Title: Enzalutamide with External Beam Radiation for Intermediate Risk Prostate Cancer: A Phase II Study
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Study Title: Enzalutamide with External Beam Radiation for Intermediate Risk Prostate Cancer: A Phase II Study

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Agent(s): Enzalutamide - Medivation

SCHEMA

Disease: Patients with Intermediate Risk Prostate Cancer:	Treatment: 6 months of enzalutamide. EBRT*** beginning 7-10 weeks after initiating enzalutamide. 7560-7920 cGy in 180cGy fractions	Endpoints: Primary-PSA level at completion of therapy compared to historical controls with LH-RH agonists Secondary: 1) Quality of Life 2) Hormonal levels 3) Body fat measurements

Timeline

Reg Start enzalutamide 6 X 28 day cycles**** End enzalutamide F/u 3 month

Start XRT** End XRT

| 30 day max | _____|_____|_____|_____ | _____ |

Fiducial*

* Fiducial placement and biopsy 3-7 weeks after initiating enzalutamide **
Radiation initiated 7-10 weeks after initiating enzalutamide.

*** Patients that are unable to complete enzalutamide therapy will still be treated with EBRT per SOC

**** 28 day cycle allows for +/- 3 day window

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1. OBJECTIVES

1.1 Study Design

The goal of this exploratory study is to assess efficacy of adding enzalutamide in the neoadjuvant and adjuvant setting in combination with external beam radiation therapy (EBRT). The population will be prostate cancer patients with intermediate risk prostate cancer, choosing radiation therapy as their primary form of therapy. This is a phase II single arm trial that has as its primary objective to estimate the proportion of patients with PSA ≤0.2 ng/ml at the completion of therapy. This endpoint has been shown to be predictive of long term response in a similar risk-group of patients treated with radiation therapy and LHRH agonists.**(1)** Secondary endpoints include measurement of serum hormone levels, health-related quality of life (HRQoL) and body fat measurements. It is expected that enzalutamide therapy in contrast to LHRH agonists has a much better profile for these secondary outcomes. Correlative studies will center on understanding enzalutamide's mechanism of action. Data from this trial, if convincing, would lead to a Phase III randomized trial comparing LHRH agonists to enzalutamide as neoadjuvant and adjuvant therapy in combination with EBRT.

On this study patients will be treated with 6 months of Xtandi (enzalutamide). Approximately one-third of the way through this treatment they will receive EBRT. Starting on Day 1, all patients will ingest enzalutamide **160 mg/day** at the same time each day without breaks (except as outlined for toxicity), with or without food, for 6 (28 day +/-3 days) cycles. Dose reduction of enzalutamide to 120 mg/day is allowed with the approval of the Medical Monitor, Dr. Glenn Bubley (Section 6.2.2.3). Patients will be instructed to return all unused capsules at each study visit to assess compliance and will receive study drug every 28 days (+/-3 days) for 6 cycles (24 weeks).

1.2 Primary Objectives

1. Estimate the proportion of patients whose PSA level at the end of six (28 day +/-3 days) cycles of enzalutamide and EBRT is ≤ 0.2 ng/ml.

1.3 Secondary Objectives

1. Assessment of the effect of treatment on health-related quality of life including fatigue, sleep quality, as well as urinary, bowel, sexual and hormonal functioning.
2. Assessment of the effect of treatment on serum sex hormones including androgens and estrogens.
3. Assessment of the effect of treatment on body fat distribution and muscle mass.
4. Assessment of safety and tolerability according to adverse event reporting during the trial.
5. Assessment of the effect of treatment on bone metabolism.

1.4 Correlative Objective

1. Assessment of cellular location of androgen receptor expression using immunohistochemistry on prostate tissue samples obtained during fiducial placement.

2. BACKGROUND

2.1 Enzalutamide

Please refer to the Investigator's Brochure for further information on the pharmacology of enzalutamide.

Enzalutamide (enzalutamide) is a potent androgen receptor signaling inhibitor that blocks several steps in the androgen receptor signaling pathway. Enzalutamide competitively binds to the androgen receptor with an IC_{50} of 36 nM, compared to 160 nM for bicalutamide (an androgen receptor antagonist commonly used for ADT **[2, 3]).** In addition, enzalutamide inhibits nuclear translocation of activated receptors and inhibits the association of the activated androgen receptor with DNA, even in the setting of androgen receptor overexpression and in prostate cancer cells resistant to anti-androgens. Enzalutamide treatment decreases the growth of prostate cancer cells and can induce cancer cell death and tumor regression. Effective inhibition of androgen receptor signaling by enzalutamide (observed in vitro) blocks the oncogenic effects of androgen metabolism by tumor cells and the up regulation of the androgen receptor. In addition, enzalutamide induces immediate prostate cancer apoptosis, an effect not seen with antiandrogens (e.g., bicalutamide) **(3)** Furthermore, enzalutamide has no known agonist activity when the androgen receptor is overexpressed.

Enzalutamide treatment in a prostate cancer xenograft model resulted in a dose-dependent reduction in tumor volume: 1/7 tumors in the low-dose group (1 mg/kg/day) and 3/7 tumors in the high-dose group (50 mg/kg/day) became unmeasurable. In contrast, bicalutamide had little effect on tumor growth.

Enzalutamide was non-mutagenic/clastogenic in in vitro genotoxicity assays (reverse mutation and mouse lymphoma). Repeat-dose oral toxicology studies were conducted with durations of up to 6 months in rats and 3 months in dogs. The most prominent effects of enzalutamide in these species were reductions in prostate, epididymis, and/or seminal vesicle weight, all of which are consistent with the expected antiandrogen pharmacology of enzalutamide. These decreases were accompanied by corresponding histopathological findings of prostatic and seminal vesicle secretory depletion and/or atrophy, with epididymal atrophy in dogs only. Hypospermatogenesis and degeneration of seminiferous tubules in testes have been observed in dogs, but not in rats. The enzalutamide-related male sex organ findings reversed, or tended to reverse, after at least 8 weeks of recovery. Reversible hepatocellular hypertrophy, associated with liver weight increases, was a consistent finding of enzalutamide in rats, but not in dogs. Several additional histopathological findings (mostly in endocrine tissues) definitively related to enzalutamide treatment in the 26-week study in rats included hypertrophy/hyperplasia in adrenals, pituitary, and thyroid; atrophy in male mammary gland; gland/lumen dilatation and lobular hyperplasia in

female mammary gland; and luminal dilatation in the uterus. In a short-term reversibility study in male dogs, enzalutamide treatment did not result in detectable permanent effects to male reproductive organs.

Cardiovascular safety was evaluated in vitro in patch-clamped mammalian cells expressing the hERG channel. The results showed that enzalutamide inhibited the hERG current with an IC50 of 16.2 μM (7.29 μg/mL). The highest free concentration of enzalutamide expected in patient plasma at a steady-state dose of 160 mg/day is well below the hERG IC50 value. The major active metabolite of enzalutamide (M2) was also shown to weakly inhibit the hERG channel with an IC50 of 18.6 μM (8.38 μg/mL).

In mice, rats, and dogs, orally administered enzalutamide had a half-life (t1/2) of approximately 0.25 to 3 days. The t1/2 did not appear to be affected by the dose size; however, bioavailability appeared to decrease with increasing dose size. Plasma protein binding of enzalutamide in human plasma ranged from 97% to 98% and was similar in mice, rats, rabbits, and dogs.

Co-administration of a strong CYP2C8 inhibitor (gemfibrozil) increased the composite area under the plasma concentration-time curve (AUC) of enzalutamide plus N-desmethyl enzalutamide in healthy volunteers. Co-administration of enzalutamide with strong CYP2C8 inhibitors should be avoided (see Appendix F).

The effects of CYP2C8 inducers on the pharmacokinetics of enzalutamide have not been evaluated in vivo. Co-administration of enzalutamide with strong CYP2C8 inducers (e.g., rifampin) may alter the plasma exposure of enzalutamide and should be avoided (see APPENDIX F).

The effects of CYP3A4 inducers on the pharmacokinetics of enzalutamide have not been evaluated in vivo. Co-administration of enzalutamide with strong CYP3A4 inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine) may decrease the plasma exposure of enzalutamide and should be avoided. (see APPENDIX F) 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.

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).

Concomitant use of enzalutamide with narrow therapeutic index drugs that are metabolized by CYP3A4 (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, fetanyl, pimozide, quinidine, sirolimus and tacrolimus), CYP2C9 (e.g., phenytoin, warfarin), pentobarbital, ketoconazole, sertaraline, digitoxin, haloperidol, ketamine, doxocycline, isoniazid, ciprofloxacin and CYP2C19 (e.g., S-mephenytoin) should be avoided if possible, as enzalutamide may

decrease their exposure. If co-administration with warfarin cannot be avoided, conduct additional INR monitoring

Additional nonclinical information can be found in the Investigator's Brochure.

2.1.1 Previous Human Experience

The tolerability, pharmacokinetics (PK), and antitumor activity of enzalutamide were studied in a multicenter, open-label, dose-escalation study of enzalutamide in 140 patients with advanced prostate cancer. Patients were treated with enzalutamide at doses of 30 to 600 mg/day until disease progression or intolerable side effects developed.

In this study, enzalutamide was absorbed rapidly after oral administration, with the median time to maximum plasma concentration (C_{max}) after a single dose occurring at 1.00 hour (range 0.42 to 4.00 hours postdose). The PK of enzalutamide was essentially linear with no major deviations from dose proportionality in C_{max} or area under the curve values in the dose range of 30 to 600 mg. The terminal $t_{1/2}$ for enzalutamide after a single dose was approximately 6 days (range 3 to 10 days) and did not appear to be affected by the dose size. In accordance with the long $t_{1/2}$, it took approximately 1 month after the start of a daily dose regimen to reach steady state. On achievement of steady state, the mean trough concentrations (Cmin) in individual patients remained constant for several months, suggesting time-linear PK. With daily oral administration of 150 mg/day, the mean accumulation index for enzalutamide was approximately 11, reflecting the long t1/2 relative to the dosing interval. Due to its slow clearance from plasma, the daily fluctuation in steady-state enzalutamide concentrations was low. The mean peak-to-trough ratios (Cmax/Cmin) was 1.2 (range 1.14 to 1.3), indicating that variability in steady-state Cmax, Cmin, and area under the curve values was low (≤ 30% CV).At 160 mg/day, the mean steady-state Cmin is expected to be approximately 12 ± 4 μg/mL. Full PK profiles were linear and consistent over the dose range studied.

