RADIATION THERAPY ONCOLOGY GROUP

RTOG 1115

PHASE III TRIAL OF DOSE ESCALATED RADIATION THERAPY AND STANDARD ANDROGEN DEPRIVATION THERAPY (ADT) WITH A GNRH AGONIST VS. DOSE ESCALATED RADIATION THERAPY AND ENHANCED ADT WITH A GNRH AGONIST AND TAK-700 FOR MEN WITH HIGH RISK PROSTATE CANCER

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Participating Sites:

☒ US and Canada

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Phase III Trial of Dose Escalated Radiation Therapy and Standard Androgen Deprivation Therapy (ADT) with a GnRH Agonist vs. Dose Escalated Radiation Therapy and Enhanced ADT with a GnRH Agonist and TAK-700 for Men with High Risk Prostate Cancer

SCHEMA

<table>
<tr><td rowspan="2">S
T
R
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F
Y</td><td><u>Risk groups</u>
1. Gleason ≥ 9, PSA ≤ 150, any T-stage

2. Gleason 8, PSA < 20, and ≥ T2

3. Gleason 8, PSA ≥ 20-150, any T-stage

4. Gleason 7, PSA ≥ 20-150, any T-stage</td><td rowspan="2">R
A
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(1:1)</td><td>Arm 1:
<u>Androgen Deprivation Therapy</u>:
GnRH agonist for 24 months with concurrent oral antiandrogen until completion of radiation
+
<u>Dose Escalated Radiation</u>:
To start 8-10 weeks after initiation of ADT. Initially, 45 Gy to prostate and pelvic lymph nodes delivered with 3DCRT/IMRT with a boost to be provided with IMRT, LDR implant, or HDR implant.</td></tr>
<tr><td><u>Type of RT Boost</u>
1. IMRT
2. Brachytherapy (LDR using PPI or HDR)</td><td>Arm 2:
<u>Androgen Deprivation Therapy</u>:
GnRH agonist for 24 months with concurrent oral antiandrogen until completion of radiation
+
TAK-700 twice daily for 24 months
+
<u>Dose Escalated Radiation</u>:
To start 8-10 weeks after initiation of ADT. Initially, 45 Gy to prostate and pelvic lymph nodes delivered with 3DCRT/IMRT with a boost to be provided with IMRT, LDR implant, or HDR implant.</td></tr>
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See pre-registration requirements in Section 5.0. See Section 7.0 for details/doses of study drug.

<u>Patient Population</u>: (See Section 3.0 for Eligibility)
Histologically confirmed diagnosis of adenocarcinoma of the prostate within 180 days prior to registration at high risk for recurrence as determined by one of the following combinations:

<u>Gleason score</u>		**<u>PSA</u>**		**<u>T-Stage</u>**
≥ 9	**and**	**≤ 150**	**and**	**Any**
8	**and**	**< 20**	**and**	**≥ T2**
8	**and**	**≥ 20-150**	**and**	**Any**
7	**and**	**≥ 20-150**	**and**	**Any**

Required Sample Size: 900

RTOG Institution #
RTOG 1115 **ELIGIBILITY CHECKLIST** (5/1/12)
Case # **(page 1 of 5)**

1. ____(Y) Does the patient have a histologically confirmed diagnosis of adenocarcinoma of the prostate within 180 days prior to registration?

2. ____(Y) Was a history/physical examination done within 60 days prior to registration?

3. ____(Y) Did the patient have clinically negative lymph nodes within 90 days prior to registration demonstrated by imaging (abdominal and pelvic CT or MRI) which if deemed equivocal or questionable the nodes are less than 2.0 cm or negative nodes per nodal sampling or dissection?

4. ____(Y) Did a bone scan demonstrate no distant metastases (M0) within 90 days prior to registration and if the bone scan was equivocal were plain films negative)?

5. ____(Y) Was the study entry (baseline) PSA performed with an FDA approved assay within 180 days prior to registration and prior to the start any hormone ablation therapy?

6. ____(N) Did the patient have testosterone administered within 90 days prior to registration?

7. ____(Y) Is the patient's performance status 0 or 1?

8. ____(Y) Is the patient's age 18 years or greater?

9. ____(Y) Has a CBC with differential been obtained within 14 days prior to registration demonstrating adequate bone marrow function as follows?
   - Absolute neutrophil count (ANC) ≥ 1800 cells/mm^3
   - Platelets ≥ 100,000 cells/mm^3
   - Hemoglobin ≥ 8.0 g/dl

10. ____(Y) Has a screening calculated ejection fraction been obtained by multiple gated acquisition (MUGA) scan or by echocardiogram (ECHO) demonstrating a result of ≥ to institutional lower limit of normal?

11. ____(Y) Has a baseline ECG been obtained within 180 days prior to registration?

12. ____(Y/N/A) If the patient is a man of child-producing potential has he agreed to use effective contraception while on treatment and for at least 120 days after treatment has been completed?

13. ____(Y) Is the patient able to provide study specific informed consent prior to study registration?

14. ____(Y) Does the patient demonstrate a high risk for prostate cancer recurrence as determined by one of the following combinations?

   - Gleason score ≥ 9 and PSA ≤ 150 and Any T-stage
   - Gleason score 8 and PSA < 20 and T-stage ≥ T2
   - Gleason score 8 and PSA ≥ 20-150 and Any T-stage
   - Gleason score 7 and PSA ≥ 20-150 and Any T-stage

_____ What is the Gleason score?

_____ What is the PSA value?

_____ What is the T-stage?

15. ____(N) Is the PSA value > 150?

16. ____(N) Is there evidence of metastatic disease?

17. ____(N) Are there pathologically positive pelvic lymph nodes or pelvic lymph nodes > 2.0 cm demonstrated by imaging (CT or MR)?

18. ____(N) Has the patient had a radical prostatectomy, cryosurgery for prostate cancer or a bilateral orchiectomy for any reason?

19. ____(N) Has the patient had a prior invasive malignancy (except non-melanoma skin cancer) unless disease free or not requiring systemic therapy for a minimum of 3 years?

20. ____(N) Has the patient had prior systemic chemotherapy for prostate cancer?

21. ____(N) Has the patient had prior radiotherapy, including brachytherapy to the region of the prostate that would result in overlap of radiation therapy fields?

22. ____(N) Has the patient had previous hormonal therapy (LHRH agonists/oral antiandrogens), estrogens or surgical castration?

23. ____(N) Does the patient have a known hypersensitivity to TAK-700 or related compounds or any other drugs being used in this study?

24. ____(N) Has the study entry PSA been obtained during either of the following time frames: 10 day period following a prostate biopsy or following the initiation of hormonal therapy?

25. ____ (N) Does the patient have a history of adrenal insufficiency?

26. ____ (N) Does this patient have any severe or active co-morbidities as defined by the following?

- Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months
- Transmural myocardial infarction within the last 6 months
- Acute bacterial or fungal infection requiring intravenous antibiotics within 14 days prior to registration
- Chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration
- Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects or severe liver dysfunction within 21 days prior to registration
- Acquired immune deficiency syndrome (AIDS) based upon current CDC definition; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive. Protocol-specific requirements may also exclude immuno-compromised patients.
- A major surgical procedure within 14 days prior to registration
- Chronic hepatitis B or C.
- Ongoing arrhythmias (greater than grade 2); thromboembolic events or any other cardiac condition (such as pericardial effusion, etc.) within 6 months prior to registration
- Class III or IV heart failure per New York Heart Association classification
- ECG abnormalities:
  -Q-wave infarction unless identified more than 6 months prior to registration
  -QTc interval greater than 460 msec

27.____(N) Does the patient have a history of Cushing's syndrome?

28. ____(N) Does the patient have a history of severe chronic renal disease demonstrated by a serum Creatinine > 2.0 mg/dl and a Creatinine clearance of < 40 mL/min?

29. ____(N) Has the patient had chronic treatment with glucocorticoids within the last year?

30. ____(N) Does the patient have uncontrolled hypertension despite appropriate medical therapy characterized by a blood pressure of greater than 150 mm Hg systolic and 90 mm Hg diastolic at two separate measurements no more than 60 minutes apart within 21 days prior to registration?

31. ____(N) Does the patient have uncontrolled nausea, vomiting or diarrhea (grade 3 or greater) despite appropriate medical therapy at the time of registration?

32. ____(N) Does the patient have a known gastrointestinal disease or procedure that might interfere with the oral absorption or tolerance of TAK-700, including difficulty swallowing tablets at the time of registration?

33. ____ State patient's height in centimeters.

34 ____ State patient's weight in kilograms.

35 ____(Y) Even if surgically sterilized (vasectomy), does the patient agree to practice effective barrier contraception during the entire study treatment period and for (4) months after the last dose of study drug or abstain from intercourse completely?

ELIGIBILITY CHECKLIST (5/1/12)

The following questions will be asked at Study Registration:
IMRT CREDENTIALING IS REQUIRED BEFORE REGISTRATION

_____ 1. Institutional person randomizing case.

_____(Y) 2. Has the Eligibility Checklist been completed?

_____(Y) 3. In the opinion of the investigator, is the patient eligible?

_____ 4. Date informed consent signed

_____ 5. Patient's Initials (First Middle Last)

_____ 6. Verifying Physician

_____ 7. Patient ID

_____ 8. Date of Birth

_____ 9. Race

_____ 10. Ethnicity

_____ 11. Gender

_____ 12. Country of Residence

_____ 13. Zip Code (U.S. Residents)

_____ 14. Method of Payment

_____ 15. Any care at a VA or Military Hospital?

_____ 16. Calendar Base Date (date hormone ablation to start)

_____ 17. Randomization date

_____ 18. Medical oncologist's name [for trials that include a drug component]

_____(Y/N) 19. Have you obtained the patient's consent for his or her tissue to be kept for use in research to learn about, prevent, treat, or cure cancer?

_____(Y/N) 20. Have you obtained the patient's consent for his or her blood to be kept for use in research to learn about, prevent, treat, or cure cancer? (**Note**: Blood collection is mandatory for patients participating in QOL—mandatory for first 410 patients enrolled).

_____(Y/N) 21. Have you obtained the patient's consent for his or her tissue to be kept for use in research about other health problems (for example: causes of diabetes, Alzheimer's disease, and heart disease)?

_____(Y/N) 22. Have you obtained the patient's consent for his or her blood to be kept for use in research about other health problems (for example: diabetes, Alzheimer's disease, or heart disease). (**Note**: Blood collection is mandatory for patients participating in QOL—mandatory for first 410 patients enrolled).

_____(Y/N) 23. Have you obtained the patient's consent to allow someone from this institution to contact him or her in the future to take part in more research?

_____(N/Y) 24. Did the patient agree to participate in the quality of life component **(mandatory participation for the first 410 patients enrolled)**?

_____ If no, please specify the reason from the following:
1. Patient refused due to illness
2. Patient refused for other reason: specify _____
3. Not approved by institutional IRB
4. Tool not available in patient's language
5. Other reason: specify_____

_____25. Risk group (specify):
1. Gleason $\geq$ 9, PSA $\leq$ 150, any T-stage
2. Gleason 8, PSA < 20, and $\geq$ T2
3. Gleason 8, PSA $\geq$ 20-150, any T-stage
4. Gleason 7, PSA $\geq$ 20-150, any T-stage

_____26. RT Modality for boost (specify):
1. IMRT
2. LDR Permanent Prostate Implant (PPI) Boost
3. HDR Boost

_____(N/Y) 27. Use of IMRT

The Eligibility Checklist must be completed in its entirety prior to web registration. The completed, signed, and dated checklist used at study entry must be retained in the patient's study file and will be evaluated during an institutional NCI/RTOG audit.

Completed by _____ Date _____

1.0 INTRODUCTION

1.1 Background

Prostate cancer is the most common cancer in men. Androgen deprivation therapy (ADT) with gonadotropin releasing hormone (GnRH) agonists is the foundation of advanced prostate cancer treatment and is given as neoadjuvant/concomitant/adjuvant treatment with radiation for intermediate and high risk localized disease. GnRH agonist therapy causes cessation of gonadal androgen production, resulting in a reduction in serum testosterone levels by more than 95% and estrogen levels by approximately 80%. Adrenal androgen synthesis accounts for most of the small persistent level of serum androgens.

TAK-700 is an oral, selective nonsteroidal inhibitor of (Keating 2006, Eri 1995) lyase that blocks synthesis of both gonadal and adrenal dehydroepiandrosterone sulfate (DHEA) and androstenedione. TAK-700 has been shown to further reduce serum testosterone levels in men already maintained on a GnRH agonist. In Phase I and II clinical trials in men with advanced prostate cancer, TAK-700 has demonstrated notable efficacy with excellent tolerability (Dreicer 2010a, Dreicer 2010b). The most common adverse effects have included fatigue, nausea and constipation, and are generally mild in nature. TAK-700 has been administered alone to a maximum recommended dose of 300 mg BID, and together with low-dose prednisone to a maximum dose of 600 mg BID. In two ongoing, pivotal phase III trials, TAK-700 is being administered at either 400 mg BID along with 5 mg daily of prednisone (metastatic prostate cancer) or 300 mg BID without prednisone (nonmetastatic prostate cancer).

1.2 Adjuvant/concurrent/neoadjuvant ADT with Radiation Therapy

Risk stratification of patients prior to primary therapy for prostate cancer yields important prognostic information and can be used to guide therapeutic choices. Three factors that are independently associated with relapse risk are clinical tumor stage, Gleason score, and pretreatment PSA level (Chism, 2004, D'Amico 2002, Levegrun 2002, Pisansky 1997, Symon 2003). Prostate cancer is categorized as high risk if it features extraprostatic extension (T3), Gleason > 8, or PSA > 20. Standard-of-care for men with high risk disease treated with external beam radiation is 2 – 3 years of ADT with a GnRH agonist based on phase III trials demonstrating an overall survival benefit (Bolla 1997, Pilepich 2005, Mohler 2010). Recently reported data from an EORTC trial comparing 6 months of ADT to 3 years of ADT for men with locally advanced disease showed a significant 5 year overall survival advantage for the longer term ADT group (15.2% vs. 19.0% mortality) (Bolla 2009). Efforts to achieve further benefit through intensified systemic therapy for this patient population led to RTOG 05-21, a randomized phase III trial in which adjuvant docetaxel chemotherapy was added to standard radiation and neoadjuvant/ concomitant/adjuvant ADT. RTOG 05-21 has completed accrual, but analysis is still several years away.

Though standard ADT with a GnRH agonist has clearly been shown to improve the efficacy of radiation therapy, no trial has yet built upon this foundation with the use of more profound androgen deprivation in this clinical setting. We propose to examine the combination of radiation with enhanced ADT using a GnRH agonist and TAK-700. This combination of hormonal agents has been shown to suppress serum testosterone to undetectable levels. Given the survival benefit conferred by lowering serum androgens with 2 – 3 years of GnRH agonist treatment in combination with radiation for high risk prostate cancer, we hypothesize that further lowering of serum androgens will produce additional clinical benefit.

1.3 Safety of Proposed Therapy

Based upon experience from phase I and ongoing II and III trials, TAK-700 is generally well tolerated when given in combination with a GnRH agonist. Adverse events that have been observed to occur frequently include fatigue, nausea, constipation, anorexia and vomiting (Dreicer 2010a, Dreicer 2010b) The most prominent safety concerns are primarily related to the risk of hypertension and electrolyte abnormalities secondary to mineralocorticoid excess, an effect that has been observed with other lyase inhibitors (Attard 2005, Attard 2008). However, this has generally not been a concern in early trials with TAK-700. In this study, electrolytes including serum potassium will be monitored regularly.

No completed study has examined the combination of TAK-700 with a GnRH agonist and concurrent radiation. Though the tolerability of this combination is anticipated to be similar to that of radiation with concurrent GnRH agonist therapy, the absence of unexpected adverse events must be verified and is a co-primary endpoint of the study. Formal toxicity assessment will be carried out after follow-up of 200 patients (100 per treatment arm) through six months of therapy. Adverse events will be measured by NCI CTCAE criteria and compared between arms. The trial will be halted if unacceptable levels of toxicity are

found among patients randomized to TAK-700 relative to standard ADT, with threshold criteria for excess incidence derived from observed adverse event data from similar patients who underwent radiation and ADT per the control arm of this trial. If the toxicity profile is acceptable as defined in Section 13.5.7.3, the trial will continue to full accrual. Quality of life measured by the EPIC (32 item) and EQ-5D (5 item) questionnaires and fatigue measured by the Patient-Reported Outcome Measurement Information System (PROMIS) Fatigue Scale also will be examined as supporting information regarding tolerability of TAK-700. In addition to this early safety assessment and continuous CTCAE adverse event monitoring throughout the trial, detailed studies with respect to both short and long term potential adverse consequences of TAK-700 will be conducted, as described in Sections 1.4 and 1.5.

1.4 Prostate Cancer Survivorship

A major consideration in the treatment of prostate cancer is achievement of a satisfactory risk-benefit ratio with respect to treatment. While men with disease meeting disease stage criteria here are deemed high-risk and thus candidates for multimodality therapy including 2-year androgen deprivation, their likelihood to non-cancer morbidity and mortality may still exceed their prostate cancer mortality risk, and thus it is necessary to carefully assess the totality of impacts treatment may exert, including adverse consequences. These are considered in a series of studies as follows.

1.4.1 Metabolic Consequences of Androgen Deprivation

Androgen deprivation therapy (ADT) can be accomplished with medical or surgical castration. This hypogonadism produces several well-described treatment-related adverse effects including insulin resistance, elevated lipoproteins, and weight gain.(Smith, Finkelstein et al. 2002; Smith, Lee et al. 2006; Saylor and Smith 2009) Consistent with these adverse effects, GnRH agonist treatment has been associated with increased risk for diabetes and cardiovascular disease.(Keating, O'Malley et al. 2006; Saigal, Gore et al. 2007; Allibhai 2008; Keating, O'Malley et al. 2010; Saylor, Keating et al. 2011) The metabolic impact of the more profound hypogonadism produced by an androgen biosynthesis inhibitor in combination with GnRH agonist therapy has not yet been evaluated.

Castrate testosterone is defined as serum testosterone < 50 ng/dL. TAK-700 is an androgen biosynthesis inhibitor that further reduces serum testosterone in men with castrate testosterone levels due to GnRH agonist therapy.(Dreicer, Agus et al. 2010) Testosterone measurement using widely-available radioimmunoassays and chemiluminescent testing is notably imprecise when measuring testosterone levels at the low end of the spectrum.(Fitzgerald and Herold 1996; Taieb, Mathian et al. 2003; Wang, Catlin et al. 2004) We therefore plan to measure on-treatment testosterone using liquid chromatography tandem mass spectrometry (LC/MS/MS), a technique that maintains precision when testosterone levels are below 50 ng/dL.(Taieb, Mathian et al. 2003; Wang, Catlin et al. 2004) It is expected that nadir testosterone will be lower among men who receive TAK-700 in addition to a GnRH agonist. Serum testosterone levels drawn at intervals throughout the 24 months of ADT will be analyzed to investigate whether there is lower cumulative androgen exposure during those 24 months, a putative mechanism of the proposed therapy.

The metabolic impact of this lower androgen exposure will be evaluated in several ways. Glycemic parameters, lipid profiles, and body mass index (BMI) will be serially evaluated during systemic treatment and during follow-up. Insulin resistance is an independent risk factor for cardiovascular disease and is present in about one fourth of adults in the general population.(Despres, Lamarche et al. 1996; Pyorala, Miettinen et al. 1998) Existing data demonstrate that standard ADT with a GnRH agonist decreases insulin sensitivity(Smith, Lee et al. 2006) and is associated with an increased incidence of type 2 diabetes.(Allibhai 2008; Keating, O'Malley et al. 2010) We will investigate whether long-term treatment with TAK-700 increases the incidence of insulin resistance, prediabetes, or diabetes. Standard ADT with a GnRH agonist causes increases in total cholesterol, triglycerides, and high density lipoprotein (HDL).(Eri, Urdal et al. 1995; Dockery, Bulpitt et al. 2003; Smith, Lee et al. 2008) We will investigate whether long-term treatment with TAK-700 results in higher lipid levels. Finally, prospective studies have demonstrated that one year of GnRH agonist therapy increases total body weight by approximately 2%.(Smith, Finkelstein et al. 2002; Smith 2004) We will investigate whether long-term treatment with TAK-700 results in higher body mass index when compared to GnRH agonist monotherapy.

1.4.2 Androgen Recovery after Treatment

Withdrawal of GnRH agonist therapy usually leads to recovery of androgen production to non-castrate levels, though the timing of this recovery is quite variable. Among studies that have described the recovery of androgen production after ADT, median time to normalization of serum testosterone varied greatly.(Hall, Fritzsch et al. 1999; Nejat, Rashid et al. 2000; Pickles, Agranovich et al. 2002; Gulley, Figg et al. 2005; Kaku, Saika et al. 2006; Gulley, Aragon-Ching et al. 2008) One study reported normalization within a median of 15.4 weeks in men who had received six months of ADT(Gulley, Aragon-Ching et al. 2008) while another reported a median of 24 months to testosterone normalization in men who had received a median of 30 months of ADT.(Kaku, Saika et al. 2006) Androgen recovery after blockade of both gonadal and adrenal androgen synthesis using a GnRH agonist with TAK-700 has not yet been described. In this phase III trial, the timing of androgen recovery after cessation of ADT will be important to the interpretation of the primary results. If the experimental arm is found to have superior overall survival when compared to the control arm, it will be essential to also know the kinetics of androgen recovery. We hypothesize that recovery of testosterone to above the accepted threshold for supplementation in the general population will be similar in the two treatment arms. We will measure serum testosterone during the first 5 years of follow-up after cessation of systemic therapy.

1.4.3 Evaluation of Clinical and Chronic Disease Outcomes

Clinical outcomes that have been shown to be associated with GnRH agonist therapy include new diagnosis of diabetes, osteoporotic fracture, coronary artery disease, myocardial infarction, stroke, pulmonary embolism, and deep vein thrombosis. Post-hoc analyses of clinical outcomes among men who participated in RTOG clinical trials (trials 85-31(Efstathiou, Bae et al. 2008), 86-10(Roach, Bae et al. 2008), and 92-02(Efstathiou, Bae et al. 2008)) have been important in clarifying these risks as they found no association between GnRH agonist treatment and cardiovascular mortality. Unfortunately, those trials were not designed to assess non-fatal cardiovascular events or other clinical endpoints relevant to prostate cancer survivorship. The proposed study presents an important opportunity to formally collect data on these clinical outcomes in a large prospective trial.

It is not known whether more intensive androgen deprivation with a GnRH agonist and an androgen biosynthesis inhibitor is associated with additional risk for these outcomes. The proposed study provides an ideal setting in which to examine this possibility as it is a randomized controlled trial with long term follow-up. Long term safety of such novel hormonal agents cannot optimally be evaluated in clinical trials in patients with more advanced disease because such patients suffer from more substantial cancer disease burden and more commonly move on promptly to subsequent therapies.

Abiraterone acetate is another androgen biosynthesis inhibitor that recently has been shown to improve survival in men with metastatic CRPC after failure of first line chemotherapy.(de Bono, Logothetis et al. 2011) With the current and planned development of TAK-700 and other agents in this class, it is likely that increasing numbers of men will be exposed to such enhanced hypogonadism, and for increasing durations. The risks for adverse clinical outcomes as a consequence of systemic therapy among prostate cancer survivors is a particularly important issue among men treated with curative intent. This study will rigorously measure the incidence of important adverse clinical outcomes and chronic diseases among men treated with standard ADT with those treated with the combination of a GnRH agonist with TAK-700.

1.5 Fatigue

A second key facet of risk-benefit evaluation for prostate cancer evaluation is patient reported outcomes relating to well-being, with fatigue being principal among these in prostate cancer. A comprehensive evaluation of fatigue is thus an integral component of this clinical trial.

Fatigue has been described as the most frequent and distressing symptom related to cancer and its treatment (Bower 2005). Radiotherapy-induced fatigue is a common early side effect reported by 80% of patients during treatment (Jereczek-Fossa 2001). There is evidence that cancer-related fatigue (CRF) has profound effects on ability to function in usual roles and activities and can linger for months or years after treatment completion (Lilleby 1999; Monga 1999; Monga 2005; Truong 2006). Following RT and/or ADT, approximately one third of prostate cancer survivors report clinically relevant fatigue one year post

treatment (Storey et al. 2011, Kyrdalen et al., 2010). The high prevalence of this symptom in persons treated for prostate cancer, as well as its association with poor quality of life, mark it as a significant problem that requires further scientific study.

