UCSF Helen Diller Family Comprehensive Cancer Center

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Phase II Trial of Definitive Radiotherapy with Leuprolide and Enzalutamide in High Risk Prostate Cancer

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Study Drug: Enzalutamide

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Protocol Signature Page

Protocol No.: 15558 **Version Date:** 09-05-2017

1. I agree to follow this protocol version as approved by the UCSF Protocol Review Committee (PRC), Committee on Human Research (CHR), and Data Safety Monitoring Committee (DSMC).
2. I will conduct the study in accordance with applicable CHR requirements, Federal regulations, and state and local laws to maintain the protection of the rights and welfare of study participants.
3. I certify that I, and the study staff, have received the requisite training to conduct this research protocol.
4. I have read and understand the information in the Investigators' Brochure (or Manufacturer's Brochure) regarding the risks and potential benefits. I agree to conduct the protocol in accordance with Good Clinical Practices (ICH-GCP), the applicable ethical principles, the Statement of Investigator (Form FDA 1572), and with local regulatory requirements. In accordance with the FDA Modernization Act, I will ensure the registration of the trial on the www.clinicaltrials.gov website.
5. I agree to maintain adequate and accurate records in accordance with CHR policies, Federal, state and local laws and regulations.

UCSF Principal Investigator / Study Chair

_____
Printed Name

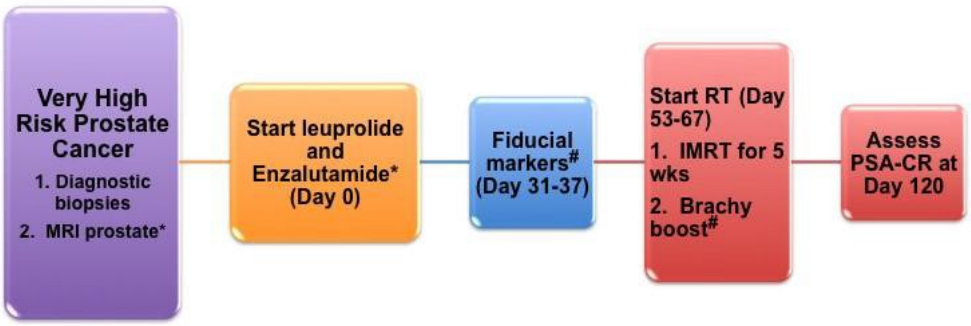
_____ _____
Signature Date

Participating Site(s): To be determined

Principal Investigator	**Site**
_____	_____
Printed Name	
_____	_____
Signature	Date

Abstract

Title	Phase II Trial of Definitive Radiotherapy with Leuprolide and Enzalutamide in High Risk Prostate Cancer
Patient population	53 Patients with high-risk, localized prostate cancer as defined by: 1) Histologically confirmed diagnosis of adenocarcinoma of the prostate within 180 days prior to registration at very high risk of recurrence as determined by 2 or more of the following combinations: a) cT3a/b b) PSA ≥20 c) Gleason score 8-10 d) ≥33% core involvement OR any patient with pelvic lymph node involvement ≥ 1 cm as determined by pelvic CT or MRI imaging will meet eligibility criteria for enrollment.
Rationale for Study	Long-term androgen deprivation therapy consisting of a LHRH agonist, with or without the addition of an anti-androgen, with radiation therapy improves the survival of patients with high risk prostate cancer.[1, 2] Enzalutamide is a potent anti-androgen with at least 9-fold higher binding affinity than other anti-androgens such as bicalutamide. Thus, more profound androgen deprivation therapy with the addition of enzalutamide to LHRH agonist therapy may improve the clinical outcomes of patients. The primary objective is to assess the safety, tolerability, and feasibility of the addition of enzalutamide to LHRH agonist therapy in patients with very high-risk prostate cancer or pelvic node positive disease receiving radiation therapy. Also, the potential efficacy of enzalutamide and leuprolide in combination with radiation therapy for improving the PSA complete response will be assessed.
Primary Objective	1) To determine the feasibility and safety of the combination of enzalutamide and leuprolide in patients undergoing definitive radiation therapy for high-risk prostate cancer or with pelvic nodal involvement. 2) To determine the PSA complete response rate with the combination of enzalutamide and leuprolide (PSA-CR as determined by PSA nadir ≤0.3) in patients undergoing radiation therapy for high-risk prostate cancer or pelvic nodal involvement.

Secondary Objectives	1) To determine time to biochemical failure as determined by the ASTRO Phoenix definition of nadir + 2 ng/mL, local progression, regional progression, and distant metastases. 2) To determine time to clinical progression free survival 3) To assess PSA nadir and PSA and testosterone levels at 3-4, 6, 12, and 24 months. 4) To assess changes in HbA1c, fasting glucose, fasting insulin and fasting lipid and cholesterol levels. 5) To document changes in quality of life outcomes.
Correlative Objectives	1) To identify potential mutations and changes gene copy number associated with enzalutamide resistance in patients with high risk prostate cancer. 2) To identify gene expression patterns, splice variants, and gene signatures associated with enzalutamide treatment and enzalutamide resistance in patients with high risk prostate cancer. 3) To identify changes in the immune response with enzalutamide treatment.
Study Design	 ***Leuprolide and enzalutamide for 24 months total.** ***MRI– Multiparametric PET/MRI with DWI, DCE, Spectroscopy** **#Biopsy will be performed at time of fiducial marker placement and at time of brachytherapy boost** Phase II study to evaluate the safety, toxicity, and feasibility of the addition of enzalutamide to leuprolide in patients with high-risk prostate cancer or pelvic node positive disease receiving radiotherapy. High-risk prostate cancer is defined as 2 or more of the following characteristics: 1) cT3a/b, 2) PSA ≥20 and <150, 3) Gleason 8-10, and 4) ≥33% core involvement. The proportion of patients obtaining a PSA complete response at day 120 will be determined. Safety will be assessed by the National Cancer Institute Common Terminology Criteria for Adverse Events v. 4.0 criteria
Number of patients	53 patients. Approximately 3 patients a month are expected to be accrued with a goal complete accrual by 24 months.

Duration of Therapy	Patients will receive a total duration 24 months of androgen deprivation therapy including leuprolide and enzalutamide with radiation therapy. The initial phase of radiation therapy will be delivered Monday-Friday, except for holidays, for a total of 15 treatment days. The boost phase (phase 2) of radiation therapy is one day for brachytherapy.
Duration of Follow up	Patients will be followed for up to 36 months after completion of radiation treatment
Duration of study	60 months
Study Treatment	Combined androgen blockade with leuprolide and enzalutamide will be administered with whole pelvic radiotherapy to a total dose of 45 Gy followed by brachytherapy boost.
Safety Assessments	Safety will be assessed through a summary of adverse events evaluated by NCI CTCAE v. 4.0.

List of Abbreviations

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical (Classification System)
AUC	area under the curve
CBC	complete blood cell (count)
CHR	Committee on Human Research (UCSF IRB)
CR	complete response
CRC	Clinical Research Coordinator
CRF	case report form
CT	computerized tomography
CTCEA	Common Terminology Criteria for Adverse Events
CTMS	Clinical Trial Management System
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HDFCCC	Helen Diller Family Comprehensive Cancer Center
HGB	hemoglobin
ICH	International Conference on Harmonization
IRB	Institutional Review Board
IV	intravenous
LFT	liver function test
MRI	magnetic resonance imaging
NCI	National Cancer Institute
PD	disease progression
PR	partial response
PRC	Protocol Review Committee (UCSF)
PSA	Prostate Specific Antigen
QOL	Quality of Life
SD	stable disease
SD	standard deviation
ULN	upper limit of normal

Table of Contents

Table of Contents

Table of Contents

List of Tables

1 Background:

1.1 High-Risk Prostate Cancer

The majority of patients with lethal prostate cancer present with clinically localized high-risk disease and will experience disease recurrence as manifested by persistently elevated or increasing PSA levels after definitive radiation therapy. Strategies to improve the outcome of these patients with high-risk disease are an unmet need.

In patients with high-risk prostate cancer receiving radiation therapy, addition of 2-3 years of androgen deprivation therapy (ADT) is the standard of care based on phase III trials demonstrating an overall survival (OS) benefit.[1, 2, 3] Five-year disease free survival (DFS) is approximately 50%. To improve outcomes, Radiation Therapy Oncology Group (RTOG) 9902 evaluated the role of adjuvant paclitaxel, estramustine, and etoposide (TEE) chemotherapy after combined androgen blockade with radiation therapy. This study failed accrual due to toxicity and did not show clinical benefit with TEE. Similarly, the GETUG-12 study evaluated the addition of docetaxel and estramustine to androgen suppression and radiation therapy in high-risk localized prostate cancer, but also did not show a significant benefit in the primary endpoint, progression free survival (PFS). Thus improvements in clinical outcome in patients with high-risk prostate cancer without added toxicity are an unmet need.

Although long-term androgen deprivation therapy improved outcomes in patients with high-risk localized prostate cancer receiving radiation, no study has evaluated the efficacy of more profound androgen blockade with enzalutamide in the same setting. Greater androgen suppression improved clinical outcomes in patients with hormone-sensitive metastatic prostate cancer. In a large phase III study, patients were randomized to greater androgen suppression with the combination of flutamide and leuprolide or to leuprolide alone. Combined androgen blockade with leuprolide and flutamide improved clinical response, PFS, and OS.[4] The greatest benefit in OS was seen in patients with limited hormone-sensitive metastatic prostate cancer,[4] which is the next step in progression after localized high-risk prostate cancer. Therefore, greater androgen blockade in patients with high-risk localized prostate cancer may also lead to improvements in clinical outcome.

1.2 Enzalutamide

Enzalutamide is a non-steroidal androgen receptor (AR) inhibitor. Enzalutamide inhibits the binding of androgens to the AR, inhibits the translocation of the AR to the nucleus, and inhibits AR mediated DNA binding. Enzalutamide has high affinity binding to the AR with 9-fold greater affinity than bicalutamide. Pre-clinical studies demonstrate that enzalutamide suppresses the proliferation of prostate cancer cells with AR gene amplification and can modulate the immune system to enhance immune recognition.[5] In two phase III trials, enzalutamide was demonstrated to improve the overall survival in patients with castrate resistant prostate cancer when compared with placebo.[6, 7] Interestingly, a large proportion of patients experienced greater than 90% reduction in PSA level in these two phase III studies[6, 7] when no further reductions were expected.

Recently, enzalutamide was demonstrated to be active in men with hormone-naïve prostate cancer, with 92.5% of men experiencing a decline of ≥80% in PSA. Approximately 25% of patients in this study had undergone radiotherapy and treatment was well tolerated.[8]

In the current study, we propose to investigate the role of more profound androgen suppression with enzalutamide in combination with an LHRH agonist in patients with high-risk prostate cancer receiving radiation therapy. Given the survival benefit with more profound androgen deprivation therapy in the hormone-sensitive setting along with the addition of 2-3 years of LHRH to radiation therapy, greater androgen blockade with the addition of enzalutamide to LHRH agonist therapy may provide an additional benefit in survival.

