy compared to the historical control data in a similar patients setting. Based on a model and nomogram by Stephenson et al for men with recurrent disease after radical prostatectomy [1], the PFS rate at 24-months among prostate cancer patients is 65%. **This trial is designed to have 84% power to reject the null hypothesis of 24 month PFS rate of 65% when the true PFS rate at 24 months is 85%.** The power of this study will be different if the enrolled patients have a lower predicted 24 month PFS rate based this nomogram, however, this study should have at least 80% power to detect a 20% improvement in 24 month PFS rate even if a 55% rate of 2 year PFS is predicted. One sample one-sided binomial test will be used to test whether the 24 month PFS rate is larger than the hypothesized value from the historical controls with a one sided alpha error of 0.05. The Kaplan-Meier product-limit estimator will be used to estimate the distribution of PFS, biochemical progression free survival, time to PSA nadir, and time to testosterone recovery. The median survival times and 95% confidence intervals will be reported. The frequency and proportion (and 95% confidence interval) of men at 1, 2, and 3 years with a PSA of <0.1 ng/ml and testosterone recovery will be reported. In addition, descriptive statistics with 95% confidence intervals will be calculated for secondary endpoints of safety profile and quality-of-life (QOL) endpoints, the continuous safety and QOL endpoints will be summarized as the patient counts, mean, standard deviation, median, $25^{th}$and 75^{th} percentiles, minimum and maximum. The

categorical safety and QOL endpoints will be categorized using frequencies and percentages. Based on one sample binomial test, the required sample size is 30. We assume the combined rate of the potential lack of testosterone recovery at 24 months and drop out is about 20% (with dropout less than 5%). The evaluable subjects are expected to be approximately 80% of total samples; the actual sample size becomes 38.

3.12 Data and Safety Monitoring

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

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

3.13 Privacy, Data Storage, and Confidentiality

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

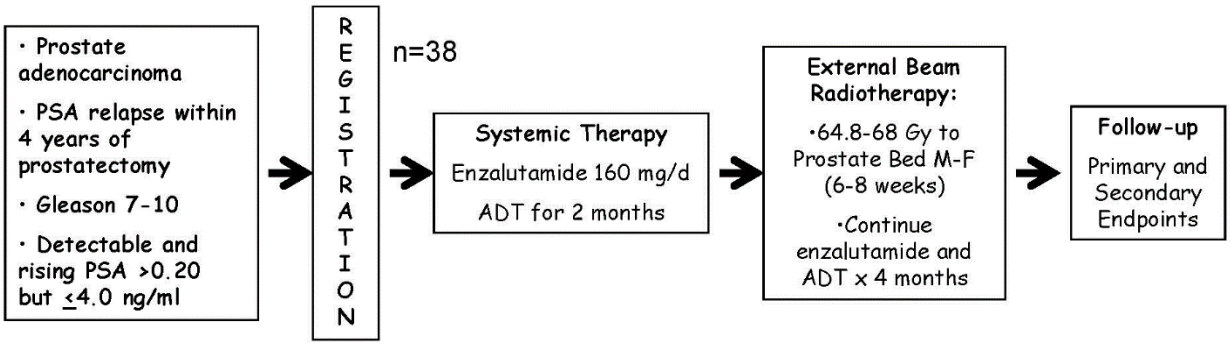
To protect privacy, every reasonable effort will be made to prevent undue access to subjects during the course of the study. All research-related interactions with the participant will be conducted by qualified research staff who are directly involved in the conduct of the research study.

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

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

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

4 STUDY SCHEMA



5 BACKGROUND AND SIGNIFICANCE

5.1 Study Disease: Prostate cancer

Worldwide, prostate cancer is the second most common cancer in men. The current lifetime risk of prostate cancer for men in the United States is approximately 1 in 6 [7]. Hormonal therapies include surgical castration or medical therapy with gonadotropin-releasing hormone analogues, AR antagonists, testosterone synthesis inhibitors, ketoconazole and/or estrogenic compounds. Tumors that progress despite castrate levels of testosterone in the blood are considered castration-resistant. Despite the early sensitivity of these tumors to hormonal strategies, castration-resistant progression generally represents a transition to the lethal variant of the illness. The median survival of castration-resistant disease is approximately 1 to 2 years [8]. Results of clinical investigations and studies on the molecular profiles of these progressing prostate tumors show that the AR remains functional and that the tumors should respond to strategies directed at the AR signaling axis. Overexpression of the AR has been documented in upwards of 50% of CRPC specimens and is believed to contribute to tumor progression [9, 10].

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

The treatment of men with PSA recurrence following radical prostatectomy has generally been unsatisfying, given the high rates of persistent or recurrent disease despite salvage radiotherapy. In most large series, the rate of distant or biochemical disease recurrence is approximately 60 to 70% following salvage radiotherapy, indicating that in these high risk individuals, only 30-40% of disease is purely localized and thus curable with salvage radiotherapy [1, 11]. Risk factors for PSA recurrence and progression despite salvage radiation therapy include increasing PSA, fast PSA kinetics, lower dose of radiation used, high Gleason sum, advanced tumor stage, and negative surgical margins [1, 12]. Additional therapeutic options for these men are needed to improve systemic control and eliminate potential micrometastatic deposits.

While radiotherapy alone in the adjuvant or salvage setting may reduce the risk of PSA and local recurrence in prostate cancer, it has an unclear benefit on reduction of metastatic disease and overall survival [13, 14]. However, recent retrospective series suggest that a survival benefit may be seen particularly in those men with rapid PSA doubling times or positive surgical margins, although benefits have been seen across nearly all subgroups [12, 15, 16]. Recent data suggests an important role for the androgen receptor in DNA repair during radiation therapy, and that blocking androgen receptor action may improve radiosensitivity [4].

5.2 Study Agent

Enzalutamide (MDV3100) is an oral androgen receptor (AR) signaling inhibitor that targets several steps in the AR signaling pathway. Enzalutamide competitively inhibits binding of androgens to ARs, inhibits nuclear translocation of receptors, and inhibits the association of the AR with DNA, even in the setting of AR overexpression and in prostate cancer cells resistant to anti-androgens.

Enzalutamide was approved in the United States on August 31, 2012 (trade name XTANDI) to treat patients with metastatic castration-resistant prostate cancer who previously received docetaxel. Clinical development is ongoing for additional treatment indications.

Enzalutamide is formulated with Labrasol (caprylocaproyl macrogoglycerides) and provided as an orally available immediate-release dosage form filled into soft gelatin capsules containing 40 mg of the active ingredient.

5.2.1 Pre-clinical experience

Enzalutamide is a novel small molecule androgen-receptor antagonist selected for its activity against prostate cancer cells overexpressing the androgen receptor. Enzalutamide has been shown in preclinical studies to provide a more complete suppression of the androgen receptor pathway than bicalutamide. Enzalutamide slows growth and induces cell death in bicalutamide-resistant cancers via three complementary actions – enzalutamide blocks testosterone binding to the androgen receptor, impedes movement of the androgen receptor to the nucleus of prostate cancer cells (nuclear translocation), and inhibits binding of DNA. Preclinical data have demonstrated that enzalutamide is superior to bicalutamide in each of these three actions. Enzalutamide has no known agonist activity when the androgen receptor is overexpressed.

In a mouse xenograft model of prostate cancer using an androgen receptor overexpresssing cell line, enzalutamide treatment resulted in a dose-dependent reduction in tumor volume. Enzalutamide treatment decreased tumor volume, resulting in unmeasurable tumors in 1/7 animals in the low-dose group and 3/7 animals in the high-dose group. Enzalutamide binds with high affinity to the human androgen receptor (Ki = 13 nM). Other targets for which measurable enzalutamide binding was detected included the human progesterone receptor and the rat gamma amino butyric acid-gated chloride channel. No significant binding was detected with the remaining 70 receptors.

5.2.1.1 Preclinical Pharmacokinetics and Metabolism

Following oral administration in animals, enzalutamide is eliminated slowly from plasma with a long half-life ($t_{1/2}$) across species. The $t_{1/2}$ did not appear to be affected by the dose size; however, the bioavailability appeared to decrease with increasing dose size. In vitro drug metabolism studies suggest that enzalutamide undergoes very slow rates of metabolism. In vitro studies show that enzalutamide is metabolized by human recombinant cytochrome P450 (CYP) isozymes CYP2C8 and CYP3A4/5. Enzalutmide or its metabolites directly inhibit CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5. Subsequent clinical data show that enzalutamide an in inducer of CYP2C9, CYP2C19, and CYP3A4/5 and has no other meaningful effects. Plasma protein binding of enzalutamide in human plasma ranged from 97% to 98% and was similar in mice, rats, rabbits, and dogs.

5.2.1.2 Preclinical Toxicology

Enzalutamide has been tested in repeat dose toxicity studies in mice, rats, dogs, and cynomolgus monkeys. Systemic exposure to enzalutamide generally increased with increasing dose size but not proportionally. In male and female rats, enzalutamide caused no deaths or clinical signs that were considered likely to be related to enzalutamide at oral doses as high as 100 mg/kg/day for 26 weeks. Enzalutamide doses ≤ 20 mg/kg/day were well-tolerated in male dogs for up to 13 weeks. Clinical signs of emesis, fecal changes, and/or salivation seen in all of the canine studies were most likely related to

the vehicle, Labrasol. Consistent with the expected anti-androgen pharmacology of enzalutamide, the most salient effects of enzalutamide in rats and dogs were on male sex organs. At least partial reversibility was noted after treatment-free periods ranging from 4-21 weeks.