Fatigue was the most frequently reported adverse event, with dose-dependent increases of Grade 3 fatigue (0% at 150 mg/day, 9% at 240 mg/day, 15% at 360 mg/day, and 20% at 480 mg/day). The dose of 240 mg/day was defined as the maximum tolerated dose. At doses of 240 mg and above, an increasing proportion of patients needed dose reductions for fatigue. Dose reductions were needed in 1 of 29 patients (3%) that received 240 mg/day, 3 of28 patients (11%) that received 360 mg/day, and 5 of 22 patients (23%) that received 480 mg/day, and 0 of 58 patients that received 30, 60, or 150 mg/day. After dose reductions, the symptoms resolved. Only 1 patient discontinued treatment due to fatigue with an onset coinciding with prostate specific antigen (PSA) rise. Overall, the most common mild (grade 2) adverse events were fatigue (n = 38 [27.1%]), nausea (n = 12 [8.6%]), dyspnea (n = 11 [7.9%]), anorexia (n = 8 [5.7%]), and back pain (n = 8 [5.7%]). Fatigue, nausea, and anorexia were the only mild adverse events with an increasing incidence as the dose of enzalutamide was increased. None of the grade 2 events required dose modification or the discontinuation of treatment, apart from 1 patient treated at 480 mg/day who had nausea at baseline and stopped therapy after 7 weeks.

In the randomized clinical trial, 7 of 800 (0.9%) patients treated with enzalutamide160 mg once daily experienced a seizure. No seizures occurred in patients treated with placebo. Seizures occurred from 31 to 603 days after initiation of enzalutamide. Patients experiencing seizure were permanently discontinued from therapy and all seizures resolved. There is no clinical trial experience re-administering enzalutamide to patients who experienced seizures.

The safety of enzalutamide in patients with predisposing factors for seizure is not known because these patients were excluded from the trial. These exclusion criteria included a history of seizure, underlying brain injury with loss of consciousness, transient ischemic attack within the past 12 months, cerebral vascular accident, brain metastases, brain arteriovenous malformation or the use of concomitant medications that may lower the seizure threshold.

The antitumor activity of enzalutamide was assessed by post-therapy changes in PSA, soft tissue and osseous disease, and circulating tumor cell count. Prostate specific antigen declines of ≥ 50% from baseline were observed in 62% of patients. Radiographic evidence of disease control (i.e., no progression) was also observed in the majority of patients **(3).**

Based on these results, 2 placebo-controlled, randomized Phase 3 studies (AFFIRM and PREVAIL) were initiated to evaluate the efficacy and safety of enzalutamide in patients with advanced prostate cancer. The AFFIRM study evaluated the safety and efficacy of enzalutamide in 1199 patients who progressed on docetaxel **(4**) This study showed a survival benefit in favor of enzalutamide (hazard ratio 0.631 $p < 0.0001$, median overall survival of 18.4 versus 13.6 months for enzalutamide and placebo, respectively **(4).** The PREVAIL study was designed to evaluate the safety and efficacy of enzalutamide in patients who have not yet received chemotherapy for their metastatic disease; this study is ongoing. The AFFIRM study, however, lead to the approval of this drug for the indication for CRPC with metastatic disease following docetaxel in September 2012.

2.2 Study Disease

Prostate cancer is the most commonly diagnosed non-cutaneous cancer diagnosed in the US male population and the second leading cause of cancer death. In 2008, 214 633 new cases were diagnosed and 28,411 men died of prostate cancer. Standard options for men with early stage prostate cancer can include active surveillance, prostatectomy, external beam or brachytherapy radiation and hormonal therapy. Treatment recommendation depends on extent of local disease and other issues such as age of the patient, pre-existing medical condition. Often patients have several management options. Including in this decision making process are the risks and toxicities associated with each treatment approach. Both retrospective reports and prospective trials have shown the usefulness of categorizing patients with prostate cancer using multimodality staging. By combining the presenting tumor stage (AJCC- T stage), the finding on rectal exam and the pre-treatment serum PSA level, patients fall into a low, intermediate or risk category.

Definitive treatment is generally recommended for men with a good life expectancy without potentially life shortening co-morbidities with Intermediate Risk prostate cancer. The addition of hormonal treatments (therapies that reduce testosterone) has been shown to be efficacious to external beam in several prospective randomized trials. The reason for this beneficial effect is not understood. One explanation for this effect is the cytoreductive effects of hormonal therapy which increases the probability of local tumor control with external beam radiotherapy. These trials where initiated in the era when the total dose external beam dose was low by contemporary standards. In fact, the RTOG is revisiting the role for androgen ablation with high dose radiotherapy in the intermediate risk prostate cancer patient (RTOG 0815).

A barrier to treatment with androgen ablation with external radiotherapy are the toxicities associated with low serum testosterone levels. These include loss of libido, erectile dysfunction, hot flashes and weight gain. Since serum testosterone levels are not affected by the androgen receptor blockade of bicalutamide, hot flashes, loss of libido and sexual side effects are less common. As stated above, these are nearly universal side effects of LH-RH agonist therapies that low serum testosterone to castrate levels. However bicalutamide is a partial agonist of the androgen receptor and there is concern regarding its efficacy as monotherapy, particularly at the 50 mg per day dose (the currently approved dose). D'Amico et al has shown that PSA nadir after external beam and 6 months of LH-RH agonist therapy with bicalutamide is predictive of disease free survival and metastasis free survival (**1**). If the PSA nadir is 0.2 ng/ml or lower, there is improvement in outcome. Potentially with longer follow-up in this study, there will be improved survival if these low PSA levels can be achieved. Therefore, PSA nadir at the end of external beam and 6 months of hormonal therapy is a surrogate endpoint for disease free survival and metastasis free survival.

2.3 Rationale

Presently most patients with intermediate risk prostate cancer receive neoadjuvant, concurrent and adjuvant hormonal therapy with external beam irradiation. Multiple studies have shown that the addition of HT improves survival to external beam radiation (**5,6)** However androgen deprivation induced by LH-RH agonists consistently results in hot flashes, loss of libido, loss of sexual functioning, weight gain, changes in metabolism, loss of muscle mass and fatigue **(7, 8)**.

In contrast, treatment with the anti-androgens bicalutamide or flutamide has minimal side effects, likely related to the fact that these agents do not suppress serum testosterone. Enzalutamide has the potential to have similar anti-tumor effects as LH-RH agonist without the toxicity associated with castrate testosterone levels. If it were shown that enzalutamide (enzalutamide) could be used as an effective adjuvant treatment for prostate cancer without androgen deprivation it would have dramatic and significant impact, including expanding its use to those patients who may have more intermediate risk and/or are unable to tolerate the toxicities associated with androgen deprivation

We have chosen as the primary endpoint the assessment of the proportion of patients whose PSA level is $\leq$0.2 ng/ml at the conclusion of therapy. This endpoint was chosen because patients that

achieve this value after treatment with LHRH analogs in combination with EBRT have an excellent prognosis compared to patients that demonstrate higher PSA levels **(1, 9).** Furthermore, demonstration of PSA levels of ≤0.2ng/ml in a significant number of patients treated on this study would be strong motivation to perform a phase III randomized trial comparing enzalutamide to LHRH analog therapy in the same setting.

2.4 Correlative Studies Background

Patients on this trial will, of necessity, have placement of fiducials that are used to guide the radiation treatment. These are placed in the outpatient setting and require exactly the same efforts as does a prostate biopsy (pre-treatment antibiotic therapy, ultrasound guidance, patient positioning etc.). Fiducials are routinely placed 3-7 weeks after initiating enzalutamide. At this juncture patients that consent will undergo two additional core samples to be obtained from the prostate, likely in the position of previous disease as documented in the core biopsy diagnostic report. The aim of obtaining these samples will be for analysis of localization of the androgen receptor by immunohistochemistry. As discussed, data suggest that one of the mechanisms behind enzalutamide's' effectiveness is to trap the AR in the cytoplasm and block its access to the nucleus where it can act as a transcription factor.**(3**). The pattern of expression from these samples can be compared to the pattern of AR localization in the patient's pre-treatment core biopsies and from patient samples available to us from our tumor bank. The latter patients have been treated with or without LHRH analogs, both of which would be important controls.

3. PARTICIPANT SELECTION

Participants must meet the following criteria on screening examination to be eligible to participate in the study:

3.1 Inclusion Criteria

Study population: Participants must have histologically confirmed malignancy and are candidates for external beam radiation therapy. Patients eligible for this study must have intermediate risk disease defined as PSA values between 10-20 ng/ml and/or T2b-c and/or Gleason grade 7. If all three are present, less than 50% of the core biopsies can be positive.

Patients previously diagnosed with low risk (Gleason score < 6, clinical stage < T2a, and PSA< 10) prostate cancer undergoing active surveillance who are re-biopsied and found to have intermediate risk disease according to the protocol criteria are eligible for enrollment within 180 days of the repeat biopsy procedure.

3.1.1 Age 18 years or more.

3.1.2 Life expectancy of greater than 1 year.

3.1.3 ECOG performance status $\leq$2 (see Appendix D).

3.1.4 Participants must have normal organ and marrow function as defined below:

- Leukocytes $\geq$ 3,000/mcL
- Platelets $\geq$ 80,000/mcL
- Total bilirubin < 2X institutional upper limit
- AST (SGOT)/ALT (SGPT) $\leq$ 2.5 X institutional upper limit of normal
- Creatinine < 2x institutional limits .

3.1.5 The effects of enzalutamide on the developing human fetus are unknown. For this reason and because enzalutamide may be teratogenic, men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation.

3.1.6 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

Patients must NOT meet any of the following exclusion criteria

3.2.1 Received an investigational agent within 4 weeks prior to enrollment (see section 5.3.12).

3.2.2 Stage T4 prostate cancer by clinical examination or radiologic evaluation.

3.2.3 Hypogonadism or severe androgen deficiency as defined by screening serum testosterone less than 50 ng/dL below the normal range for the institution.

3.2.4 Prior androgen deprivation, chemotherapy, surgery, or radiation for prostate cancer.

3.2.5 Receiving concurrent androgens, anti-androgens, estrogens, or progestational agents, or received any of these agents within the 6 months prior to enrollment or having taken finasteride or dutasteride within 30 days of registration.

3.2.6 History of another active malignancy within the previous 5 years other than curatively treated nonmelanomatous skin cancer and superficial bladder cancer. Participants treated for malignancy with no relapse within two years are eligible to participate in the study.

3.2.7 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection.

3.2.8 Severe concurrent disease, infection, or co-morbidity that, in the judgment of the Investigator, would make the patient inappropriate for enrollment.

3.2.9 Unwilling to use contraceptives while on study if relevant to patient.

3.2.10 History of seizure or any condition or concurrent medication that may predispose to seizure.

3.2.11 History of loss of consciousness or transient ischemic attack within 12 months prior to enrollment.

3.2.12 Clinically significant cardiovascular disease, including:

- Myocardial infarction within 3 months of enrollment;
- Uncontrolled angina within 3 months of enrollment;
- Congestive heart failure New York Heart Association (NYHA) class 3 or 4, or history of congestive heart failure NYHA class 3 or 4 in the past, unless a screening echocardiogram or multi-gated acquisition scan performed within 3 months results in a left ventricular ejection fraction ≥ 45%;
- History of clinically significant ventricular arrhythmias (e.g., ventricular tachycardia, ventricular fibrillation, torsades de pointes);
- History of Mobitz II second degree or third degree heart block without a permanent pacemaker in place;
- Hypotension as indicated by systolic blood pressure < 86 mmHg on 2 consecutive measurements at the Screening visit;
- Bradycardia as indicated by a heart rate < 50 beats per minute at the Screening visit;
- Uncontrolled hypertension as indicated by systolic blood pressure > 170 mmHg or diastolic blood pressure > 105 mmHg on 2 consecutive measurements at the screening visit;
- EKG demonstrating equal to or greater than grade III toxicity according the

NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0

3.2.13 History of gastrointestinal disorders (medical disorders or extensive surgery) that may interfere with the absorption of oral study drug(s) within 3 months of enrollment.