Enzalutamide, as demonstrated in phase II and phase III trials, is well tolerated. Adverse events that may occur with enzalutamide include fatigue, diarrhea, musculoskeletal pain, and headache. Recently, a phase II trail demonstrated safety with the addition of enzalutamide in the adjuvant setting after radiation therapy.[8] However, no study has been reported regarding the combination of enzalutamide with LHRH agonist and concurrent radiation.

1.3 Rationale of the Proposed Study

Long-term androgen deprivation therapy consisting of a LHRH agonist, with or without the addition of an anti-androgen, with radiation therapy improves the survival of patients with high risk prostate cancer.[1, 2] Enzalutamide is a potent anti-androgen with at least 9- fold higher binding affinity than other anti-androgens such as bicalutamide. Thus, more profound androgen deprivation therapy with the addition of enzalutamide to LHRH agonist therapy may improve the clinical outcomes of patients. The primary objective is to assess the safety, tolerability, and feasibility of the addition of enzalutamide to LHRH agonist therapy in patients with very high-risk prostate cancer or pelvic node positive disease receiving radiation therapy. Also, the potential efficacy of enzalutamide and leuprolide in combination with radiation therapy for improving the PSA complete response will be assessed. We hypothesize that greater androgen blockade with addition of enzalutamide to LHRH agonist therapy will improve the PSA complete response and provide additional clinical benefit. The primary endpoint is to assess the impact of the addition of enzalutamide to LHRH agonist therapy in improving PSA complete response (PSA-CR) after radiation therapy. PSA-CR is defined as a PSA ≤0.3 ng/mL. This metric has been validated as a predictor of clinical outcome including disease-specific survival, distant metastasis, and biochemical failure in two large studies (RTOG 9413, n=1070; MSKCC, n=1045).[9, 10] In these studies, approximately 30% of patients failed to achieve a PSA-CR while on combined androgen blockade. Failure to obtain a PSA-CR was associated with significantly worse disease-specific survival, worse disease-free survival, higher incidence of distant metastases, and increased biochemical failure. Based on prior studies evaluating PSA response with enzalutamide, we would expect that addition of enzalutamide reduce the proportion of patients failing to achieve a PSA-CR to at least 0.15.

1.4 Rationale for Correlative Studies

Mechanisms of enzalutamide resistance including AR gene amplification, truncation mutations, gain-of-function mutations, and glucocorticoid receptor overexpression have been shown in preclinical and mCRPC patient samples. However, the mechanisms of enzalutamide resistance have not been extensively studied in patients with high-risk or pelvic node positive prostate cancer. No study has evaluated the evolution of genetic alterations through primary treatment of prostate cancer. Castration and enzalutamide resistant clones may be already present in the primary tumor in patients with very high-risk, localized disease, well before the development of metastatic disease. This is suggested by the lack of a PSA-CR in 30% of patients with high-risk disease on

androgen blockade. Further evidence comes from continued AR signaling despite combined androgen blockade in localized prostate cancer. In the current proposal, mutational analysis and gene expression/gene splicing changes leading to enzalutamide resistance will be investigated in very high-risk or pelvic node positive prostate cancer.

Recently, androgen deprivation has been shown to enhance the immune response to prostate cancer as testosterone may be immunosuppressive. Androgen ablation in a mouse model reversed T-cell tolerance to a prostate restricted tumor antigen. Also, surgical castration of mice undergoing vaccination with a prostate-specific antigen enhanced CD8 T-cell response. Lastly, in patients with prostate cancer undergoing ADT, an increase in T-cell infiltration into the prostate was observed. Thus, testosterone may suppress T-cell response to tumor antigens. The mechanisms by which androgen blockade, especially with enzalutamide, regulate the immune system will be an exploratory objective in this proposal.

In summary, the goal of the correlative studies is to identify changes associated with enzalutamide response and resistance in high-risk or node positive prostate cancer. Serial biopsies and blood collection will be obtained. Genetic mutations, gene expression changes, and immune response will be evaluated from these biopsies and blood. By integrating the information gained through serial assessment, a global view of the temporal changes within the tumor(s) is obtained. These analyses will provide insight into the mechanisms of enzalutamide resistance in the very high-risk and pelvic node positive setting. Understanding the mechanisms of enzalutamide resistance in the very high-risk and node positive setting will facilitate the selection of patients benefitting from enzalutamide treatment and the development of effective treatment regimens for a personalized treatment approach.

2 Objectives of the Study

2.1 Primary

1. To determine the feasibility and safety of the combination of enzalutamide and leuprolide in patients undergoing definitive radiation therapy for high-risk prostate cancer or with pelvic nodal involvement.

2. To determine the PSA complete response rate with the combination of enzalutamide and leuprolide (PSA-CR as determined by PSA nadir ≤0.3) in patients undergoing radiation therapy for high-risk prostate cancer or pelvic nodal involvement.

2.2 Secondary

1. To determine time to biochemical failure as determined by the ASTRO Phoenix definition of nadir + 2 ng/mL, local progression, regional progression, and distant metastases.

2. To determine time to clinical progression free survival

3. To assess PSA nadir and PSA and testosterone levels at 3-4, 6, 12, and 24 months.

4. To assess changes in HbA1c, fasting glucose, fasting insulin and fasting lipid and cholesterol levels.

5. To document changes in quality of life outcomes.

2.3 Correlative Studies

1. To identify potential mutations and changes gene copy number associated with enzalutamide resistance in patients with high risk prostate cancer.

2. To identify gene expression patterns, splice variants, and gene signatures associated with enzalutamide treatment and enzalutamide resistance in patients with high risk prostate cancer.

3. To identify changes in the immune response with enzalutamide treatment.

2.4 Endpoints

2.4.1 Primary Endpoint

1. The primary endpoint of the study is to determine the rate of acute toxicity (≤90 days within the completion of radiotherapy) and late toxicity (≥91 days within the completion of radiotherapy). Adverse events will be defined according to CTCAE v. 4.0 criteria. Patients will be monitored at least weekly during treatment and every 3-6 months up to 24 months and at 36 months after radiation therapy.

2. A PSA measurement will be obtained at 120-127 days after initiation of androgen deprivation therapy. The proportion of patients achieving a PSA-CR (PSA nadir ≤0.3) at 120-127 days will be determined. The historical proportion of patients (0.7) attaining a PSA-CR from RTOG 9413 will be utilized for comparison.

2.4.2 Secondary Endpoints

1. PSA and testosterone measurements will be made at 6 weeks and then at 3-4 months, 6 months, 12 months, 18 months, 24 months, and at 36 months as part of standard of care. The time to biochemical failure will be defined from the date of randomization to the date of a rise by ≥2 ng/mL from the nadir PSA per the Phoenix Definition. PSA nadir and PSA and testosterone levels will be documented at 4, 6, 12, and 24 months.

2. The time to local failure will be defined from the date of randomization to the date of biopsy proven recurrence within the prostate gland.

3. The date of regional or distant metastases will be defined as the date from randomization to the date of 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 rising PSA, biopsy is encouraged.

4. The time to clinical progression will be defined from the date of randomization to the date of PSA failure, local failure, regional or distant metastases. Deaths prior to any of these events are treated as censoring for this endpoint.

5. Changes in HbA1c, fasting glucose, fasting insulin and fasting lipid and cholesterol levels will be assessed at 12 and 24 months during treatment.

6. Quality of life will be monitored. Changes in patient reported quality of life would be measured by the Expanded Prostate Cancer Index Composite (EPIC).

Changes in fatigue from baseline to 1 year will be measured by PROMIS. Assessment of quality adjusted survival will be performed using the EQ-5D.

2.4.3 Correlative Science Endpoints

1. To identify mutations, insertions/deletions, and changes in gene copy number associated with enzalutamide treatment and resistance, whole exome sequencing will be performed on mapped biopsies pre-enzalutamide treatment, 5-weeks post-initiation of enzalutamide therapy at the time of fiducial marker placement, and after 5 weeks of external radiotherapy. Computational analysis of raw exome data will be performed. Somatic point mutations and insertions/deletions nominated as clinically informative will be amplified and sequenced for validation.

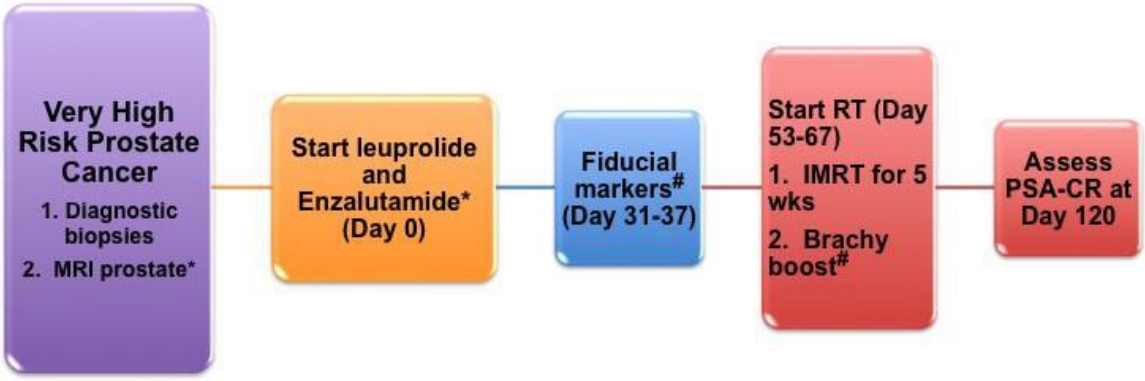
   Reads from exome sequencing of tumor and patient-matched blood cells will be aligned to target capture regions, including exons, intron/exon boundaries, and many 5' transcribed portions of promoter regions. Quality control and recalibration will be applied. To detect substitution mutations, we will use muTect (provided by K. Cibulskis/G. Getz, Broad Institute). For insertion and deletion detection, PinDel will be employed. Variant nucleotides will be merged and annotated with Annovar, followed by filtering, output, and reporting. Variant frequencies will be compared across samples as an indirect measure of non-tumor cell contamination level and abundance of mutations within the tumor cell population. Clinically informative mutations will be validated by Sanger sequencing. Tumor purity estimates from exome sequencing will be compared to estimates from tissue analyses. Tumor phylogenies will be constructed from mutations and/or copy number changes in longitudinally collected samples to understand the clonal relationships between pre and post treatment tumor biopsies.

2. To identify changes in gene expression, splice variants, and expression signatures associated with enzalutamide treatment and resistance, gene expression profiling will be performed with the Affymetrix GeneChip Human Transcriptome Array 2.0 in collaboration with GenomeDx. This array chip assesses the expression of over 1.4 million RNA features including ~22,000 known protein-coding genes as well as many thousands of non-coding RNAs. This will allow us to examine relative gene expression, splice variants, and immune response signatures.