EEG and cardiovascular assessments in a toxicity study in dogs showed no treatment related effects. In vivo and in vitro safety pharmacology studies also demonstrated the absence of cardiovascular effects.

Enzalutamide was non-mutagenic in bacteria, non-clastogenic in mammalian cells and non-genotoxic in mice. The 2 major human metabolites, the carboxylic acid derivative and N-desmethyl enzalutamide, and a minor metabolite, M6, were negative for mutagenicity in the bacterial reverse mutation assay.

5.2.2 Clinical experience

5.2.2.1 Pharmacokinetics

The pharmacokinetics (PK) and metabolism of enzalutamide have been evaluated in 7 clinical studies in 954 patients with CRPC and 140 healthy male volunteers, including 16 subjects with mild-moderate hepatic impairment. Doses have ranges from 30-600 mg/day.

Enzalutamide was absorbed rapidly after oral administration, with maximum plasma concentration occurring 30 minutes to four hours after dosing. The mean terminal half-life was 5.8 days. Steady state was achieved by day 28, and the accumulation ratio was 8.3-fold. Enzalutamide plasma concentrations exhibited a low degree of inter- and intra-patient variability and increased linearly with dose. The PK remained linear with time, and there was no evidence of inhibition or autoinduction of metabolism during chronic administration.

A mass balance and biotransformation study in healthy male volunteers showed that enzalutamide is primarily eliminated by hepatic metabolism. However, a hepatic impairment study showed that no starting dose adjustment is needed for patients with mild-moderate liver dysfunction (Child-Pugh Class A and B). Enzalutamide has not been studied in patients with baseline severe hepatic impairment (Child-Pugh Class C) or severe renal dysfunction (CrCl <30 mL/min). Age, weight, and renal function (CrCl >30 mL/min) do not have clinically meaningful effects on enzalutamide exposures and no dose adjustment is needed.

A food-effects study showed that food does not have a clinically relevant effect on the area under the plasma concentration-time curve (AUC) of enzalutamide or N-desmethyl enzalutamide, therefore enzalutamide can be taken with or without food.

Enzalutamide is a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer. Substrates of CYP3A4, CYP2C9, and CYP2C19 with a narrow therapeutic index should be avoided, as enzalutamide may decrease plasma exposure of these drugs. If enzalutamide is administered with warfarin (a CYP2C9 substrate), additional INR monitoring is necessary.

5.2.2.2 Efficacy

Efficacy has been evaluated in 3 studies, including S-3100-1-01, CRPC-MDA-1, and CRPC2 in a total of 1399 patients with CRPC.

At the pre-specified interim analysis of the large, randomized, double-blind, placebo-controlled, phase 3 study CRPC2, enzalutamide therapy (160mg/day) significantly prolonged overall survival in patients with CRPC who had progressed during or after treatment with docetaxel. There was a 37% decrease in the risk of death for patients receiving enzalutamide versus placebo (HR 0.63) and a 4.8 month increase in survival in the enzalutamide arm. The study was then stopped and placebo patients were permitted to cross over to enzalutamide treatment.

The overall survival benefit of enzalutamide was seen in all pre-specified subgroups, and also improved the secondary endpoints of time to PSA progression (HR 0.25), radiographic PFS (HR 0.4), and time to first skeletal-related event (HR 0.69). Pain was improved in 45% versus 6.7% of enzalutamide-treated patients and quality of life using the FACT-P metric was also improved. This large phase 3 efficacy study in post-chemotherapy CRPC patients (known as the AFFIRM study) is now published [17].

Additional data from other studies have supported the findings of AFFIRM. In the dose-escalation S-3100-1-01 study, enzalutamide demonstrated anti-tumor activity in men with and without previous exposure to chemotherapy, as assessed by post-therapy changes in PSA, soft tissue and osseous disease, and circulating tumor cell count. The median time to PSA progression was not reached for chemotherapy-naïve patients and was 316 days for post-chemotherapy patients. In patients with measurable disease at study entry, 22/31 (71%) of those without previous chemotherapy had radiographic partial response or stable disease. Among the post-chemotherapy patients, 23/42 (55%) had partial response or stable disease.

The PREVAIL study is a large phase 3 study evaluating the earlier use of enzalutamide in metastatic CRPC, with enzalutamide given before chemotherapy. Enrollment is complete and results from the interim analysis are expected in 2013.

Overall, enzalutamide has been well-tolerated. In the CRPC2 study, SAEs occurred in approximately 1/3 of patients but <10% discontinued treatment due to treatment-emergent adverse events. The following AEs are believed to be associated with enzalutamide: seizure, fatigue, hot flush, headache, hypertension, anxiety, hallucinations, cognitive impairment, falls, non-pathologic fractures, pruritus, and dry skin. Seizures occurred in less than 1% (7/800 patients) in the phase 3 CRPC2 study.

These safety and efficacy results support a daily dose of 160mg daily in adult men with CRPC.

5.3 Purpose/Rationale

For patients with rising PSA after prostatectomy without evidence of metastatic disease, salvage radiation therapy to the prostate bed is the standard of care, and the progression-free survival at 2 years for men receiving salvage radiation therapy is around 65% [1]. Clinically, high-risk patients with biochemical recurrence after surgery are often managed with the combination of ADT and radiation therapy, although the benefit of ADT in the salvage radiation setting remains unclear. Only

approximately 15% of men in the salvage radiation study mentioned above also received some treatment with ADT, although a recent retrospective study suggests that ADT concurrent with salvage radiation improves progression-free survival in high risk men [3]. There is also evidence that treatment with the anti-androgen bicalutamide during radiation therapy improves outcomes [18]. There are 2 large prospective studies that will likely be reported in the next few years to help further address whether giving ADT with salvage radiation therapy is beneficial. The RADICALS trial is designed to address the question of adjuvant versus delayed radiation therapy, and one arm of the RADICALS trial will look at RT alone and with 6 and 24 months of hormones in the salvage setting. The RTOG 0534 is a phase III trial of ADT with prostate bed only versus pelvic lymph node radiation therapy in the salvage setting. While awaiting the results of these studies, the use and duration of ADT or other therapies concurrent with salvage radiation therapy for biochemical recurrence is clinician-dependent. However, the available data indicates that a substantial number of patients are not cured with radiation therapy alone and that therefore additional options are necessary.

This is a non-blinded single-arm phase II study of approximately 38 subjects for feasibility of combined enzalutamide and ADT for 6 months. Enzalutamide with ADT will start 2 months prior, continue 2 months concurrent, and be completed 2 months post-salvage XRT. The endpoints are 2 year progression free survival and the proportion of men at 1, 2, and 3 years with a PSA of <0.2 ng/mL who also have testosterone recovery. Standard external beam radiotherapy will be administered to the prostate bed over 6-7 weeks.

5.3.1 Enzalutamide Therapy

Enzalutamide dosing of 160 mg once daily was found to be safe and effective in a phase III trial of men with metastatic prostate cancer [17]. LHRH agonist dosing along concurrent with radiation is standard-of-care for men with intermediate-high risk prostate cancer [19], although optimal treatment in the salvage setting remains controversial, as discussed above. The addition of enzalutamide is hypothesized improve PFS beyond the use of ADT alone in patients receiving concurrent salvage external beam radiation therapy.

5.3.2 Radiation Therapy

Radiation is a proven adjuvant therapy for high risk prostate cancer [20, 21]. In the salvage setting, radiation has improved prostate-specific survival for men with short doubling times [12]. The radiation dose in this study is based on benefit seen with dose escalation while recognizing limitations of nearby critical organs. Dose constraints are provided in Section 8 to ensure protection of nearby normal tissues.

5.3.3 Androgen Deprivation Therapy

ADT will consist of treatment with a GnRH agonist per physician and institutional preference. Either leuprolide acetate (Lupron Depot, 22.5mg IM), triptorelin pamoate (Trelstar, 11.25 mg IM), , or goserelin acetate (Zoladex, 10.8mg SC) will be administered every 3 months for 2 doses following manufacturer's instructions. Alternative dosing may be used as long as total time of active drug is no more or less than 6 months. ADT may be initiated up to 14 days prior to the start of enzalutamide.

6 OBJECTIVES AND ENDPOINTS

6.1 Objectives

Primary objective: To describe the 2 year progression-free survival in men with recurrent PSA only disease after prostatectomy receiving combined enzalutamide and standard androgen-deprivation therapy with salvage radiation therapy.

Secondary objectives:

1. To determine the proportion of men at 1, 2, and 3 years with a PSA of <0.1 ng/mL and testosterone recovery
2. To describe the 3 year progression-free survival in men receiving combined enzalutamide and standard androgen-deprivation therapy with salvage radiation therapy.
3. To describe the biochemical (PSA) progression free survival over time
4. To describe the PSA nadir
5. To describe the time to testosterone recovery
6. To describe the safety profile of combination enzalutamide, ADT, and XRT

Exploratory objectives:

1. To describe the quality of life of patients receiving the combination of enzalutamide, ADT, and XRT
2. Archived prostatectomy specimens will be collected and stored for eventual analysis of the correlation of outcomes with pre-treatment androgen receptor target genes, androgen receptor splice variants, and epithelial-mesenchymal transition (EMT) biomarkers.