3.2.14 Major surgery within 4 weeks of registration.

3.2.15 Previous use, or participation in a clinical trial, of an investigational agent that blocks androgen synthesis (e.g., abiraterone acetate, TAK-700, TAK-683, TAK-448) or targets the androgen receptor (e.g., enzalutamide, BMS 641988); ketoconazole.

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

3.2.17 Need for any of the medications on the list of drugs to be used with caution or to be avoided (see APPENDIX F).

3.2.18 Use of herbal or alternative remedies that may affect hormonal status such as Prostasol or PC-SPES.

3.3 Inclusion of Women, Minorities and Other Underrepresented Populations

Women are not affected by prostate cancer and therefore are not eligible. Efforts will be made to enroll patients that are minorities. African Americans have a higher incidence of prostate cancer and effort will be made to recruit these men to this study.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC and DF/PCC Institutions

Institutions will register eligible participants with the DF/HCC Quality Assurance Office for Clinical Trials (QACT) central registration system. Registration must occur prior to the initiation of therapy. Any participant not registered to the protocol before treatment begins will be considered ineligible and registration will be denied.

A member of the study team will confirm eligibility criteria and complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol treatment. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a participant does not receive protocol therapy following registration, the participant's protocol status must be changed. Notify the QACT Registrar of participant status changes as soon as possible.

4.2 Registration Process for DF/HCC and DF/PCC Institutions

The QACT registration staff is accessible on Monday through Friday, from 8:00 AM to 5:00 PM Eastern Standard Time. In emergency situations when a participant must begin

treatment during off-hours or holidays, call the QACT registration line at 617-632-3761 and follow the instructions for registering participants after hours.

The registration procedures are as follows:

1. Obtain written informed consent from the participant prior to the performance of any study related procedures or assessments.

2. Complete the protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical/research record. **To be eligible for registration to the study, the participant must meet each inclusion and exclusion criteria listed on the eligibility checklist.**

   Reminder: Confirm eligibility for ancillary studies at the same time as eligibility for the treatment study. Registration to both treatment and ancillary studies will not be completed if eligibility requirements are not met for all studies.

3. Fax the eligibility checklist(s) and all pages of the consent form(s) to the QACT at 617-632-2295.

4. The QACT Registrar will (a) validate eligibility, (b) register the participant on the study, and (c) enroll the participant when applicable.

5. The QACT Registrar will send an email confirmation of the registration and/or enrollment to the person initiating the registration immediately following the registration and/or enrollment.

5. TREATMENT PLAN

5.1 Pretreatment criteria: Patients with biopsy confirmed prostate cancer who meet eligibility criteria as defined in section 3.

5.2 Agent Administration

5.2.1 Treatment will be administered on an outpatient basis. Expected toxicities and potential risks as well as dose modifications for enzalutamide are described in Section 6 (Expected Toxicities and Dosing Delays/Dose Modification). No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

5.2.2 Patients will be treated in 6 (28 +/-3 days) cycles. EBRT will be initiated 7-10 weeks into enzalutamide therapy. Patients will be seen every 28 (+/-3 days) days for history and physical, adverse event and concomitant medication assessment. At these visits routine laboratory parameters will be obtained and a subset of these must be reviewed prior to dispensing the investigational agent. The routine laboratories at the beginning of each cycle should be completed per the Study Calendar in section 8.
The criteria to treat at the beginning of each cycle are:

- ANC greater than 1,000mm3
- Hgb greater than 8.0 g/dL
- Platelets greater than or equal to 50,000
- ALT less than 3.5x upper limit normal
- AST less than 3.5x upper limit normal

Any grade (3 or greater) non-hematologic adverse event (such as fatigue, etc.) must be resolved to (grade 1 or less) in order to continue therapy. The Medical Monitor should be notified of any adverse events that require holding, stopping or dose modifications of study drug.

5.2.2.1 Identity of Investigational Product

The study drug, enzalutamide, has the chemical name 3-(4-cyano-3-trifluoromethylphenyl)-1-[3-fluoro-4-(methylcarbamoyl) phenyl]-5,5-dimethyl-2-thioxoimidazolin-4-one. The drug substance has no chiral centers and no salt forms are available at ~ pH 2 to 10. It is essentially insoluble in water, but partially soluble in lipid-based solutions.

Enzalutamide inhibits androgen receptor signaling with a novel mechanism. Enzalutamide binds to the androgen receptor and is inhibited from translocation into the nuclease thereby blocking androgen receptor interaction with the chromatin and androgen inducible effects. Enzalutamide with LH-RH agonists have been shown to improve survival in castrate resistant prostate cancer (4). In an unpublished recently completed study, enzalutamide was shown to be safe in hormone-naïve prostate cancer patients with minimal toxicity. Effects on serum PSA levels and clinical outcome in this population are presently unavailable.\

5.2.2.2 Product Characteristics

The drug substance is formulated in the surfactant Labrasol. The drug product is provided as 40 mg soft gelatin capsules in 124-count bottles with induction-sealed, child-resistant caps.

5.2.2.3 Directions for Administration Enzalutamide

Study participants will self-administer the total daily dose (160 mg) of enzalutamide as a single dose, once daily. Enzalutamide can be taken with or without food. Enzalutamide may be taken at any time during the day, but should be taken at the same time each day. A missed dose should be taken as soon it is remembered. If twelve or more hours have lapsed since their regularly scheduled time, patients should not take the missed dose; rather the patient should

resume dosing at the next scheduled dose. Patients should not double up or take more than 1 dose of enzalutamide per day. Vomited doses should not be made up. Enzalutamide should not be crushed.

5.2.2.4 Storage and Labeling

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 Medivation Inc. as supplier. Patients will be instructed to store bottles containing enzalutamide capsules at room temperature

5.2.3 External Beam Radiation

5.2.3.1 Dose Specifications: 3D Conformal Radiotherapy (3DCRT) or IMRT

Dose will be normalized such that exactly 98% of the PTV (planned target volume) receives the prescription dose and will be scored as per protocol. The maximum allowable dose within the PTV is 107% of the prescribed dose to a volume that is at least 0.03 cc. The minimum allowable dose within the PTV is >95% of the prescribed dose to a volume that is at least 0.03 cc.

EBRT shall receive prescription doses to the PTV 75.6- 79.2 Gy delivered in 1.8 Gy fractions. All attempts should be made to deliver the
PTV dose with the above heterogeneity constraints with adherence to the critical structure parameters listed below:

Normal organ Limit *	No more than 15% volume receives dose that exceeds	No more than 25% volume receives dose that exceeds	No more than 35% volume receives dose that exceeds	No more than 50% volume receives dose that exceeds
Bladder Constraint	**80 Gy**	**75 Gy**	**70 Gy**	**65 Gy**
Rectum Constraint	**75 Gy**	**70 Gy**	**66 Gy**	**60 Gy**

5.2.3.2 Technical Factors

RT will be delivered with megavoltage equipment at energies ≥6 MV.

5.2.3.3 EBRT Localization, Simulation, and Immobilization

Simulation will be CT-based in all cases. The use of urethral contrast at the time of simulation is recommended but not required. The degree of bladder fullness should be made to duplicate that which is anticipated for daily treatment, i.e., if the patient is instructed to maintain a full bladder for treatment, he should be simulated as such (CT images should be acquired at a slice thickness of ≤3 mm from the top of the iliac crests superiorly to the perineum inferiorly. Target volumes and normal critical structures will be defined in the slices in which they are

visualized. The 3DCRT cases must utilize "beam's eye view" representations to define final beam aperture.

5.2.3.4 Fiducial Placement:
Fiducial markers placed within the prostate are required for this protocol. This procedure is routinely performed to permit pre-treatment imaging and position corrections to improve the precision of the external beam delivery (Image Guided Radiation Therapy). The placement of the three gold markers is performed by a Urologist. The fiducials are placed under transrectal ultrasound guidance. The fiducials are placed in the prostate so they do not overlap in the anterior and lateral x-ray projection.

Patients will be asked to participate in a procedure for correlative studies. This is not mandatory for participation. Two routine transrectal ultrasound guided biopsies will be taken in the location of previously identified disease on the diagnostic core biopsy report. These tissues samples will be stored for correlative tissue analysis.

5.2.3.5 Treatment Planning/Target Volumes
The definition of volumes will be in accordance with the ICRU Report #50: Prescribing, Recording, and Reporting Photon Beam Therapy. The Gross Tumor Volume (GTV) is defined by the physician as all known disease as defined by the planning CT, urethrogram, and clinical information. If a urethrogram is used, the GTV will encompass a volume inferiorly 5 mm superior to the tip of the dye and no less than the entire prostate. Prostate dimensions should be defined as visualized on CT scan.

The Clinical Target Volume (CTV) is the GTV plus areas considered to contain microscopic disease, delineated by the treating physician, and is defined as follows:
CTV is the GTV (prostate) plus areas at risk for microscopic disease extension plus the proximal bilateral seminal vesicles. Only the proximal 1.0 cm of seminal vesicle tissue adjacent to the prostate shall be included in the clinical target volume. This 1.0 cm of seminal vesicles refers to both radial (in plane) and superior (out of plane) extent. If both prostate and seminal vesicle are visualized in the same CT slice, this seminal vesicle tissue will contribute to the 1.0 cm of tissue. The Planning Target Volume (PTV) will provide a margin around the CTV to compensate for the variability of treatment set up and internal organ motion. A range of 5-10 mm around the CTV is required to define each respective PTV. Superior and inferior margins (capping)should be 5-8 mm depending on the thickness and spacing of the planning CT scan. Careful consideration should be made when defining the 5-8 mm margin in 3 dimensions. The ICRU Reference Points are to be located in the central part of the PTV and, secondly, on or near the central axis of the beams. Typically these points should be located on the beam axes or at the intersection of the beam axes.
Normal Critical Structures to be defined on the treatment planning CT scan will include the following: bladder, rectum (from its origin at the rectosigmoid flexure superiorly or the bottom of the SI joints, whichever is more inferior to the inferior-most extent of the ischial tuberosities), bilateral femora (to the level of ischial tuberosity), penile bulb and skin. Any

small bowel within the primary beam aperture should be defined as well. All structures will be contoured in their entirety as solid organs.
Superior and inferior margins (capping) should be 5-10 mm depending on the thickness and spacing of the planning CT scan.
Careful consideration should be made when defining the 5-10 mm margin in 3 Dimensions. The PTV forms the entire target as described. No extension of fields to specifically treat regional lymph nodes is permitted. 3D conformal beams will be shaped to include the entire PTV and minimize dose to surrounding critical structures as described. Intensity modulated radiotherapy (IMRT) using inverse planning is permitted with constraints placed to adhere to critical structure dose limitations as defined above.

