TITLE: A Phase 2 Study of Enzalutamide in patients with High-risk Prostate Cancer who have undergone local definitive therapy with Radical Prostatectomy

Coordinating Center: Cleveland Clinic

***Principal Investigator:** Jorge A. Garcia, MD., FACP.

Taussig Cancer Institute
Cleveland Clinic
9500 Euclid Ave, Cleveland, OH 44195
216-444-7774
216-444-9464
garciaj4@ccf.org

***Co-Principal Investigator:** Andrew Stephenson, MD
Glickman Urological and Kidney Institute
Cleveland Clinic
216-445-1062
216-636-4492
Stephea2@ccf.org

Co-Investigators:

Eric A. Klein, MD
Chairman
Glickman Urological and Kidney Institute
Cleveland Clinic
216-444-5601
216-636-4492
KLEINE@ccf.org

Petros Grivas, MD, PhD
Taussig Cancer Institute
Cleveland Clinic
216-636-0100
216-444-9464
grivasp@ccf.org

Timothy Gilligan, MD
Taussig Cancer Institute
Cleveland Clinic
216-444-0391
216-444-9464
gilligt@ccf.org

Cristina Magi-Galluzzi, MD., PhD.
Pathology Department
Cleveland Clinic
216-444-9251
216-445-6967
MAGIC@ccf.org

Responsible Research Nurse:
Allison Tyler, RN, BSN, OCN
Taussig Cancer Institute
Cleveland Clinic
216-445-0861
216-444-0114
tylera2@ccf.org

Responsible Data Manager:
Kimberly Schach
Taussig Cancer Institute
Cleveland Clinic
216-636-5628
216-636-5628
schachk@ccf.org

Statistician:
Paul Elson, ScD.
Taussig Cancer Institute
Cleveland Clinic
216-444-7775
216-636-2498
elsonp@ccf.org

Study Coordinator:
Kimberly Schach
Taussig Cancer Institute
Cleveland Clinic
216-636-5628
216-636-5628
schachk@ccf.org

Protocol Type / Version # / Version Date: Amendment / Version # 13 / 08/JUN/2015

SYNOPSIS

This is a pilot phase II study evaluating the clinical activity and safety of Enzalutamide (formerly known as MDV3100) a novel androgen receptor (AR) inhibitor in men with high-risk prostate cancer who have undergone local definitive therapy with radical prostatectomy. Despite the limitations of interpreting PSA outcome in this clinical setting, time to disease progression (TTP) (serologic progression) was selected as the primary endpoint of the trial. Traditional secondary endpoints in this setting will include tolerability and safety. All eligible patients will receive enzalutamide, 160mg orally daily in a 28-day cycle regimen for 24 months or until disease progression or drug intolerance. Radiographic assessment will be conducted only if patients develop biochemical recurrence.

TABLE OF CONTENTS

1. OBJECTIVES

1.1. Primary Objectives

1.1.1. To evaluate the clinical efficacy of enzalutamide in patients with high-risk prostate cancer with regards to:

1.1.1.1. Time to disease progression defined by biochemical recurrence (BCR)

1.2. Secondary Objectives

1.2.1. To further evaluate the safety of enzalutamide in patients with high-risk prostate cancer

2. BACKGROUND

2.1 Study Disease

Prostate cancer is the second-leading cause of cancer death in men in the United States. It is expected that more than 241,740 new cases will be diagnosed in 2012. [1] Despite the widespread use of prostate-specific antigen (PSA) screening, a significant number of patients are diagnosed with high-risk or locally advanced disease.

Existing risk-stratification criteria including more contemporary tools have permitted us to define this population at risk for systemic disease. [2, 3] To date, pathological stage, Gleason Score (GS) and nodal disease after surgery remain the most common features used to determine the risk of recurrence after radical prostatectomy. According to the preoperative D'Amico criteria, RP alone in patients with high-risk PCa leads to a cure in about 50% of cases. [3] Although quite heterogeneous, recurrence is mostly due to distant micrometastases and is often manifested first by a rising PSA. The goal of adjuvant therapy is to control and/or treat distant micrometastases, delay/avoid progression and ultimately improve survival. Outside of post-operative radiation therapy (RT) for those with node negative high-risk disease, no standard adjuvant systemic treatments after surgery exist. Existing data using adjuvant androgen deprivation therapy (ADT) significantly improves survival in patients with positive lymph nodes. [4, 5] The limitation of this data however is the lack of understanding of the appropriate timing to initiate ADT and the known long-term complications of testosterone suppression. In the case of negative lymph nodes, the survival advantage has not been demonstrated. [6]

Similar data exist with chemotherapy when offered to high-risk patients in the peri-operative setting. [7, 8] Neoadjuvant chemotherapy has been studied in multiple phase 2 trials. Despite the heterogeneity in the chemotherapy regimen, the utility of this approach is quite limited. Although chemotherapy prior to surgery appears to be safe, no pathological complete response (pCR) has been observed. Similarly, time to PSA

progression and overall survival remained unaffected. [9-13] Two large studies have addressed the role of adjuvant therapy for high-risk disease. The first one, TAX305 unfortunately closed due to pour accrual. [14] This trial randomized patients to either observation or treatment. Patients on the treatment arm were randomized to receive standard androgen deprivation therapy +/- 6 cycles of docetaxel based chemotherapy. Cross over to the treatment arm was allowed at the time of biochemical recurrence (BCR) for patients initially randomized to the observation arm. A similar trial, SWOG (Southwest Oncology Group) S9921 randomly assigned 983 men with high-risk features at prostatectomy to receive adjuvant therapy with androgen deprivation (ADT) alone or in combination with mitoxantrone chemotherapy. ADT consisted of goserelin and bicalutamide for 2 years. SWOG 9921 was closed to further accrual after three cases of acute myelogenous leukemia (AML) were reported of a total of 487 patients in the mitoxantrone treatment arm. [15] Although the final primary treatment comparison results have not been published, a report by Dorff et al [16] reported the outcome of patients receiving ADT-alone (n=485). The estimated 5-year biochemical failure-free survival was 92.5% (95% CI, 90 to 95), and 5-year overall survival was 95.9% (95% CI, 93.9 to 97.9).

Radiotherapy has been another modality commonly employed to treat patients with high-risk disease after RP. The rationale for immediate adjuvant RT is to gain local control by eradicating residual tumor in patients with undetectable PSA but featuring high-risk pathologic features (eg, high Gleason score, extraprostatic extension, seminal vesicle invasion [SVI], and positive surgical margins (PSM). Two recent, large, randomised trials demonstrated the impact of this approach in this cohort of patients. Adjuvant RT decreases biochemical recurrence risk with improved local control, delays time to metastases, time to ADT initiation and in the intergroup US trial improvement in OS. [17-19]

Despite of the existing data, the management of high-risk patients remains a major clinical challenge. There is no convincing evidence that either systemic therapies or local adjuvant RT truly impact outcome. As such, most patients in the US elect to undergo observation. Understanding the risk of recurrence in this cohort of patients, there is a pressing need to develop novel and non toxic therapies that can be utilized in the adjuvant setting with the goal of reducing the risk if recurrence and to improve overall survival.

2.2 **Enzalutamide and Androgen Receptor**

The androgen receptor (AR) is a well-known target in prostate cancer as disease growth is initially dependent on androgens. Depleting or blocking androgen action has been a mainstay of treatment for over 6 decades in the setting of metastatic disease or when prostate cancer recurs following resection and/or radiation. In addition, AR expression has been noted in a variety of breast cancers and an emerging body of data suggests that tumor growth may be promoted through the AR. Enzalutamide is an androgen receptor signaling inhibitor (ARSI) rationally designed to block multiple steps in the AR

signaling pathway and to be devoid of agonist activity. Enzalutamide inhibits androgen-induced receptor activation (binding of androgens to ARs in the cytosol), inhibits nuclear translocation of activated ARs, and inhibits the association of the activated AR with chromatin, even in the setting of AR overexpression and in prostate cancer cells resistant to anti-androgens such as bicalutamide. The consequence of enzalutamide AR signaling inhibition is decreased growth of prostate cancer cells, induction of cancer cell death, and tumor regression. The apoptotic effect of enzalutamide is consistent with AR blockade. Enzalutamide induces cleavage of poly (adenosine diphosphate-ribose) polymerase (PARP), a marker of apoptosis, in prostate cancer cells while bicalutamide treatment has no effect on PARP cleavage. [20] In a mouse xenograft model of castration-resistant prostate cancer, enzalutamide dose-dependently reduced tumor volume while bicalutamide treatment showed no significant benefit [Investigator's Brochure 2012].

2.3 **Non Clinical and Clinical Data**

2.3.1 **Non Clinical**

Safety pharmacology studies in mice, rats, and dogs were performed with enzalutamide to assess any acute effects on central nervous system, respiratory, and cardiovascular parameters. No enzalutamide-related effects were noted in the central nervous system study assessing a functional observation battery and in a respiratory study in rats. Enzalutamide inhibits the human ether-a-go-go-related gene (hERG) channel; however, the highest free concentrations of enzalutamide expected in patient plasma at a steady-state dose of 160 mg/day are well below the hERG IC50 value. No enzalutamide -related effects on cardiac electrophysiology were noted in a safety pharmacology study in conscious, telemetered dogs.