   Normalization and summarization of data will be performed using the SCAN Algorithm. Genes with at least a 2-fold difference in expression will be selected. All statistical analysis will be performed using the MultiExperiment Viewer. Principal component analysis will be performed by eigenvalue decomposition of the 3 principal components for tridimensional classification of the samples and an unsupervised hierarchical cluster by Pearson's correlation will be selected to group the samples. The significance analysis of microarrays statistical technique will be performed for descriptive and comparative purposes. We will use the R package DESeq to perform differential gene expression analysis between response and nonresponse patients. We will use the R package GoSeq to perform over- and under-representation analysis (ORA) of gene sets taking length bias into account.

3. Immune response signatures will be evaluated with the Affymetrix Gene Chip Array as described above. In addition, to examine the effect on T cell subsets, T cell turnover and T cell diversity, peripheral blood will be collected at pre-enzalutamide treatment, 5-weeks post-initiation of enzalutamide therapy at the time of fiducial marker placement, after 5 weeks of external radiotherapy, and at 4 months after completion of radiation therapy. T cell diversity will be performed using deep T Cell Receptor (TCR) sequencing and T cell turnover will be assessed by evaluating the number of TCR excision circles.

3 Study Design



***Leuprolide and enzalutamide for 24 months total.**
***MRI– Multiparametric PET/MRI with DWI, DCE, Spectroscopy**
#Biopsy will be performed at time of fiducial marker placement and at time of brachytherapy boost

3.1 Characteristics

This is a phase II study to evaluate the safety, toxicity, and feasibility of the addition of enzalutamide to leuprolide for a total duration of 24 months in patients with high-risk prostate cancer or pelvic node positive disease receiving radiotherapy. High-risk prostate cancer is defined as 2 or more of the following characteristics: 1) cT3a/b, 2) PSA ≥20 and <150, 3) Gleason 8-10, and 4) ≥33% core involvement.

Pre-Radiation Treatment

To be eligible, patients must have biopsy proven prostate cancer. MRI/US fusion-guided biopsy is encouraged, but not mandatory, of the dominant lesion(s), if available. Patients must also undergo serum PSA and testosterone measurement <45 days prior to biopsy or at least 18 days after biopsy. The serum PSA half life is 2.2 days, therefore any elevation due to biopsy or instrumentation of the prostate should resolve by 18 days (>5 half-lives). Patients must undergo blood sample collection prior to initiation of androgen deprivation therapy. All patients should complete the EPIC-26, PROMIS, and EQ-5D questionnaires prior to enrollment. Enrollment will begin once standard staging including above studies are completed.

4-6 wks after initiation of ADT

Patients will undergo repeat PSA and testosterone testing at 4-6 weeks after initiation of ADT. Blood collection should be performed at the time of PSA and testosterone testing. Patients should undergo fiducial marker placement to optimize patient positioning and account for prostate motion for future radiation treatment. During the fiducial marker procedure, a biopsy of the dominant lesion(s) will be obtained. The risks and discomfort of the limited biopsy are minimal as a needle is already being introduced under ultrasound guidance for fiducial marker placement as part of the standard of care. The biopsy should be mapped under MRI-guidance if available.

At time of brachytherapy (if being performed)

After 5 weeks of conventional whole pelvic radiotherapy, brachytherapy may be performed. At the time of brachytherapy, a biopsy of the dominant lesion(s) will be performed. The risks and discomfort of the limited biopsy are minimal as multiple catheters (larger in diameter) are already being introduced under ultrasound guidance into the prostate as part of the HDR procedure. Patients should complete the QOL questionnaires including EPIC-26, PROMIS, and EQ-5D.

Post-Radiation Therapy

Serum PSA and testosterone should be measured at each follow up visit as described. These follow-up visits should occur at 6 wks post-treatment, 3-4 months, 6 months, 12 months, 18 months, 24 months, and at 36 months.

Number of Subjects

A total of 53 patients with high-risk prostate cancer or with pelvic nodal involvement without distant metastases will be enrolled.

3.2 Eligibility Criteria

Patients must have baseline evaluations performed prior to the first dose of study drug and must meet all inclusion and exclusion criteria. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained from the patient prior to enrollment. The following criteria apply to all patients enrolled onto the study unless otherwise specified.

3.2.1 Inclusion Criteria

1. Histologically confirmed diagnosis of adenocarcinoma of the prostate within 25 weeks prior to registration at very high risk of recurrence as determined by 2 or more of the following combinations:

    - cT3a/b
    - PSA ≥20
    - Gleason score 8-10
    - ≥33% core involvement

    OR

    any patient with pelvic lymph node involvement ≥1cm as determined by pelvic CT or MRI imaging will meet eligibility criteria for enrollment.

2. Standard staging exams for patients with high-risk prostate cancer including bone scan or NaF PET/CT scan, and pelvic and prostate MRI.

3. No distant metastases (M0) on bone scan or NaF PET/CT within 14 weeks prior to registration. Equivocal bone scan findings are allowed if the physician determines that distant metastases are unlikely based on clinical judgment.

4. Zubrod Performance Status 0-2 within 14 weeks prior to enrollment.

5. Age ≥18

6. CBC with differential obtained within 14 weeks prior to registration on study, with adequate bone marrow function defined as follows:

    a. Absolute neutrophil count (ANC) ≥1,800 cells/mm^3
    b. Platelets ≥100,000 cells/mm^3
    c. Hemoglobin ≥8.0 g/dl (The use of transfusion or other intervention to achieve Hgb ≥ 8.0 g/dl is acceptable)
    d. Serum creatinine <2.0 mg/dl and creatinine clearance >40 mL/min
    e. Bilirubin <1.5 x ULN
    f. ALT or AST <2 × ULN

7. Patients, even if surgically sterilized (i.e., 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

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

3.2.2 Conditions for Patient Ineligibility

1) Definite evidence of metastatic disease

2) Prior radical prostatectomy or bilateral orchiectomy for any reason

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

4) Prior systemic chemotherapy for prostate cancer (Note that prior chemotherapy for a different cancer is allowed).

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

5) 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)

6) Known hypersensitivity to enzalutamide or related compounds

7) History of adrenal insufficiency

8) 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.

9) Prior allergic reaction to the drugs involved in this protocol.

11) Cushing's syndrome

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

13) Chronic liver disease (bilirubin >1.5x ULN, ALT or AST >2x ULN)

14) Active/Uncontrolled Viral Hepatitis

15) Chronic treatment with glucocorticoids within one year.

16) History of seizure including febrile seizure or any condition that may predispose to seizure (e.g., prior stroke, brain arteriovenous malformation, head trauma with loss of consciousness requiring hospitalization). Also, current or prior treatment with antiepileptic medications for the treatment of seizures or history of loss of consciousness or transient ischemic attack within 12 months prior to randomization.

17) Clinically significant cardiovascular disease including:
    a. Myocardial infarction within 6 months prior to screening
    b. Uncontrolled angina within 3 months prior to screening
    c. Congestive heart failure NYHA class 3 or 4, or subjects with history of congestive heart failure NYHA class 3 or 4 in the past, unless a screening echocardiogram or MUGA scan performed within 3 months results in a left ventricular ejection fraction that is ≥45%;
    d. History of clinically significant ventricular arrhythmias (e.g. ventricular tachycardia, ventricular fibrillation, torsades de pointes);
    e. History of Mobitz II second degree or third degree heart block without a permanent pacemaker in place;
    f. Uncontrolled hypertension as indicated by a resting systolic blood pressure >170 mm Hg or diastolic blood pressure >105 mm Hg at screening. Patients with initially elevated systolic blood pressure >170 mm Hg or diastolic blood pressure >105 mm Hg are eligible if they undergo medical management and are re-screened.

3.3 Discontinuation Criteria

If a patient decides to discontinue protocol treatment or progression of disease is detected, follow up and data collection will continue as specified in the protocol.

3.4 Criteria for Termination of Protocol

The trial will be terminated if there is a greater than 12% clinically significant, treatment-

related grade 3 or higher toxicity. The 12% clinically significant, treatment-related acute grade 3 or higher toxicity rate is acceptable as prior studies have demonstrated a 12% acute grade 3 GU and GI toxicity. The use of a urinary catheter or bladder irrigation within 14 days after brachytherapy will not be considered grade 2 toxicity as this may be a standard procedure after brachytherapy. The trial will not be terminated for non-related or non-clinically significant toxicities.

3.5 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue for up 24 months or until:

- Disease progression
- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study
- Significant patient non-compliance with the protocol
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

3.6 Duration of Follow up

After completion of radiation treatment, patients will be followed at 6 weeks, month 3-4, month 6, month 12, month 18, month 24, and at 36 months per standard of care. Patients removed from study for unacceptable treatment related adverse event(s) will be followed until resolution or stabilization of all treatment related adverse events to Grade 2 or lower.

3.7 Study Timeline

3.7.1 Primary Completion

Study accrual is to be completed by 24 months

3.7.2 Study Completion

Study completion is projected approximately 60 months from the time the study is open to accrual.

4 Radiation Therapy

Radiation therapy should begin approximately 8 weeks (+/- 1 week) after the date of the first LHRH agonist/antagonist injection of hormone therapy is given.

4.1 Two Stage Radiation Plan

4.1.1 Phase 1: Whole pelvis including prostate and seminal vesicles.

IMRT will be utilized for treatment delivery.

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: **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 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

4.1.2. Phase 2: Reduced volume to boost prostate and seminal vesicles

Acceptable Treatment Modalities: IMRT, Stereotactic body radiotherapy, permanent prostate implant (PPI) brachytherapy or high-dose rate (HDR) brachytherapy

Table 2: **Treatment Modalities and Prescription Dose for Phase 2**

Acceptable Treatment Modalities	**Prescription Dose**
Intensity-Modulated Radiotherapy	34.2 Gy in 19 fractions of 1.8 Gy each
Stereotactic Body Radiotherapy	19 Gy in 2 fractions of 9.5 Gy each
Permanent Prostate Seed Implant (PPI)	• 108 Gy for I-125 • 90 Gy for Pd-103
HDR brachytherapy	15 Gy in one fraction

4.2 Technical Factors

For Phase I, IMRT is necessary to achieve conformality. No specific field arrangement is required. External beam radiotherapy will be delivered with megavoltage equipment at energies ≥6 MV.

4.2.1 IMRT Localization, Simulation, and Immobilization

Simulation will be CT-based in all cases. A MRI is recommended to define the extent of disease and for delineation of the urethra. Rectal contrast is discouraged because it may distend the rectum and artificially displace the prostate in the anterior direction. IV contrast is permitted to assist in identifying the pelvic vessels. Patients will be positioned supine on a flat tabletop with a customized thermoplastic immobilization cast or a

molded foam cradle 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 or adaptive treatments are 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 and normal critical structures will be defined in the slices in which they are visualized.

4.2.2 Treatment Planning/Target Volumes

4.2.2.1 Target Volume for Step 1

The target volume (CTV1/PTV1) for step 1 will be the pelvic lymph node, which include the internal iliac, external iliac, obturator, and common iliac nodes, prostate, and seminal vesicles. The presacral nodes may be included if desired depending if dose constraints to the rectum are achievable. Sentinel lymph node imaging may be utilized to guide target volume delineation of CTV1. A total dose of 45 Gy in 25 fractions of 1.8 Gy each will be delivered to this volume with intensity modulated radiation therapy.