5.2.3.6 Critical Structures
Every effort should be made to deliver prescription doses to the PTV as specified while adhering to these constraints, it is recognized that certain anatomical factors may prevent this.

For purposes of compliance, up to a 5% absolute increase in the volume of critical structure receiving greater than the specified dose will be considered" variation acceptable," e.g. up to 20% of the rectum may receive a dose of > 75.6 Gy without a protocol deviation. Any increase in critical structure volume greater than 5% receiving more than the specified dose will be considered a "deviation unacceptable". The prescription dose should be the maximum deliverable up to 79.2 Gy while respecting the critical normal structure constraints. Of note, the penile bulb constraint is to be regarded as a guideline, and adherence to this should not, in any way, result in a reduction of the prescription dose or compromised dose coverage of the target volume.

5.2.3.7 Treatment Verification
First day port films or portal images of each field along with orthogonal isocenter verification films (or images) must be obtained. If modifications are made in field shaping or design, a port film of each modified field along with orthogonal isocenter verification films (or images) is required on the first day's treatment of that field. Thereafter, weekly verification films or images of orthogonal isocenter views (anterior to posterior and lateral projection) are required. The intensity profiles of each beam must be independently verified and compared to the planned field intensity. Portal films are not required for IMRT but orthogonal verification films are required. Daily on-line target localization (kV or MV imaging with fiducials) should be performed.

5.2.3.8 Quality Assurance Documentation
Requirements:
The institution will archive treatment prescription and verification images for later review by the study chair if requested. 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

5.2.3.9 Compliance Criteria

The minimum allowable dose within the PTV is >95% of the prescribed dose to a volume that is at least 0.03cc. Cases in which this small volume of at least 0.03cc receives a minimum dose that is <95% but >93% or a maximum dose that is >107% and <110% of the prescribed dose will be scored as a variation acceptable. Cases in which such a small volume receives less than 93% or >110% of the prescribed dose will be scored as a deviation and unacceptable. Acceptable dose heterogeneity will be as follows: **This maximum dose volume of the PTV must not be shared by a normal critical structure.** The maximum point dose to normal critical structures outside the PTV should not exceed the prescription dose.

The treating physician must carefully consider the tolerance dose/volume to each critical normal structure and unspecified tissue.

5.3 General Concomitant Medication and Supportive Care Guidelines

5.3.1 Prior and Concomitant Therapy

5.3.1.1 Medications taken within 14 days prior to the first dose of study drug will be documented on the appropriate case report form as a prior medication. Medications taken after the first dose of study medication and until 30 days following the last dose of any study drug (enzalutamide) will be documented on the appropriate case report form as concomitant medication. All concomitant medication(s) must be reported on the appropriate case report form. Prior and concomitant medications include all vitamins, herbal remedies, over the counter, and prescription medications. If an intermittent or as needed use of any medication during the study is due to an adverse event, then the adverse event must also be recorded on the adverse event case report form.

5.3.1.2 The following medications are prohibited within 4 weeks of first study drug administration and throughout time on study, unless otherwise indicated below:

Androgens (e.g., testosterone, dihydroepiandrosterone), estrogens, or progestational agents Ketoconazole, diethylstilbestrol, PC-SPES, and other preparations such as saw palmetto thought to have endocrine effects on prostate cancer:

- Radiopharmaceuticals such as strontium (^{89}Sr) or samarium (^{153}Sm), radium 223 ○ Aldactone, Spironol (spironolactone), eplerenone;
- Herbal medications, such as Prostasol and PC-SPES, St. Jon's Wort; ○ Cancer Vaccine therapy;
- Non-cytotoxic, non-investigational anti-tumor treatment;
- Use of an investigational agent, unless prior approval by the PI, Glenn Bubley, MD, for a shorter washout period, provided the patient has adequately recovered from any ongoing adverse events.
- Any alternative remedy that may affect hormonal status.

- Caution is advised for patients taking drugs metabolized through either CYP3A4 or CYP2C8 pathways. Please see Appendix F.

5.4 Duration of Therapy

5.4.1 Enzalutamide - 6 (28 +/-3 days) cycles-expected

5.4.2 External beam radiation up to 11 weeks-expected

5.4.3 Treatment will continue for 6 (28 day) cycles or until one of the following criteria applies:

- Disease progression;
- Intercurrent illness that prevents further administration of treatment;
- Unacceptable adverse event(s);
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements;
- Participant decides to withdraw from the study; or
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the opinion of the treating investigator.

5.5 Duration of Follow-up

5.5.1 Patients will be followed on study for 3 months after treatment (cessation of enzalutamide). Additional follow-up to assess the status of the cancer will be conducted at the discretion of the treating physicians

5.5.2 In the event a patient discontinues enzalutamide due to a related adverse event, follow up will continue until adequate resolution of the adverse event, the physician deems the adverse event to be stable, the patient initiates another systemic antineoplastic drug or an investigational drug, or the patient withdraws consent from the study.

6. EXPECTED TOXICITIES AND DOSING DELAYS/DOSE MODIFICATIONS

6.1.1 Fiducial placement for prostate tracking during external beam +/- biopsy

Likely:

- Discomfort from the placement of needles into the prostate for fiducial placement and biopsy
- Minor Rectal bleeding

Rare:

- Significant bleeding requiring transfusion and/or hospitalization Infection

Extremely Rare:

- Massive bleeding
- Death

6.1.2 External Beam Radiation

6.1.2.1Acute Reaction

Common

- Urinary frequency
- Dysuria
- Increase bowel frequency
- Exacerbation of hemorrhoids

Uncommon

- Significant fatigue

Rare

- Diarrhea
- Rectal bleeding
- Skin erythema
- Urinary obstruction

6.1.2.2 Late Reaction

Common

- Dry ejaculation
- Erectile dysfunction
- Sterility

Uncommon

- Rectal mucous discharge
- Rectal bleeding

Rare

- Gross hematuria
- Chronic diarrhea

- Rectal bleeding requiring management

Extremely Rare

- Significant rectal bleeding requiring transfusion
- Radiation induced damage of normal tissues requiring surgery
- Second cancers
- Death

6.1.3 Enzalutamide

Common

- Peripheral Edema
- Flushing
- Diarrhea
- Neutropenia
- Arthralgia
- Musculoskeletal pain
- Fatigue
- Gynecomastia

Serious

- Seizure
- Spinal cord compression
- Infectious disease

Rare

- Rash
- Neutropenia (grade 3 and 4)
- Short term memory loss

Evidence of seizure will result in cessation of enzalutamide and withdrawal from the study. Other Grade 3 or 4 possibly-related non-hematologic toxicity, including fatigue, may result in dose reduction. Based upon experience from Phase 3 studies enzalutamide is generally well tolerated. The most common adverse events related to enzalutamide include fatigue and nausea. Any dose reduction of enzalutamide requires consultation with the Medical Monitor. Instructions on dose reduction for various toxicities are provided below (section 6.2):

6.2 TOXICITY MANAGEMENT

6.2.1 Management of Radiation Toxicity

6.2.1.1 Urinary

6.2.1.1.1 Symptomatic urinary medicines, such alpha blockers for decreased urinary flow
6.2.1.1.2 NSAIDS for dysuria if no contraindication.

6.2.1.2 Rectal
6.2.1.2.1 Low fiber diet
6.2.1.2.2 Loperamide at the discretion of the treating physician.

6.2.1.3 Management of gynecomastia
At the discretion of the treating physician, at any time before or during treatment patients are permitted to receive radiation therapy to the breasts to prevent or treat gynecomastia Treatments such as tamoxifen are not permitted for gynecomastia.

6.2.2 Management of enzalutamide toxicity

6.2.2.1 If Grade 1–2 toxicities occur, give supportive care per institutional guidelines. No enzalutamide dose reduction should occur. However, at the discretion of the treating physician, an investigator can hold enzalutamide for intolerable Grade 2 toxicity for a maximum of 14 days. Participants should resume enzalutamide at the original dose (160 mg/day). If the participant is not able to resume study medication after being held for 14 days, the participant must be permanently removed from the study.

6.2.2.2 If Grade 3 fatigue occurs, hold enzalutamide and contact the medical monitor for appropriate instructions on dose reduction.

6.2.2.3 If Grade 3 or higher toxicities occur that are considered potentially related to enzalutamide including headache (that interferes with activities of daily living [ADL]), nausea (requiring total parenteral nutrition or intravenous fluids), vomiting (> 6 episodes/24 hours requiring total parenteral nutrition or intravenous fluids), diarrhea (requiring intravenous fluids or hospitalization, or resulting in hemodynamic collapse), or any other toxicity where patient safety is jeopardized, hold enzalutamide. When the toxicity has resolved to ≤ Grade 1, resume study medication at the full dose. Prophylactic medications should be considered as appropriate. If toxicity recurs, hold study medication and adjust or add medications to mitigate the toxicity. When the recurrent toxicity has resolved to ≤ Grade 1, resume enzalutamide at 120 mg/day (3 pills /day). This should be done with the approval of the PI and the medical monitor.

6.3 Dose Modification /Delays

6.3.1 Dose delays and modifications will be made using the following recommendations. NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for

Toxicity assessments will be done using the CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) which is identified and located on the CTEP website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

If possible, symptoms should be managed symptomatically. However, if a seizure occurs, stop medication immediately. Patients will be removed from study, and medical monitor will be contacted. In the case of toxicity, appropriate medical treatment should be used (including antiemetics, anti-diarrheals, etc.).

All adverse events experienced by participants will be collected from the time of the first dose of study treatment, through the study and until the final study visit. Participants continuing to experience toxicity at the off study visit may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

If a patient misses study medication for a total of 14 days, they should be discontinued from the study.

Discontinuing or temporally stopping EBRT is at the discretion of the treating physician. Treatment with radiation should be temporarily or permanently stopped due to excessive bowel and/or bladder symptoms not ameliorated with medications or other supportive measures. Temporary stopping the EBRT is not a protocol violation as long as the radiation is completed in nine and half weeks (ten missed weekday treatments during EBRT).