6.2 Endpoints

Primary endpoint: The rate of progression free survival (PFS) at 24 months, with PFS defined as the proportion of subjects with testosterone >100 at 24 months post-registration without one or more of the following:

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

Secondary endpoints:

1. To determine the proportion of men at 1, 2, and 3 years with a PSA of <0.1 ng/mL and testosterone recovery (defined as testosterone >100)
2. The rate of progression free survival (PFS) at 36 months, with PFS defined as the proportion of subjects with testosterone >100 at 36 months post-registration without one or more of the following:

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

3. To describe the biochemical (PSA) progression free survival over time. bPFS is similar to PFS but includes only PSA-based endpoints or death.
4. To describe the median PSA nadir
5. To describe the time to testosterone recovery
6. To describe the safety, feasibility, and tolerability profile of combination enzalutamide, ADT, and XRT as assessed by NCI Common Toxicity Scales

Exploratory endpoints:

1. To determine the quality of life of patients receiving the combination of enzalutamide, ADT, and XRT using the Expanded Prostate Cancer Index Composite (EPIC) short form, a validated scale of prostate-cancer specific quality of life. Surveys will be performed at baseline, week 12, at 12 months, 24, and 36 months post end-of-treatment follow-up visits

7 INVESTIGATIONAL PLAN

7.1 Study Design

This is a non-blinded single-arm phase II study of approximately 38 subjects to assess feasibility and efficacy of combined enzalutamide and androgen-deprivation (ADT) for 6 months with salvage radiation therapy. This study will be conducted at 3 centers: Duke Cancer Institute, Comprehensive Cancer Center of Wake Forest University, and the Cancer Institute of New Jersey.

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

Enzalutamide with ADT would start 2 months prior, continue during XRT, and be completed 2 months after salvage XRT for a total of 6 months of ADT. Typically ADT will be administered as 2 three-month or 6 monthly injections of leuprolide or an alternative standard of care GnRH agonist or antagonist at the treating physician's discretion. Enzalutamide will be given 160mg by mouth daily for 6 months and ADT will be administered per institutional standard for a total of 6 months. Standard external beam radiotherapy to 64.8-68 Gy will be administered to the prostate bed over 6-8 weeks. Inclusion of the pelvic nodes as part of the salvage radiation plan will be per the discretion of the treating radiation oncologist.

The endpoints are 2 year progression free survival and the proportion of men at 1, 2, and 3 years with a PSA of <0.2 ng/mL who also have testosterone recovery.

7.1.1 Definition of Dose-Limiting Toxicity (DLT)

Not applicable.

7.1.1.1 Non-hematologic:

Not applicable.

7.1.1.2 Hematologic:

Not applicable.

7.1.2 Dose Modification

Patients should be carefully monitored for toxicity related to treatment. Toxicity due to enzalutamide administration may be managed by symptomatic treatment, dose interruptions and adjustment of the enzalutamide dose. All toxicity will be reported using CTCAE v4.0. Dosage modifications are not recommended for grade 1 or 2 events. Therapy with enzalutamide should be interrupted upon the occurrence of a grade 3 adverse event. Once the adverse event has resolved or decreased in intensity to grade 2, then enzalutamide can be restarted at full dose or as adjusted according to the table below. Once the dose has been reduced it should not be increased at a later time. If grade 4 toxicity occurs, therapy should be discontinued.

Two dose reductions of enzalutamide are allowed. Doses below 80 mg daily are not permitted and require removal of the patient from the treatment phase of the study. If treatment must be held for any reason, it must be restarted **within 21 days** or the subject will be removed from the treatment part of the study. Patients removed from the treatment phase of the study will enter follow-up for a total of 3 years post-registration.

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

Dose Level	Enzalutamide Dose
-2	80 mg daily (2 tablets)
-1	120 mg daily (3 tablets)
0	160 mg daily (4 tablets)

7.1.2.1 Non-hematologic:

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

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

7.1.2.2 Hematologic:

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

7.1.3 Safety Considerations

Seizures have been infrequently reported in studies of enzalutamide. Any seizure activity while on this study will result in immediate discontinuation of enzalutamide.

7.1.4 Missed Doses

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

7.1.5 Concomitant Medications

Concomitant medication will be evaluated at each study visit during enzalutamide therapy. Concomitant medications include all vitamins, herbal remedies, over the counter, and prescription medications. ADT in the form of GnRH agonists or antagonists for 6 total months is permitted as part of the study as per standard of care practice.

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

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

The following treatments do not require study discontinuation:

- Blood transfusions and growth factor support per standard of care and institutional guidelines;
- Steroids given at a maximum equivalent daily dose of 10 mg of prednisone;
- Pain therapy per standard of care and institutional guidelines;

APPENDIX C provides a list of potent CYP enzyme inhibitors and inducers that have a theoretical concern for drug-drug interactions with enzalutamide. *In vitro* drug metabolism studies suggest that enzalutamide has the potential to inhibit or induce CYP2C8, CYP2C9, CYP2C19, and CYP3A4; therefore, concomitant medications that are substrates of any of these enzymes should be used with caution, and relevant monitoring should be considered, especially for substrates known to cause seizure, because the possibility of drug-drug interactions cannot be fully excluded.

7.1.5.1 Drugs that inhibit or induce CYP2C8

Coadministration of a strong CYP2C8 inhibitor (gemfibrozil) increased the composite AUC of enzalutamide plus N-desmethyl enzalutamide in healthy volunteers by 2.2-fold. Coadministration of enzalutamide with strong CYP2C8 inhibitors should be avoided. The effects of CYP2C8 inducers on the pharmacokinetics of enzalutamide have not been evaluated *in vivo*. Coadministration of enzalutamide with strong CYP2C8 inducers (e.g., rifampin) may alter the plasma exposure of enzalutamide and should be avoided. Selection of a concomitant medication with no or minimal CYP2C8 induction potential is recommended.

7.1.5.2 Drugs that Inhibit or Induce CYP3A4

Coadministration of a strong CYP3A4 inhibitor (itraconazole) increased the composite AUC of enzalutamide plus N-desmethyl enzalutamide by 1.3-fold in healthy volunteers. The effects of CYP3A4 inducers on the pharmacokinetics of enzalutamide have not been evaluated *in vivo*. Coadministration 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. 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.

7.1.5.3 Effect of enzalutamide on drug metabolizing enzymes

Enzalutamide is a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer in humans. At steady state, enzalutamide reduced the plasma exposure to midazolam (CYP3A4 substrate), warfarin (CYP2C9 substrate) and omeprazole (CYP2C19 substrate) by 86%, 56% and 70%, respectively. Concomitant use of enzalutamide with narrow therapeutic index drugs that are metabolized by CYP3A4 (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus and tacrolimus), CYP2C9 (e.g., phenytoin, warfarin) and CYP2C19 (e.g., S-mephenytoin) should be avoided, as enzalutamide may decrease their exposure. If coadministration with warfarin cannot be avoided, conduct additional INR monitoring.

7.1.6 Study Drug Blinding

Not applicable, this is an open-label study.

7.1.7 Randomization

Not applicable, this is a non-randomized study.

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

The dosing used for both the GnRH agonist and enzalutamide (160mg daily) is the standard-of-care dosing. Clinically, high-risk patients with biochemical recurrence after surgery are often managed with the combination of ADT and radiation therapy, although the optimal duration and benefit of ADT in the salvage radiation setting remains unclear. The treatment duration of 6 months was chosen in hopes of providing maximal efficacy while minimizing toxicity.

7.3 Rationale for Correlative Studies

Archived prostatectomy specimens will be collected and stored for eventual analysis of androgen receptor target genes, androgen receptor splice variants, and epithelial-mesenchymal transition (EMT) biomarkers. The current protocol and funding allows only for archival prostatectomy specimens to be obtained and banked.

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

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

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

The primary endpoint is the rate of PFS at 24 months, with PFS defined as the proportion of subjects with testosterone >100 at 24 months post registration, without progression as defined above. We hypothesize that ~20% of patients will not have testosterone recovery at this point and therefore will not be evaluable for the primary endpoint.

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

7.5 Early Study Termination

This study can be terminated at any time for any reason by the PI-sponsor. If this occurs, all subjects on study should be notified as soon as possible. Additional procedures and/or follow up should occur in accordance with Section 11.8, which describes procedures and process for prematurely withdrawn patients.

8 RADIATION THERAPY

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

Radiation therapy may be performed locally as standard-of-care, provided it conforms to protocol-specified treatment and dosing specifications. Weekly visits during radiotherapy may be performed locally by the treating radiation oncologist according to standard of care practice. Research visits during radiotherapy will occur at the treating institution at week 12 and week 16, according to the schedule of events.

8.1 Dose Specifications

Radiotherapy will start on week 9 (+/-14) days. Radiotherapy dose will be specified to the Planning Target Volume (PTV), as described in section 8.4. The total dose to the prostate bed must be 64.8-68 Gy in 1.8-2 Gy daily fractions. ≥ 95% of the PTV should receive the prescribed dose.

8.2 Technical Factors

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

8.3 Localization, Simulation, and Immobilization

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

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

Immobilization may be performed per institutional preference.