4.2.2.2 Step 1 Pelvic Lymph Node Irradiation

The Clinical Target Volume 1 (CTV1) will include 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. Also included will be the prostate and seminal vesicles. Please refer to the pelvic nodal atlas at the RTOG Web site (Pelvic Lymph Node Volumes for Prostate Cancer Atlas; http://www.rtog.org/atlases/PelvicLymphNodeProstateAtlas/main.html). 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 4). 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. In addition, sentinel lymph node imaging may be utilized to guide CTV1 target delineation.

For patients with gross nodal involvement (cN1) as determined by CT or MRI, a sequential boost to 59.4 Gy in 9 fractions of 1.8 Gy each is allowed to the involved node(s). It is critical to maintain small bowel dose constraints as listed in Table 4 If bowel dose constraints are unable to be met, the gross nodal boost dose should be reduced to 57.6 Gy or 55.8 Gy to meet the small bowel dose constraint. The final dose should be recorded if a gross nodal boost dose is utilized.

4.2.2.3 Planning Target Volume 1 (PTV1)

The PTV1 will provide a margin around the CTV1 to compensate for the variability of treatment set up and internal organ motion. A 5-7 mm margin around the CTV is suggested to define each PTV1. Individual selection of a PTV margin should be based

on the physician's level of confidence in patient set-up and the availability of image guidance. Superior and inferior margins (capping) is suggested to be 5-7 mm depending on the thickness and spacing of the planning CT scan. Careful consideration should be made when defining the margin in 3 dimensions.

4.2.3 Target Volume for Step 2

The target volume (CTV2/PTV2) for step 2 will be the prostate and seminal vesicle volume. The radiation for step 2 may be delivered via IMRT, LDR, or HDR treatment. If IMRT is used, the dose to CTV2/PTV2 will be 34.2 Gy in 19 fractions of 1.8 Gy each. If LDR brachytherapy is used, the dose will be 108 Gy for I-125 and 90 Gy for Pd-103. For HDR brachytherapy implant, the dose will be 15 Gy in 1 fraction.

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

4.2.3.1 Step 2 Prostate +/- Proximal Seminal Vesicle

Gross Target Volume: Gross Target Volume (GTV2) is defined by the physician as all known disease as defined by the planning CT, MRI, urethrogram, and clinical information. If an 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 1 (CTV2) will include the prostate +/- the proximal seminal vesicles (SV).

Planning Target Volume: The PTV2 margins should be a minimum of 0.2 cm and a maximum of 0.5 cm in all dimensions .

Critical Structure: The bladder, rectum (from origin at rectosigmoid flexure superiorly or bottom of SI joints, whichever is more inferior to the inferior-most extent of the ischial tuberosities, urethra, and bowel, bilateral femora (to the level of ischial tuberosity), penile bulb, and skin should be defined on the treatment planning scan. 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.

4.2.4 Target and Normal Critical Structures:

Will be defined as above for Phase I.

Table 3: Target and Normal Critical Structures

Standard Name	Description
GTV	Gross Target Volume
CTV1	Clinical Target Volume 1 – obturator, external iliac, proximal internal iliac and common iliac nodes, +/- presacral lymph nodes, prostate + seminal vesicles
CTV2	Clinical Target Volume 2 - prostate + seminal vesicles
PTV1	Planning Target Volume 1
PTV2	Planning Target Volume 2
BLADDER	Bladder
FEMUR_LT	Left Femoral Head
FEMUR_RT	Right Femoral Head
PENILE_BULB	Penile Bulb

RECTUM	Rectum
SKIN	External patient Contour

4.3 Dose Specification/Technical Considerations: IMRT

Table 4: Dose Specifications/Technical Considerations IMRT

Normal Organ	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	80 Gy	75 Gy	70 Gy	65 Gy
Rectum	75 Gy	70 Gy	65 Gy	60 Gy
Bowel	Max point dose 0.03 cc <56 Gy, 1 cc <54 Gy			
Penile Bulb	Mean dose less than or equal to 52.5 Gy			

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. 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.

4.4 IMRT Treatment Verification

For IMRT, daily on-line target localization with kilovoltage or megavoltage CT imaging of pelvic anatomy, alignment with the prostate fiducial markers using orthogonal pair imaging, or alignment to Calypso markers by radiofrequency localization is required prior to treatment delivery to ensure accurate positioning. For SBRT, orthogonal films with or without cone beam CT (if available) will be performed prior to treatment with matching fiducial markers placed in the prostate. During SBRT treatment delivery, orthogonal films will be performed to account for intrafraction motion.

4.5 Dose Specifications/Technical Considerations: LDR Brachytherapy

Low dose rate (LDR) implants will only be offered to patients with a prostate volume documented to be <60 cc by transrectal ultrasound examination. The implant may be performed under either general or spinal anesthesia.

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 PTV may be the same as the CTV or a 2-3 mm margin may be added

anteriorly and laterally and up to 5 mm craniocaudally at the discretion of the treating physician. The CTV is the prostate gland and the seminal vesicles.

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.

- For I-125, the allowable source strength for each seed is 0.277 U to 0.650 U (NIST 99 or later). For Pd-103 sources, this range is 1.29 U to 2.61 U (NIST 99 or later).
- 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.

Prescription Doses: The prescription dose for permanent seed interstitial boost will be 108 Gy for I-125 and 90 Gy for Pd-103. Doses will be prescribed as minimal peripheral dose to the PTV.

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 post implant. 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.

- Structures defined will include the prostate, bladder, rectum, and penile bulb. 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.
- Post implant 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.
    - The calculation grid should be set no larger than (2 mm x 2 mm x axial slice width).
    - Guidelines established by the American Brachytherapy Society (Nag 2000) are to be followed. DVH-based analysis must be used in the post plan 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.

- Target coverage will be documented in terms of V100, V90, V80, D90.
- Dose uniformity will be expressed in terms of V150.
- 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.

Compliance Criteria

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

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.

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

4.6 Dose Specifications/Technical Considerations: HDR Brachytherapy

HDR brachytherapy is permitted at the discretion of the treating radiation oncologist in conjunction with HT. High dose rate implants will only be offered to patients with a prostate volume documented to be <150 cc by transrectal ultrasound examination and no large TURP defects. The implant must be performed after intensity-modulated radiotherapy.

- All implants will be performed under transrectal ultrasound guidance. Epidural, spinal, or general anesthesia may be used. Epidural analgesia may be used for pain control.
- At least 14 treatment catheters should be used to ensure adequate target coverage with acceptable dose heterogeneity.
- 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.

All patients will be treated with a single implant and single HDR fraction of 15 Gy. Treatment will be delivered within a single 24-hour period measured from the beginning of the implant procedure.

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. If contrast material is used, it should be diluted to 10% or less to minimize CT artifact. 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 and normal critical structures must be outlined on all CT slices including the prostate, penile bulb, urethra, bladder, and rectum.

- Transrectal ultrasound-based planning and treatment is acceptable. However, all implant dosimetry data must be submitted on a treatment planning CT scan and evaluation of the quality of the implant will be based on the CT using criteria defined below.
- 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.

- The CTV is the prostate gland and the seminal vesicles.
- Critical structures to be defined using CT planning include the bladder, rectum, urethra, and penile bulb within the volume of interest. The outermost extent of the bladder/rectal wall will define those structures. The urethra is defined by the outer surface of the Foley catheter.
    - 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.
    - Compliance Criteria: A prescription dose of 15 Gy in one fraction will be delivered to the PTV1. Ninety percent coverage of the PTV with the prescription dose is considered per protocol, ≥85% but <90% is considered variation acceptable, and <85% coverage is considered deviation unacceptable.
    - Catheter Position Verification: Visual inspection of the catheters prior to delivery of each treatment is required. Fluoroscopy or CT may be also 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 and normal critical structure 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.
    - Catheter Removal: After completion of the treatment all catheters will be removed.

5 Drug Therapy

5.1 Dosage and Administration

Treatment will be administered on an outpatient basis. All eligible patients receive neoadjuvant, concurrent, and adjuvant androgen deprivation therapy consisting of enzalutamide combined with a LHRH (luteinizing hormone releasing hormone) agent with radiation therapy. Use of both drugs is considered combined androgen blockade (CAB). Protocol treatment must begin within 14 weeks after enrollment. Radiotherapy should begin at least 8 weeks (+/- 1 week) after starting LHRH agonist injection.

5.1.1 Anti-Androgen Therapy: Enzalutamide

Timing: Enzalutamide therapy will begin within 0-7 days (can begin before or same day as, or after) of the date of the first LHRH agonist administration and continue for a total duration of 24 months. The total duration of administered anti-androgen therapy must be documented and submitted.

Description: Enzalutamide is a nonsteroidal androgen receptor antagonist developed by the pharmaceutical company Medivation/Astellas. The chemical name is 4-(3-(4-Cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro-*N*-methylbenzamide. Enzalutamide has approximately 9-fold greater binding affinity to the androgen receptor compared to the antiandrogen bicalutamide. As opposed to

bicalutamide, enzalutamide does not promote translocation of the androgen receptor to the nucleus and in addition prevents binding of the androgen receptor to DNA and to coactivator proteins. In two clinical trials in patients with metastatic castration-resistant prostate cancer pre- and post-docetaxel (PREVAIL and AFFIRM, respectively), enzalutamide demonstrated improvements in overall survival and was well-tolerated.

Supply: From Medivation/Astellas through NCCN's vendor CRMG

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

Administration: Enzalutamide is administered orally at a dose of 160 mg (for 40 mg capsules) per day. Enzalutamide can be taken with or without food. Swallow capsules whole. Do not chew, dissolve, or open the capsules.

Administration will be suspended only if there is an apparent or suspected reaction to the drug. During RT interruptions, enzalutamide will be continued. Any treatment interruptions or failure of the patient to comply with the prescribed medication schedule must be documented.

Toxicity: Consult the package insert for comprehensive toxicity information (Table 5).