As enzalutamide inhibits the GABA-gated chloride channel, convulsion potential was assessed in single- and multiple-dose studies in mice. [21]. Oral enzalutamide daily for 7 days was associated with convulsions in a dose-dependent manner with doses ≥200 mg/kg being active. When administered as a single dose of 400 mg/kg enzalutamide treatment was also associated with convulsions. At the highest dose at which no convulsions occurred (single dose, 100 mg/kg), the maximum plasma concentration (Cmax) and area under the curve at 24 hours after dosing (AUC24) were at least 2.5-times higher than those in patients receiving 160 mg/day. Enzalutamide is metabolized primarily to 2 metabolites, M1 (a carboxylic acid derivative) and M2 (N-desmethyl enzalutamide). The metabolite M2 has a pharmacology profile similar to that of the parent molecule and may contribute to the therapeutic effects of enzalutamide in patients. M2 also binds to and inhibits the GABA-gated chloride channel with potency similar to that of the parent molecule and may contribute to convulsion risk. Metabolite M1 does not have significant pharmacological actions and probably does not contribute to the therapeutic effects of enzalutamide.

2.3.2 **Clinical**

The pharmacokinetics (PK), tolerability, and antitumor activity of enzalutamide were

first studied in a multi-center, open-label, first-in-human, dose-escalation study in 140 patients with castration-resistant prostate cancer (S-3100-1-01) [Scher, 2010]. Patients who were chemotherapy-naïve or who had previously failed docetaxel-based chemotherapy were treated with enzalutamide at doses of 30 to 600 mg/day until disease progression or intolerable side effects developed. Enzalutamide was absorbed rapidly after oral administration, with the time to Cmax after a single dose typically occurring at 1-hour post dose. No major deviations from dose proportionality were observed over the dose range 30 to 600 mg. Due to the long t1/2 (~ 5.8 days); it took approximately 1 month to reach steady state. With daily oral administration, enzalutamide accumulation was observed at steady state with an 8.3-fold higher exposure (steady-state AUC) relative to a single dose. Based on the mean peak-to-trough ratio, the average difference between the peak (Cmax) and trough (Cmin) concentrations was ≤ 25%. As a result of the low daily fluctuations, plasma profiles at steady-state resembled a constant infusion. The Cmin values in individual patients remained constant beyond Day 28 of chronic therapy, suggesting time-linear PK once steady state was achieved.

The maximum tolerated dose was determined to be 240 mg daily. Enzalutamide demonstrated antitumor activity across endpoints in patients both with and without previous exposure to chemotherapy. The antitumor activity endpoints included prostate-specific antigen (PSA) reduction from baseline, median time to PSA progression, responses on imaging, and circulating tumor cell conversion from favorable to unfavorable counts. Three potential enzalutamide-associated toxicities were identified in this study: fatigue, rash, and seizure. Three seizures (2 witnessed, 1 unwitnessed) occurred in this study at doses of 360, 480, and 600 mg/day, and were reported between 26 and 48 days after initiation of enzalutamide.

After review of all data available from the S-3100-1-01 study, the optimal dose of enzalutamide for evaluation in Phase 3 clinical trials was determined to be 160 mg/day. A Phase 3, randomized, double-blind, placebo-controlled efficacy and safety study of oral enzalutamide (160mg daily) in patients with progressive castration-resistant prostate cancer (CRPC) previously treated with docetaxel-based chemotherapy (CRPC2, also known as AFFIRM) was conducted in 1199 men, 800 of whom received treatment with enzalutamide.

A formal interim analysis of overall survival was performed at 520 events (80% of the 650 targeted number of events for final analysis) and demonstrated a statistically-significant increase in the duration of survival among patients treated with enzalutamide compared with patients treated with placebo [hazard ratio = 0.631 (95% CI 0.529, 0.752), p < 0.0001]. Median survival was 18.4 months in the enzalutamide arm and 13.6 months in the placebo arm (Ä = 4.8 months). The survival benefit was seen in all pre-specified patient subgroups defined by age, geographic region, ECOG performance status, pain score, Gleason score, number of prior chemotherapy regimens, type of disease progression at study entry, baseline level of PSA, baseline

level of hemoglobin, and baseline level of lactate dehydrogenase (LDH). There were also statistically-significant increases in radiographic progression-free survival (assessed by CT or MRI and by bone scan); time to first skeletal-related event; time to PSA progression; PSA response, and overall objective soft tissue radiographic response among patients treated with enzalutamide compared to placebo. In addition, statistically-significant differences favoring enzalutamide over placebo in pain palliation and pain progression rate at Week 13 were also observed.

2.4 **Enzalutamide Key Safety Summary Information**

The safety and tolerability of enzalutamide have been evaluated in 13 studies, including 2 completed studies (Phase 1), 7 active studies (Phase 1 through 3), and 4 enrolling studies (Phase 2 through 3). It is estimated that a total of 124 healthy volunteers, 16 subjects with hepatic impairment, and approximately 1800 patients with prostate cancer have been exposed to enzalutamide in completed, open-label, and ongoing blinded studies. In the completed interim analysis of the randomized, double-blind, placebo-controlled Phase 3 efficacy and safety study in patients with progressive castration-resistant prostate cancer previously treated with docetaxel-based chemotherapy (CRPC2), 800 patients received enzalutamide (160 mg daily). The duration of enzalutamide exposure in this study ranged from 1 day to 23.3 months (median 8.3 months).

Safety data are presented from the formal interim analysis of data from the CRPC2 study, with a data cut-off date of 25 September 2011. **Table 1** provides an overview of exposure to study drug, adverse events, and deaths.

Table 1

Treated (Safety Population) Enzalutamide	**Enzalutamide (n = 800)**	**Placebo (n = 399)**
Discontinued Treatment	569 (71.1%)	380 (95.2%)
Treatment Duration (median months)	8.3	3.0
Patients with ≥ 1 Treatment Emergent Adverse Event	785 (98.1%)	390 (97.7%)
Patients with ≥ 1 Treatment Emergent Adverse Event (Grade 3 or Higher)	362 (45.3%)	212 (53.1%)
Patients with ≥1 Serious Treatment Emergent Adverse Event	268 (33.5%)	154 (38.6%)
Patients with an Adverse Event Leading to Death	23 (2.9%)	14 (3.5%)
Patients with Adverse Events Leading to Study Drug Discontinuation	61 (7.6%)	39 (9.8%)
SUSARs (all in unique patients)	10	6
Deaths	308 (38.5%)	212 (53.1%)

Enzalutamide (160 mg daily) was generally well-tolerated in the placebo-controlled CRPC2

study of 1199 patients with progressive castration-resistant prostate cancer previously treated with docetaxel-based chemotherapy. Adverse events reported by those treated with enzalutamide (160 mg daily) with an incidence of at least 5% and by at least 2% greater than by those who received placebo included fatigue (33.6% v 29.1%), diarrhea (21.4% v 17.5%), hot flush (20.3% v 10.3%), musculoskeletal pain (13.6% v 10.0%), headache (11.6% v 5.5%), insomnia (8.6% v 6.0%), anxiety (6.4% vs. 4.0%), hypertension (6.1% v 2.8%), and nasopharyngitis (5.1% v 3.0%). Other adverse events reported less commonly than 5% but that may be associated with enzalutamide treatment after careful assessment of the adverse events include: falls (4.0% vs. 1.3%), dry skin (3.6% vs. 1.3%), and pruritus (3.5% vs. 1.3%).

A greater proportion of patients in the enzalutamide -treated group (4.1% vs. 1.8%) reporting the following adverse event terms: memory impairment, cognitive disorder, amnesia, disturbance of attention, and dementia. In addition, event terms related to hallucination (visual hallucination and tactile hallucination) were reported more frequently in the enzalutamide -treated group (1.6% vs. 0.3%). Serious adverse events that occurred at a ≥ 0.5% absolute difference in event frequency and more frequently in the enzalutamide arm than the placebo arm included: spinal cord compression (6.0% vs. 3.8%), bone pain (1.5% vs. 1.0%), metastatic pain (1.5% vs. 0.8%), pathological fracture (1.5% vs. 0.5%), urinary tract infection (0.9% vs. 0.3%), and cauda equina syndrome (0.8% vs. 0.0%). Seizure is a known potential toxicity of enzalutamide. In vitro studies have shown that Enzalutamide and its metabolite M2 bind to the GABA-gated chloride channel with IC50 values of 1.2 ìg/mL and 3.3 ìg/mL, respectively and in a cell-based assay inhibit the channel's activity with IC50 values of 1.4 ìg/mL and 1.07 ìg/mL, respectively. Some compounds that inhibit the GABA-gated chloride channel are associated with seizures. [21] In the first clinical study of enzalutamide (S-3100-1-01), a dose-escalation study in men with castration-resistant prostate cancer with and without prior exposure to chemotherapy, the following doses were evaluated: 30, 60, 150, 240, 360, 480 (as 240 mg twice per day [BID]), and 600 (as 300 mg BID) mg/day. Three patients were reported to have dose-limiting toxicities of seizure, one each at doses of 360, 480, and 600 mg/day. The results of this study led to the selection of the clinical dose of Enzalutamide of 160 mg/day.

As of the database cut-off date for the respective unblinded or open-label studies reported in the Investigator's Brochure, 7 patients out of a total of 1100 patients (0.6%) exposed to enzalutamide at a dose of 160 mg/day have reported a seizure during the enzalutamide treatment emergent adverse event reporting period. These include one patient each in studies 9785-CL-0007 and 9785-CL-0321, and 5 patients in the CRPC2 study. Two additional patients have been identified by the Sponsor to have experienced adverse events that may have been seizures, including one case reported by the Investigator as syncope (CRPC2) and the other reported as a transient ischemic attack with an abnormal electroencephalogram (CRPC-MDA-1). As of the data cut-off date, treatment with enzalutamide at a daily dose of 160 mg is associated with a 0.6-0.8% risk of seizure in men with late-stage castration-resistant prostate cancer. Taking into account information from ongoing blinded studies and events occurring after the database cut-off date, the range for seizure risk is unchanged. No

seizures have been reported in the blinded placebo controlled Phase 3 study PREVAIL with over 1300 patients enrolled (randomized 1:1 to enzalutamide 160 mg/day or placebo). One additional patient in the CRPC2 study has been reported to have had a seizure after the safety data cut-off date, and one additional patient in an ongoing blinded study (9785-CL-0222) has also reported a seizure. Please see the most current version of the Investigator Brochure for additional details.