8.4 Treatment Planning/Target Volumes

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

8.4.1 CTV (Prostate Bed)

Contrast may be used for simulation but can distort the anatomy slightly and so is not recommended. The bladder should be reasonably full for simulation, keeping in mind that patients may not be able to maintain as full a bladder during radiotherapy. The seminal vesicles or remnants thereof, if identified on CT or MRI as being present, must be included in entirety within the CTV. The immediate periprostatic bed surgical clips must also be included within the CTV. Superior nodal clips do not need to be targeted. The CTV will 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 except in the setting of node positive disease, where it may be done by physician preference. If included, the pelvic nodal CTV should include external iliac nodes to the level of the superior femoral heads, internal iliac nodes to the superior contours of the prostate/seminal vesicle CTV, and the common iliac nodes to the L5-S1 junction. Inclusion of presacral nodes is recommended but may be omitted at physician discretion

to improve organ-sparing. If nodal irradiation is performed, a cone-down to the prostate bed must occur no later than 50.4 Gy. Alternatively, simultaneous integrated boost is allowed with maximum pelvic dose of 52 Gy.

8.4.2 PTV

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

8.4.3 Normal Tissues

The critical normal structures are the bladder, rectum, and femoral heads. The normal tissues will be contoured and considered as solid organs. The bladder should be contoured from its base to the dome, excluding the 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. The penile bulb may be outlined as a reference structure. No constraints will be placed on the penile bulb.

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

8.4.4 Prostate Bed Planning for IMRT

The plan will be deemed acceptable under the following conditions.

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

Rectum: Less than or equal to 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.

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

8.5 Treatment Localization

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

8.6 Documentation Requirements

The institution will archive treatment prescription and verification images for later review if requested. For conformal RT, at least one port film or pretreatment alignment film per field along with the digital reconstructed radiographs (DRRs) from the treatment planning program or, alternatively, a simulation verification radiograph shall be acquired and kept for evaluation if requested except where geometrically impractical. For IMRT, at least 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.

8.7 Radiation Adverse Events

All patients will be seen weekly by their radiation oncologist during radiation therapy. Any observations with respect to the following symptoms/side effects will be recorded using CTCAE v4.0 grading including but not limited to:

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

- Radiation dermatitis

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

See Section 12 for Adverse Events and Adverse Event Reporting Guidelines.

9 STUDY DRUG

9.1 Names, Classification, and Mechanism of Action

Enzalutamide (MDV3100) is an androgen receptor (AR) signaling inhibitor that competitively inhibits binding of androgens to ARs, inhibits nuclear translocation of receptors and inhibits the association of the AR with DNA. Astellas Pharma Global Development, Inc. and Medivation, Inc. are developing enzalutamide for the treatment of cancer. Enzalutamide was approved in the United States on 31 August 2012 under the trade name XTANDI® for the indication of the treatment of patients with metastatic castration-resistant prostate cancer who have previously received docetaxel.

9.2 Packaging and Labeling

Enzalutamide is presented in a soft gelatin capsule filled with a formulation containing 40 mg of the active pharmaceutical ingredient. The therapeutic dose is 160 mg once daily (4 capsules, each 40 mg).

Ingredients: Fill solution: enzalutamide, caprylocaproyl macrogolglycerides, butylhydroxyanisole, butylhydroxytoluene. Capsule: gel mass (gelatin, purified water, sorbitol sorbitan solution and glycerol, titanium dioxide), ink (iron oxide black).

Appearance: Opaque white to off-white oblong liquid filled soft gelatin capsule.

Packaging: 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.

9.3 Supply, Receipt, and Storage

Treatment will be administered on an outpatient basis. Enzalutamide will be given to the patient from clinic and patients will receive 160 mg/day (four 40 mg capsules) in an unblinded fashion. Enzalutamide will be supplied by Medivation. The product is provided as gelatin capsules in bottles with pressure or induction-sealed child-resistant caps. Enzalutamide can be taken with or without food.

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

9.4 Dispensing and Preparation

After receipt of prescription by the site Investigational Pharmacy Services, a secondary label will be applied with patient's name, date, prescription, expiration, contact information, and indication. Enzalutamide 160mg daily will be dispensed monthly (120 tablets) by the site investigational pharmacy services. Enzalutamide will be given for 6 months x 30 days = 180 days total.

9.5 Compliance and Accountability

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

9.6 Disposal and Destruction

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

10 SUBJECT ELIGIBILITY

10.1 Inclusion Criteria

1. Histologically confirmed diagnosis of prostate adenocarcinoma. Variants of prostate cancer, including neuroendocrine features and small cell carcinoma of the prostate, are not permitted.

2. Gleason sum of 7, 8, 9, or 10 at the time of prostatectomy.

3. PSA relapse within 4 years of prostatectomy defined by persistently detectable or rising PSA after surgery.

4. Evidence of disease recurrence or progression as evidenced by a PSA > 0.20. This requires 2 consecutive rises in PSA, at least 1 week apart, over the post-prostatectomy nadir or one PSA value above 0.20 ng/mL if the patient failed to achieve a post-prostatectomy nadir of < 0.2 ng/mL.

5. Age ≥ 18 years

6. Karnofsky performance status ≥ 70

7. Adequate laboratory parameters
   - Adequate bone marrow function: ANC ≥1.5 x 10^9/L, Platelets ≥100 x 10^9/L, Hb >9g/dL
   - AST/SGOT and ALT/SGPT ≤ 2.5 x Institutional Upper Limit of Normal (ULN)
   - Serum bilirubin ≤ 1.5 x Institutional ULN
   - Serum creatinine ≤ 1.5 x Institutional ULN or 24-hour clearance ≥ 50 mL/min

8. A minimum of 4 weeks from any major surgery prior to registration.

9. Ability to swallow, retain, and absorb oral medication.

10. Ability to understand and the willingness to sign a written informed consent document.
11. Must use a condom if having sex with a pregnant woman.

12. Male patient and his female partner who is of childbearing potential must use 2 acceptable methods of birth control (one of which must include a condom as a barrier method of contraception) starting at screening and continuing throughout the study period and for 3 months after final study drug administration.

10.2 Exclusion Criteria

1. Radiographic evidence of metastatic disease. Patients with node-positive disease (≤2 positive nodes) at the time of radical prostatectomy are eligible. Patients with pelvic nodes up to 2 cm by short axis at the time of screening are eligible. Patients with any enlarged lymph nodes in the retroperitoneum or above the aortic bifurcation or with pelvic nodes ≥ 2 cm must be excluded.

2. PSA > 4.0 ng/mL.

3. Testosterone level ≤ 100 ng/dL.

4. More than 1 month of prior hormone exposure or hormone exposure within 30 days of registration. Prior enzalutamide, ketoconazole, abiraterone, or TAK700 prohibited. Prior 5α reductase inhibitors are allowed.

5. Prior immunotherapy including sipuleucel-T.

6. Prior systemic chemotherapy (docetaxel, cabazitaxel, estramustine, other cytotoxic agents)

7. History of solid organ or stem cell transplantation.

8. History of seizure or any condition that may predispose to seizure (e.g., prior cortical stroke, prior head or traumatic brain injury with loss of consciousness, prior or current space-occupying lesion in the brain). Also, history of loss of consciousness or transient ischemic attack within 12 months of Day 1 visit.

9. Known or suspected brain metastasis or active leptomeningeal disease.

10. Other concurrent severe and/or uncontrolled concomitant medical conditions (e.g., active or uncontrolled infection) that could cause unacceptable safety risks or compromise compliance with the protocol.

11. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of enzalutamide or increase the risk of radiation (e.g., uncontrolled nausea, vomiting, diarrhea, malabsorption syndromes, prior small bowel resection, or inflammatory bowel disease).

12. Patients who have received prior prostate or pelvic radiotherapy, including external beam or brachytherapy.

13. Patients who have undergone major surgery ≤ 4 weeks prior to starting study drug or who have not recovered from side effects of such therapy prior to registration.

14. Patients unable or unwilling to abide by the study protocol or cooperate fully with the investigator.

11 SCREENING AND ON-STUDY TESTS AND PROCEDURES

	BASELINE[a] (within 60 days)	**Monthly visits**[b]			**Week 9+**	**Monthly visits**			**End-of-treatment visit**[d] **Week 26** (+/- 7d)	**Follow-Up Visits**[e] (every 3 months)
		Day 1	**Week 4** (+/- 7d)	**Week 8** (+/- 7d)		**Week 12** (+/- 7d)	**Week 16** (+/- 7d)	**Week 20** (+/- 7d)		
Informed consent	X									
Inclusion/exclusion criteria	X									
Medical history and AE assessment	X	X	X	X		X	X	X	X	X[m,o]
Prior & concomitant medications	X	X	X	X		X	X	X	X	X[n,o]
Physical examination	X	X	X	X		X	X	X	X	X[o]
Karnofsky performance status	X	X	X	X		X	X	X	X	X[o]
Vital signs and weight[f]	X	X	X	X		X	X	X	X	X[o]
CT chest, abdomen, pelvis[g]	X									
Bone scan[g]	X									
CBC with differential[h]	X	X		X				X	X	X[o]
Serum chemistries[h]	X	X		X				X	X	X[o]
Serum PSA and testosterone[h]	X	X		X					X	X
Enzalutamide dispensing[i]		X	X	X		X	X	X		
GnRH agonist administration[j]		X				X				
Radiation therapy and weekly treatment checks[c]					X					
Archival tumor blocks[k]	X									
EPIC quality-of-life questionnaire[l]	X					X				X[l]