Table 5: Adverse Reactions

	ENZALUTAMIDE (N=800)		PLACEBO (N=399)	
General Disorders	**Grade 1-4(%)**	**Grade 3-4(%)**	**Grade 1-4(%)**	**Grade 3-4(%)**
Asthenic Conditions	50.6	9.0	44.4	9.3
Peripheral Edema	15.4	1.0	13.3	0.8
Musculoskeletal and Connective Tissue Disorders				
Back Pain	26.4	5.3	24.3	4.0
Arthralgia	20.5	2.5	17.3	1.8
Musculoskeletal Pain	15.0	1.3	11.5	0.3
Muscular Weakness	9.8	1.5	6.8	1.8
Musculoskeletal Stiffness	2.6	0.3	0.3	0.0
Gastrointestinal Disorders				
Diarrhea	21.8	1.1	17.5	0.3
Vascular Disorders				
Hot Flush	20.3	0.0	10.3	0.0
Hypertension	6.4	2.1	2.8	1.3
Nervous System Disorders				
Headache	12.1	0.9	5.5	0.0
Dizziness	9.5	0.5	7.5	0.5
Spinal Cord Compression and Cauda Equina Syndrome	7.4	6.6	4.5	3.8
Paresthesia	6.6	0.0	4.5	0.0
Mental Impairment Disorders[d]	4.3	0.3	1.8	0.0

Hypoesthesia	4.0	0.3	1.8	0.0
Infections and Infestations				
Upper Respiratory Tract Infection[e]	10.9	0.0	6.5	0.3
Lower Respiratory Tract and Lung Infection[f]	8.5	2.4	4.8	1.3
Psychiatric Disorders				
Insomnia	8.8	0.0	6.0	0.3
Anxiety	6.5	0.3	4.0	0.0
Renal and Urinary Disorders				
Hematuria	6.9	1.8	4.5	1.0
Pollakiuria	4.8	0.0	2.5	0.0
Injury, Poisoning, and Procedural Complications				
Fall	4.6	0.3	1.3	0.0
Non-pathologic Fractures	4.0	1.4	0.8	0.3
Skin and Subcutaneous Tissue Disorders				
Pruritis	3.8	0.0	1.3	0.0
Dry Skin	3.5	0.0	1.3	0.0
Respiratory Disorders				
Epistaxis	3.3	0.1	1.3	0.3

The safety and tolerability of enzalutamide as monotherapy have been evaluated in a combined safety analysis including metastatic castration resistant prostate cancer patients from 2 large randomized, placebo-controlled phase 3 studies (PREVAIL and AFFIRM). Overall enzalutamide was generally well tolerated. In these studies, adverse events included fatigue, constipation, diarrhea, hot flush, asthenia, headache, insomnia, hypertension.

Dose Modifications: If a patient experiences a ≥ Grade 3 toxicity or an intolerable side effect, withhold dosing for one week and until symptoms improve to ≤Grade 2, then resume at the same or a reduced dose (120 mg or 80 mg), if warranted.

Drug-Drug Interactions: The concomitant use of strong CYP2C8 inhibitors should be avoided if possible. If patients must be co-administered a strong CYP2C8 inhibitor,

reduce the enzalutamide dose to 80 mg once daily. If co-administration of the strong inhibitor is discontinued, the enzalutamide dose should be returned to the dose used prior to initiation of the strong CYP2C8 inhibitor.

a) Drugs that inhibit or induce CYP2C8 - Co-administration of a strong CYP2C8 inhibitor (gemfibrozil) increased the composite area under the plasma concentration-time curve (AUC) of enzalutamide plus N-desmethyl enzalutamide by 2.2-fold in healthy volunteers. Co-administration of enzalutamide with strong CYP2C8 inhibitors should be avoided if possible. If co-administration of ENZALUTAMIDE with a strong CYP2C8 inhibitor cannot be avoided, reduce the dose of enzalutamide. The effects of CYP2C8 inducers on the pharmacokinetics of enzalutamide have not been evaluated *in vivo.* Co-administration of enzalutamide with strong or moderate CYP2C8 inducers (e.g., rifampin) may alter the plasma exposure of enzalutamide and should be avoided if possible. Selection of a concomitant medication with no or minimal enzalutamide induction potential is recommended.

b) Drugs that inhibit or induce CYP3A4 - Co-administration of a strong CYP3A4 inhibitor (itraconazole) increased the composite AUC of enzalutamide plus N-desmethyl enzalutamide by 1.3-fold in healthy volunteers.

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

c) Effect of enzalutamide on drug metabolizing enzymes

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

5.1.1 Leuprolide

For additional information, consult the package inserts.

Timing: The first leuprolide administration will occur together with the start of anti-androgen treatment 2 months (+/- 1 week) prior to the start of RT. The total duration of Leuprolide therapy will be 24 months and will be determined by the physician. The total administered duration as well as the specific agent used must be documented.

Description: Leuprolide is a long-acting analog of the native LHRH peptide and are effective at reducing serum testosterone.

Supply: Commercially available.

Storage: Leuprolide should be stored as directed by the commercial supplier.

Administration: By intramuscular injection. Any duration formulation (1, 3, 4, or 6-month based on the manufacturer) is permitted to allow the duration of hormonal therapy to total 24 months at the physician's discretion. The manufacturer's instructions should be followed.

Toxicity: Consult the package insert for comprehensive toxicity information. Class-related toxicity is generally a manifestation of the mechanism of action and related to low testosterone levels. In the majority of patients testosterone levels increase above normal in 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 leuprolide 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 liability, nausea, vomiting, and rarely, allergic generalized rash and difficulty breathing.

6 Study Procedures and Observations

6.1 Schedule of Procedures and Observations

Screening assessments must be performed within 8 weeks prior to the first dose of neoadjuvant androgen deprivation therapy. Any results falling outside of the reference ranges may be repeated at the discretion of the investigator. All on-study visit procedures are allowed **a window of ±14 days** unless otherwise noted. Treatment or visit delays for public holidays or weather conditions do not constitute a protocol violation.

A written, signed, informed consent form (ICF) and a Health Insurance Portability and Accountability Act (HIPAA) authorization must be obtained before any study-specific assessments are initiated. A copy of the signed ICF will be given to the subject and a copy will be filed in the medical record. The original will be kept on file with the study records.

All patients who are consented will be registered in OnCore®, the UCSF Helen Diller Family Comprehensive Cancer Center Clinical Trial Management System (CTMS). The system is password protected and meets HIPAA requirements.

6.1.1 Pretreatment Period

Patients will be seen for an initial consultation for discussion of treatment options. Once the patient has consented to enrollment onto study, all pre-study assessments must be

completed and eligibility verified by the clinical research coordinator prior to initiation of study treatment.

The Screening procedures and assessments must be completed within 14 weeks of the Day 1 Visit unless otherwise noted below.

- Detailed history and physical exam including height, weight, and baseline evaluation of symptoms, pain, and medications
- Baseline urinary, bowel, and sexual function will be assessed with the EPIC-26, PROMIS, and EQ-5D Questionnaires
- Liver transaminases for patients undergoing androgen deprivation therapy. AST or ALT must be < 2x upper limit of normal within 60 days of initiating androgen deprivation therapy.
- Total bilirubin
- MRI pelvis and prostate to define the extent of disease as part of routine staging for high risk prostate cancer and to aid in treatment planning.
- PSA should be obtained before or at least 20 days after prostate biopsy. The PSA half-life is approximately 2.2 days. The 20-day period will allow for approximately 9 half-lives to elapse, thus minimizing the flare effect from biopsy on actual PSA value. Also, every effort should be made to obtain all serum PSA values within the year prior to treatment for calculation of PSA kinetics.
- Testosterone level
- CBC with differential
- Basic metabolic panel
- Hepatitis B and C testing
- Fasting lipid panel, glucose level, and HbA1c
- Patients must also undergo 50 mL blood sample collection. Blood collection should be performed at time of PSA, testosterone, or other lab testing.
- TRUS biopsy – may be completed up to 25 weeks prior to enrollment.
- Collection of archival tissue from a prior prostate biopsy if available
- NaF PET/CT or Tc99m bone scan

6.1.2 4-6 weeks after initiation of Androgen Deprivation Therapy

- PSA level
- Testosterone level
- CBC with differential
- Basic metabolic panel
- AST, ALT, and total bilirubin
- Patients will undergo 50 mL blood collection at the time of lab testing.
- AE assessment
- After PSA testing, patients should undergo fiducial marker placement to optimize patient positioning and account for prostate motion during radiation treatment. During the fiducial marker procedure, a biopsy of the dominant lesion(s) should be

obtained. The additional risks and discomfort of the limited biopsy during the fiducial marker placement are minimal and include bleeding as a needle is already being introduced under ultrasound guidance for fiducial marker placement as part of the standard of care. If available, the biopsy should be mapped under MRI-guidance.

- Refer to section 5.0 for details regarding androgen deprivation therapy.

6.1.3 8 weeks after initiation of Androgen Deprivation Therapy

- Refer to section 4.0 for details regarding radiation therapy.
- Patients should complete the EPIC-26, PROMIS, and EQ-5D questionnaires up to 5 days before the first day of radiation therapy.
- AE assessment - all patients will undergo weekly assessment by the radiation oncologist for any signs of acute toxicity
- After 5 weeks of conventional whole pelvic radiotherapy, patients should complete the EPIC-26, PROMIS, and EQ-5D questionnaires.
- After 5 weeks of conventional whole pelvic radiotherapy, brachytherapy may be performed as part of the radiation boost procedure (phase 2). At the time of brachytherapy, a biopsy of the dominant lesion(s) may be performed. The risks and discomfort of the limited biopsy are minimal as multiple catheters (larger in diameter) are already being introduced under ultrasound guidance into the prostate as part of the HDR procedure.
- After 5 weeks of conventional whole pelvic radiotherapy and within the first 3 days of phase 2 boost procedure (days 1-3), 50 ml blood collection will be performed.

6.1.4 Post-Treatment Assessment

Patients will be assessed at 6 weeks after completion of radiotherapy, month 3-4, month 6, month 12, month 18, month 24, and at month 36 per standard of care. All toxicity and adverse events according to CTCAE v. 4.0 criteria will be documented. At each visit, the following will be collected:

- AE assessments
- Pertinent interval history and physical exam
- Urinary, bowel, and sexual function will be assessed weekly with the EPIC-26, PROMIS, EQ-5D questionnaires
- PSA and testosterone levels
- 50 mL Blood collection will be performed at the 3-4 month follow-up visit.
- Fasting lipid panel, glucose level, and HbA1c
- CBC with differential

- Basic metabolic panel
- AST, ALT, and total bilirubin
- PSA failure will be defined as PSA nadir + 2 ng/mL. At the time of PSA failure, workup will include bone scan and/or sodium fluoride PET/CT scan and MRI of the prostate to evaluate for a source of treatment failure. Distant metastases will be noted as any site located out of the true pelvis (i.e. out of radiation field). If a local recurrence is suspected within the prostate, a transrectal ultrasound-guided biopsy of the prostate is recommended. Local recurrence will be defined as recurrence within the prostate. Regional recurrence will be documented as any site in the pelvic lymph nodes within the radiation field.

6.1.5 Discontinuation of Therapy

If a patient experiences a ≥ Grade 3 toxicity or an intolerable side effect, withhold dosing for one week and until symptoms improve to ≤Grade 2, then resume at the same or a reduced dose (120 mg or 80 mg), if warranted.

In addition, the following safety/compliance events will result in the removal of patients from therapy either permanently or until the etiology of the problem has been identified and resolved:

- Any adverse event that is intolerable to the patient and that cannot be ameliorated by the use of adequate medical intervention, or that in the opinion of the investigator would lead to undue risk to the patient if dosing continued.
- Any seizure
- Creatinine >4.0 mg/dL
- Liver function tests (AST, ALT, or total bilirubin) >2 times the upper limit of normal
- An absolute neutrophil count ≤750/μL
- A platelet count of <50,000/μL
- Patients who are in the opinion of the investigator or the medical monitor non-compliant with the protocol's requirements

The Investigator will withdraw a patient whenever continued participation is no longer in the patient's best interests. Reasons for withdrawing a patient include, but are not limited to, disease progression, the occurrence of an adverse event or a concurrent illness, a patient's request to end participation, a patient's non-compliance or simply significant uncertainty on the part of the Investigator that continued participation is prudent. There may also be administrative reasons to terminate participation, such as concern about a patient's compliance with the prescribed treatment regimen.