3 Rationale

The current standard of care for men with high-risk prostate cancer after radical prostatectomy is observation or adjuvant RT. Although RT has demonstrated to impact outcome, timing of this technique remains controversial. Similarly, the utility of RT for men with high-risk disease with microscopic disease in lymph nodes remains unknown. ADT for this patient population also remains controversial due to the long-term complications related to early testosterone suppression. The existing clinical data with enzalutamide in the castrate-resistant setting is quite robust and provides the support to test this novel AR inhibitor in an earlier state of the disease with the goal of improving outcome in patients with high-risk disease whom are destined to develop systemic disease.

4 Patient Selection

4.1 Inclusion Criteria

- 4.1.1 Understand and voluntarily sign an informed consent form.
- 4.1.2 Age ≥18 years at the time of signing the informed consent form.
- 4.1.3 Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1 **[Appendix 1]**
- 4.1.4 Histologically confirmed adenocarcinoma of the prostate.
- 4.1.5 Patients must have undergone a Radical Prostatectomy (any surgical technique is permitted) within 3 months from study entry and have high-risk disease define by any of the following:
  - 4.1.5.1 Pathological stage T3a, T3b, T4 (any grade or iPSA)
  - 4.1.5.2 Gleason' sum ≥ 8 (any stage or iPSA)
  - 4.1.5.3 Initial Pre-operative PSA ≥ 20ng/mL (any GS or pT stage)
  - 4.1.5.4 Any stage/PSA/Gleason patients with a 35% or greater chance of biochemical failure at 5 years based on Kattan's nomogram **[Appendix 2]** http://nomograms.mskcc.org/Prostate/PostRadicalProstatectomy.
  - 4.1.5.5 Patients with Lymph node (LN) positive disease, regardless of iPSA, pT stage or GS provided their post-operative PSA 6-8 weeks after surgery is ≤ 0.4ng/mL. (Lymph node dissection is desired but not mandated)
- 4.1.6 Able to swallow the study drug and comply with study requirements.
- 4.1.7 Patients must have normal organ and marrow function as defined below:
  - 4.1.7.1 Testosterone ≥ 50 ng/dL per laboratory reference range
  - 4.1.7.2 Baseline Post-RP PSA ≤ 0.4
  - 4.1.7.3 Hemoglobin ≥ 10.0 g/dL independent of transfusion
  - 4.1.7.4 Absolute neutrophil count ≥1,500/mcL
  - 4.1.7.5 Platelet count ≥100,000/ìL

4.1.7.6 Serum albumin ≥ 3.5 g/dL
4.1.7.7 Serum potassium ≥ 3.5 mmol/L
4.1.7.8 Liver function: serum bilirubin < 1.5 x ULN (except for patients with documented Gilbert's disease) and AST or ALT < 2.5 x ULN

4.2 Exclusion Criteria

4.2.1 Severe concurrent disease, infection, or co-morbidity that, in the judgment of the investigator, would make the patient inappropriate for enrollment
4.2.2 Prior radiotherapy to the prostate or pelvis (related to prostate cancer). Concurrent adjuvant radiation therapy is permitted once patient has been enrolled on trial.
4.2.3 Prior use of Abiraterone acetate or cytotoxic chemotherapy for prostate cancer
4.2.4 Prior androgen deprivation with LHRH is permitted provided that testosterone levels prior to study entry have recovered to normal limits per reference laboratory.
4.2.5 No prior anti-androgen therapy (bicalutamide, flutamide or Nilutamide) is permitted
4.2.6 Prior use of 5-alpha reductase inhibitors is permitted provided such medications were stopped 7-14 days prior to enrollment
4.2.7 Use of herbal products that may have hormonal anti-prostate cancer activity and/or are known to decrease PSA levels (e.g., saw palmetto) or systemic corticosteroids greater than the equivalent of 10 mg of prednisone per day within 2 weeks of enrollment
4.2.8 Active unresolved infection
4.2.9 Known history of CNS metastases
4.2.10 Patients must have no known history of HIV
4.2.11 Evidence of metastatic disease as evidenced by a CT or MRI of abdomen and pelvis and/or whole body bone scan (WBS). To be done prior to treatment start and up to 4 months prior to radical prostatectomy date.
4.2.12 History of seizure or any condition that may predispose to seizure (e.g., prior cortical stroke, significant brain trauma). Also, history of loss of consciousness or transient ischemic attack within 12 months of enrollment.
4.2.13 Clinically significant cardiovascular disease including:
4.2.13.1 Myocardial infarction within 6 months prior to Screening;
4.2.13.2 Uncontrolled angina within 3 months prior to Screening;
4.2.13.3 Congestive heart failure New York Heart Association (NYHA) class 3 or 4, or patients with history of congestive heart failure NYHA class 3 or 4 in the past, unless a screening echocardiogram (ECHO) or multi-gated acquisition scan (MUGA) performed within 3 months results in a left ventricular ejection fraction that is ≥ 45%
4.2.13.4 History of clinically significant ventricular arrhythmias (e.g., ventricular tachycardia, ventricular fibrillation, torsades de pointes)
4.2.13.5 History of Mobitz II second degree or third degree heart block without a permanent pacemaker in place

4.2.13.6 Hypotension as indicated by systolic blood pressure < 86 mmHg at the Screening visit

4.2.13.7 Bradycardia as indicated by a heart rate of < 50 beats per minute at the screening visit.

4.2.13.8 Uncontrolled hypertension as indicated by systolic blood pressure > 170 mmHg or diastolic blood pressure > 105 mmHg at the Screening visit

4.2.14 Gastrointestinal disorder affecting absorption (e.g., Gastrectomy, active peptic ulcer disease within last 3 months)

4.2.15 Any condition or reason that, in the opinion of the Investigator, interferes with the ability of the patient to participate in the trial, which places the patient at undue risk, or complicates the interpretation of safety data.

4.2.16 The effects of enzalutamide on the developing human fetus at the recommended therapeutic doses are unknown. Thus, men must agree to use adequate contraception (barrier method of birth control or abstinence) prior to study entry, for the duration of study participation, and for 6 months after the usage of enzalutamide. Should the patient's partner become pregnant or suspect she is pregnant while the patient is participating in this study, the patient should inform his treating physician immediately.

5 Registration Procedures

5.1 General Guidelines

Eligible patients will be entered on study centrally at the Cleveland Clinic Taussig Cancer Institute by the Study Coordinator. Following registration, patients should begin protocol treatment within 14 working days. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

5.2 Pre-treatment Evaluation: Clinical: required within 14 days before the first cycle "or as otherwise indicated"

5.2.1 History and physical examination, including height, weight, and vital signs

5.2.2 Performance status evaluation

5.2.3 Laboratory /Diagnostic: **required within 14 days before the first cycle.**

5.2.3.1 CBC, platelet count, and automated differential.

5.2.3.2 Serum chemistries: includes BUN, Creatinine, ALT, and AST, glucose, alkaline phosphatase, total bilirubin and LDH.

5.2.3.3 Testosterone level

5.2.3.4 PSA

5.2.3.5 Baseline correlative studies

5.2.3.6 Imaging/Diagnostic: **Must be performed** prior to treatment start and up to 4 months prior to radical prostatectomy date.: Baseline imaging studies to document the presence or not of measurable disease. (Whole body bone scan and MRI or CT scans of abdomen/pelvis). Pre-operative imaging, done within 4 months of surgical date may be used for screening purposes.

5.3 Registration Process

To register a patient, the following documents should be completed by the research nurse or data manager and e-mailed to Kimberly Schach at **Schachk@ccf.org** [the Study Coordinator]:

- Registration Form
- Eligibility Worksheet
- Copy of source documentation (required laboratory tests, radiographic scans, physician notes, nursing notes, list of medications, pathology/surgical reports, etc.)
- Signed patient consent form
- HIPAA authorization form

To complete the registration process, the Coordinator will

- Verify patient eligibility worksheet is complete
- Request additional documentation if necessary
- Assign a patient study number
- Register the patient on the study using the ONCORE database
- E-mail a letter of Confirmation of Registration, including the patient study number, to the responsible research nurse

6 Treatment Plan

6.1 Identity of Investigational Product

Enzalutamide has the chemical name 3-(4-cyano-3-trifluoromethylphenyl)-1-[3-fluoro-4-(methylcarbamoyl) phenyl]-5,5-dimethyl-2-thioxoimidazolin-4-one. It is a white to off-white solid that is insoluble in water and no salt forms are available at ~pH 2 to 10. The drug substance is formulated in the surfactant caprylocaproyl polyoxylglycerides, or Labrasol®. The product will be supplied as white to off white gelatin capsules containing 40 mg of enzalutamide.

6.2 Agent Administration

Treatment will be administered on an outpatient basis and will consist of 28-day cycles. A delay of cycle due to holidays, weekends, and bad weather or other unforeseen circumstances will be permitted and not counted as a protocol deviation.

6.2.1 Patients will receive daily oral therapy with enzalutamide at 160mg (4 capsules) orally once daily (QD). Patients will continue on study until progressive disease, drug intolerability, consent withdrawal or completion of study at 24 months.

6.2.2 Enzalutamide tablets should be taken at approximately the same time of day and at regular intervals (i.e., approximately every 24 hours). If a patient misses a dose of study drug, he may take the missed dose at any time up to 6 hours before the next intended dose on that day and should not be taken on a subsequent day. Patients will be instructed to notify study site personnel of any missed doses.

6.2.3 Enzalutamide can be taken with or without food

6.3 Treatment Compliance

At all times, when dispensing study drug, research center personnel will review the instructions, printed on the packaging, with subjects. Subjects will be asked to maintain a diary to record the drug administration. Subjects will be asked to bring any unused study drug and empty bottles to the research center at their next visit. Research personnel will count and record the number of used and unused study drug capsules at each visit**.** Regardless of the reason, the maximum time off enzalutamide allowed will be 21 consecutive days.