Footnotes to Study Flow Chart:

a. Screening/baseline evaluations must be completed within 60 days prior to the first dose of study agent. Radical prostatectomy report must be obtained.
b. Monthly visits will occur every 4 weeks +/- 7 days, through week 20, while receiving enzalutamide therapy.
c. Radiation therapy will begin on week 9 +/- 14 days. Radiation therapy may be performed locally as standard-of-care, provided it conforms to protocol-specified treatment and dosing specifications. Receipt of protocol-specified salvage radiation will be documented including dose, field, and timing. Weekly visits during radiotherapy may be performed locally by the treating radiation oncologist according to standard of care practice. Research visits during radiotherapy will occur at week 12 and week 16, according to the schedule of events.
d. End-of-treatment visit will occur at week 26 +/- 7 days, at which point all therapeutic intervention will be complete.
e. Follow-up visits will occur every 3 months from the end-of-treatment visit and will have a +/-21 day allowance window. Follow up will continue for 3 years post-registration or until early withdrawal.
f. Includes VAS pain and fatigue score.
g. CT scan with chest (noncontrast of chest permitted), abdomen, and pelvis (with IV contrast) and whole body Tc-99 bone scan will be performed within 60 days of initial study drug administration, as per standard-of-care to evaluate for metastatic disease. Imaging studies including CT and bone scans will be performed upon evidence of PSA or symptomatic disease progression or based on investigator concerns of disease recurrence in the absence of PSA progression.
h. Standard-of-care laboratory assessments at the times indicated include:
   Complete blood count (CBC) with differential: WBC count with differential, platelet count, hemoglobin, and hematocrit.
   Serum chemistries: Sodium, potassium, chloride, blood urea nitrogen (BUN) or urea, creatinine, glucose, carbon dioxide (CO_2) or bicarbonate, calcium, total protein, aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, total bilirubin, and alkaline phosphatase.
   Testosterone and PSA levels.

   NOTE: Day 1 lab tests do not need to be repeated if the baseline labs were obtained within 7 days of initial study drug administration.
i. Enzalutamide will be dispensed monthly and should be taken daily for a total of 6 months.
j. GnRH agonist treatment (3 month dose) will be given in clinic on day 1 and during the week 12 visit for a total of 6 months of therapy. Alternative monthly schedules are permitted provided total treatment duration of ADT is 6 months.
k. Previously archived formalin-fixed or frozen primary prostate tumor blocks or cores will be collected on this study through the Duke Cancer Institute or participating site biorepository and linked to subject outcomes if available. Slides are also acceptable in lieu of blocks. This is an optional component of the study as detailed in the ICF. At least 250 mg of tumor tissue is needed for the genomic correlative component of this study. Frozen primary tumor samples will be collected if available. See section 11.9.3 for details.
l. Quality-of-life questionnaire (EPIC Short Form) will be administered at baseline, at week 12, then at 12, 24, and 36 months (+/- 3 months) post end-of-treatment (5 per subject). The EPIC questionnaire is required to be completed by subjects during follow-up even if the associated visit is optional.
m. All AEs are collected for 30 days following the last dose of enzalutmide. During follow-up and past 30 days after the last dose of enzalutmaide, AEs definitely, probably or possibly attributed to study

drug occurring during treatment are tracked until resolution to grade 1 or lower, but new AEs are not collected.

n. During follow-up, concomitant medications tracking only includes treatments for prostate cancer (eg. ADT).

o. During follow-up visits, the CBC with differential and serum chemistries will be optional for subjects without lab abnormalities felt to be related to study treatment. In addition, follow-up visits, including medical history and AE assessment, prior & concomitant medications, physical examination, Karnofsky performance status and vital signs and weight will be optional except for subjects with an adverse event felt to be related to study treatment which has not resolved to grade 1 or returned to baseline.

11.1 Screening Examination

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

Subject data to be collected at the Screening Examination includes:

- Informed consent process utilizing a signed and dated IRB-approved ICF
- Confirmation of inclusion/exclusion criteria
- Medical history including concomitant illnesses and oncologic history. Oncologic history must include specific documentation of prostate cancer histologic diagnosis.
- Prior and concomitant medications and non-pharmacologic treatments taken within 4 weeks of screening will be recorded. In addition, all prior treatments including surgery and radiotherapy for prostate cancer will be recorded, regardless of when administered.
- CT of the chest, abdomen, and pelvis for tumor assessment, standard-of-care
- Whole body bone scan (99-Technetium), standard-of-care
- Sample collection for the following laboratory evaluations (all standard-of-care):
    - Complete blood count (CBC) with differential: WBC count with differential, platelet count, hemoglobin, and hematocrit.
    - Serum chemistries: Sodium, potassium, chloride, blood urea nitrogen (BUN) or urea, creatinine, glucose, carbon dioxide (CO_2) or bicarbonate, calcium, total protein, aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, total bilirubin, and alkaline phosphatase.
    - Testosterone and PSA levels.
- Physical examination to be conducted and height (cm), weight (kg), and vital signs (including temperature [°C], blood pressure [mmHg], heart rate [beats per minute], respiratory rate [breaths per minute] and VAS pain and fatigue score [scale of 1-10, subject reported]) to be measured and recorded
- Karnofsky performance status
- Previously archived formalin-fixed or frozen primary prostate tumor blocks or cores will be collected on this study through the Duke Prostate Center or participating site biorepository and linked to subject outcomes if available. Slides are also acceptable in lieu of blocks. This is an optional component of the study as detailed in the ICF. At least one frozen biopsy (250 mg) of tumor tissue is needed. Frozen primary tumor samples will be collected if available. See section 11.9.3 for details.
- Quality-of-life questionnaire (EPIC Short Form) will be administered at baseline.

11.2 Subject Registration

After signing informed consent and completing eligibility screening, subjects who are selected to participate will be registered with the lead site (Duke) and with their study site/institution. A record of subjects who fail to meet entry criteria (i.e., screen failures) will be maintained. Subject registration must be complete before beginning any treatment.

11.2.1 Informed Consent

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

When obtaining informed consent, study personnel should:

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

Next: Obtain dated and signed informed consent.

Finally: Confirm that the subject is eligible as defined in Section 10.0 (Inclusion/Exclusion Criteria). A record of subjects who fail to meet entry criteria (i.e., screening failures) will be maintained.

For subjects consented at the lead site ONLY, registration in the Duke clinical trial subject registry must be completed within 1 business day of the subject providing informed consent.

11.2.2 Lead Site Registration

Subject registration for all subjects signing informed consent will be completed by Duke University Medical Center Genitourinary Oncology Group. Following consent and completion of the Eligibility Checklist, documents will be submitted for review and registration of subject. Enrolled subjects will be assigned a unique study ID.

Refer to Subject Registration Instructions for details.

Subjects will be enrolled only after all pre-treatment screening evaluations are completed and all eligibility criteria are met. Once the subject has signed consent and been found to meet all eligibility criteria, the subject will be enrolled, and a unique patient study identification number will be assigned. Treatment must not commence until the subject has received his/her identification number from the lead site.

11.2.3 Institutional Registration

Subject registration at each study site/institution will be conducted according to the institution's established policies. Prior to registration, subjects will be asked to sign and date an Institutional Review Board (IRB)-approved consent form. Subjects must be registered with their local site/institution and with the lead site before beginning any treatment or study activities.

11.3 Run-In Period

Not applicable.

11.4 Treatment Period

Treatment will be administered on an outpatient basis. Enzalutamide with ADT will start 2 months prior, continue 2 months concurrent, and be completed 2 months post-salvage XRT, per the calendar of events.

11.5 End of Treatment

At week 26, or in the event of disease progression, unacceptable toxicity, or withdrawal of consent, study treatment is to be stopped and an end-of-treatment visit is to be conducted within 7 days.

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

- Concomitant medications and non-pharmacologic treatments to be reviewed and recorded.
- Sample collection for the following laboratory evaluations (all standard-of-care):
  - CBC: WBC with differential, platelet count, hemoglobin, and hematocrit.
  - Chemistries: sodium, potassium, chloride, blood urea nitrogen (BUN) or urea, creatinine, glucose, carbon dioxide (CO_2) or bicarbonate, calcium, total protein, aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, total bilirubin, and alkaline phosphatase.
  - PSA and testosterone.
- Physical examination to be conducted, including weight (kg) and vital signs (including temperature [°C], blood pressure [mmHg], heart rate [beats per minute], respiratory rate [breaths per minute] and VAS pain and fatigue score [scale of 1-10, subject reported]).
- Karnofsky performance status.
- Adverse Events.

11.6 Follow-up Period

Follow up will continue for 3 years from registration or until early withdrawal. Follow-up visits will be scheduled every three months from the end-of-treatment visit (with a 21-day window period allowance). The visits including medical history and AE assessment, prior & concomitant medications, physical examination, Karnofsky performance status, and vital signs will be optional except for subjects with an adverse event felt to be related to study treatment which has not resolved to grade 1 or returned to baseline. Imaging studies will be performed as per standard-of-care for those men with evidence of PSA recurrence or symptomatic disease or based on concerns of disease recurrence in the absence of PSA progression.

Every three months the following assessments will be performed:

- Laboratory studies:
  - Complete blood count (CBC) with differential: WBC count with differential, platelet count, hemoglobin, and hematocrit.
  - Serum chemistries: Sodium, potassium, chloride, blood urea nitrogen (BUN) or urea, creatinine, glucose, carbon dioxide (CO_2) or bicarbonate, calcium, total

protein, aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, total bilirubin, and alkaline phosphatase.
    - Testosterone and PSA levels.
    - The CBC with differential and serum chemistries will be optional for men without lab abnormalities felt to be related to study treatment.
  - Medical history and physical examination
  - Review of current medications and non-pharmacologic treatments for prostate cancer (eg. ADT) taken since the prior visit
- Quality-of-life questionnaire (EPIC Short Form) will be administered at baseline, at week 12, then at 12, 24, and 36 months (+/- 3 months) following end-of-treatment (5 per subject). The EPIC questionnaire is required to be completed by subjects during follow-up even if the associated visit is optional.