7.0 CORRELATIVE/SPECIAL STUDIES

7.1 Pharmacokinetics-N/A

7.2 Pharmacodynamics-N/A

7.3 Assessment of AR localization by IHC. (See section 10.5)

8.0 STUDY CALENDAR

	Screening (4 week period)	**Baseline (Day One Cycle 1)[5]+/- 3 day**	**At fiducial placement (3-7 weeks) (Study) (+/- 3 day)**	**Cycle 2, Day One (+/- 3 day)**	**Cycle 3, Day One (+/- 3 day)**	**Cycle 4, Day One (+/- 3 day)**	**Cycle 5, Day One (+/- 3 day)**	**Cycle 6, Day One (+/- 3 day)**	**End of cycle 6 (+/- 3 day)**	**3[6] months after completion of cycle 6**
Hx/PE	X	X		X	X	X	X	X	X	X
Vital signs	X	X		X	X	X	X	X	X	X
Height/weight[3]		X		X	X	X	x	x	x	
CBC with diff	X	X		X	X	X	X	X	X	X
Chemistry/LFTs [9]	X	X		X	X	X	X	X	X	X
Bone Metabolism markers[1,5]		X							X	X
PSA	X	X		X	X	X	X	X	X	X
Hormonal measurements[2, 5]	X[11]	X					X		X	
Anthropomorphic measurements[3] and waist circumference		X							X	
Prostate tissue samples (optional)			X							
Q of L assessment[4]		X			X		X		X	X
Dispense med/Pill diary		X		X	X	X	X	X	X[7]	
Adverse event and con med		X		X	X	X	X	X	X	
EBRT				X[8]	X[8]					
Sign Informed Consent	X									
EKG	X									
Assessment of breast enlargement[10]		X		*	*	X	*	*	X	

- 1 -bone specific alk phos, serum C-teleopeptide, serum N terminal propeptide of type I collagen (fasting)
- 2- DHEA sulfate, estrogen (estradiol), free testosterone, total testosterone, estrone, androstenedione. These should be done while fasting.
- 3 -Triceps skin fold, biceps (mid-upper arm circumference), shoulder blade and waist. Height will only be necessary at the baseline visit.
- 4- EPIC-26, PROMIS, PSQI
- 5 -Any time between Day -7 to day 1
- 6- +/- 7 days
- 7- Collect pill diary and unused drug
- 8 - EBRT 7-10 weeks after initiating enzalutamide. This could fall on cycle 2 or 3.
- 9 -Chemistries includes: creatinine, BUN, potassium, sodium, bicarbonate LFT's include AST, ALT, total bilirubin and alkaline phosphatase.
- 10- Assessment will be done with calipers. The maximum diameter of the larger breast (if there is asymmetry) at Baseline
- (Day One Cycle 1), Cycle 4/day 1, End of Cycle 6 and assess it according to these parameters: grade 1 (<=2cm), grade 2 (>2-<=4cm), grade 3 (>4-6cm), and grade 4 (>6cm).
- 11- At screening visit, the only hormonal test required is total testosterone which will not require morning collection or fasting.* We will ask you to answer a yes or no about breast tenderness and/or enlargement at every study visit.

9. MEASUREMENT OF EFFECT

9.1 Primary endpoint:

The primary endpoint is measured by PSA level. Patients achieving a PSA level ≤0.2 ng/ml at the end of six cycles of enzalutamide and EBRT treatment are considered successes.

9.2 Secondary endpoints

9.2.1. Safety and Tolerability

Safety and tolerability will be documented throughout the study by assessment of adverse events, vital signs and laboratory assessments as defined in the Schedule of Activities (Section 8). Adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.03 (NCICTCAE v4.03). Only toxicity with attribution of possibly, probably or definitely ('treatment-related') will be reported. Adverse events will be monitored and recorded until the safety follow-up visit (3 months after the completion of the drug therapy). Any glucose tests collected under previous protocol amendments will not be assessed for adverse events.

9.2.2. Health-Related Quality of Life

HRQoL will be assessed at baseline, at the beginning of cycles 3 day 1, cycle 5 day 1, end of cycle 6 and 3 months after completion of study.

Bone

Collagen type IC teleopeptide, procollagen Type I Intact N-terminal peptide, bone specific alkaline phosphatase. Should be done while fasting. Please see study calendar.

The Expanded-Prostate Index Composite – 26 (EPIC 26)

EPIC-26 evaluates patient's urinary incontinence (4 items), urinary irritation/obstruction (4 items), bowel (6 items), and vitality/hormonal function (5 items). All domains are reported on a scale of 0 – 100. EPIC is a robust prostate cancer HRQoL instrument that measures a broad spectrum of symptoms and has 50 items; however, to decrease patient burden only the domains most pertinent to this study will be used as represented in the EPIC-26. EPIC-26 has been validated in men with localized prostate cancer who underwent surgery, external beam radiation, or brachytherapy with or without the use of hormonal adjuvants. Further information on EPIC can be found at the University of Michigan website: http://www.med.umich.edu/urology/research/epic.html.

Patient-Reported Outcome Measurement Information System (PROMIS)-Fatigue Short Form

PROMIS was developed as part of the NIH Roadmap Initiative, focused on developing a publicly available resource of standardized, accurate, and efficient PRO measures of symptoms, distress, and functioning. Two content domains of fatigue, experience and impact, were identified by a panel of experts. An item pool of 58 fatigue experience and 54 fatigue impact items were developed. The psychometric properties of these items were evaluated in a sample of 450 individuals from the general US population using classical test theory indices, monotonicity, and scalability. The expert panel selected the 10 best items in each domain. These 20 items were presented to a panel of clinical experts. Only one item was dropped because of redundancy. A fatigue short-form measure of 7 items was created using items selected for consistency in the response scale, broad coverage across the fatigue continuum (i.e., high to low), and good precision of measurement (discrimination function).

Pittsburgh Sleep Quality Index (PSQI)
Sleep quality will be measured by the PSQI, a self-rated questionnaire which measures sleep quality and disturbances. The Pittsburgh Sleep Quality Index was developed to discriminate between good and poor sleepers. The PSQI has good internal consistency (Cronbach's alpha=0.83), stability (test-retest reliability=.85, P<.001) and discriminant validity. It has been used in patients with cancer and demonstrated sleep problems as expected

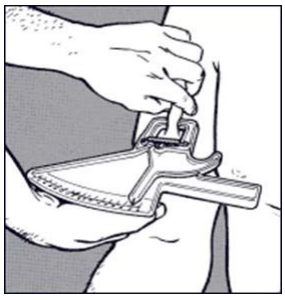
9.3 Serum Hormone Levels
Serum hormone levels include DHEA sulfate, estrone, free testosterone, total testosterone, estradiol (estrogen), androstenedione. These should be done while fasting.
See Study Calendar (Section 9) for the measurement time points.

9.4 Anthropomorphic Measures
Anthropomorphic measurements include Triceps skin fold, mid-upper arm circumference (biceps), shoulder blade and waist. (Section 8). Skin measurements will be done using Slim Guide Skinfold Caliper. Skin Measure will be taken at four different areas as below. A standard caliper will be supplied to all sites.

Measurement of body fat percentage is done using skinfold caliper by adding the measurements at four different locations (Triceps, Biceps, Shoulder blade and Waist).

Back of Upper Arm (right):
The back of upper arm (Triceps) is located halfway between the shoulder and elbow joints. The skinfold is taken in a vertical direction on the center of the back of the arm.

Front of Upper Arm (right)
The Front of upper arm (Biceps) is located halfway between the shoulder and elbow joints. The skinfold is taken in a vertical direction on the center of the front of the arm.

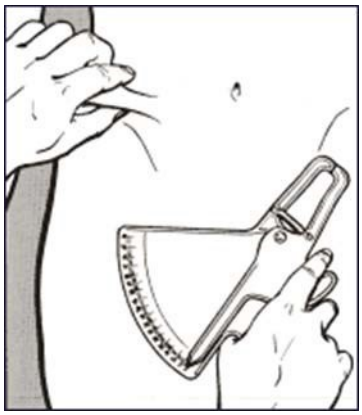


Upper Back (right):

Located just below the shoulder blade (Subscapular). The skinfold is taken at a 45° angle.

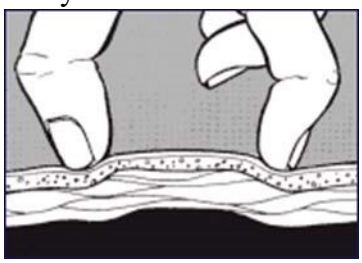
Waist (right):

Waist (Suprailiac) is located just above the iliac crest, the protrusion of the hip bone, a little towards the front from the side of the waist. The skinfold is taken horizontal.

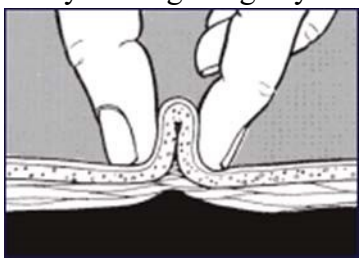


Skinfold Testing Technique

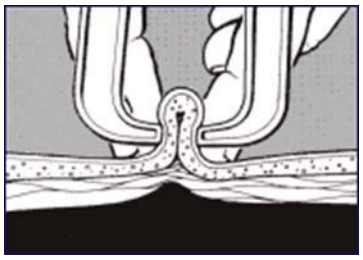
Use your thumb and index finger of your left hand to pinch an area of skin wide enough to get a good fold.



Pull out the fold of skin and underlying layer of fat with your left hand away from the body. You do not have to worry about getting any muscle as the muscle is firm and will not come into a fold with the skin and fat.



While holding the skinfold with the left hand, place the jaws of the calipers about 1/4" from the fingers of the left hand. Release the trigger of the caliper so the entire force of the jaws are on the skinfold. Without releasing the skinfold with the left hand, let the force of the caliper creep a bit for a few seconds to settle to the correct reading. Write down the measurement and proceed to the next location.



Measurement of lean muscle mass is done by multiplying the weight (in lbs.) by the body fat percentage. See Appendix G.

The breast enlargement assessment will be done with calipers. The maximum diameter of the larger breast (if there is asymmetry) at Baseline (Day One Cycle 1), Cycle 4/day 1, End of Cycle 6 and assess it according to these parameters: grade 1 (<=2cm), grade 2 (>2-<=4cm), grade 3 (>4-6cm), and grade 4 (>6cm).

Technique for measuring male breast tissue:
Proper technique is needed to examine the male breast. The thumb and index finger are used to grasp and gently pinch the periareolar area of the breast and to palpate glandular breast tissue, which is rubbery in consistency and firmer than the surrounding adipose tissue. With this technique, gynecomastia can usually be distinguished from excessive breast adipose tissue, called pseudo gynecomastia, which is often associated with generalized obesity. Gynecomastia is usually bilateral and relatively symmetric, but occasionally it is asymmetric and more prominent on one side. If present, asymmetric gynecomastia may suggest breast carcinoma, which is usually rock-hard and irregular and may be associated with skin dimpling (peau d'orange), nipple retraction or discharge, and axillary lymphadenopathy. The diameter of palpable breast tissue is used as an objective measure of gynecomastia. Gynecomastia of recent onset is usually tender on palpation, and men usually complain of nipple irritation associated with rubbing against clothing. The proper method of examining the male breast is to use the thumb and index finger to grasp the periareolar area of the breast and to gently pinch the thumb and index finger together on either side of the breast toward the nipple. Glandular breast tissue feels like a rubbery disc of tissue that extends concentrically from under the nipple and subareolar area and is firmer than the surrounding adipose tissue. The size of gynecomastia is estimated by measurement of the diameter of palpable breast tissue.[10]

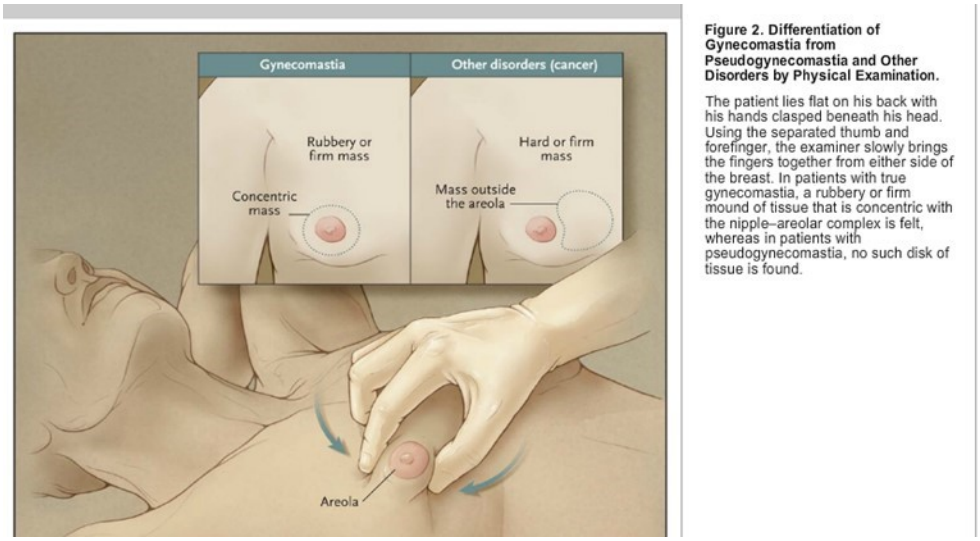


Figure 2. Differentiation of Gynecomastia from Pseudogynecomastia and Other Disorders by Physical Examination.