Table 6: Schedule of Assessments

Study Assessments	**Pre-Radiation Treatment**		**During Radiation**	**Post-Radiation Treatment**
Time period	Baseline (Diagnosis)	4-6 week after initiation of ADT (at placement of fiducial marker)	At Time of Brachytherapy Procedure (After fractionated whole pelvic radiotherapy)	Each follow up visit (6 wk, month 3-4, month 6, month 12, month 18, month 24, and month 36)[a]
Detailed medical history and physical exam	X			X (pertinent interval history and physical exam)
Collection of archival biopsy tissue if available	X			
TRUS biopsy of dominant lesion(s)[b]	X	X	X	
Serum PSA, testosterone	X	X	X	X
CBC with differential	X	X	X	X
Basic Metabolic Panel	X	X	X	X
Liver Function Tests including AST, ALT, and Total Bilirubin	X	X	X	X
Hepatitis B and C Testing	X			
Fasting Lipid Panel, glucose level, and HbA1c	X			X
50 mL blood sample collection	Y	Y	Y	Y (month 3-4)
MRI prostate and pelvis	X			X (At time of PSA failure)
NaF PET/CT or Tc99m Bone Scan	X			X (At time of PSA failure)
EPIC-26, PROMIS, EQ-5D	X		X (Before start of radiation therapy and after 5 weeks of conventional pelvic radiotherapy)	X
AE assessments		X	Each week during external beam radiation therapy	X

X = Assessments as determined by standard of care; Y = Additional procedure as part of study

[a] Patients will be assessed at 6 weeks after completion of radiotherapy and then at least every 6 months thereafter for the first 2 years.

[b] TRUS biopsies are optional and at provider discretion

6.2 Usage of Concurrent/Concomitant Medications

Clinical discretion may be used in managing radiotherapy-related and androgen deprivation-related side effects.

Bowel: Patients will be asked to adhere to a low gas, low motility diet commencing one day prior to treatment. Patients experiencing diarrhea/rectal frequency/urgency may be managed initially with psyllium fiber supplements can be used to help increase bulkiness of bowel movements. If diarrhea persists, they may then be managed with diphenoxylate or loperamide.

Urinary: Bladder irritation may be mitigated with phenazopyridine. Urinary frequency/urgency can be managed with anticholinergic agents or alpha-blockers such as tamsulosin.

Erectile Dysfunction: Erectile dysfunction can be managed with phosphodiesterase (PDE) inhibitors such as sildenafil.

Abnormal liver function tests: If liver transaminases (AST) or (ALT) are >2x the upper limit of normal, the anti-androgen may be discontinued.

Hot flashes: Frequent and bothersome hot flashes can be managed with a serotonin-norepinephrine reuptake inhibitor, venlafaxine.

Bone Health: Osteopenia and minimization of risk of osteoporosis can be managed with Calcium + Vitamin D supplementation.

7 Reporting and Documentation of Results

7.1 Definitions

Evaluable for toxicity

All patients will be evaluable for toxicity from the time of their first treatment with the study drug until 24 months after last dose of enzalutamide treatment.

7.2 Evaluation of Safety

Analyses will be performed for all patients. The study will use the CTCAE v4.0 for reporting of adverse events.

Safety will be assessed through a summary of adverse events. The maximum severity of each adverse event assessed by NCI CTCAE v. 4.0 will be summarized using summary statistics, graphical techniques, and categorical methods. Shift tables using CTCAE grades will be used to compare baseline to on-treatment values.

7.3 Definitions of Adverse Events

7.3.1 Serious Adverse Event

The term “Serious Adverse Event” (or “SAE”) shall mean any adverse drug experience occurring at any dose that results in any of the following outcomes: death, is life threatening, as defined below, requires inpatient hospitalization or prolongation of an existing hospitalization, results in a persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, results in cancer, or results in an

important medical event. Important medical events which are AEs that may not result in death, be Life-Threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the Study Participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

All SAES must be reported to ORP [redacted].

7.3.2 Adverse reaction

An adverse reaction is defined as any adverse event caused by the use of a treatment or procedure. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the treatment or procedure caused the event. Adverse events will be followed up to 60 months post-initiation of androgen deprivation therapy.

7.3.2.1 Suspected

A suspected adverse reaction is defined as any adverse event for which there is a reasonable possibility that the treatment or procedure caused the adverse event. For the purposes of IND safety reporting, “reasonable possibility” indicates that there is evidence to suggest a causal relationship between the treatment or procedure and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

7.3.2.2 Unexpected

An adverse event or suspected adverse reaction is considered *unexpected* if it is not listed in the investigator brochure or package insert(s), or is not listed at the specificity or severity that has been observed, or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

“Unexpected,” as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of treatment or procedure or as anticipated from the pharmacological properties of the treatment or procedure, but are not specifically mentioned as occurring with the particular treatment or procedure under investigation.

Adverse events that would be anticipated to occur as part of the disease process are considered *unexpected* for the purposes of reporting because they would not be listed in the investigator brochure. For example, a certain number of non-acute deaths in a cancer trial would be anticipated as an outcome of the underlying disease, but such deaths would generally not be listed as a suspected adverse reaction in the investigator brochure.

Some adverse events are listed in the Investigator’s Brochure as occurring with the same class of treatment, or as anticipated from the pharmacological properties of the drug, even though they have not been observed with the drug under investigation. Such events would be considered *unexpected* until they have been observed with the drug

under investigation. For example, although angioedema is anticipated to occur in some patients exposed to drugs in the ACE inhibitor class and angioedema would be described in the investigator brochure as a class effect, the first case of angioedema observed with the drug under investigation should be considered *unexpected* for reporting purposes.

7.3.2.3 Life-threatening

An adverse event or suspected adverse reaction is considered *life-threatening* if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

7.4 Recording of an Adverse Event

All grade 3 and above adverse events will be entered into OnCore®, whether or not the event is believed to be associated with use of the study drug. Data about these events and their severity will be recorded using the NCI CTCAE v4.0.

The Investigator will assign attribution of the possible association of the event with use of the investigational drug, and this information will be entered into OnCore® using the classification system listed below:

Relationship	Attribution	Description
Unrelated to investigational drug/intervention	Unrelated	The AE *is clearly NOT related* to the intervention
	Unlikely	The AE *is doubtfully related* to the intervention
Related to investigational drug/intervention	Possible	The AE *may be related* to the intervention
	Probable	The AE *is likely related* to the intervention
	Definite	The AE *is clearly related* to the intervention

Signs or symptoms reported as adverse events will be graded and recorded by the Investigator according to the CTCAE. When specific adverse events are not listed in the CTCAE they will be graded by the Investigator as *none*, *mild*, *moderate* or *severe* according to the following grades and definitions:

Grade 0	No AE (or within normal limits)
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local, or noninvasive intervention (e.g., packing, cautery) indicated; limiting age-appropriate instrumental activities of daily living (ADL)
Grade 3:	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
Grade 4:	Life-threatening consequences; urgent intervention indicated
Grade 5:	Death related to AE

7.5 Follow-up of Adverse Events

All adverse events will be followed with appropriate medical management until resolved. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. For selected adverse events for which administration of the treatment or procedure was stopped, a re-challenge of the subject with the investigational treatment or procedure may be conducted if considered both safe and ethical by the Investigator.

7.6 Adverse Events Monitoring

All adverse events, whether or not unexpected, and whether or not considered to be associated with the use of the study drug, will be entered into OnCore®, as noted above.

The Investigator will assess all adverse events and determine reportability requirements to the UCSF Data and Safety Monitoring Committee (DSMC) and UCSF's Institutional Review Board, the Committee on Human Research (CHR); and, when the study is conducted under an Investigational New Drug Application (IND), to the Food and Drug Administration (FDA) if it meets the FDA reporting criteria.

All adverse events entered into OnCore® will be reviewed by the Helen Diller Family Comprehensive Cancer Center Site Committee on a weekly basis. The Site Committee will review and discuss at each weekly meeting the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of the treatment or procedure.

In addition, all adverse events and suspected adverse reactions considered "serious," entered into OnCore® will be reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at DSMC meetings which take place every six (6) weeks.

7.7 Expedited Reporting

Within 24 hours of awareness of a serious adverse event, whether or not related to the study drug, the Investigator will complete and submit a Medwatch 3500A Form to FDA, containing all required information (reference 21 CFR 312.32). The Investigator will submit a copy of this MedWatch 3500A form to Astellas by either e-mail or fax, within the

same timeframe. If submission of this SAE to FDA, NCCN or Astellas is not possible within 24 hours, the Investigator's local drug safety contact (IRB, etc.) should be informed by phone.

The SAE documentation, including the Medwatch 3500A Form and available source records should be emailed or faxed to:

- Astellas Pharma Global Development – United States
- Email: [redacted]
- Fax number: [redacted]

In addition, email or fax to NCCN [redacted]. The following minimum information is required:

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

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

Reporting to the Data and Safety Monitoring Committee

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the treatment or procedure and it is determined to be related either to the treatment or procedure, the Investigator or his/her designee must notify the DSMC Chair (or qualified alternate) within 1 business day of knowledge of the event. The contact may be by phone or e-mail.

Reporting to UCSF Committee on Human Research (Institutional Review Board)

The Principal Investigator must report events meeting the UCSF CHR definition of "Unanticipated Problem" (UP) within 5 business days of his/her awareness of the event.

8 Tissue/Specimen Collection

8.1 Specimen Collection Summary for Translational Research

Specimens Taken From Patient	Time of Collection
Diagnostic Core Biopsy Specimen(s)	1) Pre-treatment 2) 4-6 wks after initiation of androgen deprivation therapy (at time of fiducial marker placement) 3) At the time of brachytherapy (if brachytherapy is being performed)
Whole blood: 50 mL of whole blood will be collected into green top tubes (sodium heparin). This should be collected, if possible, at the time of each blood draw for PSA and testosterone.	1) Pre-Treatment 2) 4-6 wks after initiation of androgen deprivation therapy (at time of fiducial marker placement) 3) Within first 3 days of phase 2 brachytherapy 4) Month 3-4 post-radiation therapy

Core biopsy specimens will be snap frozen in liquid nitrogen and stored at -80°C.

Plasma and whole blood samples will be processed and stored frozen at -80°C.

All samples will be de-identified and labeled with a case number. Samples will be sent frozen on dry ice via overnight carrier stored in a locked -80 °C freezer.

8.1.1 Plasma/Serum/Peripheral Blood Mononuclear Cell (PMBC) Banking

Immediately prior to each time point indicated above, the clinical research coordinator will assign unique specimen log numbers to be written on the specimen vials; this will ensure patient confidentiality. At the specified time points, 50 cc of whole blood will be collected in one green (sodium heparin) top tube that has been properly labeled with the unique specimen log number provided and stored at –80°C.