11.7 End of Study

Each subject will be followed q3 months following their end-of-treatment visit for a total of 3 years from study registration. The overall end of study will occur when the last enrolled subject has completed his 3 year follow-up visit.

11.8 Early Withdrawal of Subject(s)

11.8.1 Criteria for Early Withdrawal

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

Reasons for PI-initiated withdrawal may include the following:

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

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

11.8.2 Follow-up Requirements for Early Withdrawal

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

11.8.3 Replacement of Early Withdrawal(s)

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

11.9 Study Assessments

11.9.1 Medical History

At the initial visit, the detailed medical history will include concomitant illnesses and oncologic history. All prior treatments including surgery and radiotherapy for prostate cancer will be recorded, regardless of when administered. This medical history will be updated at subsequent visits. Concomitant medications and non-pharmacologic treatments taken will be recorded at each visit.

11.9.2 Physical Exam

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

11.9.3 Correlative Assessments

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

These archived specimens will be collected and stored for analysis of the correlation of outcomes with pre-treatment androgen receptor target genes, androgen receptor splice variants, and epithelial-mesenchymal transition (EMT) biomarkers for mechanisms of resistance to enzalutamide, ADT, and radiation. Prior to storage, all specimens will be labeled with the study ID and date that specimen was obtained from patient. Specimens will be stored until used according to established SOPa by in the Duke Biospecimen Repository and Processing Core (BRPC).

12 SAFETY MONITORING AND REPORTING

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

12.1 Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence in a subject administered a study drug and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not related to the study drug.

An abnormality identified during a medical test (e.g., laboratory parameter, vital sign, ECG data, physical exam) should be defined as an AE only if the abnormality meets one of the following criteria:

- Induces clinical signs or symptoms.
- Requires active intervention.
- Requires interruption or discontinuation of study medication.
- The abnormality or investigational value is clinically significant in the opinion of the investigator.

All adverse events, whether or not related to the study drug, must be fully and completely documented.

From day 1 of study treatment until 30 days after the last dose of enzalutamide, all AEs must be recorded in the subject medical record and adverse events case report form. During follow-up and past 30 days after the last dose of enzalutmaide, AEs definitely, probably or possibly attributed to study drug occurring during treatment are tracked until resolution to grade 1 or lower, but new AEs are not collected.

AEs will be assessed according to the CTCAE version 4.0. If CTCAE grading does not exist for an AE, the severity of the AE will be graded as mild (1), moderate (2), severe (3), life-threatening (4), or fatal (5).

Attribution of AEs will be indicated as follows:

- Definite: The AE is clearly related to the study drug
- Probably: The AE is likely related to the study drug

- Possible: The AE may be related to the study drug
- Unlikely: The AE is doubtfully related to the study drug
- Unrelated: The AE is clearly NOT related to the study drug

12.1.1 AEs of Special Interest

Given the concern for enzalutamide-related seizures, any and all seizure activity that occurs from the baseline visit to the end-of-treatment visit will be recorded and treated as an adverse event.

12.2 Serious Adverse Events

An AE is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Results in death,
- Is life threatening (an AE is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.),
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions,
- Results in congenital anomaly, or birth defect,
- Requires inpatient hospitalization or leads to prolongation of hospitalization (hospitalization for treatment/observation/examination caused by AE is to be considered as serious),
- Other medically important events.

12.2.1 Reporting of SAEs

Serious adverse events, whether or not considered drug related, should be reported to the lead site/sponsor (Duke) within 24 hours of becoming aware of the event, using the provided DCI SAE Report Form and the SAE Report Review Form (Site Assessment). These documents should be sent to:

The DCI Safety Desk – f[redacted]

If the safety desk cannot be reached within 24 hours, the Principal Investigator should be contacted: Dr. Andrew Armstrong [redacted] email: andrew.armstrong@dm.duke.edu).

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

- Protocol # and title
- Patient initials, study identification number, sex, age
- Date the event occurred
- Description of the SAE
- Dose level and cycle number at the time the SAE occurred
- Description of the patient's condition

- Indication whether the patient remains on study
- Causality

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

Upon receipt of the Serious Adverse Event Reporting form by the DCI Safety Desk, the PI will be notified and be required to complete the PI assessment of the DCI Safety SAE Report Review Form. The DCI safety desk will, in turn, report the event to Astellas if felt to be at least possibly related to enzalutamide using the DCI SAE Report Form.

The SAE documentation, including the DCI SAE Report Form and available source records should be emailed or faxed to:

Astellas Pharma Global Development – United States
[redacted]

The following minimum information is required:

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

Follow-up information for the event should be sent within promptly (within 7 days) as necessary.

12.3 Emergency Unblinding of Investigational Treatment

Not applicable

12.4 Procedure in case of pregnancy

The effect of enzalutamide in pregnant and lactating women is not known, and the exposure of a fetus or nursing infant is considered a potential risk. Enzalutamide can cause fetal harm when administered to a pregnant woman based on its mechanism of action. Subjects receiving enzalutamide are advised to use 2 acceptable methods of birth control (one of which must include a condom as a barrier method of contraception) starting at the time of screening for an enzalutamide study and continuing throughout the course of treatment and for at least three months after enzalutamide is discontinued.

If during the conduct of the clinical trial, a male subject impregnates his partner, the subject should report the pregnancy to the Investigator. The Investigator should report the pregnancy to the Sponsor as an SAE within 24 hours of awareness of the event. The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated fertility date, pregnancy result and neonatal data etc., should be included in this information.

The Investigator should report the outcome of the pregnancy (independent of outcome, eg. full term delivery, pre-term delivery, spontaneous abortion, induced abortion, stillbirth, death of newborn, congenital anomaly [including anomaly in a miscarried fetus, etc] in accordance with the same reporting procedure as for SAEs. The date of outcome of the pregnancy, gestational age, date of birth and neonatal data etc., should be included in this information.

12.5 Safety Oversight Committee (SOC)

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

13 QUALITY CONTROL AND QUALITY ASSURANCE

13.1 Monitoring

The Duke Cancer Institute (DCI) Monitoring Team will conduct monitoring visits to ensure subject safety and to ensure that the protocol is conducted, recorded, and reported in accordance with the protocol, standard operating procedures, good clinical practice, and applicable regulatory requirements. As specified in the DCI Data and Safety Monitoring Plan, the DCI Monitoring Team will conduct routine monitoring after the third subject is enrolled, followed by annual monitoring of 1 – 3 subjects until the study is closed to enrollment and subjects are no longer receiving study interventions that are more than minimal risk.

The DCI Safety Oversight Committee (SOC) will perform annual reviews on findings from the DCI Monitoring Team visit and additional safety and toxicity data submitted by the Principal Investigator.

Additional monitoring may be prompted by findings from monitoring visits, unexpected frequency of serious and/or unexpected toxicities, or other concerns and may be initiated upon request of DUHS and DCI leadership, the DCI Cancer Protocol Committee, the Safety Oversight Committee (SOC), the Duke School of Medicine Clinical Trials Quality Assurance (CTQA), the sponsor, the Principal Investigator, or the IRB. All study documents must be made available upon request to the DCI Monitoring Team and other authorized regulatory authorities, including but not limited to the National Institute of Health, National Cancer Institute, and the FDA. Every reasonable effort will be made to maintain confidentiality during study monitoring.

13.2 Data Management and Processing

13.2.1 Study Documentation

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

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

13.2.2 Case Report Forms (CRFs)

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

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

13.2.3 Data Management Procedures and Data Verification

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

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

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

13.2.4 Study Closure

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

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

14 STATISTICAL METHODS AND DATA ANALYSIS

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

The primary objective of this single arm, open-label, one stage phase II study is to estimate the 24 month progression-free survival rate of men with recurrent, PSA-only disease after prostatectomy receiving combined enzalutamide and standard androgen-deprivation therapy with salvage radiation therapy. The target sample size is 38. It is primarily hypothesized the 2 year PFS rate will be improved with the combined therapy compared to the historical control data in a similar patients setting. Based on a model and nomogram by Stephenson et al for men with recurrent disease after radical prostatectomy [1], the PFS rate at 24-months among prostate cancer patients is 65%. **This trial is designed to have 84% power to reject the null hypothesis of 24 month PFS rate of 65% when the true PFS rate at 24 months is 85%.** The power of this study will be different if the enrolled patients have a lower predicted 24 month PFS rate based this nomogram, however, this study should have at least 80% power to detect a 20% improvement in 24 month PFS rate even if a 55% rate of 2 year PFS is predicted. One sample binomial test will be used to test whether the 24 month PFS rate is larger than the hypothesized value from the historical controls with a one sided alpha error of 0.05. The Kaplan-Meier product-limit estimator will be used to estimate the distribution of PFS, biochemical progression free survival, time to PSA nadir, and time to testosterone recovery. The median survival times and 95% confidence intervals will be reported. The frequency and proportion (and 95% confidence interval) of men at 1, 2, and 3 years with a PSA of <0.1 ng/ml and testosterone recovery will be reported. In addition, descriptive statistics with 95% confidence intervals will be calculated for secondary endpoints of safety profile and quality-of-life (QOL) endpoints, the continuous safety and QOL endpoints will be summarized as the patient counts, mean, standard deviation, median, $25^{th}$and 75^{th} percentiles, minimum and maximum. The categorical safety and QOL endpoints will be categorized using frequencies and percentages.