The patient lies flat on his back with his hands clasped beneath his head. Using the separated thumb and forefinger, the examiner slowly brings the fingers together from either side of the breast. In patients with true gynecomastia, a rubbery or firm mound of tissue that is concentric with the nipple–areolar complex is felt, whereas in patients with pseudogynecomastia, no such disk of tissue is found.

9.5 Correlative Endpoint

Prostate biopsy samples from patients obtained during fiducial placement will be formalin fixed and paraffin embedded analogous to routine prostate biopsies. Freshly cut sections will be stained for AR using commercially available antibodies. Patient samples that have tumor will be analyzed for AR overall expression. High powered tumor sections demonstrate that at least 50% of the tumor cells express AR. These will be graded for nuclear expression as none, rare, less than expression in the cytoplasm or greater or equal to cytoplasmic expression.

Please page the study coordinator, Cesar Vazquez at 617-632-9289 and Bonnie Wong at 617-632-9279 or page through the BIDMC operator at 617-632-PAGE.

10. ADVERSE EVENT REPORTING REQUIREMENTS

10.1 Definitions 10.1.1 Adverse Event (AE)

An adverse event (AE) is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study.

Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests. **10.1.2** Serious adverse event (SAE)

A serious adverse event (SAE) is any adverse event, occurring at any dose and regardless of causality that:

- Results in death

- Is life-threatening. Life-threatening means that the person was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- Requires or prolongs inpatient hospitalization (i.e., the event required at least a 24-hour hospitalization or prolonged a hospitalization beyond the expected length of stay). Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered SAEs if the illness or disease existed before the person was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly or birth defect; or
- Is an important medical event when, based upon appropriate medical judgment, it may jeopardize the participant and require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Events **not** considered to be serious adverse events are hospitalizations for:

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

10.1.3 Expectedness

Adverse events can be 'Expected' or 'Unexpected.'

10.1.3.1 Expected adverse event

Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.

Refer to Section 6.1 for a partial listing of expected adverse events associated with the study agent(s). 10.1.3.2 Unexpected adverse event

For the purposes of this study, an adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list,

the Investigator's Brochure, the package insert or when it is not included in the informed consent document as a potential risk.

10.1.4 Attribution

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study treatment.
- Probable – The AE is likely related to the study treatment.
- Possible – The AE may be related to the study treatment.
- Unlikely - The AE is doubtfully related to the study treatment.
- Unrelated - The AE is clearly NOT related to the study treatment.

10.2 Procedures for AE and SAE Recording and Reporting

Participating investigators will assess the occurrence of AEs and SAEs at all participant evaluation time points during the study.

All AEs and SAEs whether reported by the participant, discovered during questioning, directly observed, or detected by physical examination, laboratory test or other means, will be recorded in the participant's medical record and on the appropriate study-specific case report forms.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0.
A copy of the CTCAE version 4.0 can be downloaded from the CTEP website at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

10.3 Reporting Requirements

For multi-site trials where a DF/HCC investigator is serving as the principal investigator, each participating investigator is required to abide by the reporting requirements set by the DF/HCC. The study must be conducted in compliance with FDA regulations, local safety reporting requirements, and reporting requirements of the principal investigator.

Each investigative site will be responsible to report SAEs that occur at that institution to their respective IRB. It is the responsibility of each participating investigator to report serious adverse events to the study sponsor and/or others as described below.

10.4 Reporting to the Study Sponsor 10.4.1

Serious Adverse Event Reporting

All serious adverse events that occur after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment must be reported to the DF/HCC Overall Principal Investigator on the local institutional SAE form. This includes events meeting the criteria outlined in Section 10.1.2, as well as the following:

- Grade 2 (moderate) and Grade 3 (severe) Events – Only events that are unexpected and possibly, probably or definitely related/associated with the intervention.

- All Grade 4 (life-threatening or disabling) Events – Unless expected AND specifically listed in the protocol as not requiring reporting.

- All Grade 5 (fatal) Events – When the participant is enrolled and actively participating in the trial OR when the event occurs within 30 days of the last study intervention.

Note: If the participant is in long term follow up, report the death at the time of continuing review.

Participating investigators must report each serious adverse event to the DF/HCC Overall Principal Investigator as well as the Astellas Safety Department within 24 hours of learning of the occurrence. In the event that the participating investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the adverse event. Report serious adverse events by telephone, email or facsimile both to:

DF/HCC Overall Principal Investigator and Medical Monitor:
Glenn Bubley, MD
gbubley@bidmc.harvard.edu
Phone 617-735-2062
Fax 617-735-2060

Astellas Safety Department:
Astellas Pharma Global Development – United States
Email: Safety-us@us.astellas.com
Fax number: (847) 317-1241

Within the following 24-48 hours, the participating investigator must provide follow-up information on the serious adverse event. Follow-up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation.

10.4.2 Non-Serious Adverse Event Reporting

Non-serious adverse events will be reported to the DF/HCC Overall Principal Investigator on the toxicity Case Report Forms.

10.5 Reporting to the Institutional Review Board (IRB)

Investigative sites within DF/HCC will report all serious adverse events directly to the DFCI Office for Human Research Studies (OHRS).

Other investigative sites should report serious adverse events to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. A copy of the submitted institutional SAE form should be forwarded to:

Office for Human Research Studies
Dana Farber Cancer Institute
20 Overland St., 2nd Floor (physical location)
450 Brookline Ave, OS229 (mailing location)

Boston, MA - 02215

Phone 617-632-3029

Fax 617-632-2686

The DF/HCC Principal Investigator will submit SAE reports from outside institutions to the DFCI Office for Human Research Studies according to DFCI IRB policies and procedures in reporting adverse events.

10.6 Reporting to the Food and Drug Administration (FDA)

Use on Med watch form 3500A

10.7 Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any subject safety reports or sentinel events that require reporting according to institutional policy.

10.8 Monitoring of Adverse Events and Period of Observation

All adverse events, both serious and non-serious, and deaths that are encountered from initiation of study intervention, throughout the study, and within 30 days of the last study intervention should be followed to their resolution, or until the participating investigator assesses them as stable, or the participating investigator determines the event to be irreversible, or the participant is lost to follow-up. The presence

and resolution of AEs and SAEs (with dates) should be documented on the appropriate case report form and recorded in the participant's medical record to facilitate source data verification.

For some SAEs, the study sponsor or designee may follow-up by telephone, fax, and/or monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. Participating investigators should notify the DF/HCC Overall Principal Investigator of greater or equal to grade 3 events and the IRB of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

11. DATA AND SAFETY MONITORING

11.1 Data Reporting

11.1.1 Method

The QACT will collect, manage, and monitor data for this study.

11.1.2 Data Submission

The schedule for completion and submission of case report forms (paper or electronic) to the QACT is as follows:

Form	**Submission Timeline**
Eligibility Checklist	Complete prior to registration with QACT
On Study Form	Within 14 days of registration
Baseline Assessment Form	Within 14 days of registration
Treatment Form	Within 10 days of the last day of the cycle
Adverse Event Report Form	Within 10 days of the last day of the cycle
Response Assessment Form	Within 10 days of the completion of the cycle required for response evaluation
Off Treatment/Off Study Form	Within 14 days of completing treatment or being taken off study for any reason

Follow up/Survival Form	Within 14 days of the protocol defined follow up visit date or call

11.2 Safety Meetings

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this trial. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Principal Investigator and study team.

The DSMC will meet quarterly and/or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

11.3 Ongoing Monitoring of Protocol Compliance

At the Discretion of the Overall Investigator, the Participating Institutions will be required to submit participant source documents to the DF/HCC Lead Institution for remote monitoring by the Clinical Trial Specialist and or Lead site coordinator.

At the Discretion of the Overall Investigator, the Participating Institution may require at least one on-site monitoring visit conducted by the Overall Investigator and or Clinical Trial Specialist and or Lead site Coordinator. The DF/HCC Lead Institution will implement monitoring activities ongoing to ensure that Participating Institutions are complying with regulatory and protocol requirements, data quality, and participant safety. Additional monitoring practices may include but are not limited to: source verification, review and analysis of the following: eligibility requirements of all participants , informed consent procedures, adverse events and all associated documentation, study drug administration / treatment, regulatory records and site trial master files, protocol deviations, pharmacy records, response assessments, and data management.

Monitoring can occur during any time during a site's participation up unto and including study completion.

All data submitted to the DF/HCC QACT will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. The Lead Institution or designee and if applicable QACT Data Analysts assigned to the Protocol will perform the ongoing protocol data compliance monitoring with the support of the Participating Institution's Principal Investigator and research team. The DF/HCC Lead Institution will maintain regular and ongoing communication to Participating Institutions about study related information.

12. REGULATORY CONSIDERATIONS

12.1 Protocol Review and Amendments

This protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other necessary documents must be submitted, reviewed and approved by a properly constituted IRB governing each study location.

Any changes made to the protocol must be submitted as amendments and must be approved by the IRB prior to implementation. Any changes in study conduct must be reported to the IRB. The DF/HCC Overall Principal Investigator (or Protocol Chair) will disseminate protocol amendment information to all participating investigators.

All decisions of the IRB concerning the conduct of the study must be made in writing.

12.2 Informed Consent

All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant's legally authorized representative, and by the person obtaining the consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

12.3 Ethics and Good Clinical Practice (GCP)

This study is to be conducted according to the following considerations, which represent good and sound research practice:

- E6 Good Clinical Practice: Consolidated Guidance
  www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129515.pdf

- US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki

    - Title 21 Part 11 – Electronic Records; Electronic Signatures
      www.access.gpo.gov/nara/cfr/waisidx_02/21cfr11_02.html

    - Title 21 Part 50 – Protection of Human Subjects
      www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html

    - Title 21 Part 54 – Financial Disclosure by Clinical Investigators
      www.access.gpo.gov/nara/cfr/waisidx_02/21cfr54_02.html

    - Title 21 Part 56 – Institutional Review Boards
      www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html

- Title 21 Part 312 – Investigational New Drug Application www.access.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html

- State laws

- DF/HCC research policies and procedures http://www.dfhcc.harvard.edu/clinical-researchsupport/clinical-research-unit-cru/policies-and-procedures/

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. In such case, the deviation must be reported to the IRB according to the local reporting policy.