The etiology of fatigue, its correlates, and prevalence in the context of prostate cancer treatment are poorly understood. RT field size (whole pelvis vs. prostate only RT), ADT, and TAK-700 have been associated with the development of fatigue. (Danjoux 2007, Beard et al. 1997, Fransson 2010, Saad et al. 2011, Agust et al. 2011). During prostate RT, fatigue has been found to increase significantly with the most severe fatigue being reported the last week of RT. (Jereczek-Fossa 2001; Truong 2006; Beard 1997; Danjoux 2007; Prue 2006, Fransson 2010). However, a significant increase in fatigue between baseline and all follow-up time points, including end of RT, 3 months, 1 year, 3 years, and 5 years following RT has been noted in prostate cancer patients (Fransson et al. 2010). For example, five years after RT, 66% of living patients had fatigue, while only 41% reported fatigue at baseline (Fransson et al. 2010). Patients who continued to undergo ADT for bone metastasis had the highest levels of fatigue. Other studies of prostate cancer patients support the notion that ADT has been independently associated with higher fatigue levels. When measured at baseline and 3 months post neoadjuvant ADT alone, fatigue increased in as many as two thirds of patients all before the first day of RT. (Stephens 2007; Stone 2000). In men receiving both ADT and RT, fatigue appears to be considerably worse than in men receiving RT alone. (Voermen et al. 2006) Kyrdalen et al (2010) found that 40% of >1 year prostate cancer survivors on ADT reported chronic fatigue, while only 20% of men who discontinued ADT reported fatigue at the same time point. Men who discontinued ADT had a fatigue rate comparable to men treated with RT alone and to age-matched controls from the general population. Like ADT, TAK-700 is associated with higher fatigue levels. In Phase I and II clinical trials in men with metastatic prostate cancer treated with TAK-700 [Saad et al. 2011, Agust et al. 2011] (both are abstracts), the most common adverse effect was fatigue (16 of 26 patients) but only one patient developed grade 3 or higher fatigue. The effect of TAK-700 on fatigue levels in non-metastatic prostate cancer patients treated with ADT and RT is expected to be moderate, although there is no data at this time, only the clinical experience of the investigators.

In order to minimize the potential impact of various confounding factors on fatigue, a secondary endpoint of this study, the following key information regarding potential confounds will also be collected at the time of the PROMIS-fatigue short form (using limited questions to minimize patient burden): The Anxiety/Depression Item in the EQ-5D; Overall Sleep Quality: Item from Pittsburgh Sleep Quality Index (Buysse 1989); 1 item (Q3) of the Pittsburgh Sleep Quality Index (PSQI), a self-rated questionnaire which measures sleep quality and disturbances over a 1-week or 1-month time period; and Participants' level of physical activity will be assessed using 3-items from the Godin Leisure-Time Exercise Questionnaire (GLTEQ) [Godin 1986; Gionet 1989]. Please see Section 11.0 for further details.

1.5.1 Correlation of Circulating Proinflammatory Cytokines to Fatigue

The etiology of fatigue, its correlates, and prevalence in the context of prostate cancer treatment are poorly understood. There is growing evidence that pro-inflammatory cytokines play a role in cancer-related fatigue (CRF) and fatigue from other chronic illnesses (Schubert 2007). Most of the research has been generated in breast cancer patients, and the most commonly implicated cytokines are IL-1, IL-6, TNF alpha, sTNFR2, and IFN alpha (Ryan 2007). These cytokines will be measured in the proposed study of prostate cancer patients in addition to NF-Kappa B DNA binding which has been found by our group to be elevated in fatigued women undergoing breast RT (Torres 2011). Additionally, SNPs in the promoters of cytokine genes, IL6, IL1, and TNF alpha have been associated with fatigue in breast cancer survivors (Collado-Hidalgo 2008) and prostate cancer patients (Aouizerat 2009, Miaskowski 2010). These SNPs found in genes integral to the inflammatory response will be assessed in the proposed study, as they may identify patients at risk for fatigue development. RT and ADT may initiate a constellation of molecular events that include activation of the inflammatory signaling molecule, nuclear factor kappa B (NF-kB) as well as the local and peripheral release of inflammatory cytokines (Anscher 2005). Work by Raison et al. (2009) and others have demonstrated that peripherally elaborated inflammatory cytokines can enter the brain and activate a central inflammatory response that is associated with fatigue.(Capuron 2007) Studies have shown that the development of fatigue during radiation therapy for prostate cancer is significantly correlated with increases in peripheral inflammatory markers including interleukin (IL)-1 receptor antagonist (IL-1ra), IL-6 and c-reactive protein (CRP).(Bower 2009) In contrast, the effect of hormonal therapy on inflammatory markers is less well known. Small

studies have shown altered cytokine expression by prostate tumors after hormonal therapy (Sugihara 1998), but levels of systemic cytokines after hormonal therapy for prostate cancer are not well described. Fatigue, however, is a well-known complication of hormonal therapy for prostate cancer and has been independently associated with increased inflammation (Peters 2008). Activation of the inflammatory response may be a fundamental consequence of ADT and RT leading to fatigue. Indeed, the combination of these two treatments may result in a more persistent and prolonged fatigue compared to the series evaluating fatigue after radiation alone, with as many as 32% of patients experiencing fatigue at the completion of radiation and a substantial number experiencing fatigue as late as 6.5 weeks after completion of radiation (Stone 2000). Given its primary importance in regulating the inflammatory response, NF-kB may play a prominent role in the link between cancer treatment and subsequent fatigue.(Bower In press, Torres preliminary data 2011)

It will be strongly recommended that patients consent to having a blood sample sent for storage to the RTOG Biospecimen Resource. Blood will be collected from patients enrolled on this protocol at baseline, 1 year, and 2.5 years after therapy begins to follow trends in inflammatory biomarkers that may correlate with fatigue levels. The specimens will be collected and processed according to the RTOG specimen processing guidelines and must be clearly labeled with the patient identification number. Specimens from participating institutions will be banked in the RTOG Biospecimen Resource for future translational analyses. The buffy coat will be isolated from each sample and the DNA extracted. Anticipated analyses for collected specimens include circulating markers that may correlate to patient reported outcomes. An example of one anticipated analysis is the evaluation of plasma cytokines for correlation to fatigue as measured by the PROMIS instrument in patients enrolled on this trial. Examples of inflammatory markers that will be tested include CRP, NF- kappa B, TNF alpha, IL-1, IL-1ra, sTNFR2, and IL-6.

1.5.2 Genetic Predictors of Fatigue

Evidence that specific genetic variants are associated with the development of such adverse effects arises from several studies. In one case/control study, 141 prostate cancer patients treated with radiotherapy were screened for SNPs in TGFB1 (Burri in press). Those subjects who possessed either the T/T genotype at position -509, the C/C genotype at position 869 or the G/C genotype at position 915 were significantly associated with the development of a decline in erectile function compared with those who did not have these genotypes. In addition, patients with the -509 T/T genotype had a significantly increased risk of developing late rectal bleeding compared with those who had either the C/T or C/C genotype at this position. These subjects were also genotyped for SNPs in SOD2, XRCC1, and XRCC3 (Damaraju 2006). Patients possessing the XRCC1 rs25489 G/A genotype were more likely to develop erectile dysfunction following irradiation compared to patients who had the G/G genotype. The estimated CAG haplotype frequency for XRCC1 was significantly higher in men with late rectal bleeding than in men without late rectal bleeding. In addition, patients who possessed the SOD2 rs4880 C/T genotype exhibited a significant increase in grade 2 late rectal bleeding compared to patients who had either the C/C or T/T genotype for this SNP. Furthermore, patients possessing the combination of the SOD2 rs4880 C/T genotype and XRCC3 rs861539 C/T genotype experienced a significant increase in grade 2 late rectal bleeding compared to patients without this particular genotypic arrangement. Another important study reported that possession of SNPs in the LIG4, ERCC2, and CYP2D6 was significantly associated with the development of clinical toxicity, including urinary morbidity, in patients treated with radiotherapy for prostate cancer (Dudbridge 2006). Taken together, the results of these studies provide a strong basis for the role of genetic factors in the ability to predict which prostate cancer patients will exhibit adverse radiotherapy responses. Thus, the hypothesis that forms the basis for this study is that SNPs and/or CNVs in certain genes are associated with the development of fatigue after radiotherapy for prostate cancer. This effect may be further exacerbated by profound androgen deprivation via agents such as TAK-700.

It will be strongly recommended that patients consent to having a blood sample sent for storage to the RTOG Biospecimen Resource. The buffy coat will be isolated from each sample and the DNA extracted. The specimens will be collected and processed according to the RTOG specimen processing guidelines. Anticipated analyses include evaluation of single nucleotide polymorphisms (SNPs) and copy number variants (CNVs) through screening DNA samples

derived from case and matched control subjects using Affymetrix 6.0 microarrays. Genes to be investigated for SNPs and CNVs include TNFAIP1, IL6, IL6R, CRP, NFKB1, NFKB1A, IL1R1, IL1A, IL1B. Case subjects will be patients that represent the 20% of patients in this study exhibiting the highest levels of fatigue as defined and measured by the PROMIS instrument used in this study while controls will be the 20% of patients who reported the lowest levels of fatigue as quantified using PROMIS. The goal of this study will be to identify SNPs and CNVs associated with the development of fatigue in prostate cancer patients following radiotherapy.

2.0 OBJECTIVES

2.1 Primary Objective

To evaluate the difference in overall survival in men with clinically localized prostate cancer with unfavorable prognostic features between a) standard treatment (ADT + radiotherapy) and b) standard treatment with the addition of 24 months of TAK-700.

2.2 Secondary Objectives

2.2.1 To characterize differences between the treatment groups with respect to incidence of unexpected grade $\geq$ 3 adverse events and/or clinically significant decrement in patient reported quality of life among subjects treated with TAK-700.

Additional secondary objectives are to compare the treatment groups with respect to:

2.2.2 Rates and cumulative incidence of biochemical control (freedom from PSA failure), local/regional progression, and distant metastases

2.2.3 Rate and cumulative incidence of clinical failure, defined as: PSA > 25 ng/ml, documented local disease progression, regional or distant metastasis, or initiation of androgen deprivation therapy

2.2.4 Prostate-cancer specific survival and other-cause mortality

2.2.5 Change in severity of fatigue as measured by the Patient-Reported Outcome Measurement Information System (PROMIS) fatigue short form

2.2.6 Changes in patient reported quality of life as measured by Expanded Prostate Cancer Index Composite (EPIC)

2.2.7 Assess quality adjusted survival using the EQ-5D

2.2.8 Nadir and average serum testosterone at 12 and 24 months during treatment

2.2.9 Changes in hemoglobin A1C, fasting glucose, and fasting insulin during 24 months of systemic treatment and during the first three years of follow-up

2.2.10 Changes in fasting lipid levels during 24 months of treatment and during the first three years of follow-up

2.2.11 Changes in body mass index (BMI) during 24 months of treatment and during the first three years of follow-up

2.2.12 Incidence of adverse events ascertained via CTCAE version 4.

2.2.13 Rate of recovery of testosterone to >230 ng/dL (accepted threshold for supplementation) after 12 and 24 months of follow-up

2.2.14 Median time to recovery of testosterone to >230 ng/dL during the first five years of follow-up

2.2.15 Cumulative incidence of relevant clinical survivorship endpoints including new diagnosis of type 2 diabetes, coronary artery disease, myocardial infarction, stroke, pulmonary embolism, deep vein thrombosis, or osteoporotic fracture

3.0 PATIENT SELECTION

NOTE: PER NCI GUIDELINES, EXCEPTIONS TO ELIGIBILITY ARE NOT PERMITTED

3.1 Conditions for Patient Eligibility (5/1/12)

3.1.1 Histologically confirmed diagnosis of adenocarcinoma of the prostate within 180 days prior to registration at high risk for recurrence as determined by one of the following combinations:

Gleason score		PSA		T-Stage
$\geq$ 9	**and**	**$\leq$ 150**	**and**	**Any**
8	**and**	**< 20**	**and**	**$\geq$ T2**
8	**and**	**$\geq$ 20-150**	**and**	**Any**
7	**and**	**$\geq$ 20 – 150**	**and**	**Any**

3.1.2 History/physical examination within 60 days prior to registration.

3.1.3 Clinically negative lymph nodes as established by imaging (abdominal and pelvic CT or abdominal and pelvic MRI), nodal sampling, or dissection within 90 days prior to registration.

3.1.3.1 Patients with lymph nodes equivocal or questionable by imaging are eligible if the nodes are < 2.0 cm.

3.1.4 No distant metastases (M0) on bone scan within 90 days prior to registration.

3.1.4.1 Equivocal bone scan findings are allowed if plain films are negative for metastasis.

3.1.5 Baseline serum PSA value performed with an FDA-approved assay (e.g., Abbott, Hybritech), obtained prior to any LHRH or antiandrogen therapy, within 180 days of randomization.

3.1.6 Prior testosterone administration is allowed if last administered at least 90 days prior to registration.

3.1.7 Height, weight, Zubrod Performance Status 0-1 within 21 days prior to registration

3.1.8 Age ≥ 18

3.1.9 CBC/differential obtained within 14 days prior to registration on study, with adequate bone marrow function defined as follows:

3.1.9.1 Absolute neutrophil count (ANC) ≥ 1,800 cells/mm^3

3.1.9.2 Platelets ≥ 100,000 cells/mm^3

3.1.9.3 Hemoglobin ≥ 8.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb ≥ 8.0 g/dl is acceptable.)

3.1.10 Serum creatinine < 2.0 mg/dl and creatinine clearance > 40 mL/minute within 21 days prior to registration

3.1.11 Bilirubin < 1.5x ULN and ALT or AST < 2.5x ULN within 21 days prior to registration

3.1.12 Screening calculated ejection fraction of ≥ to institutional lower limit of normal by multiple gated acquisition (MUGA) scan or by echocardiogram (ECHO).

3.1.13 Baseline ECG within 180 days prior to registration

3.1.14 Patients, even if surgically sterilized (ie, status post vasectomy), who:

(a) Agree to practice effective barrier contraception during the entire study treatment period and for 4 months (120 days) after the last dose of study drug, or

(b) Agree to completely abstain from intercourse.

3.1.15 Patient must be able to provide study-specific informed consent prior to study entry.

3.2 Conditions for Patient Ineligibility

3.2.1 PSA > 150

3.2.2 Definite evidence of metastatic disease.

3.2.3 Pathologically positive lymph nodes or nodes > 2.0 cm on imaging.

3.2.4 Prior radical prostatectomy, cryosurgery for prostate cancer, or bilateral orchiectomy for any reason.

3.2.5 Prior invasive malignancy (except non-melanoma skin cancer) unless disease-free or not requiring systemic therapy for a minimum of 3 years.

3.2.6 Prior systemic chemotherapy for prostate cancer (Note that prior chemotherapy for a different cancer is allowed, per Section 3.2.5).

3.2.7 Prior radiotherapy, including brachytherapy, to the region of the prostate that would result in overlap of radiation therapy fields.

3.2.7.1 Any patient undergoing brachytherapy must have transrectal ultrasound confirmation of prostate volume <60 cc, AUA score ≤15 within 60 days of registration, and no history of prior transurethral resection of the prostate (TURP); prior TURP is permitted for patients who receive EBRT only).

3.2.8 Previous hormonal therapy, such as LHRH agonists (e.g., goserelin, leuprolide), anti-androgens (e.g., flutamide, bicalutamide), estrogens (e.g., DES), or surgical castration (orchiectomy)

3.2.9 Known hypersensitivity to TAK-700 or related compounds

3.2.10 A history of adrenal insufficiency

3.2.11 History of myocardial infarction, unstable symptomatic ischemic heart disease, ongoing arrhythmias of Grade > 2 [NCI CTCAE, version 4.02] (U.S. Department of Health and Human Services, National Institutes of Health National Cancer Institute, 2009), thromboembolic events (eg, deep vein thrombosis, pulmonary embolism, or symptomatic cerebrovascular events), or any other cardiac condition (eg, pericardial effusion restrictive cardiomyopathy) within 6 months prior to registration. Chronic stable atrial fibrillation on stable anticoagulant therapy is allowed.

3.2.12 New York Heart Association Class III or IV heart failure (see Appendix V).

3.2.13 ECG abnormalities of:

(a) Q-wave infarction, unless identified 6 or more months prior to screening
(b) QTc interval > 460 msec

3.2.14 Patients who are sexually active and not willing/able to use medically acceptable forms of contraception; this exclusion is necessary because the treatment involved in this study may be significantly teratogenic.

3.2.15 Prior allergic reaction to the drugs involved in this protocol.

3.2.16 Study entry PSA obtained during the following time frames:
(a) 10-day period following prostate biopsy;
(b) following initiation of hormonal therapy.

3.2.17 Cushing's syndrome

3.2.18 Severe chronic renal disease (serum creatinine > 2.0 mg/dl and confirmed by creatinine clearance < 40 mL/minute)

3.2.19 Chronic liver disease (bilirubin > 1.5x ULN, ALT or AST > 2.5x ULN)

3.2.20 Chronic treatment with glucocorticoids within one year

3.2.21 Uncontrolled hypertension despite appropriate medical therapy within 21 days prior to registration (blood pressure of greater than 150 mm Hg systolic and 90 mm Hg diastolic at 2 separate measurements no more than 60 minutes apart during Screening visit)

3.2.22 Unwilling or unable to comply with the protocol or cooperate fully with the investigator and site personnel.

3.2.23 Major surgery within 14 days prior to registration

3.2.24 Serious infection within 14 days prior to registration

3.2.25 Uncontrolled nausea, vomiting, or diarrhea (CTCAE grade $\geq$ 3) despite appropriate medical therapy at the time of registration

3.2.26 Known gastrointestinal (GI) disease or GI procedure that could interfere with the oral absorption or tolerance of TAK-700, including difficulty swallowing tablets

4.0 PRETREATMENT EVALUATIONS/MANAGEMENT

NOTE: This section lists baseline evaluations needed before the initiation of protocol treatment that do not affect eligibility.

4.1 Required Evaluations/Management (5/1/12)

4.1.1 Testosterone within 21 days prior to treatment

4.1.2 Chemistry (sodium, potassium, chloride, bicarbonate, BUN, Creatinine, glucose, calcium, magnesium and phosphorous) and liver (albumin, AST, ALT, alkaline phosphatase, total and direct bilirubin) panels obtained within 21 days prior to registration.

4.1.3 Fasting glucose, fasting insulin, lipid (cholesterol, triglyceride, HDL, LDL) panel, and Hemoglobin A1C within 21 days prior to treatment

4.1.4 Review of medications at time of registration (drug names and dosages, frequency, route, start dates, etc.)

4.1.5 Completion of the Patient-Reported Outcome Measurement Information System (PROMIS)-Fatigue Short Form, Expanded Prostate Cancer Index Composite (EPIC), and EuroQol (EQ-5D) is required for the first 410 patients registered in this study.

4.1.6 Any patient undergoing brachytherapy must have transrectal ultrasound confirmation of prostatic volume < 60 cc and American Urologic Association (AUA) symptom index composite score ≤ 15 within 60 days of registration. If a patient is thought to be a poor brachytherapy candidate based on anatomy at the time of ultrasound, he may still participate in the study but must receive EBRT only per protocol guidelines. If a patient is deemed an inadequate brachytherapy candidate after he has already been enrolled on the protocol, he will no longer be eligible for study participation.

5.0 REGISTRATION PROCEDURES

Institutions that have been previously credentialed for prostate 3DCRT or IMRT on prior RTOG protocols and that have successfully irradiated a phantom and been approved by the RPC need not perform additional credentialing for RTOG 1115. However, respective institutions may only administer treatment for which they have been previously credentialed (i.e., an institution credentialed for 3DCRT only may not administer IMRT on this study without completing the IMRT credentialing process). Credentialing requirements for IMRT and 3DCRT are specified in Sections 5.1 and 5.2 below.

5.1 Pre-Registration Requirements for IMRT Treatment Approach

5.1.1 In order to utilize IMRT on this study, the institution must have met specific technology requirements and have provided baseline physics information. Instructions for completing these requirements or determining if they already have been met are available on the Radiological Physics Center (RPC) web site. Visit http://rpc.mdanderson.org/rpc and select "Credentialing" and "Credentialing Status Inquiry".

An IMRT phantom study with the RPC must be successfully completed (if the institution has not previously met this IMRT credentialing requirement). Instructions for requesting and irradiating the phantom are available on the RPC web site at http://rpc.mdanderson.org/rpc/; select "Credentialing" and "RTOG". Upon review and successful completion of the phantom irradiation, the RPC will notify both the registering institution and RTOG Headquarters that the institution has completed this requirement. Subsequently, RTOG Headquarters will notify the institution that the site can enroll patients on the study.

5.1.2 The institution or investigator must complete a new IMRT Facility Questionnaire and send it to RTOG for review prior to entering any cases, and/or set up an SFTP account for digital data submission, both of which are available on the Image-Guided Center (ITC) web site at http://atc.wustl.edu. Upon review and successful completion of the "Dry-Run" QA test, the ITC will notify both the registering institution and RTOG Headquarters that the institution has successfully completed this requirement. RTOG Headquarters will notify the institution when all requirements have been met and the institution is eligible to enter patients onto this study.

5.2 Pre-Registration Requirements for 3DCRT Treatment Approach

5.2.1 Only institutions that have met the technology requirements and that have provided the baseline physics information that are described in 3D-CRT Quality Assurance Guidelines may enter patients onto this study.

5.2.2 The new Facility Questionnaire (one per institution, available on the ATC website at http://atc.wustl.edu) is to be sent to RTOG for review prior to entering any cases. Upon review and successful completion of a "Dry-Run" QA test, the ITC will notify both the registering institution and RTOG Headquarters that the institution has successfully completed this requirement. RTOG Headquarters will notify the institution when all requirements have been met and the institution is eligible to enter patients onto this study. Institutions that have previously enrolled patients on 3D-CRT trials of this same disease site may enroll patients on this study without further credentialing.

5.3 Pre-Registration Requirements for Brachytherapy Treatment Approach

5.3.1 Brachytherapy

Institutions must be credentialed by the Radiological Physics Center (RPC) prior to registering any cases to this study. The credentialing materials may be found on the RPC website at http://rpc.mdanderson.org under the "credentialing" tab. Upon review and successful completion, the Radiological Physics Center will notify both the registering institution and RTOG Headquarters that the institution has successfully completed this requirement. RTOG Headquarters will notify the institution when all requirements have been met and the institution is eligible to enter subsequent patients onto this study.

5.3.1.1 *LDR Brachytherapy Credentialing*

Radiation Oncologists and Physicists are credentialed as a team. A completed Knowledge Assessment Questionnaire, the Facility Questionnaire and the Benchmark Cases must be completed by the team in order to enter patients on this study. If an institution has been credentialed for a previous RTOG LDR prostate brachytherapy trial (RTOG 98-05, RTOG P-0019, RTOG 0232), they do not have to be re-credentialed for this trial if the radiation oncologist and physicist are the same as on the approved credentialing request, and the institution is using the same seed model and planning system as on the approved credentialing request. A change of physician will require submission of the Knowledge Assessment Form and Clinical Test Case. A change in physicist will require submission of the Knowledge Assessment Form, the Credentialing Questionnaire, and the Reference Cases. A change in either the treatment planning computer or brachytherapy source model will require resubmission of only the Reference Cases. To be used on this protocol, low-dose rate brachytherapy sources must be listed on the joint RPC/AAPM source registry at http://rpc.mdanderson.org; select "brachy sources".

5.3.1.2 *HDR Brachytherapy Credentialing*

Radiation Oncologists and Physicists are credentialed as a team. Only institutions that have completed the Knowledge Assessment Questionnaire, the Facility Inventory, and the Benchmark Cases, as described in RTOG HDR Prostate Implant Quality Assurance Guidelines (see RPC web site http://rpc.mdanderson.org/rpc) may enter patients onto this study. The sample clinical case with complete Post Implant Data Form and other materials are to be sent to the Radiological Physics Center (RPC). If an institution has been credentialed for a previous RTOG HDR prostate brachytherapy trial (RTOG 0321, RTOG 0815), they don't have to be re-credentialed for this trial if the radiation oncologist and physicist are the same as on the approved credentialing request, and the institution is using the same seed model and planning system as on the approved credentialing request. A change of physician will require submission of the Knowledge Assessment Form and Clinical Test Case. A change in physicist will require submission of the Knowledge Assessment Form, the Credentialing Questionnaire, and the Reference Cases. A change in the treatment planning computer or brachytherapy source model will require resubmission of only the Reference Cases. To be used on this protocol, high-dose rate brachytherapy sources must be listed on the joint RPC/AAPM source registry at **http://rpc.mdanderson.org**; select "brachy sources".

5.4 Regulatory Pre-Registration Requirements

5.4.1 This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Prior to the recruitment of a patient for this study, investigators must be registered members of a Cooperative Group. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch (PMB), CTEP, DCTD, NCI. These forms are available on the CTSU registered member web site or by calling the PMB at 301-496-5725 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site by entering credentials at https://www.ctsu.org.

Requirements for RTOG 1115 site registration:

- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet
- CTSU RT Facilities Inventory Form

NOTE: Per NCI policy all institutions that participate on protocols with a radiation therapy component must participate in the Radiological Physics Center (RPC) monitoring program. For non-lead group institutions an RT Facilities Inventory Form must be on file with CTSU. If this form has been previously submitted to CTSU it does not need to be resubmitted unless updates have occurred at the RT facility.

5.4.2 **In addition to the requirements noted above, U.S. and Canadian institutions** must fax copies of the documentation below to the CTSU Regulatory Office (215-569-0206); study-related regulatory documentation also may be e-mailed to the CTSU at CTSURegulatory@ctsu.coccg.org. This must be done, prior to registration of the institution's first case:

- IRB/REB approved consent (English and native language versions*****)
  ***Note**: Institutions must provide certification/verification of IRB/REB consent translation to RTOG Headquarters (described below).
- IRB/REB assurance number renewal information as appropriate.

5.4.2.1 Translation of documents is critical. The institution is responsible for all translation costs. All regulatory documents, including the IRB/REB approved consent, must be provided in

English and in the native language. Certification of the translation is optimal but due to the prohibitive costs involved RTOG will accept, at a minimum, a verified translation. A verified translation consists of the actual REB approved consent document in English and in the native language, along with a cover letter on organizational/letterhead stationery that includes the professional title, credentials, and signature of the translator as well as signed documentation of the review and verification of the translation by a neutral third party. The professional title and credentials of the neutral third party translator must be specified as well.