6.4 Dose Reduction/Dose Adjustment

Patients who experience a Grade (G) 3 or greater toxicity that cannot be ameliorated by the use of adequate medical intervention may have their treatment interrupted until the toxicity improves to a Grade 2 or lower severity. Patients may subsequently be re-started on study drug at a reduced dose as per Section 8.

6.5 Management of Overdose

An overdose is defined as 2 days of study drug taken over the course of a 24 hour period. Neither the effects of overdose of enzalutamide nor an antidote to overdose are known. In case of overdose of enzalutamide, symptomatic treatment with frequent monitoring is recommended.

6.6 General Concomitant Mediations and Supportive Care Guidelines

Medication taken within 4 weeks prior to enrollment and any medications prescribed chronically or intermittently during the study or dose adjustments of these medications must be captured on the research nurse notes. Concomitant medications will be assessed at screening and all clinic visits. The dosage and regimen of the following medications and any chronic permitted concomitant medications should be stabilized during the screening period and held constant throughout the study.

No formal clinical drug-drug interaction studies have been completed with enzalutamide.

In vitro studies show that enzalutamide is an inhibitor of CYP2C8 and CYP2C19 with lesser inhibitory effects on CYP2B6 and CYP2C9. Substrates of CYP2B6, CYP2C8, CYP2C9, and CYP2C19 that have a narrow therapeutic index should be used with caution.

In vitro studies show that enzalutamide is an inhibitor of the efflux transporter permeability glycoprotein (P-gp). Use caution when co-administering P-gp substrates during enzalutamide treatment.

In vitro studies show that enzalutamide is an inducer of CYP3A4. Induction of CYP3A occurs via activation of the nuclear pregnane X receptor (PXR), which is expected to result in co-induction of CYP2C. Co-administration of enzalutamide with CYP3A or CYP2C

substrates may reduce oral bioavailability and/or accelerate elimination of the substrates.

In vitro studies show that enzalutamide is metabolized by CYP2C8 and CYP3A4/5. Strong inhibitors or inducers of these enzymes may affect enzalutamide exposures. Use caution when co-administering strong inhibitors of CYP2C8 or CYP3A4/5 during enzalutamide treatment, as enzalutamide concentrations may increase. Use caution when co-administering strong inducers of CYP2C8 or CYP3A4/5 during enzalutamide treatment, as enzalutamide concentrations may decrease.

6.7 Prohibited Medications while on Study Drug

- 6.7.1 Cytotoxic chemotherapy
- 6.7.2 Hormonal therapies (e.g., anti-androgens, abiraterone, estrogens; testosterone; dehydroepiandrosterone [DHEA], etc.)
- 6.7.3 Biologics and vaccines (e.g., sipuleucel-T)
- 6.7.4 Any other investigational agent.
- 6.7.5 Caution is advised when considering the concomitant use of the following medications:
  - 6.7.5.1 Medications known to lower the seizure threshold. These include but are not limited to:
    - 6.7.5.1.1 Aminophylline/theophylline
    - 6.7.5.1.2 Atypical antipsychotics (e.g., clozapine, olanzapine, risperidone, ziprasidone)
    - 6.7.5.1.3 Bupropion
    - 6.7.5.1.4 Lithium
    - 6.7.5.1.5 Pethidine
    - 6.7.5.1.6 Phenothiazine antipsychotics (e.g., chlorpromazine, mesoridazine, thioridazine)
    - 6.7.5.1.7 Tricyclic and tetracyclic antidepressants (e.g., amitriptyline, desipramine, doxepin, imipramine, maprotiline, mirtazapine)
    - 6.7.5.1.8 Substrates of CYP2B6, CYP2C8, CYP2C9, and CYP2C19 that have a narrow therapeutic index (e.g., phenytoin, warfarin). Based on in vitro data, enzalutamide is an inhibitor of CYP2B6, CYP2C8, CYP2C9, and CYP2C19 and may be an inducer of CYP3A4
    - 6.7.5.1.9 Substrates of CYP3A4/5 that have a narrow therapeutic index. Co-administration of enzalutamide with CYP3A4/5 substrates may affect oral bioavailability and/or elimination of the CYP3A4/5 substrate
    - 6.7.5.1.10 Strong CYP2C8 inhibitors (e.g., gemfibrozil) or strong CYP3A4/5 inhibitors (e.g., clarithromycin, itraconazole, ketoconazole, grapefruit, grapefruit juice and soft drinks that contain grapefruit juice). In vitro studies showed that enzalutamide is metabolized by CYP2C8 and CYP3A4/5
    - 6.7.5.1.11 Sensitive P-gp substrates (e.g., digoxin, fexofenadine). In vitro studies show that enzalutamide and metabolite M2 are potential inhibitors of P-gp. Co-administration of enzalutamide with P-gp substrates may

increase the plasma concentrations of the P-gp substrate.

6.8 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

6.8.1 Disease progression
6.8.2 Intercurrent illness that prevents further administration of treatment
6.8.3 Unacceptable adverse event(s)
6.8.4 Major violation of the study protocol
6.8.5 Enzalutamide held for greater than 21 days
6.8.6 Lost to follow up
6.8.7 Failure to recover from toxicity despite a dosing interruption of up to 21 days
6.8.8 Patient decides to withdraw from the study
6.8.9 General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.
6.8.10 Study termination by the sponsor, IRB, ethics committee, or regulatory agency.
6.8.11 Death

6.9 Duration of Follow-up

Patients will be followed for safety purposes for 4 weeks after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event. Patients will be followed for progression, via phone call or visit, every 3 months for the first year after completing therapy, then every 6 months for 2 years, then annually thereafter for 5 years.

6.10 Criteria for Study Discontinuation Treatment

Patients will be removed from study when any of the criteria listed in Section 7.8 applies. The reason for study removal and the date the patient was removed must be documented in the medical chart.

6.10.1 The primary efficacy endpoint is time to disease progression (PSA, radiographic), as defined in Section 13 Patients should ordinarily be maintained on study treatment until confirmed serologic or radiographic progression. Study treatment should be stopped and patients advised regarding available treatment options.

7 Dosing Delays/Dose Modifications

7.1 The NCI Cancer Clinical Trials Common Toxicity Criteria (version 4.0) will be utilized.
7.2 Toxicity will be evaluated as outlined by the study calendar [Table 2] during the course of the study.
7.3 All toxic events should be managed with optimal supportive care
7.4 Subjects who experience a Grade 3 or greater adverse event that cannot be ameliorated by the use of adequate medical intervention must have enzalutamide interrupted.
7.5 Enzalutamide may be resumed when the adverse event has improved to a Grade 2 or

lower severity. If the adverse event is considered not related to enzalutamide by the investigator, enzalutamide may be resumed at the same dose.

7.6 If the adverse event is considered possibly or probably related to enzalutamide, enzalutamide may be resumed either at the same dose or at an initial reduced dose of 120mg and, if needed, a second reduction to 80 mg once daily, based on the discretion of the investigator.

7.7 Enzalutamide must be permanently discontinued if subject experiences any criteria listed below:

7.7.1 Any adverse event that is intolerable to the subject and that cannot be ameliorated by the use of adequate medical intervention, or that in the opinion of the investigator would lead to undue risk to the subject if dosing continued

7.7.2 Any seizure

7.7.3 Creatinine >305 ìmol/L (4.0 mg/dL)

7.7.4 Absolute neutrophil count of ≤ 750 /ìL

7.7.5 Platelet count of < 50,000/ìL

7.7.6 LFTs that meet one of the following

7.7.7 An ALT or AST value of > 8x ULN

7.7.8 An ALT or AST value of > 5x ULN for more than 2 weeks

7.7.9 An ALT or AST value of > 3x ULN and TBL > 2x ULN

7.7.10 If close monitoring for a subject with moderate (defined in Appendix 6 as ALT or AST > 3x ULN or total bilirubin > 2x ULN) hepatic laboratory tests is not possible, study drug should be discontinued.

7.7.11 Subjects who are, in the opinion of the investigator or the medical monitor, grossly noncompliant with the protocol's requirements.

8 Pharmaceutical Information

8.1 Description of Study Drug

8.1.1 Enzalutamide is a white to off white solid. It is insoluble in water and no salts are formed from ~ pH 2 to 10. Enzalutamide drug product is formulated in a Labrasol solution containing antioxidants (butylated hydroxytoluene and butylated hydroxyanisole) and filled into gelatin capsules. Capsules are filled to contain 40 mg of active pharmaceutical ingredient and are provided in high-density polyethylene bottles with child-resistant induction seal closure.

8.1.2 Comparative Drug(s): Not applicable.

8.2 Packaging and Labeling

All medication used in this study will be prepared, packaged, and labeled under the responsibility of a qualified person at Astellas US Technologies, Inc. (AUST) in accordance with AUST Standard Operating Procedures (SOPs), Good Manufacturing Practice (GMP) guidelines, ICH GCP guidelines, and applicable local laws/regulations. Enzalutamide soft gelatin capsules will be supplied in bottles according to the study design. Subjects will be provided with a 4-week supply at the Day 1 and Week 4 visits, respectively. At and after the Week 12 visit, subjects will be provided with a 12-week

supply to allow for visits to occur every 84 days with a ± 9 day window. Information presented on the label for investigational product will comply with applicable local regulation.

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

8.3 Study drug Handling

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

8.3.1 that such deliveries are recorded

8.3.2 that study drug is handled and stored safely and properly

8.3.3 that study drug is only dispensed to study subjects in accordance with the protocol

8.3.4 That any unused study drug is returned to the sponsor or standard procedures for the alternative disposition of unused study drug are followed.