14.1 Analysis Sets

This is a non-blinded single-arm phase II study of approximately 38 subjects to assess feasibility and efficacy of combined enzalutamide and androgen-deprivation (ADT) for 6 months with salvage radiation therapy.

14.2 Patient Demographics and Other Baseline Characteristics

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

14.3 Treatments

Enzalutamide with ADT would start 2 months prior, continue 2 months concurrent, and be completed 2 months after salvage XRT. Enzalutamide will be given 160mg by mouth daily for 6 months and ADT will be administered per institutional standard for a total of 6 months. Standard external beam radiotherapy to 64.8-68 Gy will be administered to prostate bed over 6-8 weeks. Inclusion of the pelvic nodes as part of the salvage radiation plan for patients with node positive disease will be per the discretion of the treating radiation oncologist.

14.4 Primary Objective

To describe the 2 year progression-free survival in men with recurrent PSA only disease after prostatectomy receiving combined enzalutamide and standard androgen-deprivation therapy with salvage radiation therapy **and** who have had testosterone recovery to >100.

14.4.1 Variable

2 year progression-free survival time.

14.4.2 Statistical Hypothesis, Model, and Method of Analysis

The null hypothesis is that the PFS rate at 24-months among prostate cancer patients is equal to the rate for the historical control, 65%. One sample binomial test will be used to test whether the 24 month PFS rate is larger than the hypothesized value from the historical controls.

14.4.3 Handling of missing values, censoring, and discontinuations

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

14.5 Secondary Objectives

1. To determine the proportion of men at 1, 2, and 3 years with a PSA of <0.1 ng/mL and testosterone recovery
2. To describe the 3 year progression-free survival in men receiving combined enzalutamide and standard androgen-deprivation therapy with salvage radiation therapy **and** who have had testosterone recovery to >100.
3. To describe the biochemical (PSA) progression free survival over time
4. To describe the median PSA nadir
5. To describe the time to testosterone recovery

6. To describe the safety profile of combination enzalutamide, ADT, and XRT

14.5.1 Key Secondary Objective – analysis plan

To determine the proportion of men at 1, 2, and 3 years with a PSA of <0.1 ng/mL and testosterone recovery. The frequency and proportion (and 95% confidence interval) of men at 1, 2, and 3 years with a PSA of <0.1 ng/ml and testosterone recovery will be reported.

14.5.2 Other Secondary Objectives – analysis plan

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

14.6 Exploratory Objectives

7. To describe the quality of life of patients receiving the combination of enzalutamide, ADT, and XRT

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

14.6.1 Key Exploratory Objective

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

14.6.2 Other Exploratory Objectives

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

14.7 Interim Analysis

Not applicable.

14.8 Sample Size Calculation

Based on one sample binomial test, the required sample size is 30. However, because the evaluable subjects defined in section 7.4 are 80% (due to the potential lack of testosterone recovery at 24 months), the actual sample size becomes **38**. The sample size calculation assumes there is no censoring, and we will follow all patients long enough to diminish censoring effect on the sample size. This trial is designed to have 84% power to reject the null hypothesis of 24 month PFS rate of

65% when the true PFS rate at 24 months is 85%. The power of this study will be different if the enrolled patients have a lower predicted 24 month PFS rate based this nomogram, however, this study should have at least 80% power to detect a 20% improvement in 24 month PFS rate even if a 55% rate of 2 year PFS is predicted. We assume the combined rate of the potential lack of testosterone recovery at 24 months and drop out is about 20% (with dropout less than 5%). The evaluable subjects are expected to be approximately 80% of total samples; the actual sample size becomes 38.

15 ADMINISTRATIVE AND ETHICAL CONSIDERATIONS

15.1 Regulatory and Ethical Compliance

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

15.2 DUHS Institutional Review Board and DCI Cancer Protocol Committee

The protocol, informed consent form, advertising material, and additional protocol-related documents must be submitted to the DUHS Institutional Review Board (IRB) and DCI Cancer Protocol Committee (CPC) for review. The study may be initiated only after the Principal Investigator has received written and dated approval from the CPC and IRB.

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

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

15.3 Informed Consent

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

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

questions, and will be given as much time as needed to make an informed decision about participation in the study.

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

15.4 Study Documentation

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

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

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

15.5 Privacy, Confidentiality, and Data Storage

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

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

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

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

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

15.6 Data and Safety Monitoring

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

15.7 Protocol Amendments

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

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

15.8 Records Retention

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

15.9 Conflict of Interest

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

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

16 REFERENCES

[1] A. J. Stephenson, P. T. Scardino, M. W. Kattan, T. M. Pisansky, K. M. Slawin, E. A. Klein*, et al.*, "Predicting the outcome of salvage radiation therapy for recurrent prostate cancer after radical prostatectomy," *J Clin Oncol,* vol. 25, pp. 2035-41, May 20 2007.

[2] A. V. D'Amico, J. Manola, M. Loffredo, A. A. Renshaw, A. DellaCroce, and P. W. Kantoff, "6-month androgen suppression plus radiation therapy vs radiation therapy alone for patients with clinically localized prostate cancer: a randomized controlled trial," *JAMA,* vol. 292, pp. 821-7, Aug 18 2004.

[3] D. E. Soto, M. N. Passarelli, S. Daignault, and H. M. Sandler, "Concurrent androgen deprivation therapy during salvage prostate radiotherapy improves treatment outcomes in high-risk patients," *Int J Radiat Oncol Biol Phys,* vol. 82, pp. 1227-32, Mar 1 2012.

[4] W. R. Polkinghorn, J. S. Parker, M. X. Lee, E. M. Kass, D. E. Spratt, P. J. Iaquinta*, et al.*, "Androgen receptor signaling regulates DNA repair in prostate cancers," *Cancer Discov,* vol. 3, pp. 1245-53, Nov 2013.

[5] H. I. Scher, T. M. Beer, C. S. Higano, A. Anand, M. E. Taplin, E. Efstathiou*, et al.*, "Antitumour activity of MDV3100 in castration-resistant prostate cancer: a phase 1-2 study," *Lancet,* vol. 375, pp. 1437-46, Apr 24 2010.

[6] H. I. Scher, K. Fizazi, F. Saad, M. E. Taplin, C. N. Sternberg, M. D. Miller*, et al.*, "Increased Survival with Enzalutamide in Prostate Cancer after Chemotherapy," *N Engl J Med,* Aug 15 2012.

[7] R. Siegel, D. Naishadham, and A. Jemal, "Cancer statistics, 2012," *CA Cancer J Clin,* vol. 62, pp. 10-29, Jan-Feb 2012.

[8] K. Lassi and N. A. Dawson, "Update on castrate-resistant prostate cancer: 2010," *Curr Opin Oncol,* vol. 22, pp. 263-7, May 2010.

[9] C. D. Chen, D. S. Welsbie, C. Tran, S. H. Baek, R. Chen, R. Vessella*, et al.*, "Molecular determinants of resistance to antiandrogen therapy," *Nat Med,* vol. 10, pp. 33-9, Jan 2004.

[10] K. J. Pienta and D. Bradley, "Mechanisms underlying the development of androgen-independent prostate cancer," *Clin Cancer Res,* vol. 12, pp. 1665-71, Mar 15 2006.

[11] A. J. Stephenson, S. F. Shariat, M. J. Zelefsky, M. W. Kattan, E. B. Butler, B. S. Teh*, et al.*, "Salvage radiotherapy for recurrent prostate cancer after radical prostatectomy," *JAMA,* vol. 291, pp. 1325-32, Mar 17 2004.

[12] B. J. Trock, M. Han, S. J. Freedland, E. B. Humphreys, T. L. DeWeese, A. W. Partin*, et al.*, "Prostate cancer-specific survival following salvage radiotherapy vs observation in men with biochemical recurrence after radical prostatectomy," *JAMA,* vol. 299, pp. 2760-9, Jun 18 2008.

[13] M. Bolla, H. van Poppel, L. Collette, P. van Cangh, K. Vekemans, L. Da Pozzo*, et al.*, "Postoperative radiotherapy after radical prostatectomy: a randomised controlled trial (EORTC trial 22911)," *Lancet,* vol. 366, pp. 572-8, Aug 13-19 2005.

[14] I. M. Thompson, Jr., C. M. Tangen, J. Paradelo, M. S. Lucia, G. Miller, D. Troyer*, et al.*, "Adjuvant radiotherapy for pathologically advanced prostate cancer: a randomized clinical trial," *JAMA,* vol. 296, pp. 2329-35, Nov 15 2006.

[15] G. P. Swanson, M. A. Hussey, C. M. Tangen, J. Chin, E. Messing, E. Canby-Hagino*, et al.*, "Predominant treatment failure in postprostatectomy patients is local: analysis of patterns of treatment failure in SWOG 8794," *J Clin Oncol,* vol. 25, pp. 2225-9, Jun 1 2007.

[16] T. H. Van der Kwast, M. Bolla, H. Van Poppel, P. Van Cangh, K. Vekemans, L. Da Pozzo*, et al.*, "Identification of patients with prostate cancer who benefit from immediate postoperative radiotherapy: EORTC 22911," *J Clin Oncol,* vol. 25, pp. 4178-86, Sep 20 2007.