5.4.3 Pre-Registration Requirements FOR CANADIAN INSTITUTIONS

5.4.3.1 Prior to clinical trial commencement, Canadian institutions must complete and fax (215-569-0206) or e-mail (CTSURegulatory@ctsu.coccg.org) to the CTSU Regulatory Office Health Canada's Therapeutic Products Directorates' Clinical Trial Site Information Form, Qualified Investigator Undertaking Form, and Research Ethics Board Attestation Form.

5.4.4 Pre-Registration Requirements for the Initial Shipment of TAK-700:

5.4.4.1 ***U.S. and Canadian Institutions*:**
All pre-registration requirements must be met before registering the first case. Institutions must electronically complete (versus hand write) a Study Agent Shipment Form (SASF) available on the RTOG web site, www.rtog.org, under protocol-specific materials/regulatory resources. U.S. and Canadian institutions must fax the SASF to the CTSU Regulatory Office (Fax 215-569-0206) as soon as the individual responsible for the study agent has been identified. The completed SASF document also may be e-mailed to the CTSU at CTSURegulatory@ctsu.coccg.org.

5.5 OPEN Registration

5.5.1 Patient registration can occur only after pre-treatment evaluation is complete, eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

All site staff (RTOG and CTSU Sites) will use OPEN to enroll patients to this study. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' web site https://www.ctsu.org.

Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes. Site staff should use the registration forms provided on the group or CTSU web site as a tool to verify eligibility.
- All patients have signed an appropriate consent form and HIPPA authorization form (if applicable).

Access requirements for OPEN:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user id and password) used for the CTSU members' web site.
- To perform registrations, the site user must have been assigned the 'Registrar' role on the relevant Group or CTSU roster.
- To perform registrations on protocols for which you are a member of the RTOG, you must have an equivalent 'Registrar' role on the RTOG roster. Role assignments are handled through the Groups in which you are a member.
- To perform registrations to trials accessed via the CTSU mechanism (i.e., non-Lead Group registrations) you must have the role of Registrar on the CTSU roster. Site and/or Data Administrators can manage CTSU roster roles via the new Site Roles maintenance feature under RSS on the CTSU members' web site. This will allow them to assign staff the "Registrar" role.
- **NOTE**: **If you are enrolling as a non-RTOG site**: Prior to beginning the enrollment, call the RTOG Randomization desk at 215-574-3191 or 215-574-3192 to obtain an RTOG, non-Lead Group, site-specific institution number.

The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the CTSU members' web site OPEN tab or within the OPEN URL. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

5.5.2 In the event that the OPEN system is not accessible, participating sites can register a patient by calling RTOG Headquarters, at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The registrar will ask the site to fax in the eligibility checklist and will need the registering individual's e-mail address and/or return fax number. This information is required to assure that mechanisms usually triggered by the OPEN web registration system (e.g. drug shipment, confirmation of registration, and patient-specific calendar) will occur.

6.0 RADIATION THERAPY (5/1/12)

In both arms, radiotherapy should begin within 8-10 weeks after the date of the first LHRH agonist injection.

Note 1: There is no difference in radiation requirements between arms as the randomized question is in regard to hormonal therapy. However, as this protocol allows for treatment with EBRT exclusively or EBRT + a brachytherapy boost (at the discretion of the treating physician) this must be specified at the time of study enrollment. Because patients are stratified by type of boost treatment delivered (IMRT vs. brachytherapy), if a patient who was originally intended to receive brachytherapy be found, post-enrollment, to be a poor brachytherapy candidate based on transrectal ultrasound examination, he will no longer be eligible for participation in this study. Therefore, it is strongly recommended to obtain ultrasound assessment of prospective brachytherapy patients before enrollment on this study.

When an IMRT (rather than brachytherapy) boost is used to meet the dose constraints, the composite EBRT plan (see Sections 6.4 – 6.5) that includes Phases 1 and 2 must be generated and summed at the beginning of the patient's treatment to verify adherence to the required dose constraints. In the case of an inability to meet normal tissue dose-constraints on the summed plan a decrease in PTV dose to achieve normal tissue sparing is recommended (see Section 6.5).

6.1. Two Stage Radiation Plan

6.1.1 ***Phase 1***: Whole pelvis including prostate and seminal vesicles

Acceptable Treatment Modalities:
3D-CRT or IMRT

Prescription Dose (See Table 1):
45 Gy to cover 98% of PTV

- Minimum dose within PTV – 95% of prescribed dose and for a volume that is 0.03 cc
- Maximum dose within the PTV – 107% of prescribed dose and for a volume that is 0.03 cc

Table 1: 3D-CRT and IMRT Dose Objectives for Phase 1 – Pelvic and Prostate Radiation

PTV dose (encompassing 98% of PTV)	Minimum PTV dose for a point with a volume of 0.03 cc	Maximum PTV dose to a volume of 0.03 cc of the PTV[1] (Per Protocol)	Maximum PTV dose to a volume of 0.03 cc of PTV[1] (Variation Acceptable)	Maximum PTV dose to a volume of 0.03 cc of PTV[1] (Deviation Unacceptable)
45 Gy	42.8 Gy	48.2 Gy	> 48.2 - 49.5 Gy	> 49.5 Gy

[1] The maximum dose must not be within an "Organ at risk" such as the rectum, bladder, or penile bulb.

6.1.2 ***Phase 2:*** Reduce volume to boost prostate and proximal seminal vesicles

Acceptable Treatment Modalities:
IMRT or permanent prostate implant (PPI) brachytherapy or HDR brachytherapy

Prescribed Dose for IMRT boost (See Table 2):
34.2 Gy for IMRT to cover 98% of the PTV

- Minimum dose within PTV – 95% of prescribed dose and for a volume that is 0.03 cc
- Maximum dose within the PTV – 107% of prescribed dose and for a volume that is 0.03 cc

Prescription Dose for brachytherapy:
110 Gy for low dose rate PPI with I–125
100 Gy for low dose rate PPI with Pd-103
15 Gy in one fraction for HDR or two fractions of 10.5 Gy

Table 2: IMRT Dose Objectives for Prostate and Proximal Seminal Vesicle Boost

PTV dose (encompassing 98% of PTV)	Minimum PTV dose for a point with a volume of 0.03 cc	Maximum PTV dose to a volume of 0.03 cc of the PTV[1] (Per protocol)	Maximum PTV dose to a volume of 0.03 cc of PTV[1] (Variation Acceptable)	Maximum PTV dose to a volume of 0.03 cc of PTV[1] (Deviation Unacceptable)
34.2 Gy	33.4 Gy	36.6 Gy	> 36.6 – 37.6 Gy	> 37.6 Gy

[1] The maximum dose must not be within an "Organ at risk" such as the rectum, bladder, or penile bulb.

6.2 Technical Factors

6.2.1 Either 3DCRT or IMRT may be used for phase 1 of either Arm 1 or 2. For 3DCRT treating the whole pelvis (WPRT), a minimum of 4-fields should be used and a 4 field plan is recommended. For IMRT, no specific field arrangement is required.

6.2.2 RT will be delivered with megavoltage equipment at energies ≥ 6 MV. Typically, except for tomotherapy and VMAT techniques, 5 to 9 gantry angles are employed for the boost IMRT treatment.

6.2.3 Patients who receive brachytherapy as a boost component of their RT will undergo EBRT for Phase 1 implementing either 3DCRT or IMRT as described. The prostate and seminal vesicles will be treated to a dose of 45 Gy in 1.8 Gy fractions prescribed to a PTV dose as above.

6.3 EBRT Localization, Simulation, and Immobilization

Simulation will be CT-based in all cases. The use of urethral contrast at the time of simulation is not required to help identify the apex of the prostate. Rectal contrast is discouraged because it may distend the rectum and artificially displace the prostate in the anterior direction. Intravenous contrast is permitted but not required to assist in identifying the pelvic vessels. Patients will be positioned supine or prone on a flat tabletop with a customized thermoplastic immobilization cast or a molded foam cradle or similar immobilization for stabilization and setup reproducibility. The degree of bladder fullness should be made to duplicate the degree of fullness anticipated for daily treatment, i.e., if the patient is instructed to maintain a full bladder for treatment, he should be simulated as such (especially for cases in which image guidance is not implemented). The rectum should be kept as empty as possible; consider an enema 1-2 hours prior to simulation. 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 (Section 6.4) and normal critical structures (Section 6.4.4) will be defined in the slices in which they are visualized. The 3DCRT cases (Phase 1) must utilize "beam's eye view" representations to define final beam aperture.

6.4 Treatment Planning/Target Volumes

6.4.1 Patients treated with an IMRT boost (Phase 2) must have a composite treatment plan generated at the beginning of Phase 1 so that the final EBRT dose to critical structures is evaluated before any dose delivery has begun.

Dose for Phase 1 (CTV1/PTV1) will be 45.0 Gy at 1.8 Gy per fraction in both arms. Once Phase 1 is completed, a cone down boost to the prostate and proximal vesicles will be delivered in Phase 2 by any one of the three acceptable methods: IMRT, HDR or LDR permanent prostate

implant. If an EBRT boost is planned, the prostate will receive 34.2 Gy at 1.8 Gy per fraction, for a total prostate dose of 79.2 Gy. For pelvic 3D-CRT, a 4-field technique, using opposed anterior-posterior and opposed lateral fields, is recommended. All fields should conform to the beam's-eye-view of the target. No specific field arrangement is required for IMRT, although typically 5-9 fields are used for fixed gantry treatment. Tomotherapy and VMAT also are allowed for IMRT treatment on this protocol. However, both of these techniques must be credentialed separately from general IMRT credentialing.

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

6.4.2.1 *Phase 1 Pelvis, including prostate and seminal vesicles (Arms 1 and 2)*

Gross Target Volume (GTV1)

The GTV1 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.

Clinical Target Volume (CTV1)

The CTV1 will include the prostate and entire seminal vesicles (SV), the obturator, external iliac, proximal internal iliac and common iliac nodes, using the vascular structures, up to a level corresponding to the top of L4-L5. Please refer to the pelvic nodal atlas at the RTOG Web site (Pelvic Lymph Node Volumes for Prostate Cancer Atlas; **http://www.rtog.org/CoreLab/ContouringAtlases/ProstatePelvicLymphNodes.aspx**).

The presacral nodes from L5-S1 to S3 may be included if desired depending on whether the dose constraints to the rectum are achievable (see Table 1). The CTV1 will extend superiorly from L4-L5 to 0.5 cm below the tip of the urethral contrast dye (if used) and no less than the entire prostate gland. Lateral borders will be at least 1 cm from the pelvic brim. In the lateral fields, the external and internal iliac lymph nodes below the SI joints, and the posterior extension of the seminal vesicles should be covered. The usual posterior border is approximately S2-3, but CT anatomy should take precedence. The inferior extent of the external iliac lymph nodes is at the top of the femoral heads. The inferior extent of the obturator lymph nodes is at the top of the symphysis pubis. The CTV1 will include a 7 mm margin in 3-dimensions to the contoured iliac vessels, but not extend outside of the true pelvis, into the pelvic musculature nor into adjacent identifiable organs, such as the bladder, rectum or other bowel. Extension of the CTV into adjacent bone may be carved out.

Planning Target Volume

The PTV1 margins should be a minimum of 0.5 cm and a maximum of 1.5 cm in all dimensions.

6.4.2.2 *Phase 2 Prostate and Proximal Seminal Vesicles Boost with IMRT (Arms 1 and 2)*

Gross Target Volume (GTV 2)

See Section 6.4.2.1 above for GTV1.

Clinical Target Volume (CTV2)

The CTV2 is the GTV2 plus areas considered to contain microscopic disease, delineated by the treating physician. The CTV2 includes 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 as seen on the CT simulation scan. For patients with clinical biopsy proven involvement of the seminal vesicles treatment of the entire seminal vesicles is acceptable as long as it does interfere with the ability to achieve dose constraints to the critical normal structures (see section 6.5).

Planning Target Volume (PTV2)

The PTV2 will provide a margin around the CTV2 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. Individual selection of a PTV margin should be based on the institution's level of confidence in patient set-up and the availability of image guidance. 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.

6.4.3 Normal Critical Structures

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. The normal tissues will be contoured and considered as solid organs. The bladder should be contoured from its base to the dome, and the rectum from the anus (at the level of the ischial tuberosities) for a length of 15 cm or to the rectosigmoid flexure. This generally is below the bottom of the sacroiliac joints. If IMRT is being used to treat the pelvic nodes, the potential bowel space (not just individual loops of bowel) where the small and large bowel may fall should be outlined. The borders are the abdominal wall anteriorly, pelvic sidewalls laterally (excluding the pelvic lymph node regions), superiorly to one cut above the last axial CT image on which the lymph nodes are outlined and inferiorly from the level of the top of CTV1 (outlining around the sides of the bladder near the top of the bladder to encompass the bowel that may fall into these regions). See the ITC web site (http://atc.wustl.edu) to view examples of target and normal tissue contours.

The following table summarizes the naming of targets and critical structures for submission of data to the ITC.

Standard Name	***Description***
GTV	Gross Target Volume
CTV	Clinical Target Volume
PTV	Planning Target Volume
BLADDER	Bladder
FEMUR_LT	Left Femoral Head
FEMUR_RT	Right Femoral Head
PENILE_BULB	Penile Bulb
RECTUM	Rectum
SKIN	External Patient Contour
SEM_VES	Seminal Vesicles
PELVIC_LN	Pelvic Lymph Nodes

6.4.4 The PTV forms the entire target as described. 3D conformal beams will be shaped to include the entire PTV and minimize dose to surrounding critical structures as described. IMRT using inverse planning is permitted with constraints placed to adhere to critical structure dose limitations as defined below.

6.5 Critical Structures

Critical structure dose constraints shall remain consistent with those represented in prior RTOG 3DCRT/IMRT prostate protocols (see Table 3 below).

Table 3: Critical Structure Dose Constraints

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	65 Gy	60 Gy
Penile Bulb	Mean dose less than or equal to 52.5 Gy			

†Normal organ limit refers to the volume of that organ that should not exceed the dose limit.

While 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. As mentioned in Section 6.1, a prescription dose reduction to a level of 77.4 Gy or 75.6 Gy is permitted if constraints cannot be met at a prescription dose of 79.2 Gy. 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." It is at this point that a dose reduction to 77.4 Gy or 75.6 Gy should be implemented. 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.

6.6 Treatment Verification

6.6.1 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/image 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.

For IMRT the intensity profiles of each beam must be independently verified and compared to the planned field intensity. Portal films/images are not required for IMRT but orthogonal verification films/images are required, just as for 3DCRT. Real-time ultrasound localization and on-line cone beam CT image guidance are important complements to conventional port films or portal imaging and should be used when available. When not available, weekly port filming/imaging is required in this study.

6.6.2 Daily on-line target localization (kV or MV imaging with fiducials, trans-abdominal ultrasound, or other) or off-line adaptive approaches to account for interfraction organ motion and setup variability are permitted on this study but not required.

6.7 Quality Assurance

6.7.1 Compliance Criteria for Cases Treated with EBRT

Cases that are treated entirely with external beam radiation therapy must meet the criteria as stated in Sections 6.1.1 and 6.1.2 (see also Tables 1 and 2) to be scored as per protocol. That is, each case will have to meet the requirements in these sections depending on the particular arm of the study selected during randomization. Both the Phase 1 and 2 requirements for a particular arm must be met in order to be scored as per protocol. If only one phase of treatment meets the requirement, the case will be scored with the lower score of either variation acceptable or deviation unacceptable. In addition, the critical structure dose constraints of Section 6.5 and Table 3 must be met. In this case also, the patient's treatment will be scored lower when the critical structure score is lower.

The compliance criteria for the situation where the Phase 2 boost is accomplished with brachytherapy is given in Sections 6.8 and 6.9 below.

6.7.1.1 Acceptable dose heterogeneity for external beam treatment is summarized in Tables 1 and 2. The treating physician must carefully consider the tolerance dose/volume to each critical normal structure and unspecified tissue.

6.7.1.2 *Dose Distribution*

RTOG Headquarters QA will display, and compare with isodose distributions for the axial and coronal planes through the planning target volume to verify correct digital submission and conversion. The submitted DVHs for the PTV will then be compared with those generated by the RTOG. Per protocol scoring will be considered for those cases in which 98% of the PTV receives the prescription dose.

6.8 Dose Specifications/Technical Considerations: LDR Brachytherapy Boost

Note: As this protocol allows for treatment with exclusively EBRT or EBRT + a brachytherapy boost (at the discretion of the treating physician) this must be specified at the time of study enrollment. If a patient who was originally intended to receive brachytherapy be found, post-enrollment, to be a poor brachytherapy candidate based on transrectal ultrasound examination, he will no longer be eligible for participation in this study. Therefore, it is strongly recommended to obtain ultrasound assessment of prospective brachytherapy patients before enrollment on this study.

6.8.1 LDR, permanent seed, brachytherapy boost is permitted at the discretion of the treating radiation oncologist in conjunction with EBRT as described in Section 6.2.3. Implants will only be offered to patients with a prostate volume documented to be <60 cc by transrectal ultrasound examination, an AUA score ≤15, and no prior history of TURP (Section 3.2.7.1). The implant may be performed under either general or spinal anesthesia and will be performed following the EBRT portion of treatment no more than 2 weeks after its completion.

6.8.2 Preplanning

This will be carried out prior to the procedure or intra-operatively via transrectal ultrasound examination. The prostate will be defined from base to apex in the axial plane at 5 mm slice intervals. The treatment length and prostate volume will be recorded. The CTV is the prostate gland and the proximal seminal vesicles (CTV2). The PTV may be the same as the CTV or a 2-3 mm margin may be added anteriorly and up to 5 mm craniocaudally and laterally at the discretion of the treating physician.

6.8.3 Isotope Selection

Iodine-125 or Palladium-103 seeds may be used. The sources will be received and inventoried in accordance with state and federal regulations. If nonsterile loose sources or cartridges are used, at least 10% of the sources will be assayed in such a manner that direct traceability to either the National Institute of Standards and Technology (NIST), an Accredited Dosimetry Calibration Lab (ADCL) or for international participants, the national standards laboratory in their respective country, is maintained. NIST 1999 standards will be used. If sterile source assemblies or strands are used, alternatively non-stranded loose seeds equal to 5% of the total, or five seeds, whichever is fewer, may be ordered and assayed. Agreement of the average measured source strength shall agree with that indicated in the vendor's calibration certificate to within 5%. No measured source strengths should fall outside 10% of that indicated in the vendor's calibration certificate.

6.8.3.1 For I-125, the allowable source strength for each seed is 0.277 U to .650 U (NIST 99 or later). For Pd-103 sources, this range is 1.29 U to 2.61 U (NIST 99 or later).

6.8.3.2 The vendor's stated source strength shall be used in all dosimetry calculations. Calculations will be performed in accordance with NIST 1999 calibration standards, the point source formalism described in the report generated by AAPM Task Group 43 and subsequent published AAPM Subcommittee Reports. The AAPM's recommendations for Pd-103 dose specifications and prescription are being followed.

6.8.4 Prescription Doses

The prescription dose for permanent seed interstitial boost will be **110 Gy for I-125 and 100 Gy for Pd-103**. Doses will be prescribed as minimal peripheral dose to the PTV.

6.8.5 Postimplant Imaging

A pelvic x-ray with seed count verification will be obtained immediately postimplant. If the seed count does not match the number of seeds implanted, PA and lateral chest x-rays will be obtained to rule out pulmonary seed migration. CT scan for postimplant dosimetric analysis will be obtained following implant completion. Use of a Foley catheter for this test is encouraged for accurate urethral dosimetry but not required. This may be obtained immediately postoperative on the day of the implant if desired but no later than 5 weeks postimplant. The use of intravesical contrast is encouraged. CT slices should be acquired at ≤3 mm thickness and should encompass the pelvis from, at minimum, the bottom of the sacroiliac joints superiorly to 2 cm caudal to the prostatic apex.

6.8.5.1 Structures defined will include the prostate, bladder, and rectum. The rectum will be defined from the bottom of the sacroiliac joints to the ischial tuberosity and will extend to the outer surface of the visualized rectal wall. The postimplant, CT-defined prostate will be defined as the "evaluated target volume" (ETV) and will form the basis for dosimetric analysis.

6.8.6 Dosimetry

Postimplant evaluation will be performed on equipment capable of providing structural and volume-based dosimetric assessment on both the target and critical structures. Volume acquisition will be based on contiguous axial CT slices as described above. Both target volume and critical structures will be contoured on each applicable axial slice. Isodose line displays and dose-volume histograms for all structures will be generated.

6.8.6.1 The calculation grid should be set no larger than (2 mm x 2 mm x axial slice width).

6.8.6.2 The planning system shall be capable of transmitting data via DICOM RT to the ITC electronically.

6.8.6.3 Guidelines established by the American Brachytherapy Society (Nag 2000) are to be followed. DVH-based analysis must be used in the postplan evaluation. The following values shall be reported. Vn is the percentage of the ETV that received at least n% of the prescription dose. Dm is the minimum dose received by m% of the ETV.

6.8.6.4 Target coverage will be documented in terms of V100, V90, V80, D90.

6.8.6.5 Dose uniformity will be expressed in terms of V150.

6.8.6.6 The rectum will be defined from the bottom of the SI joints to the ischial tuberosity. The maximum rectal dose as well as the volume and percentage of rectum receiving > 100% of the prescription dose will be recorded.

6.8.7 Compliance Criteria

6.8.7.1 *Per protocol*: D90 for the ETV is greater than 90% of the prescription dose but less than 130% of the prescription dose.

6.8.7.2 *Variation acceptable*: D90 for the ETV is greater than 80% of the prescription dose, but less than 90% of the prescription dose, or greater than 130% of the prescription dose.

6.8.7.3 *Deviation unacceptable*: D90 for the ETV is less than 80% of the prescription dose.

6.8.8 Dosimetric Data to be Submitted to the ITC

6.8.8.1 Copies of preimplant TRUS images with CTV and PTV annotated

6.8.8.2 A copy of the implant record generated during the procedure

6.8.8.3 A copy of the image taken after the procedure and a copy of the image or scout taken during the post implant CT

6.8.8.4 A copy of the postimplant CT scan, ETV and bladder and rectum delineation and dosimetry calculations (must be submitted electronically)

6.8.8.5 A copy of the postimplant dosimetry report that contains the information required in Section 6.8.6 above.

6.9 Dose Specifications/Technical Considerations: HDR Brachytherapy Boost

Note: As this protocol allows for treatment with exclusively EBRT or EBRT + a brachytherapy boost (at the discretion of the treating physician) this must be specified at the time of study enrollment. If a patient who was originally intended to receive brachytherapy be found, post-enrollment, to be a poor brachytherapy candidate based on transrectal ultrasound examination, he will no longer be eligible for participation in this study. Therefore, it is strongly recommended to obtain ultrasound assessment of prospective brachytherapy patients before enrollment on this study.

6.9.1 HDR brachytherapy boost is permitted at the discretion of the treating radiation oncologist in conjunction with EBRT as described in Section 6.2.3. Implants will only be offered to patients with a prostate volume documented to be <60 cc by transrectal ultrasound examination, AUA symptom index ≤15, and no prior history of TURP (Section 3.2.7.1). The implant may be performed during the EBRT portion of the treatment or within 1 week prior to its initiation or following its completion. The RT should start within 56 days (+/-7 days) following the first LHRH administration. The date of HDR brachytherapy implant will constitute the start of RT for those patients receiving implants prior to EBRT.

6.9.2 All implants will be performed under transrectal ultrasound guidance. Epidural, spinal, or general anesthesia may be used. Epidural analgesia may be used for interfraction pain control.

6.9.3 At least 14 treatment catheters should be used to ensure adequate target coverage with acceptable dose heterogeneity.

6.9.4 Fiducial markers identifying the prostatic base and apex could be placed at the time of the implant procedure unless previously placed for guidance of EBRT.

6.9.5 The use of intraoperative cystoscopy is encouraged to ensure the absence of treatment catheters within the urethra or bladder. The cystoscope should be retroflexed within the bladder for visualization of the bladder neck. Light pressure on the treatment catheters should result in mucosal tenting confirming adequate coverage at the prostatic base.

6.9.6 Patients will be treated with either a single implant-single HDR fraction, a single implant-2 HDR fractions delivered over 24 hours with a minimum of 6 hours in between or 2 implants-2 HDR fractions. For patients receiving 2 fractions over 2 implants, the insertions should be 7 days prior to initiation of EBRT following its completion if not done during the EBRT. No EBRT treatment will be delivered on the day of HDR treatment.

6.9.7 Implant Dosimetry (CT or US-based)

6.9.7.1 The treatment planning CT scan must be performed with the patient in the supine position with the Foley catheter in place. Metallic obturators or non-CT compatible dummy ribbons must be removed prior to the CT scan. The scan must include all of the CTV with at least 9 mm superior and inferior margin, and the scan must include the tips of all the implanted catheters. The scan thickness must be ≤0.3 cm and the slices must be contiguous. The brachytherapy target volume (Section 6.9.8) and normal critical structures (Section 6.9.9) must be outlined on all CT slices including the prostate, seminal vesicles, urethra, bladder, and rectum.