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

8.3.5.1 The investigator agrees not to supply study drugs to any persons except the subjects in this study.

8.3.5.2 The investigator/pharmacist/designee will keep the study drugs in a pharmacy or other locked and secure storage facility under controlled storage conditions, accessible only to those authorized by the investigator to dispense these test drugs.

8.3.5.3 A study drug inventory will be maintained by the investigator/pharmacist/designee. The inventory will include details of material received and a clear record of when they were dispensed and to which subject.

8.3.5.4 At the conclusion or termination of this study, the investigator/pharmacist/designee agrees to conduct a final drug supply inventory and to record the results of this inventory on the Drug Accountability Record. It must be possible to reconcile delivery records with those of used and returned medication. Any discrepancies must be accounted for. Appropriate forms of deliveries and returns must be signed by the person responsible.

8.3.5.5 Used or unused study drug may be destroyed at the study center according to standard institutional procedures after drug accountability has been conducted by the Sponsor or representative, only if agreed upon by the Sponsor. A copy of the standard institutional procedure for destroying investigational drugs will be provided to the Sponsor or designee upon request. Unused study drug not destroyed at the site must be returned to the Sponsor or designee at the end of the study or upon expiration.

8.3.5.6 Enzalutamide should be stored in a secure location with limited access at 77°F (25°C), with excursions permitted to 59°F to 86°F (15°C to 30°C). Bottles

will be labeled with the study protocol number, medication or bottle number, contents, directions for use, storage directions, clinical trial statement, and the sponsor.

8.4 Availability

Enzalutamide is an investigational agent supplied to investigators by Astellas Pharmaceutical.

9 Correlative/Especial Studies; NONE

10 Study Calendar

Baseline evaluations are to be conducted within 14 days prior to start of protocol therapy. Imaging studies must be done prior to the start of therapy and up to 4 months prior to radical prostatectomy date. Patients will be evaluated on C1D1 of therapy and every 28 days thereafter for the first 4 cycles. If patients are stable and do not have any major issues with AEs, patients will then be evaluated every 3 cycles until the completion of study.

Table 2. Study Calendar- Enzalutamide in High-risk Patients

	Pre-Study	C1D1 (± 3 days)	Day 1 of Cycle 2-4 (± 3 days)	Day 1 of every 3 cycles (± 7 days)	End of Treatment[d] (± 7 days)	Safety[e,f] follow up
Enzalutamide[a]		X	X	X		
Informed consent	X					
Demographics	X					
Medical history	X					
Concurrent meds	X	X	X	X	X	X
Physical exam	X	X[h]	X	X	X	X
Vital signs	X	X	X	X	X	X
Height	X					
Weight	X	X	X	X	X	X
Performance status	X	X	X	X	X	X
CBC w/diff, plts	X		X	X	X	X
Testosterone	X		X		X	
Serum Chemistry including PSA, LDH[b]	X	X[g]	X	X	X	X
AE evaluation		X	X	X	X	X
Radiologic Evaluation[c]	X				X	

a: Enzalutamide: 160mg PO daily - continuous dosing

b: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride,

creatinine, glucose, LDH, potassium, total protein, SGOT [AST], SGPT [ALT], sodium

c: Baseline scans done pre-operatively may be used, as long as done prior to study treatment start and up to 4 months prior to surgical date. At the time of serologic progression, patient will undergo CT Abdomen/Pelvis and Bone scan .

d: EOT procedures to be completed at the time of drug discontinuation

e Safety follow up visit to be completed within 30 days of last dose of enzalutamide.

f: Progression follow up for survival and disease progression [PSA or radiographic], via phone call, or some type of clinic visit, will be done every 3 months for the first year after completing therapy, then every 6 months for 2 years, then annually for 5 years.

g: Laboratory studies drawn at screening may be used as baseline prior to starting treatment.

h: Physical exam does not need to be repeated on C1 D1 if done within the 7 days prior to C1 D1.

11 Study Assessments

11.1 Screening Period: The following activities/procedures will be conducted during the screening period which may occur over 14 days:

- Medical history including prior prostate cancer therapies, PSA, clinical and pathological T stage, and Gleason score at diagnosis
- Demographics
- Physical examination, weight, and height with baseline signs and symptoms
- Vital signs including blood pressure, heart rate, respiratory rate, height and weight.
- Assessment of ECOG Performance Status. Appendix 1
- Laboratory tests including: CBC/differential and Platelets; CMP (Sodium, Potassium, Chloride, CO2, BUN, Creatinine, SGPT [ALT], SGOT [AST], Glucose, Alkaline Phosphatase, Total Bilirubin, and LDH); PSA and testosterone.
- Documentation of all concomitant medications and procedures.
- Baseline tumor assessment including a CT/MRI of the abdomen/pelvis and a whole body scan [To be done prior to study treatment start and up to 4 months prior to radical prostatectomy date.].

Treatment Period (Cycle 1 Day 1 to end of Study Treatment):

Cycle 1 Day 1:

Visit may occur on the same day as the Screening visit provided that all screening assessments have been completed and screening results are reviewed prior to the commencement of Cycle 1 Day 1 assessments. The following procedures should be completed prior to receiving study drug.

- Concomitant Medications listing

- Physical exam [if not done within 7 days prior to C1D1] including vital signs including blood pressure, heart rate, respiratory rate and weight
- Assessment of ECOG Performance Status by investigator
- Laboratory studies from screening can be used as baseline prior to starting treatment.

Day 1of each subsequent Cycle (2-4):

- Physical exam including vital signs including blood pressure, heart rate, respiratory rate and weight
- Assessment of ECOG Performance Status
- Concomitant Medications listing
- Toxicity evaluation
- Laboratory tests including: CBC/differential and Platelets; CMP (Sodium, Potassium, Chloride, CO2, BUN, Creatinine, SGPT [ALT], SGOT [AST], Glucose, Alkaline Phosphatase, Total Bilirubin, and LDH) testosterone, and PSA

Day 1 of every 3 cycles:

- Physical exam including vital signs including blood pressure, heart rate, respiratory rate and weight
- Assessment of ECOG Performance Status
- Concomitant Medications listing
- Toxicity evaluation
- Laboratory tests including: CBC/differential and Platelets; CMP (Sodium, Potassium, Chloride, CO2, BUN, Creatinine, SGPT [ALT], SGOT [AST], Glucose, Alkaline Phosphatase, Total Bilirubin, and LDH) and PSA

Radiographic evaluation will be completed at baseline and at the time of PSA failure. Earlier scans will be performed at the discretion of the treating physician.

Treatment Discontinuation

The Treatment Discontinuation Visit can occur at any scheduled or unscheduled visit when applicable. At this visit, documentation to confirm progressive disease (serologic or radiographic) is required. If a patient discontinues therapy due to reasons other than PD (ie: adverse events), then patient's PSA will be followed at the discretion of the treating physician.

End of Study Treatment Visit

The End of Study Treatment Visit should be scheduled to collect safety assessments at the time the patient stops treatment. The following safety assessments should be carried out at the End of Treatment Visit after patients discontinue study treatment for any reason:

- Physical exam including vital signs including blood pressure, heart rate, respiratory

rate and weight
- Assessment of ECOG Performance Status by investigator
- Toxicity Evaluation. Treatment-related AEs will be followed until resolved.
- Documentation of all concomitant medications and procedures.
- Laboratory tests including: CBC/differential and Platelets; CMP (Sodium, Potassium, Chloride, CO2, BUN, Creatinine, SGPT [ALT], SGOT [AST], Glucose, Alkaline Phosphatase, Total Bilirubin, and LDH) and PSA.
- Radiographic tumor assessment (if not done within the last 6 weeks)

Safety Visit

The Safety Visit should be scheduled to collect safety assessments within 30 days after the patient stops treatment/last dose of study drug. The following safety assessments should be carried out:

- Physical exam including vital signs including blood pressure, heart rate, respiratory rate and weight
- Assessment of ECOG Performance Status by investigator
- Toxicity Evaluation. Treatment-related AEs will be followed until resolved.
- Documentation of all concomitant medications and procedures.
- Laboratory tests including: CBC/differential and Platelets; CMP (Sodium, Potassium, Chloride, CO2, BUN, Creatinine, SGPT [ALT], SGOT [AST], Glucose, Alkaline Phosphatase, Total Bilirubin, and LDH) and PSA.

Follow-up (every 3 months for the first year after completing treatment, then every 6 months for two years and then yearly thereafter) for 5 years:

- Progression-free survival follow-up can be done by phone contact or clinic visit.
- Follow treatment-related adverse events until resolved.

12 Measurement of Effect

12.1 Progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

12.2 PSA progression will be defined by a PSA value > 0.4ng/mL repeated in two consecutive occasions at least 2 weeks apart.

12.3 Definitions

12.3.1 Evaluable for Toxicity: All patients will be evaluable for toxicity from the time of their first treatment with enzalutamide

12.3.2 Time to PSA Progression: The start of the time to PSA progression is the day treatment is initiated. The end date is the time of PSA progression as defined in

section above.

12.3.2.1 Radiographic Progression-Free Survival
A patient is considered to have progressed by scans if

12.3.2.2 The first bone scan with ≥1 new lesions compared to baseline is observed

12.3.2.3 The first CT A/P with any new evidence of disease as per RECIST 1.1 compared with baseline scans.

13 Adverse Events/Data Safety Monitoring Plan

13.1 Definition of Adverse Event

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, physical exam) should be defined as an AE only if the abnormality meets one of the following criteria:

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

13.2 Definition of a Serious Adverse Event (SAEs)

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

13.2.1.1 Results in death

13.2.1.2 Is life threatening (an adverse event 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 adverse event that, had it occurred in a more severe form, might have caused death)

13.2.1.3 Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions

13.2.1.4 Results in congenital anomaly, or birth defect

13.2.1.5 Requires inpatient hospitalization or leads to prolongation of hospitalization (hospitalization for treatment/observation/examination caused by AE is to be considered as serious).