[17] H. I. Scher, K. Fizazi, F. Saad, M. E. Taplin, C. N. Sternberg, K. Miller*, et al.*, "Increased survival with enzalutamide in prostate cancer after chemotherapy," *N Engl J Med,* vol. 367, pp. 1187-97, Sep 27 2012.

[18] W. U. Shipley, D. Hunt, H. Lukka, P. Major, N. M. Heney, D. Grignon*, et al.*, "Initial Report of RTOG 9601: A Phase III Trial in Prostate Cancer: Anti-androgen Therapy with Bicalutamide during and after Radiation Therapy Improves Freedom from Progression and Reduces the Incidence of Metastatic Disease in Patients following Radical Prostatectomy with pT2-3, N0 Disease, and Elevated PSA Levels," *International Journal of Radiation Oncology,* vol. 78, p. S27, 2010.

[19] C. U. Jones, D. Hunt, D. G. McGowan, M. B. Amin, M. P. Chetner, D. W. Bruner*, et al.*, "Radiotherapy and short-term androgen deprivation for localized prostate cancer," *N Engl J Med,* vol. 365, pp. 107-18, Jul 14 2011.

[20] I. M. Thompson, C. M. Tangen, J. Paradelo, M. S. Lucia, G. Miller, D. Troyer*, et al.*, "Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term followup of a randomized clinical trial," *J Urol,* vol. 181, pp. 956-62, Mar 2009.

[21] M. Bolla, H. van Poppel, B. Tombal, K. Vekemans, L. Da Pozzo, T. M. de Reijke*, et al.*, "Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomised controlled trial (EORTC trial 22911)," *Lancet,* vol. 380, pp. 2018-27, Dec 8 2012.

17 APPENDICES

17.1 APPENDIX A: ECOG and Karnofsky Performance Status Criteria

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

17.2 APPENDIX B: VAS Pain and Fatigue Score Criteria

17.2.1 VAS Pain Score Criteria

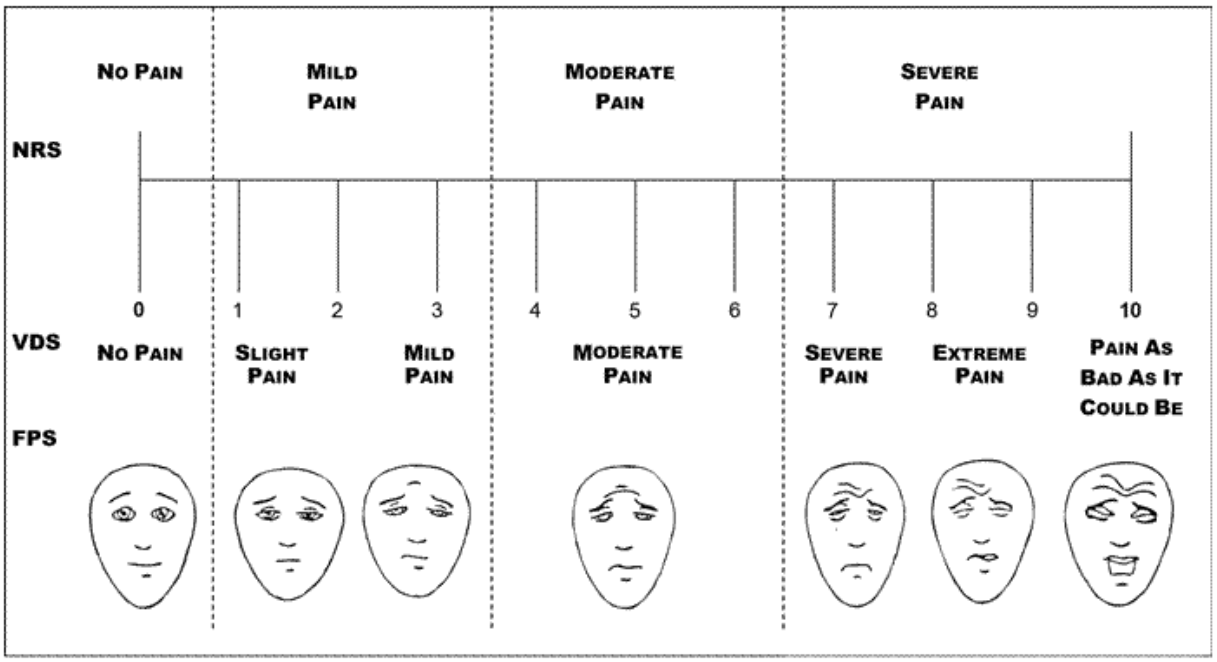


Figure.

17.2.2 Fatigue Score Criteria

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

17.3 APPENDIX C: Concomitant medications to be avoided

Strong inhibitors or inducers of CYP2C8

- Gemfibrozil
- Rifampin

Strong inhibitors or inducers of CYP3A4

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

Substrates of CYP3A4, CYP2C9, CYP2C19

- Alfentanil
- Cyclosporine
- Dihydroergotamine and ergotamine
- Fentanyl
- Midazolam
- Phenytoin and S-mephenytoin
- Pimozide
- Quinidine
- Sirolimus
- Tacrolimus
- Warfarin (If coadministration with warfarin cannot be avoided, must monitor INR at least weekly while on enzalutamide)

17.4 Summary of Changes

Amendment 1 (3/12/14)

Section 2 – Added GnRH and LHRH to List of Abbreviations

Section 3.8 – clarified that study duration is three years post-registration (not after last dose of study drug).

Section 5.3.3 – removed duplication of drug leuprolide acetate / Lupron Depot.

Section 6.2 – clarified time points for administration of quality of life surveys

Section 7.1; Section 7.1.5; Section 11 footnote i – clarified ADT administration guidelines, allowing for alternative ADT therapy at treating physician's discretion, provided that drug is administered for 6 months.

Section 7.1.5 – indicate the medications are prohibited within 2 weeks of enrollment AND while on study drug

Section 11 footnote f – indicate noncontrast of chest permitted

Updated lead coordinator and table of contents

Amendment 2 (4/21/14)

Section 3.4 – clarified inclusion criteria #3 to state "PSA relapse within 4 years of prostatectomy defined by persistently detectable or rising PSA after surgery."

Section 10.1 - clarified inclusion criteria #3 to state "PSA relapse within 4 years of prostatectomy defined by persistently detectable or rising PSA after surgery."

Amendment 3 (6/12/14)

Section 11.9.3 – Tissue specimens will be stored in the Duke Biospecimen Repository and Processing Core (BRPC).

Updated study staff on cover page

Amendment 4 (7/7/14)

Sections 3.3, 3.8, 4, 7.1, 8.1, 8.4.1, 8.4.4, 14.3 – Allowed a range of Radiotherapy Dose, still within standard of care.

Section 4 – Updated schema.

Section 7.1 – Corrected site name for Comprehensive Cancer Center of Wake Forest University

Amendment 5 (9/8/14)

Sections 3.4, 10.2 – clarified first statement in exclusion criteria 4.

Section 7.1.5, 11 – clarified monthly study visit schedule. Previous versions stated that visits/ evaluation of concomitant medications would occur every 4 weeks while subjects are taking enzalutamide. This is true through week 20, and then the next visit occurs at week 26.

Amendment 6 (2/24/15)

Sections 3.4, 10.2 – Exclusion 1- limited number of nodes at time of surgery to 2.

Amendment 7 (10/5/15)

Sections 11, 11.1, 11.5, 11.9.2 and 17.2 – Added assessment of VAS pain and fatigue score to each study visit (included as part of vital signs).

Section 17.3 – Concomitant medications to be avoided moved to Appendix C.

Amendment 8 (12/2/15)

Cover page – added contact information for the multi-site coordinator and data manager.

Sections 11, 11.6 – Clarified that during follow-up only prostate cancer treatments are tracked as concomitant medications.

Sections 11, 12.1 – Clarified collection of AEs during follow-up.

Amendment 9 (5/26/16)

Section 6.2: Clarified the primary endpoint. A serum PSA value of 0.2 ng/mL or more above the PSA and confirmed (at least) 4 weeks later by a second PSA measurement higher than the first by any amount.

Section 11: Follow-up will continue for 3 years post-registration or until early withdrawal.

Section 11.8.1: Corrected an error: Progression of disease defined as PSA rise 0.2 ng/ml above nadir or imaging consistent with metastatic disease;

Amendment 10 (11/28/16)

Sections 11, 11.6 - During follow-up visits, the CBC with differential and serum chemistries will be optional for subjects without lab abnormalities felt to be related to study treatment. In addition, follow-up visits, including medical history and AE assessment, prior & concomitant medications, physical examination, Karnofsky performance status and vital signs and weight, will be optional except for subjects with an adverse event felt to be related to study treatment which has not resolved to grade 1 or returned to baseline.

Amendment 11 (11/10/17)

Cover page - The primary regulator coordinator section was deleted. The Primary Study Coordinator was updated from Beth Leith to Diane Pinder

Section 11, (footnote for "l"); 11.6 - Amended to state that "Quality-of-life questionnaire (EPIC Short Form) will be administered at baseline, at week 12, then at 12, 24, and 36 months (+/- 3 months) post end-of-treatment follow-up visits (5 per subject)

Exploratory Endpoints – Clarifed that surveys will be performed at baseline, at week 12, then at 12, 24, and 36 months post end-of-treatment follow-up visits

Section 11.6 - Follow up period clarified to state that "Follow up will continue from registration or until early withdrawal"