6.9.7.2 Real-time, transrectal ultrasound-based planning is acceptable. The prostate must be defined from base to apex in axial slices with a maximum slice thickness of 5 mm. A Foley catheter must be in place for definition of the urethra.

6.9.7.3 Dwell times in positions located outside of the PTV should be turned down or off to minimize normal tissue irradiated. A dwell time optimization program based on implant geometry or an inverse planning algorithm may be used. Manual optimization is also accepted.

6.9.8 The CTV2 includes the prostate and proximal vesicles.

6.9.9 Critical structures to be defined include the bladder, rectum, urethra, and penile bulb within the volume of interest defined in Section 6.9.7.1. The outermost extent of the bladder/rectal wall will define those structures. The urethra is defined by the outer surface of the Foley catheter.

6.9.9.1 The volume of bladder and rectum receiving 75% of the prescription dose must be kept to less than 1 cc (V75 <1 cc) and the volume of urethra receiving 125% of the prescription dose must be kept to less than 1 cc (V125 <1 cc) and urethral V150 should be 0%. If the dose to normal critical structures cannot be kept below the specified level, we recommend readjusting the implant or repeating the implant procedure until a more optimal implant is obtained.

6.9.10 Ultrasound-Based Planning

For ultrasound-based planning, the urethra will be defined by the Foley catheter in slices extending from the base to the prostate apex. The anterior rectal wall must be defined along the length of the prostate.

6.9.10.1 Attempts should be made to limit the volume of urethra receiving ≥115% of the prescription dose to ≤5%. Up to 10% will be considered variation acceptable. Dose to > 1 cc of the anterior rectal wall should not exceed 75% of the prescription dose.

6.9.11 Compliance Criteria

The prescription dose and fractionation is at the discretion of the prescribing physician (Section 6.9.6).

6.9.11.1 *Single implant-single fraction*:

A prescription dose of 15 Gy will be delivered to the PTV.

Single implant-2 fractions:

A prescription dose of 21 Gy will be delivered to the PTV in two equal fractions of 10.5 Gy. The first fraction of 10.5 Gy will be delivered as soon as possible following completion of the implant procedure and treatment planning. Both fractions must be delivered within a single 24-hour period and separated by a minimum of 6 hours. Overnight hospital stay is permitted between fractions if necessary.

2 implants-2 fractions:

A prescription dose of 21 Gy will be delivered to the PTV in two equal fractions of 10.5 Gy, using one implant for each fraction. Both fractions of 10.5 Gy will be delivered as soon as possible following completion of the implant procedure and treatment planning. All catheters will be removed following completion of the treatment after each fraction. Both fractions must be separated by a minimum of 7 days.

6.9.11.2 Ninety-five percent coverage of the PTV with the prescription dose is considered per protocol, ≥90% but <95% is considered variation acceptable, and <90% coverage is considered deviation unacceptable.

6.9.12 Catheter Position Verification

Visual inspection of the catheters prior to delivery of each treatment is required. Fluoroscopy or CT may also be used to verify the position of the catheters in relation to the Foley catheter balloon and fiducial markers. The physician may adjust the catheters if catheter displacement is identified prior to the treatment. If the catheters cannot be satisfactorily repositioned and the PTV (Section 6.9.11) and normal critical structure (Section 6.9.10.1) DVH parameters are not met with a new plan, then the treatment should be postponed until a satisfactory implant is done. If the planning process is repeated, then a second set of data should be submitted.

6.9.12 Catheter Removal

After completion of the treatment all catheters will be removed.

6.9.13 Data Submission

All data will be digitally submitted to ITC and include CT data, normal critical structures, all PTV contours, and digital DVH data for all normal critical structures, the PTV for dose plan, a copy of the daily treatment chart for EBRT and Brachytherapy.

6.9.13.1 *Contours and Isodose Distributions*

For CT-planned cases contours of the PTV and normal critical structures with at least 9 mm in the cephalad and caudal directions must be submitted digitally to ITC. Electronic data transmission will be used after the institution has successfully completed a practice run with the ITC. Institutions credentialed for previous prostate brachytherapy protocols need not complete a practice run. For ultrasound-planned cases, at least 3 axial slices with the above overlying isodose curves will be submitted. These must include the base plane, apex, and widest axial dimension.

6.10 R.T. Quality Assurance Reviews

The study co-chairs for the respective RT modalities offered in this trial will oversee quality assurance reviews for patients treated in those respective fashions. These reviews will be ongoing and performed remotely. RT quality assurance reviews will be facilitated by RTOG RTQA.

6.11 Radiation Therapy Adverse Events

6.11.1 All patients will be seen weekly by their treating radiation oncologist while undergoing EBRT. Any observations with respect to the following symptoms/side effects will be recorded:

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

6.11.2 Clinical discretion may be used in managing radiotherapy-related side effects. Diarrhea/rectal frequency/urgency may be managed with diphenoxylate or loperamide. Bladder irritation may be mitigated with phenazopyridine. Urinary frequency/urgency can be managed with anticholinergic agents or alpha-blockers such as tamsulosin. Erectile dysfunction can be managed with phosphodiesterase (PDE) inhibitors such as sildenafil.

6.12 Radiation Therapy Adverse Event Reporting

See Section 7.16.

7.0 DRUG THERAPY

7.1 Treatment

Androgen suppression (AS) must begin within 6 weeks after registration and will be administered in both Arms 1 and Arm 2. TAK-700 will begin at the same time as AS. Radiation therapy will begin 8-10 weeks after the initiation of AS and will be given as specified in Section 6.0.

7.1.1 Arm 1

Patients on Arm 1 will receive standard AS with LHRH agonist and oral antiandrogen. LHRH agonist will continue for 24 months from initiation. Oral antiandrogen will be discontinued at the end of radiation therapy.

7.1.2 Arm 2

Patients on Arm 2 will receive the same standard AS with LHRH agonist and oral antiandrogen as Arm 1, but also will receive the study drug TAK-700 as detailed in Section 7.5 below.

7.2 LHRH agonists (such as leuprolide, goserelin, buserelin, triptorelin)

For further information, consult the package inserts.

7.2.1 Description: LHRH agonists are long-acting analogs of the native LHRH peptide and are effective at reducing serum testosterone. Analogs approved by the FDA (or by Health Canada for Canadian institutions) can be used in this study.

7.2.2 Supply: Commercially available. (NOTE: Buserelin is not commercially available in the United States. It is commercially available for use in Canada and other countries outside of the United States.)

7.2.3 Storage: LHRH analogs should be stored as directed by the commercial supplier.

7.2.4 Administration: LHRH analogs are administered with a variety of techniques, including subcutaneous insertion of a solid plug in the abdominal wall (Zoladex), intramuscular injection (Lupron), subcutaneous injection (Eligard), or insertion of a long-acting cylinder that slowly releases the agent (Viadur). The manufacturer's instructions should be followed.

7.2.5 Toxicity: Consult the package insert for comprehensive toxicity information. Class-related toxicity is generally a manifestation of the mechanism of action and due to low testosterone levels. In the majority of patients testosterone levels increased above baseline during the first week, declining thereafter to baseline levels or below by the end of the second week of treatment. The most common side effect of LHRH analogs is vasomotor hot flashes; edema, gynecomastia, bone pain, thrombosis, and gastrointestinal disturbances have occurred. Potential exacerbations of signs and symptoms during the first few weeks of treatment is a concern in patients with vertebral metastases and/or urinary obstruction or hematuria which, if aggravated, may lead to neurological problems such as temporary weakness and/or paresthesia of the lower limbs or worsening of urinary symptoms. Other side effects include impotence and loss of libido, weight gain, depression, dizziness, loss of bone density, anemia, increased thirst and urination, unusual taste in the mouth, skin redness or hives, pain at injection site, and muscle mass and strength loss, hair changes, penile length and testicular volume loss, increased cholesterol, hypertension, diabetes exacerbation, emotional lability, nausea, vomiting, and rarely allergic generalized rash and difficulty breathing.

7.3 Eulexin (flutamide)

For further information, consult the package insert.

7.3.1 Description: Flutamide is a substituted anilide. It is a fine, light, yellow powder, insoluble in water but soluble in common organic solvents such as aromatic or halogenated hydrocarbons. Its concentration in plasma can be determined by gas chromatography. Flutamide is a nonsteroidal antiandrogen that is metabolized into a hydroxylated derivative, which effectively competes with the hydrotestosterone for androgen receptor sites.

7.3.2 Supply: Commercially available.

7.3.3 Storage: Flutamide should be stored at temperatures ranging from 20-30 °C (36 °-86 °F) and protected from excessive moisture.

7.3.4 Administration: The drug is administered orally at a dose of 250 mg (two 125-mg capsules) three times a day for a total daily dose of 750 mg. Flutamide will begin 8-10 weeks prior to radiotherapy and continue throughout radiotherapy. Radiotherapy should begin 8-10 weeks after start of LHRH therapy. Administration will be suspended only if there is an apparent or suspected reaction to the drug. See Section 7.3.6. Flutamide will be terminated on the last day of radiotherapy. During radiotherapy interruptions, flutamide will be continued.

7.3.5 Toxicity: Consult the package insert for comprehensive toxicity information. The reported side effects of treatment include diarrhea and anemia. A high percentage of patients treated with flutamide alone developed gynecomastia within 2 to 8 months. There have been post-marketing reports of hospitalization, and, rarely, death due to liver failure in patients taking flutamide. Evidence of hepatic injury included elevated serum transaminase levels, jaundice, hepatic encephalopathy, and death related to acute hepatic failure. The hepatic injury was reversible after prompt discontinuation of therapy in some patients. Approximately half of the reported cases occurred within the initial 3 months of treatment with flutamide. Other side effects include impotence and loss of libido, fatigue, and rarely photosensitivity.

7.3.6 Dose Modifications: If gastrointestinal disturbances (cramps, diarrhea) occur prior to initiation of radiotherapy, flutamide will be withheld until the side effects subside; the drug will then be reintroduced at a dose of 250 mg/day and increased (at 3-day intervals) to 500 mg/day and then to 750 mg/day as tolerated. If gastrointestinal disturbances occur after administration of radiotherapy, it might be difficult to identify their cause. However, if severity of diarrhea exceeds

the level commonly observed during pelvic irradiation, the toxicity will be ascribed to flutamide and the drug will be permanently discontinued. ALT will be measured pretreatment, then monthly during oral antiandrogen therapy. If ALT increases ≥ 2 x upper institutional limit of normal, flutamide must be discontinued.

7.4 Casodex (bicalutamide)

For further information, consult the package insert.

7.4.1 Description: Bicalutamide is a nonsteroidal antiandrogen, which has no androgenic or progestational properties. The chemical name is propanamide, N-[4-cyano-3(trifluoromethyl)phenyl]- 3- [(4-fluorophenyl)sulphonyl]- 2- hydroxy- 2- methyl, (+,-). Bicalutamide is a racemic mixture with the antiandrogen activity residing exclusively in the (-) or R-enantiomer. Bicalutamide has a long half-life compatible with once-daily dosing. Bicalutamide is well tolerated and has good response rates in phase II trials (Kennealey and Furr, 1991, Tyrrell 1994).

7.4.2 Supply: Commercially available.

7.4.3 Storage: Bicalutamide should be stored in a dry place at room temperature between 68°-77°F.

7.4.4 Administration: Bicalutamide is administered orally at a dose of one 50 mg tablet per day. Bicalutamide will begin 8-10 weeks prior to radiotherapy and continue throughout radiotherapy. Radiotherapy should begin 8-10 weeks after start of LHRH therapy. Administration will be suspended only if there is an apparent or suspected reaction to the drug. Bicalutamide will be terminated on the last day of radiotherapy. During radiotherapy interruptions, bicalutamide will be continued.

7.4.5 Toxicity: Consult the package insert for comprehensive toxicity information. In animal experiments, birth defects (abnormal genitalia, hypospadias) were found in male offspring from female animals dosed with bicalutamide during pregnancy. Although offspring from male animals dosed with bicalutamide did not show any birth defects, patients enrolled in this trial are advised not to cause pregnancy nor donate sperm while receiving protocol therapy or during the first 3 months after cessation of therapy. The use of barrier contraceptives is advised. The most frequent adverse events reported among subjects receiving bicalutamide therapy are breast tenderness, breast swelling, and hot flashes. When bicalutamide 50 mg was given in combination with an LHRH analog, the LHRH analog adverse event profile predominated with a high incidence of hot flashes (53%) and relatively low incidences of gynecomastia (4.7%) and breast pain (3.2%). Other side effects include impotence and loss of libido, fatigue, and rarely photosensitivity and diarrhea.

7.4.6 Dose Modifications: Bicalutamide should be discontinued in instances of chemical liver toxicity. ALT will be measured pretreatment and then monthly during antiandrogen therapy. If the ALT rises ≥ 2 x the institutional upper limit of normal, bicalutamide must discontinued.

7.5 Study Drug (TAK-700) Administration

7.5.1 Dose and Regimen

TAK-700 will initially be given at 300 mg BID (600 mg per day) orally, continuously for 2 years, beginning at the same time as androgen suppression (AS). See Section 7.6 for dose modification and supportive care guidelines. TAK-700 should be taken twice daily at the same time each day, but not less than 6 hours apart, and may be taken with or without food. Missed doses of study drug will not be made up. Patients will be given a diary to record study drug dosing. If a dose is missed, the missed dose will be recorded as “not taken.” The next dose will be taken at the next scheduled time.

7.6 Dose Modification and Supportive Care Guidelines

The investigator should determine if an AE is related to TAK-700. Adverse events considered at least possibly related to TAK-700 may require a dose reduction (Table 7-1), a temporary hold, or permanent discontinuation.

Depending on the AE, following partial or complete resolution of symptoms, the dose of TAK-700 may be increased at 2-week intervals to the next higher dose level until the original dose level has been reached. Guidelines for modification of the dose based on the severity of the AE are provided in this section.

7.6.1 Dose Levels for TAK-700

The TAK-700 dose levels to be applied for all dose modifications are defined in Table 7-1.

Table 7-1 Dose Modifications for TAK-700	
Dose Level	TAK-700 Dose (Tablets and Timing of Administration)
0	300 mg BID (100 mg x 3 BID)
-1	200 mg BID (100 mg x 2 BID)
-2	None (dosing hold or temporary discontinuation)

7.6.2 Dose Modifications

Dose modifications should be based on CTCAE version 4.0. Dose reduction for Grade 1 AEs is not required. Dose reduction for Grade 2 events should only be considered when the AE is judged by the investigator to be clinically intolerable. For TAK-700 Grade ≥2 AEs, the dose modification of TAK-700 should follow the Dose Reduction and Re-escalation guidelines (Sections 7.6.3 and 7.6.4, respectively). For events of fatigue, nausea, vomiting, diarrhea, and hypertension, refer to Section 7.6.6, Specific Guidelines for Possible TAK-700 Related Toxicities.

7.6.3 Criteria for TAK-700 Initial Dose Reduction

Asymptomatic Grade 3 or 4 laboratory findings may not require dose modification (i.e. dose hold or reduction) especially if these are not considered to be clinically significant or related to study drug. The decision to modify the dose should be based on the investigator's clinical judgment.

Grade 3 or 4 AEs that are considered at least possibly related to study drug require a dosing hold, i.e. hold for a minimum of 2 weeks. The investigator should identify other potential causes of AEs. For a clinically intolerable Grade 2 AE that is considered at least possibly related to study drug, the dose should be decreased by 1 dose level for 2 weeks.

Once the dose is reduced, reassessment is required at least every 2 weeks until the event is resolved or stabilized. However, the frequency of reassessment should be increased as clinically indicated. If the grade worsens at any time, the dose should be decreased in accordance with the guidelines for the worst grade.

7.6.4 Criteria for TAK-700 Dose Re-escalation

7.6.4.1 *Re-escalation for Grade 2 Intolerable Adverse Events*

Re-escalation of TAK-700 after resolution or improvement of a Grade 2 intolerable AE will follow the criteria below:

(1) If the AE grade improves to Grade 0, 1, or Grade 2 tolerable AE, re-escalate the dose by 1 level.

(2) If the AE remains at intolerable Grade 2 or worsens to Grade > 3, hold TAK-700 for 2 weeks followed by a reassessment. Follow the re-escalation guidelines for Grade 3 or 4 AEs as defined in Section 7.6.4.2.

Reassess the AE after 2 weeks, or sooner if the AE worsens. Continue to reassess at least every 2 weeks until the event is resolved or stabilized. Continue to adjust the TAK-700 dose until the dose is optimally titrated. If the dose has been held for 6 weeks, TAK-700 should be discontinued permanently.

7.6.4.2 *Re-escalation of TAK-700 Following a Grade 3 or 4 Adverse Event*

Re-escalation following a Grade 3 or 4 AE will follow the criteria below:

(1) If the AE grade improves to Grade 0, 1, or Grade 2 tolerable AE, re-escalate the TAK-700 dose by 1 level.

(2) If the AE improves to Grade 2 but is still intolerable, hold dosing for another 2 weeks. Follow the re-escalation guidelines for Grade 2 intolerable AEs as defined in Section 7.6.4.1.

(3) If the AE is Grade 3 or 4 after 2 weeks, hold dosing for another 2 weeks and reassess again after 2 weeks.

Reassess the AE after 2 weeks, or sooner if the AE worsens. Continue to reassess at least every 2 weeks until the event is resolved or stabilized. Continue TAK-700 dose adjustment until the dose is optimally titrated.

7.6.5 Criteria for Discontinuation of TAK-700

If the adverse event persists at ≥ Grade 3 for more than 6 weeks, permanently discontinue treatment with TAK-700. The TAK-700 dose may also be discontinued permanently if judged by the investigator to be clinically intolerable despite dose reduction, and the dose cannot be optimally titrated.

7.6.6 Specific Guidelines for Possible TAK-700-Related Toxicities

This section provides the required dose modifications for study drugs and recommended clinical management of patients who experience AEs that are considered by the investigator to be related to TAK-700.

7.6.6.1 *Fatigue*

Grade 2 to Grade 3 fatigue has occurred in some patients receiving TAK-700 without concomitant prednisone. Less severe Grade 1 or Grade 2 fatigue has been reported in some men receiving concomitant prednisone; other factors such as acute androgen deprivation may also contribute to symptoms.

Dose modification for Grade 2 fatigue is optional but may be helpful by slowing the induction to full androgen deprivation. Grade 3 fatigue should be treated according to the general outlines in Section 7.6.2, including initial hold and re-introduction of TAK-700 with subsequent titration at 2 week intervals to the patient's tolerated dose level.

7.6.6.2 *Gastrointestinal Adverse Events*

In previous and ongoing clinical studies, episodic and not necessarily dose-related gastrointestinal toxicities have occurred.

Nausea and/or Vomiting

Grade 1 – No action required

Grade 2 – Concomitant antiemetics may initially be administered without dose reduction. If Grade 2 nausea or vomiting persists and is intolerable, dose reduction and re-escalation should follow Grade 2 Dose Reduction and Dose Re-escalation guidelines.

Grade 3 or 4 – Supportive care regimen should follow local standard of care. Follow Dose Reduction and Dose Re-escalation guidelines.

Note: It is possible that nausea and vomiting could be secondary to acute adrenal insufficiency. If nausea and vomiting occur in the setting of severe fatigue, prostration, or hypotension, blood should be obtained to check the electrolytes. Institutional standard of care should be followed in the presence of electrolytes imbalance. Even if the vomiting occurs shortly following the TAK-700 dose, no re-dosing of TAK-700 will be done.

Diarrhea

Prophylactic antidiarrheals will not be used in this protocol; however, patients will be treated according to institutional standard of care. Fluid intake should be maintained to avoid dehydration.

7.6.6.3 *Hypertension*

If new onset or worsening of established hypertension occurs and the potassium level is < 3.5 mEq/L, in the absence of other causes such as new diuretic therapy, it suggests a TAK-700-related mineralocorticoid syndrome. A plasma renin activity that is undetectable or low also suggests such a syndrome rather than a secondary cause. While addressing underlying factors or compliance with current antihypertensives, dose modification should be initiated according to the general guidelines outlined in Section 7.6.3.

If other causes are identified as the reason for new or worsening hypertension, the investigator should follow the institution's local standard of care treatment and the dose of TAK-700 can be adjusted upwards in accordance with the general guidelines in Section 7.6.3.

7.6.6.4 *Suspected or Possible Adrenal Insufficiency*

If patients experience adrenal insufficiency, the adrenal insufficiency may have the more nonspecific manifestations of glucocorticoid insufficiency, rather than the more specific electrolyte abnormalities of mineralocorticoid insufficiency. Patients experiencing severe physiological stress (eg, surgery, severe infection) should be carefully monitored for adrenal

insufficiency. Concomitant medications may complicate the picture of adrenal insufficiency, in particular in patients who are on beta-blockers or diuretics. Concomitant illness such as infection might similarly trigger or worsen symptoms of otherwise mild adrenal insufficiency. Grading of adrenal insufficiency should follow CTCAE criteria (version 4.0). In all cases, actions should include a thorough review for other possible causes or contributors to the presenting symptoms (eg, infection, anemia, or newly introduced concomitant medications).

7.6.6.5 *Abnormal Liver Enzymes*

Table 7-2 Management of Abnormal AST or ALT Bearing a Possible Relationship to TAK-700 Treatment

AST and/or ALT Elevation Grade (Per NCI CTCAE)	Concurrent Bilirubin Level	TAK-700 Dose Modification
Grade 1	≥ 1.5 x ULN	Hold until bilirubin resolves to < 1.5 ULN Dose at the next lower dose level
Grade 2	< 1.5 x ULN	Hold until ALT/AST resolve to Grade 1 Dose at the next lower dose level
Grade 2	≥ 1.5 x ULN	Discontinue TAK-700
Grade ≥ 3	Any	Discontinue TAK-700

Note: Following TAK-700 dose de-escalation due to AST/ALT and/or bilirubin abnormalities, no re-escalation is permitted.

7.6.7 Overdose

The maximum tolerated or efficacious dose for TAK-700 has not been determined. An overdose is defined as deliberate or accidental administration of study medication at a dose above that which is assigned to that individual subject. In the event of drug overdose, the principal investigator should be notified immediately and the patient observed closely for adverse effects. The patient should be treated symptomatically as appropriate, and the incident of overdose and related AEs and/or treatment-documented in the patient's medical record. Patients who may have overdosed and who have possible manifestations of adrenal insufficiency may be treated acutely with oral steroids as tolerated.

7.7 Excluded Concomitant Medications and Procedures

The following medications and procedures are prohibited during the study:

- Any investigational agent other than TAK-700
- Other anticancer therapy, except for GnRH analogs, antiandrogens, and radiation therapy
- Hormonal therapies including estrogens or herbal products
- Ketoconazole or aminoglutethimide
- Chronic use of systemic corticosteroids, such as oral prednisone
- Patients must be instructed not to take any medications, including over-the-counter products and vitamins, minerals and other dietary supplements, without first consulting with the investigator.

7.8 Precautions and Restrictions

It is not known what effects TAK-700 has on human pregnancy or development of the embryo or fetus. Therefore, male patients should avoid impregnating a female partner. Patients should use effective methods of contraception through defined periods during and after study treatment as specified below. If a female partner of a male patient becomes pregnant during the male patient's participation in this study, this must be reported to Millennium Pharmacovigilance (or designee) immediately (see below). Every effort should be made to follow the pregnancy for the final pregnancy outcome (i.e. delivery, still birth, miscarriage).

Millennium Pharmacovigilance
SAE and Pregnancy Reporting Contact Information:
North America
PPD, Inc.
Safety and Medical Management, US
Fax: +1 888-488-9697
Hotline number (available 24/7): 1-800-201-8725

Male patients, even if surgically sterilized (eg, status postvasectomy) must agree to either practice effective barrier contraception during the entire study treatment period and through 4 months after the last dose of study drug, or completely abstain from intercourse.

Nonclinical studies of TAK-700 biotransformation by human hepatic and intestinal microsomes indicate that CYP enzymes have only a minor role in the metabolism of TAK-700. Based on these findings, there is very low risk that the metabolism of TAK-700 will be affected by CYP-mediated interactions due to other drugs.

In vitro studies indicate that TAK-700 is a weak to moderate inhibitor of CYP1A2, 2C9, and 2C19 (Kis of 8.9, 15.4, and 19.4 µmol/L, respectively). These findings indicate that TAK-700 has the potential to inhibit the metabolism of drugs that are substrates of CYP1A2 and may possibly inhibit the metabolism of drugs that are substrates of 2C9 and 2C19.

Drugs that are primarily metabolized by these CYP isoforms should be used with caution when administered concomitantly with TAK-700.

In vitro studies demonstrate that TAK-700 is a substrate for P-gp but the affinity of TAK-700 for P-gp is low. Studies show that TAK-700 was not an inhibitor of P-gp. Based on these findings, there is very low risk of a P-gp-based interaction of TAK-700 with other drugs.

No single-dose effect of TAK-700 on QTc interval has been observed in healthy male subjects, and no trend in QTc interval has been observed to date in patients with mCRPC in the open-label phase 1/2 TAK-700_201 study. Until more data are available, patients with underlying cardiac rhythm abnormalities or in patients on other drugs that may affect the QTc interval should be monitored closely.

7.9 Blinding and Unblinding

This is an open-label study.

7.10 Description of Investigational Agent

TAK-700 is manufactured by Takeda Pharmaceutical Company, Ltd., Osaka, Japan. TAK-700 will be supplied as pale red film-coated tablets. Each tablet will contain 100 mg of TAK-700. Further details are provided in the TAK-700 Investigator's Brochure.