13.2.1.6 Other medically important events.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These events, including those that may

result in disability/incapacity, should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse. Additionally, Astellas requests that all medical events listed in Appendix 3 (Adverse Events Always Considered to be Serious), Appendix 4 (Liver Safety Monitoring and Assessment) and Appendix 5 (Common Serious Adverse Events) be reported by the Investigator as SAEs, even if none of the above criteria apply.

13.3 Criteria for Causal Relationship to the Study Drug

Adverse events that fall under either "Possible" or "Probable" should be defined as "adverse events whose relationship to the study drugs could not be ruled out".

Table 3. Adverse Events

Causal relationship to the study drug	**Criteria for causal relationship**
Not Related	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and/or in which other drugs, chemicals or underlying disease provide plausible explanations.
Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
Probable	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on re- administration (rechallenge) or withdrawal (dechallenge).

13.4 Criteria for Defining the Severity of an Adverse Event

Severity of adverse events will be graded according to the Cancer Therapy and Evaluation Program (CTCAE) Common Terminology Criteria for Adverse Events v. 4.03. For terms not specified within NCI-CTCAE, the following guideline should be used to determine grade:

Table 4 Criteria for Severity of Adverse Event Terms Not Specified Within NCICTCAE

Grade	Description
Grade 1	Mild; asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self care activities of daily living
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

13.5 General Requirements

13.5.1 Investigators are required by Federal Regulations to report serious adverse events as defined in the table below. Investigators are required to notify the Investigational Drug Branch (IDB), Study Chair, and their Institutional Review Board if a patient has a reportable serious adverse event (follow guidelines in the table below). This study will utilize the Common Toxicity Criteria version 4.0 to determine the severity of the reaction for adverse event reporting.

13.5.2 Reporting requirements and procedures depend upon: (1) whether agents are suspected of causing the adverse event, (2) whether the possibility of such an adverse event was reported in the protocol, consent form, or manufacturer's literature (expected or unexpected adverse event), (3) the severity or grade of the adverse event, (4) the phase of the study and attribution (the determination of whether an adverse event is related to a medical treatment or procedure).

13.5.3 All reactions in a "reportable" category must be reported. Reactions attributable to a regimen that includes commercial agents must be reported using the FDA Form #3500 (MedWatch).

13.6 Monitoring And Reporting Guidelines

Data related to these trials are discussed at weekly scheduled study group or site committee meetings where the result of each patient's treatment is discussed. The discussion will include for each treatment arm/dose level, the number of patients, significant toxicities as described in the protocol, dose adjustments, and responses observed. Additionally, the study team will meet quartly to review protocol and evaluate accurance of data entered into the OnCore database. Twice yearly, summaries will be submitted to the Data Monitoring Committee for review.

13.7 Review and Oversight Requirements will be communicated to: XTANDI Adverse Event Reporting: 800-888-7704 ext. 8224 or email: safety-us@usastellas.com

13.7.1 Adverse Event – Reported By Phone Within 24 Hours

13.7.2 Adverse events requiring expedited reporting by phone within 24 hours (as described in the protocol) will also be reported by phone to the Clinical Research Support Services (CRSS) administrator within one working day. Confirmation that all appropriate parties (including the CCF Committee on Human Research) were notified will be done at this time. Hardcopies or electronic versions of FDA Form #3500 (MedWatch) and/or any other documentation available at that time will also be reviewed by the DMC Committee Chair who will determine if immediate action is required. Within ten working days all subsequent SAE documentation that is available will be submitted to the DMC Committee Chair who will determine if further action is required. All information will be tracked in the Case Comprehensive Cancer Center's database.

13.7.3 If the AE occurs on a multiple-institutional clinical trial coordinated by the Case Comprehensive Cancer Center, the Principal Investigator will insure that all participating sites are notified of the event and resulting action within one working day of the determination.

13.7.4 Adverse Event – Reported within 10 Days

13.7.4.1 Adverse events requiring expedited AE reports in writing within 10 working days (as described in the protocol) will be sent to the CRSS office. Hardcopies or electronic versions of FDA Form #3500 (MedWatch), or other required forms will be submitted for review by the DMC Committee Chair to determine if further action is required. This information will be tracked in the Case Comprehensive Cancer Center's database.

13.8 Study Progress – Quarterly Review

13.8.1 Principal Investigators are required to submit quarterly study progress reports to determine whether accrual projections are being met, to summarize adverse reactions reported, and to determine if the trial should be continued based upon the likelihood of timely completion. These quarterly reports are reviewed at Data Monitoring Committee meetings. Failure to submit such reports will result in trial suspension.

13.8.2 An overall assessment of accrual, toxicities as described in the protocol, and responses will enable the committee members to assess whether significant benefits or risks are occurring that would warrant study closure. This information is provided by study committee/site committee meeting minutes, internal data quality audits, and annual DMC audits, all of, which is required of all research studies at Case Comprehensive Cancer Center. The committee will also receive all external DSMB reports and external data audits and may request further information from the Principal Investigator or Site Committee.

13.8.3 The Data Monitoring Committee recommendations for modifications to the trial or corrective actions are forwarded to the Protocol Review Committee and the Clinical Research Steering Committee. The Principal Investigator is notified of this recommendation in order that he/she may alert all investigators, at the Case Comprehensive Cancer Center and at external sites involved in the trial, about

the potential action. At this time the Principal Investigator may submit to the Clinical Research Steering Committee additional information that could affect the Committee's decision. The Clinical Affairs Committee will notify the Principal Investigator if they concur with the Data Monitoring Committee recommendations, including suspension or closure. The DMC Chair will notify all investigators involved with the study at Case Comprehensive Cancer Center and external sites, the IRB, the sponsor and the funding agency and provide written documentation of these notifications to the Clinical Research Steering Committee. The Case Comprehensive Cancer Center Clinical Research Steering Committee (CRSC), composed of Cancer Center senior leaders oversees these activities.

13.9 Review of Adverse Event Rates

13.9.1 Once a month, adverse event rates will be monitored utilizing the Case Comprehensive Cancer Center Clinical Trials database. If any study has had two or more of the same AE reported in a month or more than six of the same AE in six months, the DMC Chair will review the summary of SAEs, discuss events with Principal Investigator, and conduct a more detailed review with the Principal Investigator or the external DSMB if warranted. The Committee Chair will determine if further action is required. If this occurs on a multiple-institutional clinical trial coordinated by the Case Comprehensive Cancer Center, the Safety Coordinator will insure that all participating sites are notified of the resulting action.

13.9.2 Astellas instructions for rapid notification of serious adverse events

13.9.3 The principle investigator has the obligation to report all serious adverse events to the FDA, IRB, and XTANDI Adverse Event Reporting: 800-888-7704 ext. 8224 or email: safety-us@usastellas.com

13.9.4 All events reported to the FDA by the investigator are to be filed utilizing the Form FDA 3500A (MedWatch Form).

13.9.5 All events must be reported to XTANDI Adverse Event Reporting: 800-888-7704 ext. 8224 or email: safety-us@usastellas.com within 24 hours of learning of its occurrence. This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences. All deaths during treatment or within 30 days following completion of active protocol therapy must be reported within 5 working days.

13.9.6 Any serious adverse event occurring after the patient has initiated study treatment dosing and until 4 weeks after the patient has stopped dosing study drug must be reported. This includes the period in which the study protocol interferes with the standard medical treatment given to a patient (e.g. treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant medication).

13.9.7 Serious adverse events occurring more than 4 weeks after last dose of study drug need only be reported if a relationship to the Astellas study drug (or therapy) is suspected.

13.9.8 For Comparator Drugs/Secondary Suspects (Concomitant Medications), all serious adverse experiences will be forwarded to the product manufacturer by the investigator.

13.10 Pregnancies

Any pregnancy that occurs during study participation should be reported. To ensure patient safety each pregnancy must also be reported to Astellas within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects, congenital abnormalities or maternal and newborn complications.

14 Statistical Considerations

14.1 Study Design/Endpoints

This is a pilot phase II single institutional open label study. The primary endpoint of the trial is time to progression, defined by serologic criteria. That is a PSA value $\geq$ 0.4 in two separate occasions at least two weeks apart.

Secondary endpoints include safety based on CTCAE version 4.03 criteria.

14.2 Statistics

The primary goal of this trial is to assess the efficacy of enzalutamide in high risk patients following radical prostatectomy as measured by the biochemical failure-free (BFF) interval. Historically the 5-year BFF interval in this population is approximately 55% (Hernandez et al., *Urology,* 70:931-935, 2007). Assuming the BF interval follows an exponential distribution, accrual will take approximately 24 months. There will be at least 12 months of additional follow-up once accrual is completed. A sample size of 40 eligible and evaluable patients is recommended in order to have 80% power to detect a 75% decrease in the risk of biochemical failure (based on a 2-sided exponential MLE test that makes use of a Normal approximation, and a 5% type I error). To allow for a 5% exclusion rate, a total of 42 patients will be accrued. A secondary goal of the trial is to assess safety. Adverse events will be coded and graded according to CTCAE version 4.03 criteria. With 40 eligible and evaluable patients the likelihood of a specific type and/or grade of adverse event can be estimated using an exact 95% confidence interval that has a maximum half-width of 17%. BFF interval will be summarized using the Kaplan-Meier method; and proportional hazards models will be used to assess the impact of factors such as Gleason Score, PSA at diagnosis, seminal vesicle invasion, and nodal status.

14.3 Sample Size/Accrual Rate

The required sample size will be based upon evaluating the primary study objective. A total of 42 patients, 40 of whom are expected to be eligible and evaluable, will be entered into the study and treated with enzalutamide. Similar studies in high-risk

populations previously conducted at our institution have accrued an average of 2-3 patients per month. Thus it is estimated that 24 months will be required to complete total accrual for the clinical trial.