8.1.2 Tumor biopsy

Image guided biopsies will be performed prior to any treatment as part of the patient's diagnosis (may be performed up to 180 days prior to registration to confirm diagnosis of adenocarcinoma of the prostate; archival tissue will be collected if available), at 5 weeks post-initiation of enzalutamide therapy at the time of gold marker placement, and after 5 weeks of external beam radiation therapy at the time of brachytherapy (if patient decides to undergo brachytherapy). The biopsies will be performed by urologic surgical oncology and radiation oncology under transrectal ultrasound guidance with a 16-18 gauge needle. There will be minimal risk to these biopsies as similar or larger-gauge needles are already being inserted for fiducial marker placement (routinely used for daily setup for external beam radiation therapy) and HDR brachytherapy. Core biopsies will be extracted and will be immediately frozen on a pre-frozen bed of OCT (Optimal Cutting Temperature compound used for frozen sections), covered with additional OCT, and kept on dry ice or at –80°C.

All biopsies and blood samples will be delivered to the laboratory of Dr. Lawrence Fong at UCSF, [redacted] or to the laboratory of Dr. Hao Nguyen at UCSF, [redacted]. Both locations are secured, locked rooms with a locked liquid nitrogen storage tank and –80°C freezer. These samples will receive a patient-insensitive identifier and the link to patient identity will be kept in a locked file with access only by the principal investigators and the clinical research coordinator. Other co-investigators will have access to samples by submitting a request to the Committee on Human Research. Patients have the right at any time to request that all remaining samples be destroyed. Patients will be asked to consent to future, additional research on stored samples. Additional written consent will be required if additional samples are to be taken.

Deep whole exome sequencing of the tumor specimens with matched germ line samples (blood) will be performed on paired samples pre- and 5 weeks post-initiation enzalutamide treatment. The results will be compared across patients that do and do not obtain a biochemical complete response. Whole exome sequencing will allow for the identification of mutations, insertions/deletions, and copy number alterations involved in enzalutamide resistance. For exome sequencing, exons will be captured in solution from one microgram of sonicated genomic DNA using an Agilent SureSelect target capture system. Libraries of captured exons will be sequenced using 75 bp paired-end sequencing on an Illumina HiSeq with a goal of 100X coverage. Libraries will be constructed with indexing to allow sequencing of 3 or more exomes/lane. Computational analysis will of raw exome data will be performed as described by our group. Somatic point mutations and indels nominated as clinically informative will be amplified and sequenced for validation.

Total RNA will be extracted, amplified, fragmented, and labeled. Gene expression profiling will be performed with the Affymetrix GeneChip Human Transcriptome Array 2.0. This microarray chip assesses the expression of over 1.4 million RNA features including ~22,000 known protein-coding genes as well as many thousands of non-coding RNAs. This will allow us to examine relative gene expression, splice variants, and immune response signatures.

9 Statistical Considerations and Evaluation of Results

9.1 Study Design

Phase II single arm study evaluating the potential efficacy in improving the PSA-CR with combined enzalutamide and leuprolide therapy in patients with high-risk prostate cancer or pelvic node involvement undergoing definitive radiation therapy. Also the safety and feasibility of combined enzalutamide and leuprolide therapy in patients undergoing radiation therapy will be determined.

9.2 Determination of Sample Size and Accrual Rate

9.2.1 Sample Size and Power Estimate

Sample size is determined based on the primary objective of the PSA-CR. This is a single arm study with the primary endpoint evaluating the proportion of patients experiencing a PSA-CR. From historical controls (RTOG 9413 and MSKCC as mentioned in background information), we expect 70% of patients to experience a PSA-CR. With addition of enzalutamide, at least 85% of patients are expected to attain a PSA-CR. With 53 patients (10% dropout rate), we would have 80% power to detect thus improvement at significance level of 0.05 based on directional binomial test.

As we expect the combined enzalutamide and leuprolide regimen does not significantly increase grade 3 or greater acute or late toxicity for treatment of intermediate- to high-risk prostate cancer and the usual rate of 3 or greater toxicity is approximately 12%. If the true grade 3 or greater acute or late toxicity rate is 12%, with 47 patients we will have 80% confidence in the toxicity rate estimate with precision of 4.7% (i.e. a confidence interval width of 9.4%).

9.2.2 Accrual estimates

A total of 53 patients with very high-risk prostate cancer or with pelvic nodal involvement without distant metastases will be enrolled. Study accrual is anticipated to be approximately 3 patients per month, with a goal complete accrual by 24 months.

9.3 Interim Analyses and Stopping Rules

Continuous safety monitoring will be performed throughout the trial. The trial will be terminated if there is a greater 12% acute grade 3 toxicity. This rate is acceptable as prior studies have demonstrated 8-15% acute grade 3 GU and GI toxicity when irradiating the pelvis using standard fractionated technique to 45 Gy in 1.8 Gy fractions followed by brachytherapy boost

9.4 Analyses Plans

9.4.1 Analysis Population

Analyses will be performed for all patients. The study will use the NCI CTCAE v4.0.

9.4.2 Primary Analysis (or Analysis of Primary Endpoints)

Point estimates and 95% confidence intervals of PSA-CR will be obtained. The PSA-CR will be compared with the historical rate by binomial test.

Toxicity will be assessed by CTCAE v4.0. Point estimation and its 95% confidence interval will be calculated for the rate of acute Grade 3 or greater toxicity within 24 months of completing treatment with radiotherapy. Furthermore, one sample proportion test will be used to test hypothesis that the addition of enzalutamide to leuprolide and radiation therapy does not significantly increase acute or late toxicity.

9.4.3 Secondary Analysis (or Analysis of Secondary Endpoints)

The time to local failure will be defined from the date of randomization to the date of biopsy proven recurrence within the prostate gland. The distribution of the time to event data will be estimated by Kaplan-Meier method.

The time to clinical progression will be defined from the date of randomization to the date of PSA failure, local failure, regional or distant metastases. Deaths prior to any of these events are treated as censoring for this endpoint. The distribution of the time to event data will be estimated by Kaplan-Meier method.

To assess PSA nadir, PSA, testosterone levels, HbA1c, fasting glucose, fasting insulin and fasting lipid and cholesterol levels at each time point, the summary statistics for continuous variables will be used.

To assess their changes across the time, the random effect model for longitudinal data will be used for each outcome measurement.

Patient-reported quality of life outcomes will be assessed by EPIC, PROMIS, and EQ-5D questionnaires and will be described by summary statistics for categorical data.

10 Study Management

10.1 Pre-study Documentation

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as stated in 21 CFR §312.120(c)(4); consistent with GCP and all applicable regulatory requirements.

Before initiating this trial, the Investigator will have written and dated approval from the Institutional Review Board for the protocol, written informed consent form, subject recruitment materials, and any other written information to be provided to subjects before any protocol related procedures are performed on any subjects.

The clinical investigation will not begin until either FDA has determined that the study under the Investigational Drug Application (IND) is allowed to proceed or the Investigator has received a letter from FDA stating that the study is exempt from IND requirements.

The Investigator must comply with the applicable regulations in Title 21 of the Code of Federal Regulations (21 CFR §50, §54, and §312), GCP/ICH guidelines, and all applicable regulatory requirements. The IRB must comply with the regulations in 21 CFR §56 and applicable regulatory requirements.

10.2 Institutional Review Board Approval

The protocol, the proposed informed consent form, and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the UCSF CHR (UCSF Institutional Review Board). Prior to obtaining CHR approval, the protocol must be approved by the Helen Diller Family Comprehensive Cancer Center Site Committee and by the Protocol Review Committee (PRC). The initial protocol and all protocol amendments must be approved by the IRB prior to implementation.

10.3 Informed Consent

All participants must be provided a consent form describing the study with sufficient information for each participant to make an informed decision regarding their participation. Participants must sign the CHR-approved informed consent form prior to participation in any study specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

10.4 Changes in the Protocol

Once the protocol has been approved by the UCSF CHR, any changes to the protocol must be documented in the form of an amendment. The amendment must be signed by the Investigator and approved by PRC and the CHR prior to implementation.

If it becomes necessary to alter the protocol to eliminate an immediate hazard to patients, an amendment may be implemented prior to CHR approval. In this circumstance, however, the Investigator must then notify the CHR in writing within five (5) working days after implementation. The Study Chair and the UCSF study team will be responsible for updating any participating sites.

10.5 Handling and Documentation of Clinical Supplies

The UCSF Principal Investigator and each participating site will maintain complete records showing the receipt, dispensation, return, or other disposition of all investigational drugs. The date, quantity and batch or code number of the drug, and the identification of patients to whom study drug has been dispensed by patient number and initials will be included. The sponsor-investigator will maintain written records of any disposition of the study drug.

The Principal Investigator shall not make the investigational drug available to any individuals other than to qualified study patients. Furthermore, the Principal Investigator will not allow the investigational drug to be used in any manner other than that specified in this protocol.

10.6 Case Report Forms (CRFs)

The Principal Investigator and/or his/her designee, will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific Case Report Forms (CRFs) will document safety and treatment outcomes for safety monitoring and data analysis. All study data will be entered into OnCore® via standardized CRFs in accordance with the CTMS study calendar, using single data entry with a secure access account. The Clinical Research Coordinator (CRC) will complete the CRFs as soon as possible upon completion of the study visit; the Investigator will provide oversight.

The information collected on CRFs shall be identical to that appearing in original source documents. Source documents will be found in the patient's medical records maintained by UCSF personnel. All source documentation should be kept in separate research folders for each patient.

In accordance with federal regulations, the Investigator is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto CRFs. The PI will approve all completed CRFs to attest that the information contained on the CRFs is true and accurate.

All source documentation and CTMS data will be available for review/monitoring by the UCSF DSMC and regulatory agencies.

The Principal Investigator will be responsible for ensuring the accurate capture of study data. At study completion, when the CRFs have been declared to be complete and accurate, the database will be locked. Any changes to the data entered into the CRFs after that time can only be made by joint written agreement among the Study Chair, the Trial Statistician, and the Protocol Project Manager.

Each participating site will complete study specific CRFs for safety monitoring and data analysis. Each site will enter the study data into OnCore® via standardized CRFs in accordance with the CTMS study calendar, using single data entry with a secure access account. The participating site's Clinical Research Coordinator (CRC) will complete the

CRFs; the Investigator will review and approve the completed CRFs – this process must be completed within 10 business days of the visit. Study data from the participating site will be reported and reviewed in aggregate with data from patients enrolled at the coordinating center, UCSF. All source documentation and CTMS data will be available for review/monitoring as needed.

10.7 Oversight and Monitoring Plan

The UCSF Helen Diller Family Comprehensive Cancer Center DSMC will be the monitoring entity for this study. The UCSF DSMC will monitor the study in accordance with the NCI-approved Data and Safety Monitoring Plan (DSMP). The DSMC will routinely review all adverse events and suspected adverse reactions considered "serious". The DSMC will audit study-related activities to ensure that the study is conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). Significant results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as applicable. See Appendix 2 Data and Safety Monitoring Plan for a Phase 2 or 3 Institutional Study, for additional information.

10.8 Record Keeping and Record Retention

The Principal Investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects, as well as written records of the disposition of the drug when the study ends.