7.11 Preparation, Reconstitution, and Dispensation

TAK-700 is an antineoplastic agent, and as with other potentially toxic compounds, caution should be exercised when handling TAK-700.

7.12 Packaging and Labeling

TAK-700 supplied as 100 mg tablets packaged in high density polyethylene bottles with child-resistant cap and with a 3 gram desiccant. Each bottle will be labeled in accordance with all regulatory requirements appropriate for the country(ies) in which the study will be conducted.

7.13 Storage, Handling, and Accountability

TAK-700 supplied as 100-mg film-coated tablets should be stored in the original dispensing bottle at the conditions described in the product label. The drug supply must be kept in an appropriate, limited-access, secure place until it is dispensed to study enrollees, returned to the sponsor, or

forwarded to the sponsor's designee for destruction. Drug supplies will be counted and reconciled at the site before being returned.

The investigator must maintain 100% accountability for all study medication received and dispensed during his or her entire participation in the study. Proper drug accountability includes, but is not limited to:

- Continuously monitoring expiration dates if retest date is provided to the investigator.
- Frequently verifying that actual inventory matches documented inventory. Verifying that the drug accountability log is completed for the drug lot used to prepare each dose.
- Verifying that all containers used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.

If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately. The investigator must maintain a current inventory (drug accountability log) of all study medication delivered to the site, inventory at the site, and patients' use records. This log must accurately reflect the drug accountability of the study medication at all times. The following information will be recorded at a minimum: protocol number and title, name of the investigator, site identifier and number, description of the study medication, expiry and/or retest date, date and amount dispensed, and the date and amount returned to the site by the patient, including the initials of the person dispensing and receiving the study medication. The log should include all required information as a separate entry for each patient to whom study medication is dispensed. Prior to site closure or at appropriate intervals, a representative from the sponsor or its designee will perform clinical study material accountability and reconciliation before TAK-700 clinical study materials are returned to the sponsor or its designee for destruction. The investigator will retain the original documentation regarding clinical study material accountability, return, and/or destruction, and copies will be sent to the sponsor. The investigator will be notified of any expiry date or retest date extension of clinical study material during the study conduct. On expiry date notification from the sponsor or designee, the site must complete all instructions outlined in the notification, including segregation of expired clinical study material for return to the sponsor or its designee for destruction. In the event of expiry date extension of supplies already at the study site, supplies will be relabeled with the new expiry date at that site. In such cases, the sponsor or its designee will prepare additional labels, certificates of analyses, and all necessary documentation for completion of the procedure at the sites.

7.14 Supply (5/1/12)

This study will be conducted under an IND to be held by RTOG and will require FDA submission and approval as part of the IND. TAK-700 will be supplied to patients in the study free of charge.

The Study Agent Shipment Form [SASF; available on the RTOG web site, www.rtog.org, under protocol-specific materials/regulatory resources] for U.S. and Canadian sites must be submitted to the CTSU Regulatory Office (Fax 215-569-0206) as soon as the individual responsible for the study agent has been identified. This must be done prior to registration of the institution's first case. The drug supply will not be shipped by Biologics, Inc. until the patient has been registered. Canadian shipments may require additional time. RTOG will notify Biologics, Inc. to initiate each of these shipments after registration of the patient. Drug shipments may not be immediate if the protocol includes a delay in the initial dosing. Drug will be delivered in time for the patient's first dose.

7.14.1 Biologics, Inc. TAK-700 Distribution

Upon receipt of patient registration/randomization, RTOG will notify Biologics via e-mail.

Biologics will then perform the following process:

- Confirm SASF and Registration/Randomization;
- Place call directly to the study site contact listed on the SASF confirming that the registration/randomization was received and to:
  - Collect any additional patient or shipping information required per protocol;
  - Arrange the date and time of arrival for the study drug;
- Ship the initial shipment of study drug supply per protocol directly to SASF address; any discrepancies will be addressed with the CTSU.

Biologics, Inc. ships study drug the same day of receipt of patient registration/randomization if received before 2:00pm ET on Monday through Friday. Ambient drug like TAK-700 allows for Friday shipment with Monday delivery. Authorized and complete orders received after 2:00pm ET Monday through Friday will be processed and shipped the next business morning.

TAK-700 Shipment Schedule				
Patient registered with RTOG	**E-order transmitted by RTOG**	**E-order Received by Biologics (before 2PM ET)**	**Order shipped**	**Order received at site**
Monday	Monday	Monday	Monday	Tuesday
Tuesday	Tuesday	Tuesday	Tuesday	Wednesday
Wednesday	Wednesday	Wednesday	Wednesday	Thursday
Thursday	Thursday	Thursday	Thursday	Friday
Friday	Friday	Friday	Friday	Monday

All shipments are sent via *FedEx for Priority Overnight* delivery. Study Drug (TAK-700) is shipped in a Biologics, Inc. branded container appropriate to maintain temperature stability.

Shipment Schedule

Initial shipment – 18 Bottles of study drug to be taken continuously
- 6 months at 300mg (3 tabs/100mg each) PO BID

Biologics places follow-up call during month 5 for subsequent shipment of study drug
Subsequent shipment 2 – 18 Bottles of study drug to be taken continuously
- 6 months at 300mg (3 tabs/100mg each) PO BID

Biologics places follow-up call during month 11 for subsequent shipment of study drug
Subsequent shipment 3 – 18 Bottles of study drug to be taken continuously
- 6 months at 300mg (3 tabs/100mg each) PO BID

Biologics places follow-up call during month 17 for subsequent shipment of study drug
Subsequent shipment 4 – 18 Bottles of study drug to be taken continuously
- 6 months at 300mg (3 tabs/100mg each) PO BID

For all drug shipments from Biologics, Inc.:

- Study Drug will be shipped in original manufacturers packaging. Bottles are placed in a Ziploc bag with a patient specific label adhered to the outside of the bag.

- Each shipment includes a patient label on the Ziploc bags with the following information:
  - The Study Number (i.e. RTOG 1115);
  - IND caution statement and/or local regulatory statements;
  - Drug identification (TAK-700)
  - Expiration
  - Storage conditions
  - Dosing instructions (Take as Directed per Protocol)
  - Subject ID number (e.g. 1115-YYY, where the study number and sequence number represents the unique patient identifier assigned by RTOG at registration);
  - The patient's initials (i.e. first, middle, last)
  - A blank line for the site pharmacist to enter the patient's name;
  - Administration instructions (i.e. "Take xx tablets every day for xx days");
  - Storage instructions (i.e. "Store at controlled room temperature, xx degrees");
  - Emergency contact instructions;

- Enclose a packing slip that includes the quantity of drug provided with a section to be completed once received by the site coordinator. This section includes confirmation of drug receipt, verification of package contents, and instruction to fax the completed packing slip to Biologics.

- Packages are tracked until confirmed delivered and delivery exceptions are managed with the highest level of urgency to ensure therapy start date adherence. Packing slips with the shipment tracking number included will be faxed to the designated site coordinator for all shipments.

Please contact the drug distributor, as listed below, directly for shipment tracking information and anticipated delivery dates or if a shipment has not been received by the expected date.

Unused supplies at the sites will be destroyed on site per local guidelines/standard operating procedures. Additional questions about supply and delivery should be directed to:

Clinical Trial Services
Biologics, Inc.
120 Weston Oaks Court
Cary, NC 27513
(800) 693-4906
clinicaltrials@biologicstoday.com

7.14.2 Study Agent Accountability

Drug accountability records must be maintained at all sites according to good clinical practices and NCI guidelines using the Investigational Agent Accountability Record (IAAR) form.

7.15 Adverse Events

This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for AdEERS reporting of adverse events (AEs). **All AE reporting on the study case report forms (CRFs) should follow grading criteria instructions on the specific CRF.** The CTCAE version 4.0 is identified and located on the CTEP web site at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0.

All adverse events (AEs) as defined in the tables below will be reported via the AdEERS (Adverse Event Expedited Reporting System) application accessed via the CTEP web site (https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main$.startup).

Serious adverse events (SAEs) as defined in the tables below will be reported via AdEERS. Sites also can access the RTOG web site (http://www.rtog.org/ResearchAssociates/AdverseEventReporting.aspx) for this information.

In order to ensure consistent data capture, serious adverse events reported on AdEERS reports also must be reported on an RTOG case report form (CRF). In addition, sites must submit CRFs in a timely manner after AdEERS submissions.

A 24-hour notification is to be made to RTOG Data Management by telephone at 215-717-2762 only when internet connectivity is disrupted. Once internet connectivity is restored, an AE report submitted by phone must be entered electronically into AdEERS by the original submitter at the site.

7.15.1 Adverse Events (AEs)

Definition of an AE: Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). [CTEP, NCI Guidelines: Adverse Event Reporting Requirements. July 26, 2011; http://ctep.cancer.gov/reporting/adeers.html]

The following guidelines for reporting adverse events (AEs) apply to **all** NCI/RTOG research protocols. AEs, as defined above, experienced by patients accrued to this protocol should be reported on the AE section of the appropriate case report form (see Section 12.1). **Note: AEs indicated in the AdEERS Expedited Reporting Requirements in text and/or table in Section 7.16 also must be reported via AdEERS.**

NOTE: If the event is a Serious Adverse Event (SAE) [see next section], further reporting will be required. Reporting AEs only fulfills Data Management reporting requirements.

7.15.2 Serious Adverse Events (SAEs) — **All SAEs that fit any one of the criteria in the SAE definition below must be reported via AdEERS. Contact the AdEERS Help Desk if assistance is required.**

Certain SAEs as outlined below will require the use of the 24 Hour AdEERS Notification:

- **Phase II & III Studies: All unexpected potentially related SAEs**
- **Phase I Studies: All unexpected hospitalizations and all grade 4 and 5 SAEs regardless of relationship**

Definition of an SAE: Any adverse experience occurring during any part of protocol treatment and 30 days after that results in any of the following outcomes:

- Death;
- A life-threatening adverse drug experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. Any pregnancy occurring on study must be reported via AdEERS as a medically significant event.

Pharmaceutically supported studies will require additional reporting over and above that which is required by CTEP.

SAEs (more than 30 days after last treatment) attributed to the protocol treatment (possible, probable, or definite) should be reported via AdEERS.

All supporting source documentation indicated as being provided in the Additional Information Section of the AdEERS Report must be properly labeled with the study/case numbers and the date of the event and must be faxed to the RTOG dedicated SAE FAX, 215-717-0990, before the five or ten-calendar-day deadline to allow RTOG to comply with the reporting requirements of the pharmaceutical company/companies supporting the RTOG trial. The RTOG Case Number without any leading zeros should be used as the Patient ID when reporting via AdEERS. Non-RTOG intergroup study and case numbers must also be included, when applicable. Submitted AdEERS Reports are forwarded to RTOG electronically via the AdEERS system. Use the patient's case number as the patient ID when reporting via AdEERS.

SAE reporting is safety related and separate and in addition to the Data Management reporting requirements as outlined in the previous AE reporting section. **Any event that meets the above outlined criteria for an SAE but is assessed by the AdEERS System as "expedited reporting NOT required" must still be reported for safety reasons and to fulfill the obligations of RTOG to the pharmaceutical company/companies supporting the RTOG trial. Sites must bypass the "NOT Required" assessment and complete and submit the report. The AdEERS System allows submission of all reports regardless of the results of the assessment. Note:** Sites must select the option in AdEERS to send a copy of the report to the FDA or print the AdEERS report and fax it to the FDA, FAX 1-800-332-0178.

7.15.3 Acute Myeloid Leukemia (AML) or Myelodysplastic Syndrome (MDS)

AML or MDS that is diagnosed during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported via the AdEERS system within 30 days of AML/MDS

diagnosis. If you are reporting in CTCAE version 4, the event(s) may be reported as either: 1) Leukemia secondary to oncology chemotherapy, 2) Myelodysplastic syndrome, or 3) Treatment-related secondary malignancy. Any malignancy possibly related to cancer treatment (including AML/MDS) also should be reported via the routine reporting mechanisms outlined in each protocol.

7.16 AdEERS Expedited Reporting Requirements

CTEP defines expedited AE reporting requirements for phase 3 trials as described in the table below. **Important:** All AEs reported via AdEERS also must be reported on the AE section of the appropriate case report form (see Section 12.1).

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention[1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via AdEERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via AdEERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/ intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

8.0 SURGERY

Not applicable to this study

9.0 OTHER THERAPY

9.1 Permitted Supportive Therapy

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site's source documents as concomitant medication.

9.1.1 Anticonvulsants
9.1.2 Antiemetics
9.1.3 Anticoagulants
9.1.4 Antidiarrheals
9.1.5 Analgesics
9.1.6 Hematopoietic Growth Factors
9.1.7 Herbal products
9.1.8 Nutritional supplementation

9.2 Non-permitted Supportive Therapy

Patients must be instructed not to take any medications, including over-the-counter products and vitamins, minerals and other dietary supplements, without first consulting with the investigator, as noted in Section 7.7 above.

10.0 TISSUE/SPECIMEN SUBMISSION

NOTE: Patients must be offered the opportunity to participate in the tissue/specimen submission component of the protocol. If the patient consents to participate in this component of the study, the site is required to submit the patient's specimens as specified below.

Sites are not permitted to delete the tissue/specimen submission component from the protocol or from the sample consent (Appendix I).

10.1 Tissue/Specimen Submission

The RTOG Biospecimen Resource at the University of California San Francisco acquires and maintains high quality specimens from RTOG trials. Tissue from each block is preserved through careful block storage and processing. The RTOG encourages participants in protocol studies to consent to the banking of their tissue. The RTOG Biospecimen Resource provides tissue specimens to investigators for translational research studies. Translational research studies integrate the newest research findings into current protocols to investigate important biologic questions.

10.2 Specimen Collection for Translational Research (Mandatory) (5/1/12)

For patients who have consented to participate in the tissue/blood component of the study (See Appendix I).

10.2.1 Specimen Submission

See Section 10.5 for the address information for sending specimens.

10.2.2 Specimen Collection Summary for Translational Research (Mandatory)

Specimens for Translational Research (mandatory)			
Specimens taken from patient:	**Collected when:**	**Submitted as:**	**Shipped:**
SERUM for baseline and follow up Testosterone, processed as per local laboratory requirements *Note: Collect testosterone in the a.m. at same time of day as collection of Fasting Insulin/Fasting Glucose/ Fasting Lipids/Hemoglobin A1C*	**(1) Baseline/ pre-treatment:** Within 21 days prior to treatment **(2)** At 30 months **(3) Follow Up:** Every 12 months for 3 years	Testing performed on site at local laboratory	Not applicable
SERUM for Testosterone (LC/MS/MS): 5 mL (no-additive red-top), processed as detailed in Appendix VI *Note: Collect testosterone in the a.m. at same time of day as collection of Fasting Insulin/Fasting Glucose/ Fasting Lipids/Hemoglobin A1C*	**(1) During ADT:** (a) At 12 months (b) At 24 months	Frozen serum samples containing 0.5 mL per aliquot in 1 mL cryovials	Serum sent frozen on dry ice via overnight carrier to the RTOG Biospecimen Resource
SERUM for Fasting Insulin: 5 mL (no-additive red-top), processed as detailed in Appendix VI *Note: Collect in the a.m. at same time of day as testosterone*	**(1) Baseline/ pre-treatment:** Within 21 days prior to treatment **(2) During ADT:** (a) At 12 months (b) At 24 months **(3) Follow Up:** Every 12 months for 3 years	Frozen serum samples containing 0.5 mL per aliquot in 1 mL cryovials (five to ten)	Serum sent frozen on dry ice via overnight carrier to the RTOG Biospecimen Resource
SERUM for Fasting Glucose/Fasting Lipids/Hemoglobin A1C, processed as per local laboratory requirements *Note: Collect in the a.m. at same time of day as testosterone*	**(1) Baseline/ pre-treatment:** Within 21 days prior to treatment **2) During ADT:** (a) At 12 months (b) At 24 months **(3) Follow Up:** Every 12 months for 3 years	Testing performed on site at local laboratory	Not applicable

10.3 Specimen Collection for Tissue Banking and Translational Research (Strongly Recommended) (5/1/12)

For patients who have consented to participate in the tissue/blood component of the study (See Appendix I). **Note: Blood collection is mandatory for patients participating in QOL.**

The following must be provided in order for the case to be evaluable for the Biospecimen Resource:

10.3.1 One H&E stained slide

10.3.2 A paraffin-embedded tissue block of the tumor or 10-15 unstained sections cut onto positive charged slides from the tumor tissue. Block or slides must be clearly labeled with the pathology identification number that corresponds to the Pathology Report.

10.3.3 A Pathology Report documenting that the submitted block or slides contains tumor. The report must include the RTOG protocol number and patient's case number. The patient's name and/or other identifying information should be removed from the report. The surgical pathology numbers and information must NOT be removed from the report.

10.3.4 A Specimen Transmittal Form (STF) clearly stating that tissue is being submitted for the RTOG Biospecimen Resource; if for translational research, this should be stated on the form. The form must include the RTOG protocol number and patient's case number.

10.3.5 Specimen Collection Summary for Tissue Banking and Translational Research (strongly recommended)

Specimens for Tissue Banking and Translational Research (strongly recommended)			
Specimens taken from patient:	**Collected when:**	**Submitted as:**	**Shipped:**
Representative H&E stained slides of the primary tumor	Pre-treatment	H&E stained slide Pre-treatment	Slide shipped ambient
A paraffin-embedded tissue block of the primary tumor taken before initiation of treatment or 10-15 unstained slides	Pre-treatment	Paraffin-embedded tissue block or 15 unstained slides	Block or slides shipped ambient
PLASMA: 5-10 mL of anticoagulated whole blood in EDTA tube #1 (purple/ lavender top) and centrifuge *[For inflammatory cytokines and markers including CRP, NF- kappa B, TNF alpha, IL-1, IL-1ra, sTNFR2, and IL-6]*	(1) Pre-treatment (2) 1 year (12 months) after therapy starts (3) 2.5 years (30 months) after therapy starts	Frozen plasma samples containing 0.5 mL per aliquot in 1 mL cryovials (five to ten)	Plasma sent frozen on dry ice via overnight carrier to the RTOG Biospecimen Resource
WHOLE BLOOD for DNA: 5-10 mL of anticoagulated whole blood in EDTA tube #2 (purple/ lavender top) and mix *[For SNPs and CNVs in TNFAIP1, IL6, IL6R, CRP, NFKB1, NFKB1A, IL1R1, IL1A, IL1B]*	Pre-treatment Note: If site missed this collection time point they may collect this specimen at any other time point instead but must note this on the STF.	Frozen whole blood samples containing 1 mL in 1mL cryovials (three to five)	Whole blood sent frozen on dry ice via overnight carrier to the RTOG Biospecimen Resource
PBMCs: 5-10ml of whole blood in two separate purple/lavender top tubes (tubes #3 and #4). See Appendix VII for processing instructions.	(1) Pre-treatment (2) 1 year (12 months) after therapy starts (3) 2.5 years (30 months) after therapy starts	Frozen PBMC samples (one to five). See Appendix VII for processing instructions.	PBMC sent frozen on dry ice via overnight courier to the RTOG Biospecimen Resource

[For NF Kappa B]			

10.3.6 **See Appendix VI for the specimen collection kit and detailed collection instructions. See Appendix VII for detailed PBMC collection, processing, and shipping information.** Note: Kit includes a label for shipping. The following materials must be provided to the RTOG Biospecimen Resource: A Specimen Transmittal Form (STF) documenting the date of collection of the biospecimen; the RTOG protocol number, the patient's case number, time point of study, and method of storage, for example, stored at -80° C, must be included.

10.4 Storage Conditions (5/1/12)

Store frozen specimens at -80°C (-70°C to -90°C) until ready to ship. Frozen specimens can be stored -80°C (-70°C to -90°C) for up to six months before shipping. If a -80°C freezer is not available:

Samples can be stored short term in a -20° C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only; Canada: Monday-Tuesday).

OR:

Samples can be stored in plenty of dry ice for up to one week, replenishing daily (ship out Monday-Wednesday only; Canada: Monday-Tuesday).

OR:

Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only; Canada: Monday-Tuesday).

Please indicate on the STF the storage conditions used and time stored.

For PBMC Specimens Only:

Store frozen specimens immediately at -80°C. Samples must then be kept at -80°C during storage and shipping (please ship out Monday-Wednesday only; Canada: Monday-Tuesday)

OR:

If a -80°C freezer is not available: Samples can be stored in plenty of dry ice for up to one week, replenishing daily (ship out Monday-Wednesday only; Canada: Monday-Tuesday).

Please indicate on the STF the storage conditions used and time stored. **See Appendix VII for detailed PBMC collection, processing, and shipping information.**

10.5 Submit materials for Tissue Banking and Translational Research as follows:

U. S. Postal Service Mailing Address: For Non-frozen Specimens Only
RTOG Biospecimen Resource
University of California San Francisco
Campus Box 1800
2340 Sutter Street, Room S341
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): For Frozen Specimens
RTOG Biospecimen Resource
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115

Questions: 415-476-RTOG (7864)/FAX 415-476-5271; RTOG@ucsf.edu

10.6 Reimbursement

RTOG will reimburse institutions for submission of protocol specified biospecimen materials sent to the Biospecimen Resource at the University of California San Francisco and other protocol-specified collection repositories/laboratories. After confirmation from the RTOG Biospecimen Resource or other designated repository/laboratory that appropriate materials have been received, RTOG Clinical Trials Administration will authorize payment according to the schedule

posted with the Reimbursement and Case Credit Schedule found on the RTOG web site (http://www.rtog.org/LinkClick.aspx?fileticket=Csxzt1v1hEk%3d&tabid=323). Biospecimen payments will be processed quarterly and will appear on the institution's summary report with the institution's regular case reimbursement.

10.7 Confidentiality/Storage

(See the RTOG Patient Tissue Consent Frequently Asked Questions, http://www.rtog.org/Researchers/BiospecimenResource/BiospecimenResourceFAQs.aspx for further details.)

10.7.1 Upon receipt, the specimen is labeled with the RTOG protocol number and the patient's case number only. The RTOG Biospecimen Resource database only includes the following information: the number of specimens received, the date the specimens were received, documentation of material sent to a qualified investigator, type of material sent, and the date the specimens were sent to the investigator. No clinical information is kept in the database.

10.7.2 Specimens for tissue banking will be stored for an indefinite period of time. Specimens for the translational research component of this protocol will be retained until the study is terminated, unless the patient has consented to storage for future studies. If at any time the patient withdraws consent to store and use specimens, the material will be returned to the institution that submitted it.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters: See Appendix II for assessments and timeframes. See Sections 11.1.1 and 11.1.2 below for details and/or exceptions to Appendix II.

11.1.1 Chemistry and liver panels (sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, magnesium, phosphorus, albumin, AST, ALT, alkaline phosphatase, total bilirubin, direct bilirubin) will be checked monthly during ADT until three consecutive normal potassium values have been obtained, then the chemistry panels will be spaced to every 3 months.

11.1.2 Collect blood for testosterone in the morning at the same time of day as collection of blood for Fasting Insulin/Fasting Glucose/ Fasting Lipids/Hemoglobin A1C.

11.2 PROMIS-Fatigue Short Form

Note: Participation in quality of life (QOL) is mandatory for the first 410 patients enrolled in this study. Sites are required to administer the PROMIS, EPIC-26, and the EQ-5D assessments at baseline and as specified in Appendix II of the protocol. Sites are not permitted to delete the quality of life component from the protocol or from the sample consent. **Blood collection is mandatory for patients participating in the QOL.**

The PROMIS Fatigue Scale (7 items) was developed by the Patient-Reported Outcome Measurement Information System (PROMIS), part of the NIH Roadmap Initiative, focused on developing a publicly available resource of standardized, accurate, and efficient patient-reported outcome (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 preliminary 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).

The following items are being measured due to the fact that sleep quality and exercise are documented confounders of fatigue:

Muscle weakness question (scale of 1-5, from none to very much)
Overall Sleep Quality: Item from Pittsburgh Sleep Quality Index (Buysse 1989):

Sleep quality will be measured by 1 item (Q3) of the Pittsburgh Sleep Quality Index (PSQI), a self-rated questionnaire which measures sleep quality and disturbances over a 1-week or 1-month time period.

	Very bad	*Fairly bad*	*Fairly good*	*Very good*
1. During the past week, how would you rate your sleep quality overall?	***0***	***1***	***2***	***3***

Participants' level of physical activity will be assessed using the three item Godin Leisure-Time Exercise Questionnaire (GLTEQ) [Godin 1986; Gionet 1989], which measures time spent per week in each of light, moderate, and vigorous activities. A score can be computed for each level of exercise. A total score is computed by summing the three levels weighted by their respective MET equivalents of 3, 5, and 9. The GLTEQ has good test-retest reliability and has shown convergent validity with both objective and other self-report measures of physical activity (Godin 1986; Gionet 1989).

The following questions are about your average weekly exercise. When answering the questions only count exercise that you do during free time (ignore exercise associated with your occupation and housework). Considering a typical week (7 days), how many times, on average, do you perform mild, moderate, or strenuous exercise? And when you engage in exercise, how long do you exercise, on average?