15 References

1. Siegel R, Naishadham D, Jemal A. Cancer Statistics 2012. *CA Cancer J Clin* 2012 Jan-Feb;62(1):10-29.

2. Kattan MW, Wheeler TM, Scardino PT. Postoperative nomogram for disease recurrence after radical prostatectomy for prostate cancer. *J Clin Oncol*. 1999;17(5):1499–507.

3. D'Amico AV, Whittington R, Malkowicz SB, Schultz D, Blank K, Broderick GA, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *JAMA*. 1998;280(11):969–74.

4. Messing EM, Manola J, Sarosdy M, Wilding G, Crawford ED, Trump D. Immediate hormonal therapy compared with observation after radical prostatectomy and pelvic lymphadenectomy in men with node-positive prostate cancer. *N Engl J Med*. 1999;341(24):1781–8.

5. Messing EM, Manola J, Yao J, Kiernan M, Crawford D, Wilding G, et al. Immediate versus deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy. *Lancet Oncol*. 2006;7(6):472–9.

6. McLeod DG, Iversen P, See WA, Morris T, Armstrong J, Wirth MP. Bicalutamide 150 mg plus standard care vs standard care alone for early prostate cancer. *BJU Int*. 2006;97(2):247–54.

7. Kibel AS, Rosenbaum E, Kattan MW, Picus J, Dreicer R, Klein EA, et al. Adjuvant weekly docetaxel for patients with high risk prostate cancer after radical prostatectomy: a multi-institutional pilot study. *J Urol*. 2007;177(5):1777–81.

8. Montgomery B, Lavori P, Garzotto M, Lee K, Brophy M, Thaneemit-Chen S, et al. Veterans Affairs Cooperative Studies Program study 553: Chemotherapy after prostatectomy, a phase III randomized study of prostatectomy versus prostatectomy with adjuvant docetaxel for patients with high-risk, localized prostate cancer. *Urology*. 2008;72(3):474–80.

9. Pettaway CA, Pisters LL, Troncoso P, et al. Neoadjuvant chemotherapy and hormonal therapy followed by radical prostatectomy: feasibility and preliminary results. *J Clin Oncol* 2000;18:1050–7.

10. Febbo PG, Richie JP, George DJ, et al. Neoadjuvant docetaxel before radical prostatectomy in patients with highrisk localized prostate cancer. *Clin Cancer Res* 2005;11: 5233–40.

11. Prayer-Galetti T, Sacco E, Pagano F, et al. Long-term follow- up of a neoadjuvant chemohormonal taxane-based phase II trial before radical prostatectomy in patients with non-metastatic high-risk prostate cancer. *BJU Int* 2007;100:274–80.

12. Kelly WK, Halabi S, Elfiky A, et al., Cancer and Leukemia Group B. Multicenter phase 2 study of neoadjuvant paclitaxel, estramustine phosphate, and CBDCA plus androgen deprivation before radiation therapy in patients with unfavorable-risk localized prostate cancer: results of Cancer and Leukemia Group B 99811. *Cancer* 2008;113:3137–45.

13. Nakabayashi M, Oh WK. Neoadjuvant and adjuvant chemotherapy for high-risk localized prostate cancer. *Curr Treat Options Oncol*. 2004 Oct;5(5):349-55.

14. Ozen H, Yazici S, Inci K. Management of High-Risk Localised Prostate Cancer. *European urology supplements*. 2009:8:439–47.

15. Flaig TW, Tangen CM, Hussain MH, et al. Randomization reveals unexpected acute leukemias in Southwest Oncology Group prostate cancer trial. *J Clin Oncol*. 2008 Mar 20;26(9):1532-6.

16. Dorff TB, Flaig TW, Tangen CM, et al. Adjuvant androgen deprivation for high-risk prostate cancer after radical prostatectomy: SWOG S9921 study. *J Clin Oncol*. 2011 May 20;29(15):2040-5

17. Bolla M, van Poppel H, Collette L, et al. European Organization for Research and Treatment of Cancer. Postoperative radiotherapy after radical prostatectomy: a randomized controlled trial (EORTC trial 22911). *Lancet* 2005;366: 572–8.

18. Thompson Jr IM, Tangen CM, Paradelo J, et al. Adjuvant radiotherapy for pathologically advanced prostate cancer: a randomized clinical trial. *JAMA* 2006;296:2329–35.

19. Thompson IM, Tangen CM, et al. Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term follow-up of a randomized clinical trial. *J Urol*. 2009;181(3):956.

20. Tran C, Ouk S, Clegg NJ, et al. Development of a second generation antiandrogen for treatment of advanced prostate cancer. *Science*. May 2009:324(5928):787-90.

21. Foster WR, Car, BD, Hong S, et al. Drug safety is a barrier to the discovery and development of new androgen receptor agonists. *The Prostate*. 2011:71:480-8.

22. Mocellin S, Keilholz U, Rossi CR, Nitti D. Circulating tumor cells: the 'leukemic phase' of solid cancers. *Trends Mol Med*. Mar 2006:12(3):130-9.

23. Hayes DF, Cristofanilli M, Budd GT, et al. Circulating tumor cells at each follow-up time point

during therapy of metastatic breast cancer patients predict progression-free and overall survival. *Clin Cancer Res.* Jul 2006:12(14):4218-24.

24. Larson CJ, Moreno JG, Piento KJ, et al. Apoptosis of circulating tumor cells in prostate cancer patients. *Cytometry A.*Nov 2004:62(1):46-53.

25. Meng S, Tripathy D, Frenkel EP. Circulating tumor cells in patients with breast cancer dormancy. *Clin Cancer Res.* Dec 2004:10:8152-62.

26. Smirnov DA, Zweitzig DR, Foulk BW, et al. Global gene expression profiling of circulating tumor cells. *Cancer Res.* Jun 2005:65(12):4993-7.

27. Shaffer DR, Leversha MA, Danila DC, et al. Circulating tumor cell analysis in patients with progressing castration-resistant prostate cancer. *Clin Cancer Res.* Apr 2007:13(7):2023-9.

28. Olmos D, Arkenau HT, Ang JE, et al. Circulating tumour cell (CTC) count as intermediate end points in castration-resistant prostate cancer (CRPC): a single-centre experience. *Ann Oncol.* Jan 2009:20(1):27-33.

29. Danila DC, Heller G, Gignac GA, et al. Circulating tumor cell number and prognosis in progressive castration-resistant prostate cancer. *Clin Cancer Res.* Dec 2007:13(23):7053-8.

30. Hayashi N, Yamauchi H. Role of circulating tumor cells and disseminated tumor cells in primary breast cancer. *Breast Cancer.* Apr 2012:19(2):110-7.

31. Wong NS, Kahn HJ, Zhang L, et al. Prognostic significance of circulating tumour cells enumerated after filtration enrichment in early and metastatic breast cancer patients. *Breast Cancer Res Treat.* Sep 2006:99(1):63-9.

32. Allard WJ, Matera J, Miller MC, et al. Tumor cells circulate in the peripheral blood of all major carcinomas but not in healthy subjects or patients with nonmalignant disease. *Clin Cancer Res.* Oct 2004:10(20):6897-904.

33. Hayes DF, Smerage JB. Circulating tumor cells. *Prog Mol Biol Transl Sci.* 2010:95:95-112.

34. O'Hara SM, Moreno JG, Zweitzig DR, Gross S, Gomella LG, Terstappen LW. Miltigene reverse transcription-PCR profiling of circulating tumor cells in hormone-refractory prostate cancer. *Clin Chem.* May 2004:50(5):826-35.

35. Fehm T, Hoffman O, Aktas B, et al. Detection and characterization of circulating tumor cells in blood of primary breast cancer patients by RT-PCR and comparison to status of bone marrow disseminated cells. *Breast Cancer Res.* Apr 2009:11(4):R59.

36. Kosaka N, Iquchi H, Ochiya T. Circulating microRNA in body fluid: a new potential biomarker

for cancer diagnosis and prognosis. *Cancer Sci*. Oct 2010:101(10):2087-92.