12.4 Study Documentation

The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified.

Original source documents supporting entries in the case report forms include but are not limited to hospital records, clinical charts, laboratory and pharmacy records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays.

12.5 Records Retention

All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

13. STATISTICAL CONSIDERATIONS

13.1 Sample Size/Accrual Rate

The primary objective is to estimate the proportion of patients having intermediate risk CaP treated with external beam radiation therapy (EBRT) and enzalutamide whose PSA level at the end of six cycles of enzalutamide and EBRT is ≤0.2 ng/ml. In a single stage design, seventy-one patients will be enrolled. Assuming 10% ineligibility, the target evaluable sample size is 64 patients. The null hypothesis is 60% of patients achieving PSA nadir ≤0.2 ng/ml. The historical rate will serve as the alternative in this design. Based on research by D'Amico et al, the proportion of patients achieving PSA level ≤0.20 ng/ml at the end of EBRT and 6 months of leuprolide acetate neo-adjuvant/adjuvant treatment is 75%. With a sample size of 64 evaluable patients, if the number achieving PSA level ≤0.2 ng/ml is 44 or more, then the hypothesis that the percentage achieving PSA level ≤0.2 ng/ml is ≤60% is rejected with a target error rate of α=0.10 (actual error 0.095), whereas if the number is 43 or less, then the hypothesis that the percentage achieving PSA level ≤0.2 ng/ml is ≥75% is rejected with a target error rate of β=0.10 (actual β=0.099). We also will report exact binomial 90% confidence intervals on the observed proportion. Patients that discontinue early or are missing the end of treatment (cycle 6) PSA will be considered failures. Sensitivity analysis on the primary endpoint that includes counting a patient as a success if there is record of PSA level ≤0.20 ng/ml ever on treatment will be performed. We expect to accrue 2-3 patients per month at the three DF/HCC hospitals, BWH and DFCI and therefore accrual duration is expected to be 24-36 months.

13.2 Analysis of Secondary Endpoints

13.2.1 Health related quality of life

The primary HRQoL aim is to assess the change from baseline to the end of cycle 6 in the vitality or hormonal function score as well as the sexuality score on the EPIC-26 questionnaire. It is anticipated approximately 75% of patients will have both scores for each domain. A one-sample t-test will be used to assess the overall change in score. To be considered a clinically meaningful difference will be defined as half historical standard deviation for the specific domain. Given 48 evaluable patients, there is 80% power to detect a 0.41 change in the hormonal domain score of the EPIC-26 assuming 2-sided 5% alpha. Results in this study will be evaluated in the context of past research by Sanda et al showing patients that received radiotherapy with non-hormonal therapy had a score on the vitality or hormonal function domain of approximately 80 and a score on the sexuality domain of 26.

Descriptive statistics at each time point and changes over time will be provided for each of the EPIC-26 domains as well as for the PROMIS-Fatigue and PSQ1. Mixed models will be used to explore the impact of time on quality of life adjusting for prognostic baseline factors.

13.2.2 Safety and Tolerability: We will monitor toxicities experienced by all treated patients. Frequency and severity of worst grade 3 or higher treatment-related AEs by type will be reported along with the incidence of overall grade 3 or higher treatment-related AEs. With 71 treated patients, the maximum width of a 90% CI for a given toxicity is 21%. The probability of observing one rare severe toxicity (true rate=5%) is 97%. Tolerability endpoints include the number of dose reductions and treatment interruptions as well as the number of patients that discontinue treatment due to AEs. The safety summary will include clinical laboratory, ECG and vital signs data.

13.2.3 Hormone Levels: Descriptive statistics at each time point and changes over time will be provided for all hormone measures. Paired t-tests and two-sample t-tests (or non-parametric equivalents) will be used to assess significance of change over 6 cycles of treatment in hormone levels for the overall cohort and by status on primary clinical endpoint (yes or no achieving PSA level $\leq$0.20 ng/ml at the end of 6 cycles of treatment with enzalutamide and EBRT).

13.2.4. Anthropomorphic Measurements: Descriptive statistics at each time point and change over 6 cycles will be provided for all anthropomorphic measures.

13.3 Analysis of Correlative Endpoint

We anticipate that at approximately 75% of patients will consent to have prostate samples removed at the time of the fiducial placement. We expect to detect tumor from samples from at least half of these patients. Therefore we expect that we will have conservatively ~24 patients that have samples that are evaluable. Nuclear expression grade will be tabulated. This unique resource will serve as a pilot to help in the understanding of the mechanism of enzalutamide action when the pattern of AR expression is compared to pre-treatment biopsy samples and samples from other patient tumors.

14. REFERENCES

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15. APPENDICES

Appendix A: PROMIS Sleep Survey

Appendix B: Pittsburg Sleep Quality Index

Appendix C: EPIC-26

Appendix D: Eastern Cooperative Oncology Group Performance Status

Appendix E: Research Labs

Appendix F: Drugs to be used with caution or avoided

Appendix G: Charts to calculate body fat %

Appendix H: Pill Diary

Appendix A:

PROMIS Item Bank v1.0 – Pain Interference – Short Form 8a

Pain Interference – Short Form 8a

Please respond to each question or statement by marking one box per row.

In the past 7 days…

		Not at all	A little bit	Somewhat	Quite a bit	Very much
PAININ9 1	How much did pain interfere with your day to day activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ22 2	How much did pain interfere with work around the home?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ31 3	How much did pain interfere with your ability to participate in social activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ34 4	How much did pain interfere with your household chores?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ12 5	How much did pain interfere with the things you usually do for fun?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ36 6	How much did pain interfere with your enjoyment of social activities?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ3 7	How much did pain interfere with your enjoyment of life?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ13 8	How much did pain interfere with your family life?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

https://www.sleep.pitt.edu/wp-content/uploads/Study_Instruments_Measures/PSQI-Instrument.pdf

Version 13.0 Protocol Version Date: 1/09/2015

Appendix B:

PITTSBURGH SLEEP QUALITY INDEX

INSTRUCTIONS:
The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month.
Please answer all questions.

1. During the past month, what time have you usually gone to bed at night?

BED TIME _____

2. During the past month, how long (in minutes) has it usually taken you to fall asleep each night?

NUMBER OF MINUTES _____

3. During the past month, what time have you usually gotten up in the morning?

GETTING UP TIME _____

4. During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spent in bed.)

HOURS OF SLEEP PER NIGHT _____

For each of the remaining questions, check the one best response. Please answer all questions.

5. During the past month, how often have you had trouble sleeping because you . . .

a) Cannot get to sleep within 30 minutes

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

b) Wake up in the middle of the night or early morning

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

c) Have to get up to use the bathroom

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

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d) Cannot breathe comfortably

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

e) Cough or snore loudly

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

f) Feel too cold

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

g) Feel too hot

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

h) Had bad dreams

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

i) Have pain

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

j) Other reason(s), please describe_____

_____

How often during the past month have you had trouble sleeping because of this?

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

6. During the past month, how would you rate your sleep quality overall?

Very good _____

Fairly good _____

Fairly bad _____

Very bad _____

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7. During the past month, how often have you taken medicine to help you sleep (prescribed or "over the counter")?

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

8. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

9. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?

No problem at all _____

Only a very slight problem _____

Somewhat of a problem _____

A very big problem _____

10. Do you have a bed partner or room mate?

No bed partner or room mate _____

Partner/room mate in other room _____

Partner in same room, but not same bed _____

Partner in same bed _____

If you have a room mate or bed partner, ask him/her how often in the past month you have had . . .

a) Loud snoring

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

b) Long pauses between breaths while asleep

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

c) Legs twitching or jerking while you sleep

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

d) Episodes of disorientation or confusion during sleep

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

e) Other restlessness while you sleep; please describe_____

_____

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

https://www.sleep.pitt.edu/instruments/

SCORING INSTRUCTIONS FOR THE PITTSBURGH SLEEP QUALITY INDEX:

The Pittsburgh Sleep Quality Index (PSQI) contains 19 self-rated questions and 5 questions rated by the bed partner or roommate (if one is available). Only self-rated questions are included in the scoring. The 19 self-rated items are combined to form seven "component" scores, each of which has a range of 0-3 points. In all cases, a score of "0" indicates no difficulty, while a score of "3" indicates severe difficulty. The seven component scores are then added to yield one "global" score, with a range of 0-21 points, "0" indicating no difficulty and "21 " indicating severe difficulties in all areas.

Scoring proceeds as follows:

Component 1: Subjective sleep quality

Examine question #6, and assign scores as follows:

Response	Component 1 score
"Very good"	0
"Fairly good"	1
"Fairly bad"	2
"Very bad"	3

Component 1 score: _____

Component 2: Sleep latency

1. Examine question #2, and assign scores as follows:

Respo\nse	Score
≤15 minutes	0
16-30 minutes	1
31-60 minutes	2
> 60 minutes	3

Question #2 score: _____

2. Examine question #5a, and assign scores as follows:

Response	Score
Not during the past month	0
Less than once a week	1
Once or twice a week	2
Three or more times a week	3

Question #5a score: _____

3. Add #2 score and #5a score

Sum of #2 and #5a: _____

4. Assign component 2 score as follows:

Sum of #2 and #5a	Component 2 score
0	0
1-2	1
3-4	2
5-6	3

Component 2 score: _____

Component 3: Sleep duration

Examine question #4, and assign scores as follows:

Response	Component 3 score
> 7 hours	0
6-7 hours	1
5-6 hours	2
< 5 hours	3

Component 3 score:_____

Component 4: Habitual sleep efficiency

1. Write the number of hours slept (question #4) here:_____
2. Calculate the number of hours spent in bed:

   Getting up time (question #3):_____

   Bedtime (question #1):_____

   _____

   *Number of hours spent in bed:*_____

3. Calculate habitual sleep efficiency as follows:

   (Number of hours slept/Number of hours spent in bed) X 100 = Habitual sleep efficiency (%)

   (_____/_____) X 100 = %

4. Assign component 4 score as follows:

Habitual sleep efficiency %	Component 4 score
> 85%	0
75-84%	1
65-74%	2
< 65%	3

Component 4 score:_____

Component 5: Step disturbances

1. Examine questions #5b-5j, and assign scores for each question as follows:

Response	Score
Not during the past month	0
Less than once a week	1
Once or twice a week	2
Three or more times a week	3

5b score: _____

5c score: _____

5d score: _____

5e score: _____

5f score: _____

5g score: _____

5h score: _____

5i score: _____

5j score: _____

2. Add the scores for questions #5b-5j:

Sum of #5b-5j: _____

3. Assign component 5 score as follows:

Sum of #5b-5j	Component 5 score
0	0
1-9	1
10-18-4	2
19-27	3

Component 5 score: _____

Component 6: Use of sleeping medication

Examine question #7 and assign scores as follows:

Response	Component 6 score
Not during the past month	0
Less than once a week	1
Once or twice a week	2
Three or more times a week	3

Component 6 score: _____

Component 7: Daytime dysfunction

1. Examine question #8, and assign scores as follows:

Response	Score
Never	0
Once or twice	1
Once or twice each week	2
Three or more times each week	3

Question#8 score: _____

2. Examine question #9, and assign scores as follows:

Response	Score
No problem at all	0
Only a very slight problem	1
Somewhat of a problem	2
A very big problem	3

Question #9 score: _____

3. Add the scores for question #8 and #9:

Sum of #8 and #9: _____

4. Assign component 7 score as follows:

Sum of #8 and #9	Component 7 score
0	0
1-2	1
3-4	2
5-6	3

Component 7 score: _____

Global PSQI Score

Add the seven component scores together:

Global PSQI Score: _____

Appendix C

EPIC -26

The Expanded Prostate Cancer Index Composite

EPIC-26

The Expanded Prostate Cancer Index Composite

Short Form

This questionnaire is designed to measure Quality of Life issues in patients with Prostate cancer. To help us get the most accurate measurement, it is important that you answer all questions honestly and completely.