	Times Per Week **(a)**	Average Duration **(b)**
1. Mild exercise – that is, minimal effort exercise that did not make you perspire, such as easy walking, yoga, bowling, lawn bowling, shuffleboard, or golf	_____	_____ mins.
2. Moderate exercise – that is, exercise that is not exhausting and which made you perspire lightly, such as fast walking, tennis, easy bicycling, easy swimming, or popular and folk dancing	_____	_____ mins.
3. Strenuous exercise – that is, exercise that made your heart beat rapidly and made you sweat, such as running, aerobics classes, cross country skiing, vigorous swimming, or vigorous bicycling	_____	_____ mins.

11.3 Health Related Quality of Life (HRQOL) Assessments

Note: Participation in quality of life is mandatory for the first 410 patients enrolled in this study. Sites are required to administer the PROMIS, EPIC-26, and the EQ-5D assessments at baseline and as specified in Appendix II of the protocol. Sites are not permitted to delete the quality of life component from the protocol or from the sample consent. **Blood collection is mandatory for patients participating in QOL.**

The following instruments will be used to assess health related quality of life (HRQOL), including quality adjusted survival: the Expanded Prostate Cancer Index (EPIC)-26, and the EuroQol (EQ-5D) instrument. **These outcomes measurements will be administered to the first 410 patients (205 in each arm).** Of note, these are essentially the same instruments (and similar time points) that are being studied in two related trials, RTOG 0815 and 0924, which are currently accruing patients. In RTOG 0815, patients with "lower" intermediate risk prostate cancer all receive high dose RT and are randomized to +/- short term hormones. In RTOG 0924, patients with intermediate to high risk prostate cancer are randomized to +/- whole pelvic RT and are

stratified by short (6 months) or long term (32 months) ADT. Ultimately, use of essentially the same instruments and time points in all three studies (RTOG 0815, RTOG 0924, and RTOG 1115) will create a large database of relevant information related to QOL, QAS, and fatigue issues in prostate cancer patients that will facilitate a large combined analysis in the future. The outcomes instruments in this study are as follows:

11.3.1 Prostate Cancer-Specific Health-Related Quality of Life: EPIC-26

The Expanded Prostate Cancer Index Composite (EPIC) is a prostate cancer health-related quality of life (HRQOL) patient self-administered instrument that measures a broad spectrum of urinary, bowel, sexual, and hormonal symptoms related to radiotherapy and hormonal therapy (van Andel 2003;Wei 2000). To minimize patient burden, the abbreviated, validated EPIC-26 will be used (Szymanski 2010).

11.3.2 Quality-Adjusted Survival Analysis: EuroQol (EQ-5D)

The EQ-5D is a patient self-administrated questionnaire that takes approximately 5 minutes to complete (Schulz 2002). The first part consists of 5 items covering 5 dimensions including: mobility, self care, usual activities, pain/discomfort, and anxiety/depression. Each dimension can be graded on 3 levels: 1-no problems, 2-moderate problems, and 3-extreme problems. Health states are defined by the combination of the leveled responses to the 5 dimensions, generating 243 (35) health states to which unconsciousness and death are added (Badia 1998).

The 5-item index score is transformed into a utility score between 0, “Worst health state,” and 1, “Best health state.” The index score or the cost-utility equation can be used in the quality adjusted survival analysis depending on the health state(s) of interest (Wu 2002). For this study we plan to report the multidimensional utilities for comparative purposes. The EQ-5D has been used across numerous disease sites (Milne 2006; Wildi 2004) and has been used to assess quality adjusted survival of prostate cancer screening and treatment (Essink-Bok 1998; Sandblom 2004; Sennfalt 2004).

11.4 Criteria for Discontinuation of Protocol Treatment

- Progression of disease;
- A delay in protocol treatment, as specified in Sections 6.0 and/or 7.0.

If protocol treatment is discontinued, follow up and data collection will continue as specified in the protocol.

12.0 DATA COLLECTION (5/1/12)

This study will utilize Medidata Rave® for remote data capture (RDC) of all data.

Each person responsible for data entry must be on the RTOG roster in order to receive access to Medidata Rave®. To be added to the RTOG roster, complete the RTOG Roster Update Form (http://www.rtog.org/LinkClick.aspx?fileticket=q61ShTwNbFQ%3d&tabid=217) and e-mail the completed form to RTOG-Membership@acr.org. The RTOG roster update form must be submitted at least 2 business days prior to the first patient registration.

All CRAs at participating sites will receive e-mail invitations from iMedidata-Notification@mdsol.com to activate their account. Once an account is activated, eLearning modules will be available for Rave RDC instructions. All modules must be completed before access to data entry is granted. Further training opportunities will be communicated through the web site.

Medidata Rave® can be accessed through the iMedidata portal at https://login.imedidata.com

12.1 Summary of Data Submission

Folder	Form/Item	Due
Registration via the OPEN System	• *Subject Enrollment Form (1)*	**At time of registration**
Enrollment When pushed into RAVE there will be 5 forms representing registration	• *Demography Form (2)* • *Step Information Form (3)* • *Treatment Assignment Form (4)* • *Eligibility Checklist Form (5)*	
Concomitant Medications		**Review at baseline and then every 3 months during treatment (24 months) for changes** (in frequency, dose, additional drugs or discontinuation of drugs)
PSA Measurements		**All required measurements will be collected in this folder—every 3 months during treatment; then every 6 months for 3 years; then annually--**the follow up form will prompt reporting of these measurements
Quality of Life (**mandatory** for the first 410 patients; when QOL accrual achieved this folder will not be available for future patients)	• *EQ-5D (QF)* • *EPIC-26 (FA)* • *PROMIS (HP)* • *PSQI/GLTEQ (QL)*	**Collected at 5 time points (**only if answer to quality of life participation = *yes* at registration**):** 1) Prior to the start of protocol hormone treatment (baseline); 2) Prior to RT; 3) During the last week of RT; 4) At one year (12 months) after the start of protocol treatment; 5) At 2.5 years (30 months) after the start of protocol treatment
Baseline Folder	• *Patient History Form* (formerly known as the A5; voluntary form completed by the patient or with help from site staff or family) • *Work Up Form* • *Diagnostic Staging Form* • *Prior Treatment Form*	**Within 2 weeks after registration**

Folder	Form/Item	Due
	• *Pathology Report Form* (a copy of this report will be scanned and uploaded into RAVE) • *Chemistry Panel Form* • *Liver Panel Form* • *Fasting Lipid Panel Form* • *CBC w/Differential Form* • *Hemoglobin A1C Form* • *Serum Testosterone Form*	
Month 1 visit	• *Chemistry Panel Form* • *Liver Panel Form*	**After 30 days of hormonal treatment** For relevant labs necessary during hormonal treatment +/- TAK700
Month 2 visit	• *Chemistry Panel Form* • *Liver Panel Form*	**After 60 days of hormonal treatment** For relevant labs necessary during hormonal treatment +/- TAK700
Follow-Up Folders **Month 3** **Month 6** **Month 9** **Month 12** **Month 15** **Month 18** **Month 21** **Month 24**	• *Follow up Form – if* Patient Contacted = "yes" • *Primary Cause of Death Form – if* Patient's Vital Status = 'dead' • *Disease Assessment Form – if* Documented clinical assessment = 'yes' • *New Primary Cancer Form – if* New Primary Cancer = 'yes' • *Non-protocol Treatment Form – if* patient started on non-protocol cancer therapy = 'yes' • *Complete Appropriate Lab Form* - if labs performed = 'yes' (chemistry and liver panel forms every 3 months and at 12 and 24 month visits fasting lipid panel form and hemoglobin A1C form will be added*)* • *PSA Measurement Form – if* PSA assessed = 'yes' • Adverse *Event Form – if* new or continuing adverse events = 'yes' • *Concomitant Medication Form if* Changes in Medication = 'yes'	**Every 3 months from the start of treatment** during years 1 and 2 (to capture hormone +/- TAK-700 administration);
Hormonal Treatment with or without TAK-700	• *Oral Antiandrogen Form* • *LHRH Agonist Form* • *Agent TAK700 Form*	**Every 3 months for 2 years**

Folder	Form/Item	Due
Month 30 Visit • Marks the start of follow up without treatment • Questions answered as 'yes' generate additional forms—similar to 'filter questions' being asked **Month 36** **Month 42** **Month 48** **Month 54** **Month 60** **Month 72** • Start of annual visits	• *Follow up Form – if* Patient Contacted = "yes" • *Primary cause of death form – if* Patient's Vital Status = 'dead' • *Disease Assessment Form – if* Documented clinical assessment = 'yes' • *New Primary Cancer Form – if* New Primary Cancer = 'yes' • *Non-protocol Treatment Form – if* patient started on non-protocol cancer therapy = 'yes' • *Complete Appropriate Lab Form* - if labs performed = 'yes' (at 36, 48 and 60 month visits *a chemistry panel form*-- for fasting glucose*; fasting lipids form; testosterone form and hemoglobin A1C form)* • *PSA Measurement Form – if* PSA assessed = 'yes' • *Adverse Event Form – if* new or continuing adverse events = 'yes'	**Every 6 months for 3 years** **Annual visits**

12.2 Summary of Dosimetry Digital Data Submission (Submit to ITC; see Section 12.2.1)

Folder	Form/Item	Due
N/A	**Preliminary Dosimetry Information** Digital Data Submission – Treatment Plan submitted to ITC via SFTP account exported from treatment planning machine by Physicist Digital data submission includes the following: • CT data, critical normal structures, all GTV, CTV, and PTV contours • Digital beam geometry for initial and boost beam sets • Doses for initial and boost sets of concurrently treated beams • Digital DVH data for all required critical normal structures, GTV, CTV, and PTVs for total dose plan *Digital Data Form* → ***Upload confirmation email from ITC that digital data was received***	**Within 1 week of start of RT**
RT Administration→ If answered as 'yes' then *RT Treatment* form will be added	**Final Dosimetry Information** *RT Treatment form* [for EBRT +/- brachytherapy] Daily Treatment Record **[copy to ITC]** **Please note**: Daily Treatment Record will be uploaded via Rave to RTOG HQ Modified digital patient data as required through consultation with Image-Guided Therapy QA Center **NOTE:** All Simulation and Portal Films and/or Digital Images will be kept by the Institution and only submitted if requested.	**Within 1 week of RT end (external beam RT +/- brachytherapy)**
	LDR Brachytherapy Post-implant evaluation CT scan Post-implant structure set Post-implant plan Post-implant dose distribution RTOG Prostate Brachytherapy Protocol Compliance Form-Available on the ATC website, http://atc.wustl.edu	**If applicable**: 3-5 weeks post implant—submit listed items to ITC
	HDR Brachytherapy Implant CT scan Implant structure set Implant plan	**If applicable**: 3-5 weeks post implant—submit listed items to ITC

Folder	Form/Item	Due
	Implant dose distribution RTOG Prostate Brachytherapy Protocol Compliance Form-Available on the ATC website, http://atc.wustl.edu **NOTE:** Copies of simulation and port films/images will be submitted to RTOG Headquarters ONLY if specifically requested.	

12.2.1 *Digital Data Submission to ITC*

Digital data submission may be accomplished using media or the Internet.

For network submission: The SFTP account assigned to the submitting institution by the ITC shall be used, and e-mail identifying the data set(s) being submitted shall be sent to:

itc@wustl.edu

For media submission: Please contact the ITC about acceptable media types and formats.

Hardcopies accompanying digital data should be sent by mail or Federal Express and should be addressed to:

Image-Guided Therapy Center (ITC)
ATTN: Roxana Haynes
4511 Forest Park, Suite 200
St. Louis, MO 63108
314-747-5415
FAX 314-747-5423

13.0 STATISTICAL CONSIDERATIONS

13.1 Primary Endpoint

13.1.1 Overall Survival (failure: death due to any cause)

13.2 Secondary Endpoints

13.2.1 Incidence of unexpected grade $\geq$ 3 adverse events and/or clinically significant decrement in patient reported quality of life among subjects treated with TAK-700

13.2.2 Rates and cumulative incidence of biochemical control (freedom from PSA failure), local/regional progression, and distant metastases

13.2.2.1 Biochemical failure will be defined by the Phoenix definition (PSA ≥ 2 ng/ml over the nadir PSA, the presence of local, regional, or distant recurrence, or the initiation of salvage androgen deprivation therapy) [Roach 2006].

13.2.2.2 Local failure will be defined as biopsy proven recurrence within the prostate gland.

13.2.2.3 Regional or distant metastasis will be defined as imaging or biopsy demonstrated evidence for recurrence in the pelvic lymph nodes (regional) or systemically. Biopsy is not required to define regional or distant metastasis; however, in absence of a rising PSA biopsy is encouraged.

13.2.3 General clinical treatment failure free interval (general clinical treatment failure [GCTF] is defined as: PSA > 25 ng/ml, documented local disease progression, regional or distant metastasis, or initiation of androgen deprivation therapy). Deaths prior to any of these events are treated as censoring for this endpoint.

13.2.4 Prostate cancer specific survival (failure: death due to prostate cancer) and other-cause survival (failure: death due to other causes)

13.2.5 Change in fatigue from baseline to 1 year, as measured by PROMIS

13.2.6 Changes in patient reported quality of life as measured by Expanded Prostate Cancer Index Composite (EPIC)

13.2.7 Assessment of quality adjusted survival using the EQ-5D

13.2.8 Nadir and average serum testosterone at 12 and 24 months during treatment

13.2.9 Lipid profiles at 12 and 24 months
13.2.10 Fasting plasma glucose, fasting plasma insulin, and hemoglobin A1c at 12 and 24 months
13.2.11 Changes in body mass index (BMI) during 24 months of treatment and during the first three years of follow-up
13.2.12 Incidence of adverse events ascertained via CTCAE version 4
13.2.13 Rate of recovery of testosterone to >230 ng/dL (accepted threshold for supplementation) after 12 and 24 months of follow-up
13.2.14 Median time to recovery of testosterone to >230 ng/dL during the first five years of follow-up
13.2.15 Cumulative incidence of relevant clinical survivorship endpoints including new diagnosis of type 2 diabetes, coronary artery disease, myocardial infarction, stroke, pulmonary embolism, deep vein thrombosis, or osteoporotic fracture

13.3 Sample Size Determination (5/1/12)

13.3.1 Sample Size for Primary Endpoint

Patients with disease characteristics meeting the eligibility criteria for this study (Section 3.0) historically have 5-year survival of 78% and 8-year survival of 61.5%. We assume an annual hazard rate of 0.055, and aim to detect a 33% reduction in failure rate for the experimental arm. Assuming a two-sided alpha level of 0.05 (adjusted for interim analysis, see below), observation of 239 events is required for 85% statistical power to detect this effect. This relative hazard reduction implies an absolute survival difference of 7% at five years.

It is anticipated that patients can be accrued to this study at a rate of 30 per month. If 875 patients are accrued over 29 months, then the requisite events for definitive analysis would be accumulated after an additional 67 months, or 96 months from commencement of accrual. To account for a potential ineligibility rate of 3%, 900 patients will be enrolled.

13.3.2 Statistical Power for Other Time to Event Endpoints

Patients in this risk class have biochemical failure rates of approximately 8% per year between years 5 and 8. The trial will provide for detection of a 30% relative reduction in biochemical failure rate with statistical power approaching 90% at eight years. The distant failure rate for these patients is 2.0% per year. A 50% relative reduction in hazard of distant metastases for the experimental treatment group can be detected with statistical power of 88% at eight years.

13.3.3 Statistical Power for Primary Survivorship Endpoints

Hemoglobin A1c will be measured at baseline, 12 months and 24 months, with scores reflecting change from baseline compared at the follow-up time-points. A 0.1% difference in A1c between treatments would be considered of clinical interest. Given the precision of measurement in HB A1c in prior studies involving men receiving GnRH therapy (mean to standard error ratio greater than 10), power for detection of such differences would easily exceed 90%, even after controlling for multiple comparisons.

For diabetes/pre-diabetes incidence, the standard treatment frequency is expected to be in the range of 12-15%. Odds ratios of 1.5 or greater for the TAK-700 group will be detectable with power exceeding 80%.

13.3.4 Statistical Power for Primary Quality of Life Endpoint

It is not anticipated that the entire trial participant cohort will be enrolled in the QOL correlative study. However, it is of interest to establish whether the addition of TAK-700 contributes to diminished quality of life scores and increased fatigue, and thus is desirable to have a sufficient sample to rule out smaller differences that would be considered clinically material. Fatigue, as measured by the PROMIS, will be the primary QOL analysis and therefore will be used in the sample size calculation. If we consider a 0.33 standard deviation effect size and a two-sided type I error = 0.05, we obtain a required sample size of 390 patients (195 patients per arm) for 90% power. To account for losses, 5% inflation in sample size is applied, resulting in 410 patients. The first 410 patients enrolled in the study will be required to participate in the QOL portion of the trial.

13.3.5 Software for Sample Size Calculations

For the above calculations, the statistical software package EAST was used. Additional calculations verifying study duration and power for time to event endpoints were performed with user-written programs in the SAS statistical language.

13.4 Randomization

Patients will be stratified before randomization by the composite risk score (based on Gleason score, PSA, and tumor stage) defined in Section 3.1.1. Treatment arms will be balanced with respect to risk score via a permuted block procedure (Zelen 1974).

13.5 Analysis Plan

13.5.1 Primary Efficacy Endpoint

Primary analysis will include all eligible randomized patients with follow-up information, with patients included in the group to which they were assigned, regardless of whether they started treatment. Overall survival will be compared between treatment arms using the log-rank test (Mantel 1966). The Kaplan-Meier estimator will be used to estimate overall survival by treatment group (Kaplan 1958). Event times are measured from the date of study registration to the date of failure, or last follow up.

13.5.2 Other Efficacy Endpoints

Cumulative probability over time of PSA failure, local/regional recurrence, distant metastases and clinical failure will be estimated via the cumulative incidence function, which correctly accounts for competing risks (Korn 1992). Primary putative treatment effect comparisons for these endpoints will be based on cause-specific hazards using logrank tests (Friedlin 2005, Dignam 2008). To evaluate differences specifically in cumulative incidence of these events, we may also employ Gray's test (Gray 1988).

If there are imbalances in covariates by treatment arm, then hazard regression models will be used to produce adjusted treatment effect estimates and tests. Appropriate models will be applied based on which metric is being examined (cause-specific hazard or cumulative incidence) [Prentice 1978, Fine 1999]. If model-specific assumptions are not met (for example, proportionality), then alternative approaches will be sought.

13.5.3 Longitudinal Quality of Life (QOL) and Patient Reported Outcome (PRO) Endpoints

The primary hypothesis of the QOL endpoints are that QOL and fatigue scores will not differ significantly between the control group and the experimental group receiving both a GnRH agonist and TAK-700. Quality of life will be measured with the prostate cancer-focused 32-question EPIC (The Expanded Prostate Cancer Index Composite) questionnaire and by the 5-question EQ-5D global quality of life assessment. Fatigue will be measured by the 7-question PROMIS (Patient-Reported Outcome Measurement Information System) fatigue short form questionnaire. The EPIC-26, PROMIS-fatigue short form, and EQ-5D will be collected at pretreatment (baseline), the week prior to starting RT, the last week of RT, and 1 year and 2.5 years after initiation of therapy.

The primary objective in the fatigue analysis is to determine the QOL differences at 1 year. The response will be the change of measurement from baseline for each measurement. Using the sample size calculated in section 13.3.3 of 195 patients per arm, we will have 77.3% statistical power assuming a type I error = 0.05 (with appropriate type I error control for multiplicity using the Bonferroni correction) to detect a standard deviation effect size of 0.33 between the treatment arms for the 4 domains of the EPIC.

For these investigations, a longitudinal analysis will be conducted that will focus on patterns of scores over time points (baseline, the week prior to starting RT, the last week of RT, and 1 year and 2.5 years after initiation of therapy) for the QOL and PRO instruments (EPIC, PROMIS and EQ-5D). Following descriptive statistics on assessments and tests of the primary endpoint of change from baseline to 1 year, repeated measures analysis of covariance (ANCOVA) will be used on scores for the assessment measures, where time points are considered the within-patient factor and treatment groups is considered the between-patient factor (Diggle 1994). While scales for the individual instrument questions are quantitative, they represent ordinal values on a bounded range rather than continuous quantities. Nonetheless, in aggregate these approximate continuous distributions, and appropriate transforms will be applied to improve consistency with model assumptions. The hierarchical analytic approach described below permits tests of omnibus hypotheses that control for multiple comparisons among time points and treatment groups. The analysis will be conducted as follows:

(1) The ANCOVA model will be used to carry out an omnibus test of the hypothesis that there is a common mean score across time point within the treatment groups: H_0: $\mu_{it} = \mu_{i.}$, where i =

treatment group 1 or 2, *t* = time point (baseline, the week prior to starting RT, the last week of RT, 1 year and 2.5 years) and μ_{it} is the mean score in treatment group *i* at time *t*.

(2) If the hypothesis in (1) is rejected, individual comparisons of the post-RT and subsequent scores will be conducted within treatment groups. Additional modeling and graphical methods to determine trends or patterns of change in scores over time points will be conducted.

(3) The ANCOVA model will be used to carry out an omnibus test of the hypothesis that there is a common mean score at each time point among the treatments: H_0: $\mu_{it} = \mu_{.t}$, where again μ_{it} is the mean score in treatment group *i* at time *t*.

(4) Assuming the result of the hypothesis test in (3) is significant (H_0 rejected), individual tests will be carried out to determine differences between treatment groups at specific time points. If there are no significant treatment differences identified in (3), an overall test of trend in scores can be aggregated over treatment groups. Additional modeling to characterize patterns of change over time will be conducted.

Information regarding potential confounds will be collected in a short form (QL) using limited questions to minimize patient burden. This information can be used to evaluate the potential impact of these confounding factors on fatigue. Patient responses to the following will be collected in the QL form: muscle weakness (one item), overall sleep quality as measured by one item from the Pittsburgh Sleep Quality Index (PSQI) [Buysse 1989] and level of physical activity as measured by the Godin Leisure-Time Exercise Questionnaire (GLTEQ) (Godin 1986; Gionet 1989). Anxiety/depression is also a potential confound with fatigue and patient responses to the anxiety/depression item in the EQ-5D can be used. At the same time points, the QL form (i.e., one item from the PSQI, 3 items from the GLTEQ, and one question regarding general muscle weakness) will be collected. In addition, in order to correlate fatigue with the cytokine changes, the PROMIS-fatigue short form (and the associated questions) will be collected at the following time points: at baseline, the week prior to starting RT, the last week of RT, 1 year and 2.5 years after therapy starts.

These confounding factors may be incorporated into the above hypothesis tests via the ANCOVA model. The effects of these covariates on scores may also be evaluated separately in exploratory analyses. Also note that baseline scores will be analyzed in relation to subsequent impairment or decline for both treatment groups (hypothesis (1) above). The use of change scores (relative to baseline) for the main analysis also may be explored to account for the influence of per patient conditions prior to undergoing treatment.

A certain degree of attrition from the study, due to both patient withdrawal and mortality, is expected. Characteristics of patients with missing data will be evaluated to identify imbalance in factors such as treatment, baseline scores, and other clinical and demographic features. In the absence of apparent systematic missing data patterns, data will be analyzed assuming that the observations are missing at random, employing appropriate methodology for this purpose (Little 1992). In the case of evidence for systematic patterns of missing data ('informative' missingness), alternative strategies for analyzing such data, depending on the pattern (e.g., intermittent versus complete dropout pattern) will be investigated (Wu 1988, Little 1992).

In this study, the addition of TAK-700 is hypothesized to improve overall survival (OS), without having a significant a negative impact on health related quality of life (HRQOL). As there are competing pros and cons of this treatment, it is useful to combine these factors into one equation to determine whether the potential benefits of this treatment (dose-escalated RT combined with short-term androgen deprivation), in terms of OS, outweigh the potential risks, in terms of negatively impacting on global HRQOL, compared to RT and ADT alone. Such a quality adjusted survival analysis can be invaluable for assisting in the decisions of future patients as well as clinicians faced with these treatment options.

Quality-adjusted survival can be defined by the weighted sum of different time episodes added up to a total quality-adjusted life-year [U= sum of quality (qi) of health states K times the duration (si) spent in each health state] (Glasziou 1990):

$$\mathbf{U} = \sum_{i=1}^{K} \mathbf{q}_i \mathbf{s}_i$$

We will use Glasziou's multiple health-state (Q-TwiST) models to use the repeated measures of EQ-5D. Because Glasziou's method incorporates longitudinal QOL data into an analysis of quality-adjusted survival, the health stated model must be constructed on the following assumptions:

A1) QOL is independent from treatment.
A2) A health state is independent from previous states.
A3) Proportionality of quality-adjusted duration and duration of the actual state of health

Assumption A1 can be checked by plotting QOL over time according to treatment, and the t-test can be used to compare the mean QOL scores of each treatment arm. Assumption A2 can be checked by comparing the QOL for patient groups in a given health state where the groups are defined by duration of previous health state experience using a regression model. Suitable checks for assumption A3 at minimum would be a simple plot. If data does not support these assumptions, we will use a method which uses the longitudinal QOL data directly. We will use the 5-item utility score in EQ-5D for the cost-utility analysis. We will use the Z-test to test the hypothesis that the cost-utility in the 2 treatment arms is the same at 1 year after initiation of treatment with a significance level of 0.05 and a 2-sided test. The remaining timepoints in which the EQ-5D is collected will also be assessed using similar longitudinal analysis techniques as described for the primary endpoint.