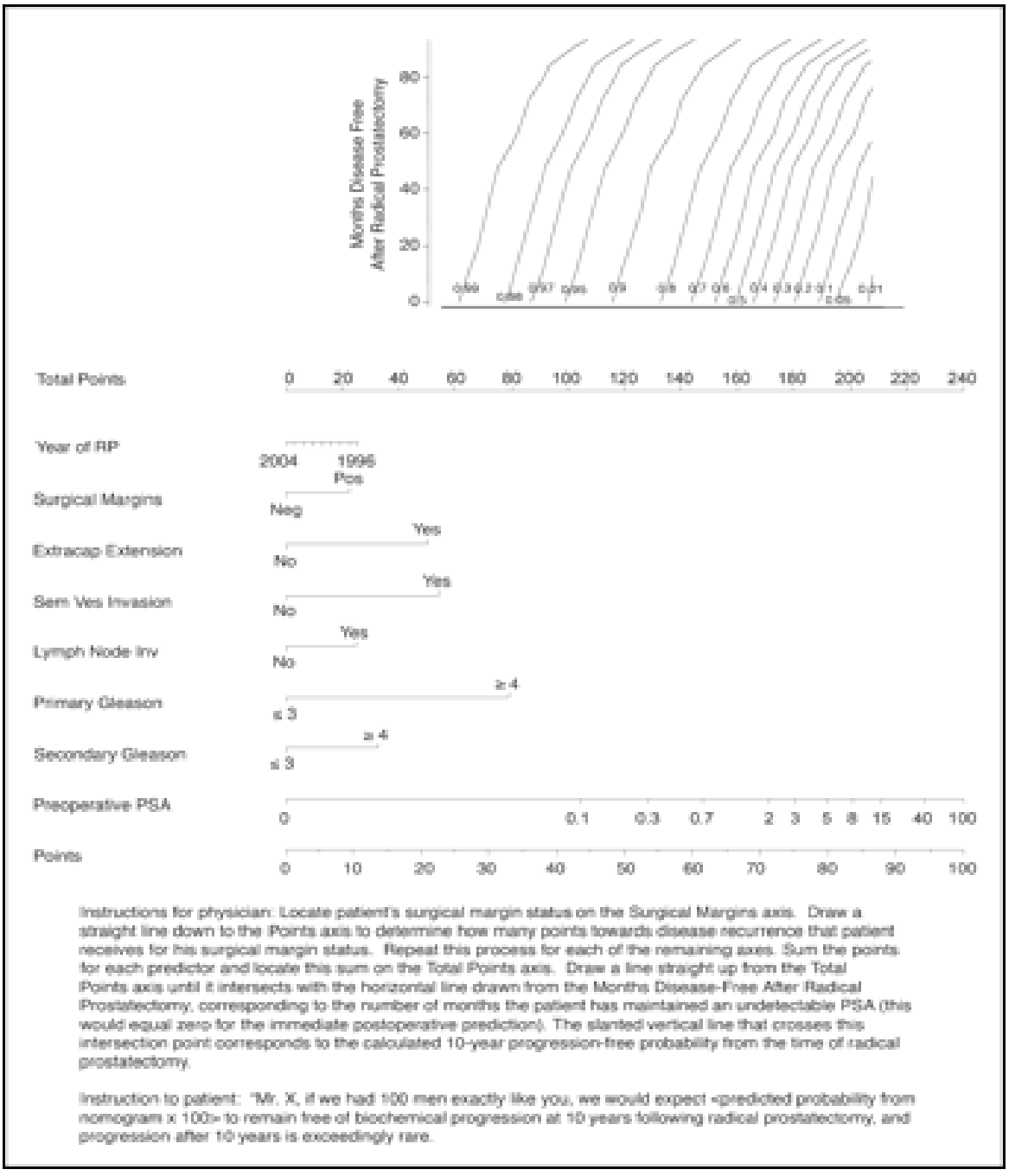
APPENDIX 1

Performance Status Criteria

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease 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 of his/her 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 more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX 2

MSKCC Nomogram – Post-RP
http://nomograms.mskcc.org/Prostate/PostRadicalProstatectomy.aspx



Instructions for physician: Locate patient's surgical margin status on the Surgical Margins axis. Draw a straight line down to the Points axis to determine how many points towards disease recurrence that patient receives for his surgical margin status. Repeat this process for each of the remaining axes. Sum the points for each predictor and locate this sum on the Total Points axis. Draw a line straight up from the Total Points axis until it intersects with the horizontal line drawn from the Months Disease-Free After Radical Prostatectomy, corresponding to the number of months the patient has maintained an undetectable PSA (this would equal zero for the immediate postoperative prediction). The slanted vertical line that crosses this intersection point corresponds to the calculated 10-year progression-free probability from the time of radical prostatectomy.

Instruction to patient: "Mr. X, if we had 100 men exactly like you, we would expect <p>redicted probability from nomogram x 100> to remain free of biochemical progression at 10 years following radical prostatectomy, and progression after 10 years is exceedingly rare.

APPENDIX III

Adverse Events Always Considered To Be Serious

If any of the following adverse events occur during the study, they should be considered as serious adverse events and reported as per protocol.

- acute liver failure
- acute renal failure
- acute respiratory failure
- agranulocytosis
- anaphylaxis
- any new primary malignancy
- aplastic anemia
- confirmed or suspected endotoxin shock
- confirmed or suspected transmission of infectious agent by marketed product
- congenital anomalies
- liver necrosis
- malignant hypertension
- pulmonary fibrosis
- pulmonary hypertension
- sclerosing syndromes
- seizure
- torsade de pointes
- toxic epidermal necrolysis
- ventricular fibrillation

APPENDIX IV
Liver Safety Monitoring and Assessment

If laboratory testing for a subject enrolled in study and receiving study drug reveals an increase of serum aminotransferases (AT) to > 3x ULN, or bilirubin > 2x ULN, at least all four of the usual serum hepatic measures (ALT, AST, ALP, and TBL) should be repeated. Testing should be repeated within 48-72 hours of notification of the test results. If applicable, for studies for which a central laboratory is used, alerts will be generated by the central lab regarding moderate and marked liver abnormality to inform the investigator, study monitor and study team. Subjects should be asked if they have any symptoms suggestive of hepatobiliary dysfunction.

Definition of Liver Abnormalities
Confirmed abnormalities will be characterized as moderate and marked where ULN:

	ALT or AST		Total Bilirubin
Moderate	> 3x ULN	*or* >	2x ULN
Marked	> 3x ULN	*and*	> 2x ULN

In addition, the subject should be considered to have marked hepatic abnormalities for any of the following:

- ALT or AST > 8x ULN
- ALT or AST > 5x ULN for more than 2 weeks
- ALT or AST > 3x ULN and INR > 1.5
- ALT or AST > 3x ULN with the appearance of fatigue, nausea, vomiting, right upper
- quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).

The investigator may determine that abnormal liver function results, other than as described above, may qualify as moderate or marked abnormalities and require additional monitoring and follow-up. Discontinuation of treatment must occur if subject has marked abnormalities. In addition, if close monitoring for a subject with moderate hepatic laboratory tests is not possible, drug should be discontinued.

Follow-up Procedures
Confirmed moderate and marked abnormalities in hepatic functions should be thoroughly characterized by obtaining appropriate expert consultations, detailed pertinent history, physical examination and laboratory tests. The site should complete the Liver Abnormality Case Report Form (LA-CRF) or an appropriate document. Subjects with confirmed abnormal liver function testing should be followed as described below.
Confirmed moderately abnormal LFTs should be repeated 2-3 times weekly then weekly or less if abnormalities stabilize or the study drug has been discontinued and the subject is asymptomatic.
Marked hepatic liver function abnormalities, in the absence of another etiology, may be considered an important medical event and reported as a Serious Adverse Event (SAE). The sponsor should be contacted and informed of all subjects for whom marked hepatic liver

function abnormalities possibly attributable to study drug are observed.

To further assess abnormal hepatic laboratory findings, the investigator is expected to:

- Obtain a more detailed history of symptoms and prior or concurrent diseases. Symptoms and new onset-diseases should be recorded as 'adverse events' on the AE page of CRF. Illnesses and conditions such as hypotensive events, and decompensated cardiac disease that may lead to secondary liver abnormalities should be noted. Non-alcoholic steatohepatitis (NASH) is seen in obese hyperlipoproteinemic, and/or diabetic subjects and may be associated with fluctuating aminotransferase levels. The investigator should ensure that the medical history form captures any illness that pre-dates study enrollment that may be relevant in assessing hepatic function.
- Obtain a history of concomitant drug use (including non-prescription medication, complementary and alternative medications), alcohol use, recreational drug use, and special diets. Medications, including dose, should be entered on the concomitant medication page of CRF. Information on alcohol, other substance use, and diet should be entered on the LA-CRF or an appropriate document.
- Obtain a history of exposure to environmental chemical agents
- Based on the subject's history, other testing may be appropriate including:
    a. Acute viral hepatitis (A,B, C, D, E or other infectious agents).
    b. ultrasound or other imaging to assess biliary tract disease
    c. other laboratory tests including INR, direct bilirubin
- Consider gastroenterology or hepatology consultations
- Submit results for any additional testing and possible etiology on the LA-CRF or an appropriate document.

Study Discontinuation

In the absence of an explanation for increased LFTs, such as viral hepatitis, pre-existing or acute liver disease or exposure to other agents associated with liver injury, the subject may be discontinued from the study. The investigator may determine that it is not in the subject's best interest to continue study enrollment.

Discontinuation of treatment must occur if:

- ALT or AST > 8x ULN
- ALT or AST > 5x ULN for more than 2 weeks
- ALT or AST > 3x ULN and TBL > 2x ULN or INR > 1.5

Discontinuation of treatment should be considered if:

- ALT or AST > 3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).
- In addition, if close monitoring for a subject with moderate hepatic laboratory tests is not possible, drug should be discontinued.

APPENDIX V

Common Serious Adverse Events

The following list of serious adverse events are considered common for the study population defined in this protocol and should be reported by the investigator as described in the protocol.

For IND safety reporting, single occurrences of the following events may be excluded from expedited reporting. If aggregate analysis of these events indicates they occur more frequently with study drug, an expedited IND safety report may be submitted to FDA

- Anemia
- Anorexia
- Asthenia / Fatigue
- Back pain
- Bone pain
- Catheter related infection
- Dyspnea
- Hematuria
- Hydronephrosis
- Metastases to bone
- Metastases to central nervous system
- Nausea
- Obstructive uropathy
- Pain
- Prostate cancer metastatic
- Renal failure
- Renal failure acute
- Spinal compression fracture
- Spinal cord compression
- Urinary retention
- Urinary tract infection
- Urinary tract obstruction
- Vomiting

APPENDIX VI

Subject Registration Form

Protocol No: **CASE 12812**	Title: **A Pilot Phase II study of Enzalutamide in men with High-risk PCa after Radical Prostatectomy**	Date: ___/___/_____

Subject Demographics

Study Site:			
MRN:	Last Name:	First Name	MI:
Gender: X Male	Ethnicity: □ Hispanic □ Non-Hispanic □ Unknown	Race: □ American Indian or Alaska Native □ Asian □ Black or African American □ Native Hawaiian or Other Pacific Islander □ Unknown □ White	
Date of Birth: ___/___/_____	On Study Date: ___/___/_____	Study Patient No:	
Disease Site: PROSTATE			
Histology: PROSTATE			
Registrar's Name		Registrar's Signature	