The Principal Investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

Study documentation includes all CRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, CHR correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

In accordance with FDA regulations, the investigator shall retain records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

11 Protection of Human Subjects

11.1 Protection from Unnecessary Harm

Each clinical site is responsible for protecting all subjects involved in human experimentation. This is accomplished through the CHR mechanism and the process of informed consent. The CHR reviews all proposed studies involving human experimentation and ensures that the subject's rights and welfare are protected and that the potential benefits and/or the importance of the knowledge to be gained outweigh the risks to the individual. The CHR also reviews the informed consent document associated with each study in order to ensure that the consent document accurately and clearly communicates the nature of the research to be done and its associated risks and benefits.

11.2 Protection of Privacy

Patients will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. Following this discussion, they will be asked to sign the HIPAA form and informed consent documents. The original signed document will become part of the patient's medical records, and each patient will receive a copy of the signed document. The use and disclosure of protected health information will be limited to the individuals described in the informed consent document.

REFERENCES:

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Appendices

Appendix 1 Performance Status Criteria

ECOG (Zubrod) Performance Status Scale	
Grade	Descriptions
0	Normal activity Fully active, able to carry on all pre-disease performance without restriction
1	Symptoms, but ambulatory Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work)
2	In bed < 50% of the time Ambulatory and capable of all self-care, but unable to carry out any work activities Up and about more than 50% of waking hours
3	In bed > 50% of the time Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	100% bedridden Completely disabled Cannot carry on any self-care Totally confined to bed or chair
5	Dead

Appendix 2 Data and Safety Monitoring Plan for Multicenter Institutional Study (Phase 2 or 3 Institutional Study)

The UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) Data and Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and subject safety for all HDFCCC institutional clinical studies. A summary of DSMC activities for this study includes:

- Review of subject data
- Review of suspected adverse reactions considered "serious"
- Monthly monitoring (depending on study accrual)
- Minimum of a yearly regulatory audit

Monitoring and Reporting Guidelines

All institutional Phase 2 or 3 therapeutic studies are designated with a moderate risk assessment. The data is monitored every six months, with twenty percent of the subjects monitored (or at least three subjects if the calculated value is less than three).

The UCSF Coordinating Center provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. The UCSF Coordinating Center will also coordinate quarterly conference calls with the participating sites to communicate the review of adverse events, safety data, and other study matters.

The Principal Investigator at the UCSF Coordinating Center will hold the role of Study Chair. The Study Chair is responsible for the overall conduct of the study and for monitoring its safety and progress at all participating sites. The Study Chair will conduct continuous review of data and subject safety and discuss each subject's treatment at monthly UCSF Site Committee meetings. The discussions are documented in the UCSF Site Committee meeting minutes.

<u>Multicenter communication</u>

The UCSF Coordinating Center provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. The UCSF Coordinating Center will also coordinate, at minimum, monthly conference calls with the participating sites at the completion of each cohort or more frequently as needed to discuss risk assessment. The following issues will be discussed as appropriate:

- Enrollment information
- Adverse events (i.e. new adverse events and updates on unresolved adverse events and new safety information)
- Protocol violations
- Other issues affecting the conduct of the study

Adverse events reporting to the DSMC will include reports from both the UCSF Coordinating Center, as well as the participating sites. The DSMC will be responsible for monitoring all data entered in OnCore® at the UCSF Coordinating Center and the participating sites. The data (i.e. copies of source documents) from the participating sites will be sent electronically or faxed over to the UCSF Coordinating Center prior to

the monitoring visits in order for the DSMC to monitor the participating site's compliance with the protocol, patient safety, and to verify data entry.

Adverse Event Review and Monitoring

Adverse Event Monitoring

All Grade 3-5 Adverse Events, whether or not unexpected, and whether or not considered to be associated with the use of study drug, will be entered into OnCore®, UCSF's Clinical Trial Management System.

All Grade 3-5 adverse events entered into OnCore® will be reviewed on a monthly basis at the UCSF Site Committee meetings. All clinically significant adverse events must be reported to the UCSF Coordinating Center by the participating sites within 10 business days of becoming aware of the event or during the next scheduled quarterly conference call, whichever is sooner. The UCSF Site Committee will review and discuss the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of the study drug(s) from the UCSF Coordinating Center and the participating sites.

In addition, all suspected adverse reactions considered "serious" must be entered in OnCore® and reported to the UCSF Coordinating Center within 1 business day. The suspected adverse reactions considered "serious" will be reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at the DSMC meeting, which take place every six (6) weeks.

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and is determined to be related either to the investigational drug or any research related procedure, the Study Chair at the UCSF Coordinating Center or the assigned designee must be notified within 1 business day from the participating site(s) and the Study Chair must then notify the DSMC Chair or qualified alternate within 1 business day of this notification. The contact may be by phone or e-mail.

Increase in Adverse Event Rates

If an increase in the frequency of Grade 3 or 4 adverse events (above the rate reported in the Investigator Brochure or package insert), the Study Chair at the UCSF Coordinating Center is responsible for notifying the DSMC at the time the increased rate is identified. The report will indicate if the incidence of adverse events observed in the study is above the range stated in the Investigator Brochure or package insert.

If at any time the Study Chair stops enrollment or stops the study due to safety issues, the DSMC Chair and DSMC Manager must be notified within 1 business day via e-mail. The DSMC must receive a formal letter within 10 business days and the CHR must be notified.

Data and Safety Monitoring Committee Contacts:

DSMC Chair:	[redacted]	DSMC Monitors
Phone:	[redacted]	Box 0128
Email:	[redacted]	UCSF Helen Diller Family Comprehensive Cancer Center
Address:	Box 1705 UCSF San Francisco, CA 94158	San Francisco, CA 94143

* DSMP approved by NCI 09/February2012

Appendix 3 UCSF Policy/Procedure for Required Regulatory Documents for a UCSF Multicenter Investigator-Initiated Oncology Clinical Trials with an Investigator held Investigational New Drug (IND)

Purpose

This policy defines the required Regulatory Documents for Single Site and Multicenter Investigator Initiated Oncology Clinical Trials at the Helen Diller Family Comprehensive Cancer Center (HDFCCC) where the Principal Investigator (PI) holds the IND.

Background

The International Conference on Harmonization (ICH) Good Clinical Practices (GCP) Guidelines define Essential Regulatory Documents as those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of data produced. These documents serve to demonstrate compliance with standards of GCP and with all applicable regulatory requirements. Filing essential documents in a timely manner can greatly assist in the successful management of a clinical trial.

The Regulatory Documents will consist of electronic files in both iMedRIS and OnCore®, as well as paper files in the Regulatory Binders for both the Coordinating Site and the Participating Site(s) in the HDFCCC Investigator Initiated Oncology Clinical Trials.

Procedures

1. HDFCCC Essential Regulatory Documents

Documents Filed in iMedRIS:

- CHR approvals for initial submission of application, all modifications, and continuing annual renewals
- Current and prior approved protocol versions with signed protocol signature page(s)
- Committee for Human Research (CHR) approval letters and Informed Consent Form(s) (ICF)
- Current and prior versions of the Investigator Brochure (IB).
- Serious Adverse Event Reporting
- Protocol Violations and Single Patient Exception (SPE) Reports to CHR with supporting fax documentation

Documents Filed in OnCore®:

- Package Insert (if the study drug is commercial) or Investigator Brochure
- Protocol Review Committee (PRC) approved protocols, protocol amendments and Summary of Changes (SOC)
- Patient handouts
- Screening/enrollment log
- Data and Safety Monitoring Committee (DSMC) monitoring reports
- OnCore® Case Report Form (CRF) completion manual

Documents Filed in Regulatory Binder:

- Completed Food and Drug Administration (FDA) 1572 document with Principal Investigator's signature
- For all Principal Investigators and Sub-Investigators listed on the FDA 1572, will need Financial Disclosure Forms, CVs, MD Licenses, Drug Enforcement Agency (DEA) Licenses, and Staff Training Documents (i.e. Collaborative Institute Training Initiative (CITI), etc.)
- Site Initiation Visit (SIV) minutes and correspondence with participating site(s).
- As applicable, approvals for Biosafety Committee, Radiation Committee, and Infusion Center
- Serious Adverse Event (SAE) reports to CHR and sponsor.
- MedWatch reporting to FDA and sponsor
- Delegation of Authority Form
- Drug Destruction Standard Operating Procedure (SOP)
- For all laboratories listed on the FDA 1572, will need CLIA certifications, CAP certifications, lab licenses, CVs of Lab Directors, and laboratory reference ranges

2. Additional Essential Documents for Multicenter Trials for the Coordinating Center (filed in Regulatory Binder or OnCore)

- Institutional Review Board (IRB) approval letters, IRB roster, Informed Consent Form (ICF), and Health Insurance Portability and Accountability Act (HIPAA) Consent Form for the Participating Site(s)
- For all Principal Investigators and Sub-Investigators listed on the 1572 at the Participating Site(s) – Financial Disclosure Forms, CVs, MD Licenses, and Staff Training documents (i.e. Collaborative Institute Training Initiative (CITI), etc.) (for Investigational New Drug Application
- Site Initiation Visit (SIV) minutes and correspondence with Participating Site(s).
- As applicable, approvals for Biosafety Committee, Radiation Committee, and Infusion Center for the Participating Site(s)
- Protocol Violations and Single Patient Exception (SPE) reports to IRB with supporting fax documentation for Participating Site(s)
- Drug Destruction Standard Operating Procedure (SOP) for the Participating Site(s)
- Data and Safety Monitoring Committee (DSMC) monitoring reports for the Participating Site(s)
- For all laboratories listed on FDA 1572, will need CLIA certifications, CAP certifications, lab licenses, CVs of Lab Directors, and laboratory reference ranges for the Participating Site(s)
- Copy of the Data and Safety Monitoring Plan (DSMP) Monitoring Plan for all participating site(s) in Multicenter studies or Contract Research Organization (CRO) Monitoring Plan (if an outside CRO is used for the study)
- Serious Adverse Event (SAE) forms submitted to both the IRB and the sponsor for the Participating Site(s)

Required Regulatory Documents for Sub-sites Participating in a UCSF Investigator Initiated Multicenter Trial (Checklist)

Directions:

1) Fax the documents listed below to the UCSF Coordinating center [redacted] *or*

2) Scan the documents and upload to OnCore® and create a Note to File for the on-site Regulatory binder to indicate where these documents may be found

1572

☐ PI and Sub investigators:

CV and Medical license

Financial disclosure form

NIH or CITI human subject protection training certification

☐ Laboratories

CLIA and CAP

CV of Lab Director and Lab Licenses

Laboratory reference ranges

Local Institutional Review Board

☐ IRB Approval letter

☐ Reviewed/Approved documents

- Protocol version date: _____
- Informed consent version date: _____
- Investigator Brochure version date: _____
- HIPAA

☐ Current IRB Roster

Other

☐ Delegation of Authority Log

- Include NIH or CITI human subject protection training certificates or GCP training certification

☐ Pharmacy

- Drug destruction SOP and Policy

☐ Protocol signature page

☐ Executed sub contract