13.5.4 Testosterone Kinetics

Comparison of testosterone levels at designated time points will be conducted via t-tests on baseline-corrected and appropriately transformed measurement values. Nonparametric tests to compare medians may also be conducted.

Time to recovery of testosterone to >230 ng/dL (accepted threshold for supplementation) after treatment will be estimated using time to event data methods. Specifically, the cumulative incidence of >230 ng/dL level achievement will be computed, accounting for competing events in the form of 1) interventions due to clinical failure that may suppress recovery and 2) deaths.

13.5.5 Lipid Profiles, Glycemic Parameters, and Body Mass Index

Comparison of baseline-adjusted values for fasting glucose, fasting insulin, lipid levels, and hemoglobin A1c will be carried out between treatment groups at designated time points. Additionally, longitudinal models as described above may be used to characterize changes in these parameters over time within and between treatment groups. Body mass index will similarly be contrasted at specific time points and modeled as a function of time from treatment initiation.

13.5.6 Clinical Survivorship Endpoints

Incidence rates (events/person years of exposure) and cumulative incidence over time of specific clinical events (type 2 diabetes, coronary artery disease, myocardial infarction, stroke, pulmonary embolism, deep vein thrombosis, osteoporotic fracture) will be estimated by treatment arm. Poisson regression or other appropriate methods will be used to investigate the role of other explanatory risk factors in conjunction with treatment exposure.

13.5.7 Trial Monitoring

13.5.7.1 *Data Monitoring Committee*

Phase III trials are required by NCI Cooperative Group Program Guidelines to be reviewed by a Data and Safety Monitoring Committee (DSMC). This study will be reviewed by the RTOG Data Monitoring Committee (DMC) on a semi-annual basis in January and June.

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0 (CDUS Abbreviated). Cumulative CDUS data will be submitted quarterly by electronic means. Reports are due January 31, April 30, July 31, and October 31.

13.5.7.2 *Interim Efficacy and Futility Analysis Plan*

There will be three interim analyses of the primary hypotheses, at equally spaced increments of 25%, 50%, and 75% of the requisite events for definitive analysis. A

conservative upper superiority bound, based on a Lan-DeMets approximation to the O'Brien and Fleming boundary (DeMets 1994) provides test criteria of Z > 4.33 at the first interim analysis, Z > 2.96 at the second interim analysis, and Z > 2.36 at the third interim analysis. At the final analysis, a test statistic of Z > 2.01 will be required to reject H_0.

Interim futility analysis will be based on the rule of Freidlin, Korn, and Gray (Freidlin 2010). This rule provides the opportunity to terminate early for evidence that the experimental arm will not prove superior, but protects against aggressive early termination for treatment effect sizes smaller than planned.

The following table summarizes the interim efficacy/futility monitoring schedule with respect to the primary endpoint:

Analysis	Time (month)	Prop. Total events	Cumulative Total Events (Both Arms)	Efficacy boundary		Futility boundary	
				Z>	P<	Z<	P>
Interim 1	33	0.25	60	4.33	0.00001	-1.64*	0.05*
Interim 2	54	0.50	120	2.96	0.0015	0.06	0.476
Interim 3	75	0.75	180	2.36	0.009	0.31	0.378
final	96	1.00	239	2.01	0.022	-	-

* Early look for detriment in experimental arm, left-tail p < 0.05 will prompt stopping

In addition to the futility boundary for the primary endpoint, we will also implement a futility rule based on an intermediate endpoint for which evidence of efficacy is expected if there is eventual efficacy on the primary endpoint. Specifically, hormone deprivation agents that have shown favorable survival benefit typically demonstrate reductions in clinical outcomes such as time free from PSA progression or clinical failure (local, regional, or distant disease progression). Thus, early evidence of activity will be assessed by comparing the rate of general clinical treatment failure (GCTF, defined as time to any of the following events: PSA failure, local/regional recurrence, distant recurrence, hormone initiation) between treatment groups. The approach will involve testing for a difference in GCTF with adequately high power but a rather less stringent alpha level, following the strategy in multi-arm multi-stage clinical trials, where regimens are evaluated early based on intermediate endpoints to assure some level of activity before continuing to definitive endpoints (Sydes 2009).

Assuming an annual GCTF hazard rate of 0.125, a one-sided alpha of 0.10 and statistical power of 0.90, detection of a 40% reduction in GCTF hazard for patients receiving TAK-700 requires observation of 100 events. Because the most frequent GCTF event is PSA failure, and this event is delayed during active treatment, analysis will take place only on the cohort of patients consisting of those entering through the first 1.5 years (450 patients). This cohort will be observed for an additional 1.75 years, or to approximately 3.25 years from commencement of accrual, when the requisite number events for the above comparison will have been observed. At this time, GCTF will be compared between treatments, and if the null hypothesis of no difference in GCTF rate cannot be rejected in favor of a lower GCTF rate for patients receiving TAK-700 (one-sided 0.10 test), then discontinuation of the trial for futility will be considered. Within the time frame described above, there will be at least 80% power for any treatment difference equal to or greater than a 33% relative reduction in GCTF events. Results of this analysis will be reported only to the RTOG Data Monitoring Committee and not in any scientific forum or publication.

13.5.7.3 *Interim Safety Analysis Plan*

After the accrual and follow-up of 100 patients per treatment arm through completion of six months of therapy, adverse event (CTCAE) frequencies will be formally compared between treatment arms.

Analysis will focus on specific organ system class and specific adverse event types, in addition to frequency of grade 3 and higher adverse events overall (i.e., any type). Adverse events of interest are shown below, accompanied by expected frequencies for the control

arm of this trial, based on observed rates in previous RTOG prostate cancer trials using prolonged androgen suppression.

CTCAE (4.0) category	CTCAE specific	Expected % grade ≥3 or greater on standard ADT
Any	Any	22.0
Renal and urinary disorders	Any	3.0
Gastrointestinal disorders	Any	3.6
Reproductive system and breast disorders	Any	10.4
General disorders and administration site conditions	Fatigue	1.9
Vascular disorders	Hypertension	0.0
Metabolism and nutrition disorders	Hypokalemia	0.0

Frequencies will be compared between treatment arms via Fisher's exact test. A one-sided criterion will be used to determine whether there is higher frequency of a given adverse event in the ADT+TAK700 arm. Including 200 patients with six months of follow-up (100 in each treatment group) and using a one-sided 0.01 alpha level, a 15% absolute increase in event types with expected frequency < 4% under standard ADT (for example, GU, GI, fatigue) can be detected with statistical power of 85% or greater. For those events with expected frequency in the range of 10%-25% in the control arm, statistical power for detecting a 25% absolute increase exceeds 85%. If there are imbalances between treatments in patient demographic or radiation treatment parameters that may affect adverse event rates, then stratification or modeling methods will be used.

In addition, scores for EPIC, EQ-5D, and PROMIS in this cohort will be compared between treatment groups, using the scheduled post-RT assessment. Differences will be assessed via t-tests on suitably transformed score sums, corrected for baseline values. A formal stopping criterion for these scores will not be specified.

13.5.8 Trial Reporting

The primary trial endpoint will be reported when specific criteria described in Section 13.5.7.2 are met. In particular, when either the number of events for definitive analysis is reached or an interim analysis indicates that early stopping is warranted, then the primary endpoint will be considered eligible for reporting.

13.6 Gender and Minorities

Men of all races and ethnic groups are eligible for this study. Clinically important race/ethnicity differences are not expected from the intervention effect.

Projected Distribution of Gender and Minorities

	Gender		
Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	N/A	27	27
Not Hispanic or Latino	N/A	873	873
Ethnic Category: Total of all subjects	N/A	900	**900**
	Gender		
Racial Category	**Females**	**Males**	**Total**
American Indian or Alaskan Native	N/A	2	2
Asian	N/A	4	4
Black or African American	N/A	135	135
Native Hawaiian or other Pacific Islander	N/A	3	3
White	N/A	756	756
Racial Category: Total of all subjects	N/A	900	**900**

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APPENDIX I

RTOG 1115
Informed Consent Template for Cancer Treatment Trials
(English Language)

Phase III Trial of Dose Escalated Radiation Therapy and Standard Androgen Deprivation Therapy (ADT) with a GnRH Agonist vs. Dose Escalated Radiation Therapy and Enhanced ADT with a GnRH Agonist and TAK-700 for Men with High Risk Prostate Cancer

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this study because you have prostate cancer.

Why is this study being done?

The purpose of this study is to compare the effects of hormone therapy (androgen deprivation) and TAK-700 plus radiation therapy with hormone therapy (androgen deprivation) and radiation therapy on you and your prostate cancer to find out which is better.

TAK-700 is a new drug that is experimental, which means that this drug is not approved by the United States Food and Drug Administration (FDA). TAK-700 is a pill intended to further reduce the levels of testosterone and other male hormones that may also cause continued growth of your prostate cancer.

There are 2 treatment groups in this study:
1) Patients who receive hormone therapy plus radiation therapy only
2) Patients who receive hormone therapy and TAK-700 plus radiation therapy

If you agree to participate in this study, you will receive one of these two treatments.

How many people will take part in the study?

About 900 people will take part in this study.

What will happen if I take part in this research study?

Before you begin the study …

You will have to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- A complete medical history will be collected including information on your general health, past surgeries and past treatments for prostate cancer and medications that you are taking (pain medications, over the counter medications, herbal remedies, vitamins, and supplements)
    - Tell the study doctor if you have any changes in your medication while on study. You should also talk to your study doctor before taking any other drugs, herbal supplements or therapy, including over the counter drugs and drugs prescribed by another doctor
- Blood tests to measure your blood chemistry, blood counts, the health of your arteries and heart (for example, cholesterol), and blood sugar level
- The following additional blood tests will be performed to evaluate your cancer:

    - Stress and male sex hormone levels such as testosterone
    - Prostate Specific Antigen (PSA), which is a tumor marker that may be used to track your prostate cancer
- A complete physical examination including vital signs (blood pressure, heart rate, and temperature), height and weight
- Certain imaging tests may be performed if you haven't had them done within the 90 days of starting the study. These are routinely performed to evaluate your disease. You could have a computed tomography (CT) scan (with contrast) or magnetic resonance imaging (MRI) of your abdomen (stomach area) and pelvis (hip area). In addition, bone scans will be completed to measure your disease.
- Electrocardiogram (ECG) to measure the health of your heart
- MUGA scan (Multi Gated Acquisition Scan) or Echocardiogram (ECHO) also to measure the health of your heart

Screening tests may require more than 1 visit to the clinic. Your study doctor will review the test results and tell you whether or not you are eligible for the study.

During the study …

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will have the following tests and procedures. They are part of regular cancer care:

- Physical exam with vital signs, height and weight (every 3 months during treatment)
- Safety blood tests to monitor your blood chemistry and blood counts (monthly and then every 3 months during treatment, as determined by your doctor)
- Blood tests to monitor levels of Prostate Specific Antigen [PSA] (every 3 months during treatment)
- For patients who will receive brachytherapy only: Transrectal ultrasound assessment of the prostate and an assessment of urinary symptoms and function

You will have these tests and procedures that are either being tested in this study or being done to see how the study is affecting your body:

- Blood tests to measure the following:
    - Stress and male sex hormone levels (testosterone at 12 and 24 months during treatment)
    - The health of your arteries and heart (for example, cholesterol)
    - Blood sugar levels
- You will be asked to record when you take your TAK-700 in a diary
- You will be asked about all medications you take (every 3 months during treatment)
- You will be asked to complete questionnaires that ask about how your cancer and your treatment affects your energy level, your quality of life, and your overall health status

The first 410 patients enrolled in this study will be required to complete three questionnaires: PROMIS-Fatigue Short Form, Expanded Prostate Cancer Index Composite (EPIC), and EuroQol (EQ-5D). Completion of these questionnaires is mandatory for this study. It takes about 25 minutes to fill out the questionnaires. If any questions make you feel uncomfortable, you may skip those questions and not give an answer. You will be asked to complete the questionnaires at the following times: *prior to study treatment, the week prior to radiation therapy, the last week of radiation therapy, one year and two and a half years after therapy starts.*

In addition, the first 410 patients enrolled in this study will be required to have an additional blood draw to evaluate particular biomarkers and how they relate to fatigue that you may be experiencing. Biomarkers are either proteins or genes that may be related to or predict how someone reacts to a treatment. This procedure would require an additional 10mL, or approximately 2 teaspoons, of blood to be drawn at three visits *in addition* to the other tests *(prior to study treatment, 1 year after therapy starts, and two and a half years after therapy starts)*. Your doctor will tell you if you will have this additional blood sample drawn.

You will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance. A computer program will place you in one of the study groups. Neither you nor your study doctor can choose the group you will be in. You will have an equal chance of being placed in any group.

If you are in group 1 (often called "Arm 1"): You will receive radiation treatments to the whole pelvis once daily, 5 days a week, Monday through Friday, for a total of 25 treatments. Each radiation treatment will take

approximately 20 minutes but may be specific to the center in which you are being treated. If you choose to receive brachytherapy (permanent or temporary radiation seed implant), the total number of daily treatment sessions will be 25. If you are treated with external beam as a boost you will receive a total of 44 treatments. The logistics of the brachytherapy implant procedure (if you have chosen to undergo this type of treatment) should be thoroughly reviewed by your treating physician.

You also will receive hormone therapy for 24 months. Hormone therapy will begin 2 months before the start of the radiation treatments. There are two parts to the hormone therapy. You will take injections of a luteinizing hormone releasing hormone (LHRH) agonist, either under the skin or in the muscle (typically every 1 to 3 months), and you will take a pill, either flutamide three times per day or bicalutamide once per day. The pills will be taken from 2 months prior to radiation therapy until the end of radiation therapy while the injections will be given for a total of 24 months. The injected LHRH agonist will reduce the amount of circulating testosterone and the pill will interfere with the action of any remaining testosterone.

If you are in group 2 (often called "Arm 2"): You will receive radiation treatments to the whole pelvis once daily, 5 days a week, Monday through Friday, for a total of 25 treatments. Each radiation treatment will take approximately 20 minutes but may be specific to the center in which you are being treated. If you choose to receive brachytherapy (permanent or temporary radiation seed implant), the total number of daily treatment sessions will be 25. If you are treated with external beam as a boost you will receive a total of 44 treatments. The logistics of the brachytherapy implant procedure (if you have chosen to undergo this type of treatment) should be thoroughly reviewed by your treating physician.

You also will receive hormone therapy for 24 months. Hormone therapy will begin 2 months before the start of the radiation treatments. There are two parts to the hormone therapy. You will take injections of a luteinizing hormone releasing hormone (LHRH) agonist, either under the skin or in the muscle (typically every 1 to 3 months), and you will take a pill, either flutamide three times per day or bicalutamide once per day. The pills will be taken from 2 months prior to radiation therapy until the end of radiation therapy while the injections will be given for a total of 24 months In addition, you will take an additional pill twice daily for 2 years which interferes with the body's ability to make the male hormone testosterone. The injected LHRH agonist will reduce the amount of circulating testosterone and the pill will interfere with the action of any remaining testosterone. This study is testing if the combination of these 3 drugs further suppresses the action of testosterone and leads to an improved chance to cure the prostate cancer.

In addition, you will take TAK-700 by mouth (pill) two times a day for 24 months. As noted above, TAK-700 is a new drug that is experimental, which means that it is not approved by the United States Food and Drug Administration (FDA). TAK-700 is a pill intended to further reduce the levels of testosterone and other male hormones that may also cause continued growth of your prostate cancer.

When you are finished hormone therapy plus radiation therapy or hormone therapy and TAK-700 plus radiation therapy, you will need these tests and procedures:

- At 30 months:
    - Blood for testosterone
- Every 6 months for 3 years, then at least annually:
    - A complete physical examination including vital signs (blood pressure, heart rate, and temperature), height and weight
    - Blood tests to measure prostate specific antigen (PSA)
    - You will be asked about all medications you take
    - Evaluation of any side effects you may be having
- Every 12 months for 3 years:
    - Blood tests to measure the health of your arteries and heart (for example, cholesterol), blood sugar level, and testosterone
- As clinically indicated; every 6 months after PSA relapse
    - A bone scan

Study Plan

Another way to find out what will happen to you during the study is to read the chart below. Start reading at the top and read down the list, following the lines and arrows.

Randomization
(You will be in one Group or the other)

Group 1

Hormone Therapy (ADT)
LHRH agonist for 24 months with concurrent oral antiandrogen until completion of radiation

Plus

Dose Escalated Radiation Therapy
44 treatments if no brachytherapy
- or -
25 treatments *plus* brachytherapy implant

Group 2

Hormone Therapy (ADT)
LHRH agonist for 24 months with concurrent oral antiandrogen until completion of radiation

Plus

TAK-700 twice daily for 24 months

Plus

Dose Escalated Radiation Therapy
44 treatments if no brachytherapy
- or -
25 treatments *plus* brachytherapy implant

How long will I be in the study?

You will receive hormone therapy for 24 months. Radiation therapy will be given in 44 treatments over approximately 2 months. Or, if you choose to receive the brachytherapy implant, you will receive 25 daily treatments plus the implant procedure over a timeframe of approximately 6 weeks. If you are in Group 2 ("Arm 2"), you also will take TAK-700 for 24 months.

After you are finished receiving therapy, the study doctor will ask you to visit the office for follow-up exams every 6 months for 3 years and then once a year. The study doctors would like to keep track of your medical condition by seeing you every year for your lifetime.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the hormone therapy and radiation can be evaluated by him/her. Another reason to tell your study doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

What side effects or risks can I expect from being in the study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, researchers don't know all the side effects that may happen. Side effects may be mild or

very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop treatment. In some cases, side effects can be serious, long lasting, or may never go away.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks and side effects related to the *radiation therapy* include those which are:

Likely

- Increased urinary frequency or urgency
- Burning or discomfort/straining with urination
- Increased frequency of bowel movements or change in stool consistency
- Increased straining/discomfort with bowel movements
- Mild fatigue

Less Likely

- Rectal bleeding (usually mild)
- Chronic bowel/bladder symptoms as described above
- Temporary blockage of urination requiring use of a catheter
- Erectile dysfunction

For patients undergoing brachytherapy, risks associated with aspects of an invasive procedure such as those associated with anesthesia, infection, and bleeding must be considered and discussed with your treating physician. If permanent seed brachytherapy is used, there is a possibility of loss or migration of seeds leading to areas of under- or overdosage in certain parts of the prostate or elsewhere. Rectal or bladder complications may occur if these organs are affected because of seed misplacement.

Rare but serious

- Permanent rectal or bladder injury requiring surgery for treatment

Possible risk and side effects related to the *hormone therapy and TAK-700*:

Most Common (30% or more)	**Very Common (10% or more to less than 30%)**	**Common (5% or more to less than 10%)**
• Hot flashes • Erectile Dysfunction • Feeling tired • Nausea	• Constipation • Headache • Loss of appetite • Diarrhea • Dizziness • Skin rash, covering part or most of body • Joint pain • Increase in a type of fat in blood • Difficulty breathing during physical activity • Changes in electrocardiogram (QTc, length) • Hot flush • Bone or liver enzyme increased in blood • High blood sugar (glucose) • Dizziness • Protein in urine • Change in sense of taste • High blood pressure • Low white blood cells	• Back pain • Cough • Low blood cell count (red blood cells) • Vomiting • Depression • Upset stomach • Muscle spasms or cramps • Pain in the arms or legs • Trouble or difficulty breathing • Increased gas in the intestines • Low potassium in blood • Swelling of feet or legs • Infection of bladder or kidneys • Weight loss • Swelling of the stomach or abdomen • Anxiety or worry • Increase in creatinine in blood (decreased kidney function) • Blood in the urine • High potassium in blood • Low sodium in blood • Trouble sleeping • Muscle weakness

	(lymphocytes) • Decrease in number of blood platelets	• Sore throat or head cold

Less Common Risks (<5%)

Some other risks were observed in less than 5% of patients treated with TAK-700. The measurement of heart function (ejection fraction) was decreased in some patients. A few patients developed blood clots in the leg or lung. With limited experience we do not know if TAK-700 will cause such clots. In addition, several patients who had previous problems with urination, such as blockage in the tubes leading to and from the bladder, developed worsening symptoms during the study that led to a brief decrease in kidney function.

With any drug, unusual, unexpected, or previously unreported side effects could occur, including side effects that are not listed or detailed above. You could also have an allergic reaction to the drug (your body has a reaction to the study medication). Therefore, it is important that you report all unusual symptoms and side effects that you experience as soon as they occur.

RISK TO THE UNBORN CHILD

The effect of TAK-700 on human sperm has not been studied. The effects on a developing fetus and the risks of birth defects are also unknown or may be unforeseeable. Therefore, men should not father a baby or donate sperm while on this study. If sexually active, an effective method of birth control should be used. Even if you are surgically sterilized (i.e. have had a vasectomy) you must agree to use an appropriate method of barrier contraception (latex condom with a spermicidal agent) during the entire study drug treatment period, and for 4 months after the last dose of study drug treatment. Or, you should completely avoid having heterosexual intercourse.

If your partner becomes pregnant while you are participating in this study, it is important that you notify your study nurse/physician immediately. The doctor will advise you of the possible risks to your unborn child and discuss options for managing the pregnancy with you.

All possible adverse effects from the combination therapy of prednisone, and other testosterone reducing drugs and the study drug, TAK-700, are unknown at this time. Your study doctor will discuss with you the possible risks involved with the other medicines that you are required to take in this study such as prednisone and GnRH analogue.

Risks associated with LHRH (GnRH) agonists:
Patients receiving treatment with LHRH agonists should undergo periodic monitoring of blood glucose and/or glycosylated hemoglobin (HbA1c) for signs of developing diabetes or worsening of blood glucose control in patients with diabetes, and also for the signs and symptoms suggestive of the development of cardiovascular disease.

Possible risks or side effects of other study procedures:
There are also risks associated with some of the study procedures. The risks are described below; however, any unknown risks that cannot be predicted are possible.

CT scans may use a contrast which in rare occurrences can cause an allergic reaction. There are also low levels of radiation used to produce an image and risk from radiation is minimal.

You may experience some pain, bruising, dizziness or (rarely) infection from the blood draws. Some patients may feel faint, may have nausea and/or feel cold and clammy as a result of a blood draw.

Your doctor will answer any questions you may have about these tests or procedures.

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. The information from this study will help researchers learn more about hormone therapy and radiation therapy as a treatment for prostate cancer. This information could help future cancer patients.

What other choices do I have if I do not take part in this study?

Your other choices may include:

- Getting treatment or care for your cancer without being in a study; this could include the following options, either alone or in combination with each other:
    - Radiation therapy
    - Hormone therapy
    - Surgery to the prostate
- Taking part in another study
- Getting no treatment

Talk to your study doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

Data are housed at RTOG Headquarters in a password-protected database. We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The Radiation Therapy Oncology Group (RTOG)
- The National Cancer Institute (NCI) and other government agencies involved in keeping research safe for people, like the Central Institutional Review Board (CIRB) and the Food and Drug Administration (FDA)
- The Cancer Trials Support Unit (CTSU), a service sponsored by the National Cancer Institute (NCI) to provide greater access to cancer trials
- Medidata Solutions Worldwide, the developers of Medidata Rave®

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of study results. You can search this Web site at any time.

[Note to Informed Consent Authors: The above paragraph complies with the new FDA regulation found at 21 CFR 50.25(c) and must be included verbatim in all informed consent documents. The text in this paragraph cannot be revised.]

[Note to Local Investigators: The NCI has recommended that HIPAA regulations be addressed by the local institution. The regulations may or may not be included in the informed consent form depending on local institutional policy.]

What are the costs of taking part in this study?

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

Millennium Pharmaceuticals, Inc will supply theTAK-700 at no charge while you take part in this study. Millennium Pharmaceuticals, Inc does not cover the cost of getting the TAK-700 ready and giving it to you, so you or your insurance company may have to pay for this.

Even though it probably won't happen, it is possible that the manufacturer may not continue to provide the TAK-700 for some reason. If this would occur, other possible options are:

- You might be able to get the TAK-700 from the manufacturer or your pharmacy but you or your insurance company may have to pay for it.
- If there is no TAK-700 available at all, no one will be able to get more, and the study would close.

If a problem with getting TAK-700 occurs, your study doctor will talk to you about these options.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, _____ *[investigator's name(s)],* if you feel that you have been injured because of taking part in this study. You can tell the study doctor in person or call him/her at _____ *[telephone number].*

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

A Data Monitoring Committee (DMC) will be regularly meeting to monitor safety and other data related to this study. The Committee members may receive confidential patient information, but they will not receive your name or other information that would allow them to identify you by name.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* at _____ *[telephone number].*

For questions about your rights while taking part in this study, call the _____ *[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at _____ *(telephone number). [Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]*

*You may also call the Operations Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only). *[*Only applies to sites using the CIRB.]*

Please note: This section of the informed consent form is about additional research that is being done with people who are taking part in the main study. You may take part in this additional research if you want to. You can still be a part of the main study even if you say 'no' to participating in this additional research.

You can say "yes" or "no" to the following study. Please mark your choice below.

About Using Tissue for Research

You are going to have a biopsy (or surgery) to see if you have cancer. Your doctor will remove some body tissue to do some tests. The results of these tests will be given to you by your doctor and will be used to plan your care.

We would like to keep some of the tissue that is left over for future research to learn more about cancer and other diseases. If you agree, this tissue will be sent to a laboratory to evaluate biomarkers. Biomarkers are either proteins or genes (also called DNA) that may be related to or predict how someone responds to a treatment. Please read the information sheet called "Providing your Tissue for Research" to learn more about tissue research. This information sheet is available to all at http://cdp.cancer.gov/humanSpecimens/ethical_collection/patient.htm.