Remember, as with all medical records, information contained within this survey will remain strictly confidential.

Today's Date (please enter date when survey completed): Month_____Day_____Year_____

Name (optional): _____

Date of Birth (optional): Month_____Day_____Year_____

Do Not Mark in This Space

1. Over the **past 4 weeks**, how often have you leaked urine?

   More than once a day..... 1
   About once a day..... 2
   More than once a week..... 3 (Circle one number) 23/
   About once a week..... 4
   Rarely or never..... 5

2. Which of the following best describes your urinary control **during the last 4 weeks**?

   No urinary control whatsoever..... 1
   Frequent dribbling..... 2 (Circle one number) 26/
   Occasional dribbling..... 3
   Total control..... 4

3. How many pads or adult diapers per day did you usually use to control leakage **during the last 4 weeks**?

   None 0
   1 pad per day..... 1
   2 pads per day..... 2 (Circle one number) 27/
   3 or more pads per day..... 3

4. How big a problem, if any, has each of the following been for you **during the last 4 weeks**?

   (Circle one number on each line)

	No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem	
a. Dripping or leaking urine	0	1	2	3	4	28/
b. Pain or burning on urination.....	0	1	2	3	4	29/
c. Bleeding with urination.....	0	1	2	3	4	30/
d. Weak urine stream or incomplete emptying.....	0	1	2	3	4	31/
e. Need to urinate frequently during the day.....	0	1	2	3	4	33/

5. Overall, how big a problem has your urinary function been for you **during the last 4 weeks**?

   No problem..... 1
   Very small problem..... 2
   Small problem..... 3 (Circle one number) 34/
   Moderate problem..... 4
   Big problem..... 5

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6. How big a problem, if any, has each of the following been for you? (Circle one number on each line)

	No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem	
a. Urgency to have a bowel movement	0	1	2	3	4	49/
b. Increased frequency of bowel movements.....	0	1	2	3	4	50/
c. Losing control of your stools.....	0	1	2	3	4	52/
d. Bloody stools	0	1	2	3	4	53/
e. Abdominal/ Pelvic/Rectal pain...	0	1	2	3	4	54/

7. Overall, how big a problem have your bowel habits been for you **during the last 4 weeks**?

No problem..... 1
Very small problem..... 2
Small problem..... 3 (Circle one number) 55/
Moderate problem..... 4
Big problem..... 5

8. How would you rate each of the following **during the last 4 weeks**? (Circle one number on each line)

	Very Poor to None	Poor	Fair	Good	Very Good	
a. Your ability to have an erection?.....	1	2	3	4	5	57/
b. Your ability to reach orgasm (climax)?.....	1	2	3	4	5	58/

9. How would you describe the usual QUALITY of your erections **during the last 4 weeks**?

None at all..... 1
Not firm enough for any sexual activity..... 2
Firm enough for masturbation and foreplay only..... 3 (Circle one number) 59/
Firm enough for intercourse..... 4

10. How would you describe the FREQUENCY of your erections **during the last 4 weeks**?

I NEVER had an erection when I wanted one..... 1
I had an erection LESS THAN HALF the time I wanted one..... 2
I had an erection ABOUT HALF the time I wanted one ..... 3 (Circle one number) 60/
I had an erection MORE THAN HALF the time I wanted one..... 4
I had an erection WHENEVER I wanted one..... 5

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11. Overall, how would you rate your ability to function sexually **during the last 4 weeks**?

Very poor	1		
Poor	2		
Fair	3	(Circle one number)	64/
Good	4		
Very good	5		

12. Overall, how big a problem has your sexual function or lack of sexual function been for you **during the last 4 weeks**?

No problem	1		
Very small problem	2		
Small problem	3	(Circle one number)	68/
Moderate problem	4		
Big problem	5		

13. How big a problem **during the last 4 weeks**, if any, has each of the following been for you? (Circle one number on each line)

	No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem	
a. Hot flashes	0	1	2	3	4	74/
b. Breast tenderness/enlargement	0	1	2	3	4	75/
c. Feeling depressed	0	1	2	3	4	77/
d. Lack of energy	0	1	2	3	4	78/
e. Change in body weight	0	1	2	3	4	79/

THANK YOU VERY MUCH!!

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Appendix D:

https://ecog-acrin.org/resources/ecog-performance-status/

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982 Dec;5(6):649-655. PMID: 7165009

Appendix E: Research Labs

Bone Metabolism Markers (should be drawn in AM and fasting)

1. **Collagen Type I C-telopeptide**
   Serum; 1 ml; red top without serum separator; CPT4 code: 82523
2. **Bone Specific alkaline phosphatase**
   Serum, 1 ml serum separator tube;
3. **Procollagen Type I Intact N terminal propeptide** Serum, 1 ml CPT code 83519

Hormone Metabolism Markers (should be drawn in AM and fasting)

1. **DHEA-S (also called DHEA-sulfate or dehydroepiandrosterone sulfate** Serum; .25 ml; serum separator tube; CPT4 code 80158
2. **Androstenedione**
   Serum; 1 ml; red top tube without serum separator; CPT4 code 82157
3. **Testosterone**
   Serum; 0.5 ml; serum separator tube
4. **Free testosterone**
   Serum; 0.5ml. serum separator tube
5. **Estrone (precursor or estradiol which is also called estrogen)**
   Serum; 2 ml. serum separator tube; CPT4 code 82679
6. **Estradiol (estrogen)**
   Serum; 2 ml. serum separator tube; CPT4 code 84231

These tubes are to be drawn through their normal process for ordering blood work and should be sent to the clinical laboratory.

Appendix F:

Drugs to avoid because of interaction with CYP2C8 or CYP3A4 metabolic pathways

Gemfibrizil, carbamazepine, phenobarbital, pentobarbital, phenytoin, rifabutin, rifampin, rifapentine, nafcillin,modafinial, etavirenz, efavirenz, bosentan, cyclosporin, ergotamine, quininide, sirolimus tacrolimus, alfentanil, pimozide, St. John's Wort, ketoconazole, sertraline, digitoxin, haloperidol, ketamine, doxocycline, isoniazid, etravirine, dihydroergotamine and fentanyl.

Drugs to be used with caution

Warfarin (will likely require a change in warfarin dosing), omeprazole, midazolam, ciprofloxacin.

Appendix G

Charts to calculate body fat %

Chart (Men)

% Fat for Sum of Measurements at All 4 Locations

Sum in mm	Age 16-29	Age 30-49	Age 50+
20	8.1	12.1	12.5
22	9.2	13.2	13.9
24	10.2	14.2	15.1
26	11.2	15.2	16.3
28	12.1	16.1	17.4
30	12.9	16.9	18.5
35	14.7	18.7	20.8
40	16.3	20.3	22.8
45	17.7	21.8	24.7
50	19.0	23.0	26.3
55	20.2	24.2	27.8
60	21.2	25.3	29.1
65	22.2	26.3	30.4
70	23.2	27.2	31.5
75	24.0	28.0	32.6
80	24.8	28.8	33.7
85	25.6	29.6	34.6
90	26.3	30.3	35.5
95	27.0	31.0	36.5
100	27.6	31.7	37.3
110	28.8	32.9	38.8
120	29.9	34.0	40.2
130	31.0	35.0	41.5
140	31.9	36.0	42.8
150	32.8	36.8	43.9
160	33.6	37.7	45.0
170	34.4	38.5	46.0
180	35.2	39.2	47.0
190	35.9	39.9	47.9
200	36.5	40.6	48.8

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Appendix H: Pill Diary

Study Participant_____

Self-Administration

Study Drug Diary

Dana-Farber/Harvard Cancer Center

Participant Identifier: _____

Protocol # : **Enzalutamide with External Beam Radiation for Intermediate Risk Prostate Cancer: A Phase II study**

Your MD _____ Phone _____

Your RN _____ Phone _____

STUDY DRUG INSTRUCTIONS:

Study Drug: Enzalutamide

How Much: Your dose is160 mg

How Often: You will take 4 (40mg) capsules per day

When: You should take your capsules at the same time each day.

SPECIAL INSTRUCTIONS: Do not make up missed or vomited doses if It has been longer than 12 hours since you were supposed to take your dose. Do not chew or crush capsules. Take with or without food. Bring in your Used pill bottles at each visit.

Study Participant Initials _____ Date _____

FOR STUDY TEAM USE ONLY	
Staff Initials:	
Date Dispensed:	Date Returned:
# pills/caps/tabs dispensed:	# pills/caps/tabs returned:
# pills/caps/tabs that should have been taken:	
Discrepancy Notes:	

DOSING LOG

Cycle: ___

For each dose take:

Please indicate the date, time, amount taken and any comments.

	Date	Amount Taken Time/ Dose	Comments
Ex:	6/1/2009	8 AM 4 capsules	took with breakfast
Day 1			
Day 2			
Day 3			
Day 4			

SYMPTOMS/SIDE EFFECTS

Please record any side effects experienced during this cycle.
Include the date the particular symptom started and when it ended.
Please evaluate the severity of the symptom according to the following scale:

Mild: Awareness of sign or symptom; easily tolerated and did Not affect ability to perform normal daily activities. Symptom did not require medication or therapeutic intervention. **Moderate:** Significant discomfort which interfered with ability to perform normal daily activities. Symptom was easily resolved with at home medication or simple therapeutic intervention. **Severe:** Marked discomfort with an inability to carry out normal daily activities. Symptom required new medication and/or therapeutic intervention in order to resolve

Day 5			
Day 6			
Day 7			
Day 8			
Day 9			
Day 10			
Day 11			
Day 12			
Day 13			
Day 14			
Day 15			
Day 16			
Day 17			
Day 18			
Day 19			
Day 20			
Day 21			
Day 22			
Day 23			
Day 24			
Day 25			
Day 26			

Day 27			
Day 28			

Please Note: The severity should reflect the most severe level experienced during the time period.

Symptom	Start Date	End Date