In addition, you will have blood tests before you start treatment and at 1 year and 2.5 years after treatment starts. We would like to keep about four teaspoons of blood for future research as well. If you agree, this blood will be kept and may be used in research to learn more about cancer and other diseases.

Your tissue and blood specimens may be helpful for research whether you do or do not have cancer. The research that may be done with your specimens is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your specimens will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Things to Think About

The choice to let us keep the left over tissue and blood for future research is up to you. No matter what you decide to do, it will not affect your care or your participation in the main part of the study.

If you decide now that your specimens can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your tissue or blood specimens. Then any tissue or blood that remains will no longer be used for research and will be returned to the institution that submitted it.

In the future, people who do research may need to know more about your health. While the study doctor/ institution may give them reports about your health, the study doctor/institution will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes specimens are used for genetic research (about diseases that are passed on in families). Even if your specimens are not used for this kind of research, the results will not be put in your health records. Your specimens will be used only for research and will not be sold. The research done with your specimens may help to develop new treatments for cancer in the future.

Benefits

The benefits of research using tissue and blood specimens include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

Risks

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, check "Yes" or "No". If you have any questions, please talk to your doctor or nurse, or call our research review board at _____ [IRB's phone number].

No matter what you decide to do, it will not affect your care.

1. My specimens may be kept for use in research to learn about, prevent, or treat cancer, as follows:
   - Tissue ☐Yes ☐ No
   - Blood ☐Yes ☐ No

2. My specimens may be kept for use in research to learn about, prevent, or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease), as follows:
   - Tissue ☐Yes ☐ No
   - Blood ☐Yes ☐ No

3. My specimens may be kept for use in research to evaluate biomarkers.
   - Tissue ☐Yes ☐ No
   - Blood ☐Yes ☐ No

4. Someone may contact me in the future to ask me to take part in more research.
   ☐Yes ☐ No

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237)

You may also visit the NCI Web site at http://cancer.gov/

- **For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/**
- **For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/**

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all _____ *[insert total of number of pages]* pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant _____

Date _____

APPENDIX II: STUDY PARAMETER TABLE

***Note**: See Sections 3.0 and 4.0 (pre-study entry), 10.0 (specimen collection), and 11.1 (during treatment/follow up) for details and/or exceptions to this table.*

Assessments	**Pre-Treatment (may be required for eligibility)**					**During 24 months of ADT +/- TAK-700**					**Follow Up (beginning at 36 months)**
	Within 180 days prior to registration	Within 90 days prior to registration	Within 60 days prior to registration	Within 21 days (3 wks) prior to registration or treatment	Within 14 days (2 wks) prior to registration	q 1 month	q 3 months	12 months	24 months	30 months	q 6 months for 3 years and then annually
Biopsy	X										
History/physical			X				X				X
Ht/Wt/PS				X			X				X
PSA	X						X				X
CBC/diff					X						
Chemistry & liver panels				X (prior to treatment)		See 11.1					
Testosterone (standard assay unless otherwise noted) *Note: Collect blood for testosterone in the a.m. at same time of day as collection of fasting insulin/ fasting glucose/ fasting lipids/ hemoglobin A1C*				X (prior to treatment)				X (by LC/MS/MS; ship specimen to UCSF BSR)	X (by LC/MS/MS; ship specimen to UCSF BSR)	X	q 12 months for 3 years
Fasting glucose/ fasting lipids/ hemoglobin A1C *Note: Collect blood in the a.m. at same time of day as collection of testosterone*				X (prior to treatment)				X	X		q 12 months for 3 years

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APPENDIX II: STUDY PARAMETER TABLE (continued) (5/1/12)

***Note*: See Sections 3.0 and 4.0 (pre-study entry), 10.0 (specimen collection), and 11.1 (during treatment/follow up) for details and/or exceptions to this table.**

Assessments continued	**Pre-Treatment (may be required for eligibility**					**During 24 months of ADT +/- TAK-700**					**Follow Up (beginning at 36 months)**
	Within 180 days prior to registration	Within 90 days prior to registration	Within 60 days prior to registration	Within 21 days (3 wks) prior to registration or treatment	Within 14 days (2 wks) prior to registration	q 1 month	q 3 months	12 months	24 months	30 months	q 6 months for 3 years and then annually
Fasting insulin (ship specimen to UCSF) *Note: Collect blood in the a.m. at same time of day as collection of testosterone*				X (prior to treatment)				X	X		q 12 months for 3 years
MUGA scan or echocardiogram	X										
Bone scan		X									As clinically indicated, q 6 months after PSA relapse
CT or MRI		X									
Transrectal ultrasound and AUA			X (for brachy patients only)								
Review of medications	At registration						X				X
AE evaluation						X					X
*Clinical survivorship		X*					X				X
†PROMIS-fatigue, EPIC, EQ-5D, PSQI/GLTEQ	(1) Pretreatment; (2) in the week prior to RT start; (3) during the last week of RT; (4) at 1 year (12 months); and (5) at 2.5 years (30 months) after therapy starts (Note: Mandatory for the first 410 patients enrolled in this study)										

*See Section 1.0 of protocol under Evaluation of Clinical and Chronic Disease Outcomes (1st sentence)

†Blood collection is mandatory for patients participating in QOL.

- Continued on next page -

APPENDIX II: STUDY PARAMETER TABLE (continued) (5/1/12) ***Note**: See Sections 3.0 and 4.0 (pre-study entry), 10.0 (specimen collection), and 11.1 (during treatment/follow up) for details and/or exceptions to this table.*											
Assessments continued	**Pre-Treatment (may be required for eligibility)**					**During 24 months of ADT +/- TAK-700**					**Follow Up (beginning at 36 months)**
	Within 180 days prior to registration	Within 90 days prior to registration	Within 60 days prior to registration	Within 21 days (3 wks) prior to registration or treatment	Within 14 days (2 wks) prior to registration	q 1 month	q 3 months	12 months	24 months	30 months	q 6 months for 3 years and then annually
Tissue for banking (if patient consents)											
†Blood for banking/QOL(if patient consents)	(1) Pre-treatment; (2) 1 year (12 months); and (3) 2.5 years (30 months) after therapy starts *(see also Section 10.0)*										

†Blood collection is mandatory for patients participating in QOL.

APPENDIX III

ZUBROD PERFORMANCE SCALE

0	**Fully active, able to carry on all predisease activities without restriction**
1	**Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature. For example, light housework, 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 50% or more of waking hours**
4	**Completely disabled. Cannot carry on self-care. Totally confined to bed**
5	**Death**

APPENDIX IV
Staging System, Prostate, 7th Edition
DEFINITIONS OF TNM

Primary Tumor, Clinical (T)

TX Primary tumor cannot be assessed

T0 No evidence of primary tumor

T1 Clinically inapparent tumor neither palpable nor visible by imaging
- T1a Tumor incidental histologic finding in 5% or less of tissue resected
- T1b Tumor incidental histologic finding in more than 5% of tissue resected
- T1c Tumor identified by needle biopsy (e.g., because of elevated PSA)

T2 Tumor confined with prostate*
- T2a Tumor involves one-half of one lobe or less
- T2b Tumor involves more than one-half of one lobe but not both lobes
- T2c Tumor involves both lobes

T3 Tumor extends through the prostate capsule**
- T3a Extracapsular extension (unilateral or bilateral)
- T3b Tumor involves the seminal vesicle(s)

T4 Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles and/or pelvic wall

*Note: Tumor found in one or both lobes by needle biopsy, but not palpable or reliably visible by imaging, is classified as T1c

**Note: Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is classified not as T3 but as T2.

Primary Tumor, Pathologic (pT) *

pT2 Organ confined
- pT2a Unilateral, one-half of one side or less
- pT2b Unilateral, involving more than one-half of side but not both sides
- pT2c Bilateral disease

pT3 Extraprostatic extension
- pT3a Extraprostatic extension or microscopic invasion of bladder neck**
- pT3b Seminal vesicle invasion

pT4 Invasion of rectum, levator muscles, and/or pelvic wall

*Note: There is no pathologic T1 classification
**Note: Positive surgical margin should be indicated by an R1 descriptor (residual microscopic disease).

Regional Lymph Nodes (N)

Clinical

NX Regional lymph nodes were not assessed
N0 No regional lymph node metastasis
N1 Metastasis in regional lymph node(s)

Pathologic

pNX Regional nodes not sampled
pN0 No positive regional nodes
pN1 Metastases in regional node(s)

APPENDIX IV
Staging System, Prostate, 7th Edition
DEFINITIONS OF TNM

Distant Metastasis (M)*

M0 No distant metastasis
M1 Distant metastasis
- M1a Nonregional lymph node(s)
- M1b Bone(s)
- M1c Other site(s) with or without bone disease

*Note: When more than one site of metastasis is present, the most advanced category is used; pM1c is most advanced.

Histologic Grade (G)

Gleason X	Gleason score cannot be processed
Gleason ≤6	Well-differentiated (slight anaplasia])
Gleason 7	Moderately differentiated (moderate anaplasia)
Gleason 8-10	Poorly differentiated/undifferentiated (marked anaplasia)

Anatomic Stage/Prognostic Groups*

Stage I	T1a-c	N0	M0	PSA <10	Gleason ≤6
	T2a	N0	M0	PSA <10	Gleason ≤6
	T1-2a	N0	M0	PSA X	Gleason X
Stage IIA	T1a-c	N0	M0	PSA <20	Gleason 7
	T1a-c	N0	M0	PSA ≥10<20	Gleason ≤6
	T2a	N0	M0	PSA <20	Gleason ≤7
	T2b	N0	M0	PSA <20	Gleason ≤7
	T2b	N0	M0	PSA X	Gleason X
Stage IIB	T2c	N0	M0	Any PSA	Any Gleason
	T1-2	N0	M0	PSA ≥20	Any Gleason
	T1-2	N0	M0	Any PSA	Gleason ≥8
Stage III	T3a-b	N0	M0	Any PSA	Any Gleason
Stage IV	T4	N0	M0	Any PSA	Any Gleason
	Any T	N1	M0	Any PSA	Any Gleason
	Any T	Any N	M1	Any PSA	Any Gleason

*Note: When either PSA or Gleason is not available, grouping should be determined by T stage and/or either PSA or Gleason as available.

Source: Edge, SB, ed. *AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer; 2010.

APPENDIX V
New York Heart Association Classification of Cardiac Disease

The following table presents the NYHA classification of cardiac disease.

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Source: The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, MA: Little, Brown & Co; 1994:253-256.

APPENDIX VI
APPENDICES FOR RTOG BIOSPECIMEN COLLECTION
(as specified by the protocol)

Shipping Instructions:

U.S. Postal Service Mailing Address: For FFPE or Non-frozen Specimens Only
RTOG Biospecimen Resource
University of California San Francisco
Campus Box 1800
2340 Sutter Street, Room S341
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): For Frozen or Trackable Specimens
RTOG Biospecimen Resource
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115

- ❑ Include all RTOG paperwork in pocket of biohazard bag.
- ❑ Check that the Specimen Transmittal Form (STF) has the consent boxes checked off.
- ❑ Check that all samples are labeled with the RTOG study and case number, and include date of collection as well as collection time point (e.g., pretreatment, post-treatment).

- ❑ **FFPE Specimens:**
  - o Slides should be shipped in a plastic slide holder/slide box. Place a small wad of padding in top of the container. If you can hear the slides shaking it is likely that they will break during shipping.
  - o FFPE Blocks can be wrapped with paper towel, or placed in a cardboard box with padding. Do not wrap blocks with bubble wrap. Place padding in top of container so that if you shake the container the blocks are not shaking. If you can hear the slides shaking it is likely that they will break during shipping.
  - o Slides, Blocks, or Plugs can be shipped ambient or with a cold pack either by United States Postal Service (USPS) to the USPS address (94143) or by Courier to the Street Address (94115). **Do NOT ship on Dry Ice**.

- ❑ **Frozen Specimens:**
  - o Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and clearly identified.
  - o Place specimens and absorbent shipping material in Styrofoam cooler filled with dry ice (at least 7 lbs). There should be plenty of dry ice under and above the specimens. If the volume of specimens is greater than the volume of dry ice then ship in a larger Styrofoam box, or two separate boxes. Any Styrofoam box can be used, as long as it is big enough.
  - o Specimens received thawed due to insufficient dry ice or shipping delays will be discarded and the site will be notified.
  - o Send frozen specimens via overnight courier to the address above. Specimens should only be shipped Monday through Wednesday (Monday-Tuesday for Canada) to prevent thawing due to delivery delays. Saturday or holiday deliveries cannot be accepted. Samples can be stored frozen at -80° C until ready to ship.

- ❑ **For Questions regarding collection/shipping please contact the RTOG Biospecimen Resource by e-mail: RTOG@ucsf.edu or phone: 415-476-RTOG(7864) or Fax: 415-476-5271.**

APPENDIX VI (continued)

RTOG BLOOD COLLECTION KIT INSTRUCTIONS

Note: There is a separate appendix for PBMC preparation not included in this instruction (See Appendix VII). This Kit is for collection, processing, storage, and shipping of serum, plasma, or whole blood *(as specified by the protocol)*:

Kit contents:

- One Red Top tube for serum (A)
- One Purple Top EDTA tube for plasma (B)
- One Purple Top EDTA tube for Whole Blood (C)
- Twenty-five (25) 1 ml cryovials
- Biohazard bags (3) and Absorbent shipping material (3)
- Styrofoam container (inner) and Cardboard shipping (outer) box
- UN1845 DRY Ice Sticker and UN3373 Biological Substance Category B Stickers
- Specimen Transmittal Form (STF) and Kit Instructions

PREPARATION AND PROCESSING OF SERUM, PLASMA AND WHOLE BLOOD:

(A) Serum (if requested): Red Top Tube

- ❑ Label as many 1ml cryovials (5 to 10) as necessary for the serum collected. Label them with the RTOG study and case number, collection date, time, and time point, and clearly mark cryovials "serum".

Process:

1. Allow one red top tube to clot for 30 minutes at room temperature.
2. Spin in a standard clinical centrifuge at ~2500 RPM for 10 minutes at 4°C (preferred). If sites are unable to process samples at 4°C then spinning at room temperature is acceptable if done within 2 hours of draw but must be noted on the STF.
3. Aliquot 0.5 ml serum into as many cryovials as are necessary for the serum collected (5 to 10) labeled with RTOG study and case numbers, collection date/time, protocol time-point collected (e.g. pretreatment, post-treatment), and clearly mark specimen as "serum".
4. Place cryovials into biohazard bag and immediately freeze at -70 to -90° C, and store frozen until ready to ship. See below for storage conditions.
5. Store serum at -70 to -90° C until ready to ship on dry ice. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and include collection time point on the STF.

(B) Plasma (If requested): Purple Top EDTA tube #1

- ❑ Label as many 1ml cryovials (5 to 10) as necessary for the plasma collected. Label them with the RTOG study and case number, collection date, time, and time point, and clearly mark cryovials "plasma".

Process:

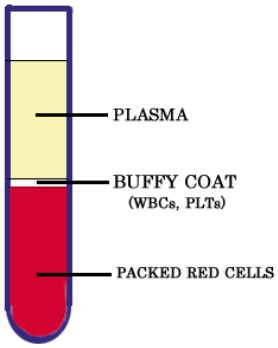
1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA.
2. Centrifuge specimen(s) within one hour of collection in a standard clinical centrifuge at ~2500 RPM for 10 minutes at 4°C (preferred). If sites are unable to process samples at 4°C then spinning at room temperature is acceptable if done within 2 hours of draw but must be noted on the STF..
3. If the interval between specimen collection and processing is anticipated to be more than one hour, keep specimen on ice until centrifuging is performed.
4. Carefully pipette and aliquot 0.5 ml plasma into as many cryovials as are necessary for the plasma collected (5 to 10) labeled with RTOG study and case numbers, collection date/time, time point collected and clearly mark specimen as "plasma". Avoid pipetting up the buffy coat layer.
5. Place cryovials into biohazard bag and immediately freeze at -70 to -90°C.
6. Store frozen plasma until ready to ship on dry ice.
7. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and include collection time point on the STF.

(continued on next page)

APPENDIX VI

RTOG BLOOD COLLECTION KIT INSTRUCTIONS (continued)



(C) Whole Blood for DNA (if requested): Purple Top EDTA tube #2

- ❑ Label as many 1ml cryovials (3 to 5) as necessary for the whole blood collected..Label them with the RTOG study and case number, collection date/time, and time point, and clearly mark cryovials "blood".

Process:

1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA. Blood can also be mixed for 5 minutes on a mixer at room temperature.
2. Carefully pipette and aliquot 1.0 ml blood into as many cryovials as are necessary for the blood collected (3 to 5) labeled with RTOG study and case numbers, collection date/time, time point collected and clearly mark specimen as "blood".
3. Place cryovials into biohazard bag and freeze immediately at -70 to -80° Celsius.
4. Store blood samples frozen until ready to ship on dry ice.
5. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and include collection time point on STF.

Freezing and Storage:

- ☐ Freeze Blood samples in a -80°C Freezer or on Dry Ice or snap freeze in liquid nitrogen.
- ❑ Store at –80°C (-70°C to -90°C) until ready to ship.
  If a -80°C Freezer is not available,
  - Samples can be stored short term in a -20°C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only; Canada: Monday-Tuesday only).

    OR:
  - Samples can be stored in plenty of dry ice for up to one week, replenishing daily (please ship out on Monday-Wednesday only; Canada: Monday-Tuesday only).

    OR:
  - Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only; Canada: Monday-Tuesday only).
- ❑ Please indicate on Specimen Transmittal Form the storage conditions used and time stored.

Shipping/Mailing:

- ❑ Ship specimens on Dry Ice overnight **Monday-Wednesday (Monday-Tuesday from Canada)** to prevent thawing due to delivery delays. Saturday and holiday deliveries cannot be accepted.
- ❑ Include all RTOG paperwork in a sealed plastic bag and tape to the outside top of the Styrofoam box.
- ❑ Wrap frozen specimens of same type (i.e., all serum together, plasma together and whole bloods together) in absorbent shipping material and place each specimen type in a separate biohazard bag. Place specimen bags into the Styrofoam cooler and fill with plenty of dry ice (7-10 lbs/3.5kg minimum). ***Add padding to avoid the dry ice from breaking the tubes.***
- ❑ Place Styrofoam coolers into outer cardboard box, and attach shipping label and UN3373 and UN1895 stickers to outer cardboard box.

(continued on next page)

APPENDIX VI

RTOG BLOOD COLLECTION KIT INSTRUCTIONS (continued)

- *Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and that there is enough room for plenty of dry ice.* ***Add padding to avoid the dry ice from breaking the tubes.***
- **For questions regarding collection, shipping or to order a Blood Collection Kit, please e-mail RTOG@ucsf.edu or call (415)476-7864.**

Shipping Address:

Courier Address (FedEx, UPS, etc.): For all Frozen Specimens
RTOG Biospecimen Resource
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115
For questions, call 415-476-RTOG (7864) or e-mail: RTOG@ucsf.edu

APPENDIX VII (5/1/12)

PBMC PREPARATION INSTRUCTIONS
Peripheral blood mononuclear cell (PBMC) isolation

1. Collect whole blood into two lavender top tubes (total volume about 6 ml per tube). **Keep blood at room temperature (RT)**.

2. *Within 10 min*, transfer the whole blood from collection tubes into a 50 ml conical tube. Note the volume of blood.

3. Dilute whole blood. Adjust blood volume to 1:1 with 1X PBS (e.g. 11 whole blood + 11 ml 1X PBS), invert to mix.

4. Add 5 ml lymphocyte separation medium (LSM) per tube to two 15 ml conical tubes.

5. Carefully add ***the diluted whole blood*** on the top of LSM (split evenly between the two 15 ml conical tubes) with disposable blunt tip transfer pipette, pipetting slowly along side of the tube to get two layers. Do not mix diluted whole blood with LSM.

6. Carefully transfer the tube with diluted whole blood/ LSM into a swing bucket centrifuge. Spin at 705 RCF for 10 minutes, RT, **with the brake off**.

7. Collect PBMCs with a disposable thin tip transfer pipet, and deposit to two new 15ml tubes.

8. Wash cells: bring volume in these tubes up to 14ml with 1X PBS (still RT) in each tube.

9. Centrifuge for 10 min at 194 RCF, RT, brake on.

10. Discard supernatant and wash again with 14ml of 1X PBS, RT.

11. Centrifuge for 10 min again at 194 RCF, RT, brake on.

12. Discard supernatant and re suspend pellets in 1.5 ml of ***freezing serum*** **(FBS + 10% DMSO)**.

13. **Store immediately at -80°C** in 2 ml cryovial**. Samples must then be kept at -80°C during storage and shipping.**

APPENDIX VII

PBMC PREPARATION INSTRUCTIONS (continued)
Peripheral blood mononuclear cell (PBMC) isolation

14. SHIPPING INSTRUCTIONS:

- Ship specimens on Dry Ice overnight **Monday-Wednesday (Monday-Tuesday from Canada)** to prevent thawing due to delivery delays. Saturday and holiday deliveries cannot be accepted.
- Include all RTOG paperwork in a sealed plastic bag and tape to the outside top of the Styrofoam box.
- Wrap frozen specimens in absorbent shipping material, and place inside zip-lock biohazard bags. Place specimen bags into the Styrofoam cooler and fill with plenty of dry ice (7-10 lbs/3.5kg minimum). ***Add padding to avoid the dry ice from breaking the tubes.***
- Place Styrofoam coolers into outer cardboard box, and attach shipping label and UN3373 and UN1895 stickers to outer cardboard box.
- **For questions regarding collection, shipping or to order a PBMC Collection Kit, please e-mail RTOG@emory.edu or call (404)778-5564.**

Shipping Address:

Courier Address (FedEx, UPS, etc.): For all Frozen Specimens
RTOG Biospecimen Resource
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115
Phone: +1 415-476-7864

PBMC Collection Kit Contents

Lavender top tubes: Becton Dickson 366450

1X PBS: made from 10X DPBS, Cellgro # 20-031-CV

50 ml conical tube: Becton Dickson 352070

lymphocyte separation medium: Mediatech 25-072-CL

disposable blunt tip transfer pipette: Fisher 13-711-7M

disposable thin tip transfer pipette: Thermo Scientific Samco 232

15 ml conical tube: Becton Dickson 352097

cryovial: Corning 430915

freezing medium: Fetal Bovine Serum, Hyclone SH30071.03; DMSO, Sigma D2650

APPENDIX VIII

MONTHLY PILL DIARY FOR RTOG 1115 TAK-700

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
Date:	**Date:**	**Date:**	**Date:**	**Date:**	**Date:**	**Date:**
AM DOSE 300mg____ **PM DOSE** 300mg____	**AM DOSE** 300mg____ **PM DOSE** 300mg____	**AM DOSE** 300mg____ **PM DOSE** 300mg____	**AM DOSE** 300mg____ **PM DOSE** 300mg____	**AM DOSE** 300mg____ **PM DOSE** 300mg____	**AM DOSE** 300mg____ **PM DOSE** 300mg____	**AM DOSE** 300mg____ **PM DOSE** 300mg____
Date:	**Date:**	**Date:**	**Date:**	**Date:**	**Date:**	**Date:**
AM DOSE 300mg____ **PM DOSE** 300mg____	**AM DOSE** 300mg____ **PM DOSE** 300mg____	**AM DOSE** 300mg____ **PM DOSE** 300mg____	**AM DOSE** 300mg____ **PM DOSE** 300mg____	**AM DOSE** 300mg____ **PM DOSE** 300mg____	**AM DOSE** 300mg____ **PM DOSE** 300mg____	**AM DOSE** 300mg____ **PM DOSE** 300mg____
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Date:	**Date:**	**Date:**	**Date:**	**Date:**	**Date:**	**Date:**
AM DOSE 300mg____ **PM DOSE** 300mg____	**AM DOSE** 300mg____ **PM DOSE** 300mg____	**AM DOSE** 300mg____ **PM DOSE** 300mg____	**AM DOSE** 300mg____ **PM DOSE** 300mg____	**AM DOSE** 300mg____ **PM DOSE** 300mg____	**AM DOSE** 300mg____ **PM DOSE** 300mg____	**AM DOSE** 300mg____ **PM DOSE** 300mg____
Date:	**Date:**	**Date:**	**Date:**	**Date:**	**Date:**	**Date:**
AM DOSE 300mg____ **PM DOSE** 300mg____	**AM DOSE** 300mg____ **PM DOSE** 300mg____	**AM DOSE** 300mg____ **PM DOSE** 300mg____	**AM DOSE** 300mg____ **PM DOSE** 300mg____	**AM DOSE** 300mg____ **PM DOSE** 300mg____	**AM DOSE** 300mg____ **PM DOSE** 300mg____	**AM DOSE** 300mg____ **PM DOSE** 300mg____

Patient Instructions:

Place a (✓) next to each dose taken on a daily basis. If you were instructed to take a different daily dose, write that dose in the box. If you missed a dose or a day, indicate that by placing an '**M**' after the dose rather than a (✓).

Be sure to bring your pill bottles and diaries with you for your return appointment.

Return appointment date:

____/____/_____

____**1115**___/______________
Study number/case number

____
Date

Comments____
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****Please file this diary in the patient's research chart. Do not mail to RTOG HQ.**