

Neoadjuvant Androgen Deprivation Therapy and Chemotherapy followed by Radical Prostatectomy in Patients with Prostate Cancer

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**Neoadjuvant Androgen Deprivation Therapy and Chemotherapy followed by
Radical Prostatectomy in Patients with Prostate Cancer**

Protocol No: GU-14-101

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The study is to be conducted according to the protocol and in compliance with Good Clinical Practice (GCP) and other applicable regulatory requirements.

Signature: _____ Date: _____
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PROTOCOL SYNOPSIS

TITLE	Neoadjuvant Androgen Deprivation Therapy and Chemotherapy followed by Radical Prostatectomy in Patients with Prostate Cancer
PROTOCOL NUMBER	GU-14-101
PHASE OF DEVELOPMENT	Phase 2
STUDY OBJECTIVES	<p>Primary Objective To assess rates of complete pathologic response or near-complete pathologic response of androgen deprivation therapy (ADT) plus chemotherapy prior to radical prostatectomy in prostate patients presenting with localized high-risk prostate cancer.</p> <p>Secondary Objectives</p> <ul style="list-style-type: none">• To assess the efficacy of therapy prior to prostatectomy based on:<ul style="list-style-type: none">○ Prostate-specific antigen (PSA) response○ Circulating tumor cell (CTC) response○ Volume and perfusion of the prostate utilizing multiparametric prostate magnetic resonance imaging (mpMRI)• To assess the safety of preoperative administration of ADT and chemotherapy• To assess the surgical morbidity following therapy with ADT and chemotherapy <p>Tertiary Objective To assess the effect of ADT and chemotherapy administered in the neoadjuvant setting on the natural disease history of patients with locally advanced prostate cancer who undergo radical prostatectomy</p>
STUDY DESIGN	<p>This is an open-label, single-arm of neoadjuvant ADT and chemotherapy in subjects with non-metastatic, locally-advanced prostate cancer who are eligible for radical prostatectomy.</p> <p>Patients will be treated with 4 monthly injections of degarelix along with two 8-week cycles of chemotherapy. Each cycle of chemotherapy will consist of 6 weeks of chemotherapy and 2 weeks of rest. In the absence of toxicity or disease progression, patients will receive 2 cycles of treatment prior to radical prostatectomy.</p> <p>The primary endpoint will be complete or near-complete pathologic response.</p> <p>Safety will be assessed on any patient receiving at least one dose of study drug by the reporting of adverse events, vital signs and by the assessment of findings on physical exam and routine safety laboratory determinations. The severity of adverse events and certain abnormal laboratory findings will be assessed according to the NCI CTCAE V4.03.</p> <p>Laboratory-based studies will evaluate the following:</p> <ul style="list-style-type: none">• Complete metabolic profile<ul style="list-style-type: none">○ BUN, creatinine, alkaline phosphatase, ALT/AST, total

	<p>bilirubin, LDH, calcium, albumin, glucose, magnesium, uric acid, phosphorous</p> <ul style="list-style-type: none"> • Electrolytes <ul style="list-style-type: none"> ○ Sodium, potassium, chloride, CO₂ content • Hematology <ul style="list-style-type: none"> ○ CBC with differential, platelet count ○ PT, INR, PTT • Testosterone • Biomarkers <ul style="list-style-type: none"> ○ PSA ○ CTCs
NUMBER OF PATIENTS	Up to 24 evaluable patients
INCLUSION CRITERIA	<ul style="list-style-type: none"> • Pathologic proof of prostatic adenocarcinoma without evidence of regional and/or distant metastasis, clinical stage T1c or T2a with high grade disease (Gleason 8-10) on initial biopsy, clinical stage T2b-T2c with Gleason grade 7 (4+3), or clinical stage T3. No neuroendocrine differentiation or small cell features. • Recent (<6 weeks prior to study entry) negative bone scan and CT of the chest and abdomen. • Appropriate surgical candidate for radical prostatectomy and a performance status of <2 (ECOG scale). • Adequate bone marrow function as defined as an absolute peripheral granulocyte count >1500 and platelet count >100,000. • Adequate hepatic function per the following criteria: <ul style="list-style-type: none"> ○ Albumin ≥2.8 g/dL ○ AST and ALT ≤5 x ULN ○ Total bilirubin <2 mg/dL • Adequate renal function per the following criteria: <ul style="list-style-type: none"> ○ Serum creatinine ≤1.5 x ULN • Normal coagulation profile (INR ≤ 1.5, aPTT ≤ 1.5 x ULN for the lab) and no history of substantial non-iatrogenic bleeding diatheses. Use of anticoagulants is limited to local use only (for control of central line patency). • Age ≥ 18 years • Written informed consent to participate in this study.
EXCLUSION CRITERIA	<ul style="list-style-type: none"> • Prostatic adenocarcinoma with neuroendocrine differentiation or small cell features • Surgical resection or major surgery within 4 weeks or stereotactic biopsy within 1 week of first ADT and chemotherapy treatment • Previous or current hormonal treatment, chemotherapy, radiation therapy, immunotherapy, or investigational study drug. • Unable to tolerate multiparametric MRI or is contraindicated. • Patients not appropriate surgical candidates for radical prostatectomy based on the evaluation of coexistent medical diseases and competing causes of death. • Patients with uncontrolled cardiac, hepatic, renal, or neurologic/psychiatric disorder. • Severe gastrointestinal bleeding within 12 weeks of treatment with

	<p>ADT and chemotherapy</p> <ul style="list-style-type: none"> • Patients who are HIV positive or have chronic hepatitis B or C infections. • Congestive heart failure New York Heart Association (NYHA) class 3 or 4, or history of congestive heart failure New York Heart Association (NYHA) class 3 or 4, unless a 2D echocardiogram or multi-gated acquisition scan (MUGA) performed within 3 months of enrollment demonstrates a left ventricular ejection fraction >45%. • Sensory neuropathy grade >1. • History of another malignancy within the previous 5 years other than curatively treated non-melanoma skin cancer. • Use of herbal products that may decrease PSA levels (e.g., saw palmetto) or systemic corticosteroids greater than the equivalent of 10 mg of prednisone per day within 4 weeks of enrollment. • Any other condition, including concurrent medical condition, social circumstance or drug dependency, which in the opinion of the investigator could compromise patient safety and/or compliance with study requirements
<p>DURATION OF TREATMENT AND STUDY PARTICIPATION</p>	<p>Patients may remain on study for two 8-week cycles or until any of the following:</p> <ul style="list-style-type: none"> • Progressive disease • Initiation of treatment with an alternative therapy • Patient withdraws consent to continue in the trial • Patient develops an adverse event or intercurrent condition that precludes further participation or requires a prohibited treatment • The investigator withdraws the subject in the subject's best interest • The subject is lost to follow-up
<p>STUDY DRUG ADMINISTRATION</p>	<p>Treatment will be ADT plus chemotherapy.</p> <ul style="list-style-type: none"> • ADT Patients will be treated with degarelix monthly for 4 months. • Chemotherapy Patients will receive two 8-week cycles of chemotherapy (6 weeks of chemotherapy followed by 2 weeks of rest). In weeks 1, 3, and 5, patients will receive doxorubicin (20 mg/m² as a 24-hour intravenous infusion on day 1 of each applicable week) and ketoconazole (400 mg orally 3 times daily for 7 days); in weeks 2, 4, and 6, patients will receive docetaxel (35 mg/m² intravenously on day 1 of each applicable week) and estramustine (280 mg orally 3 times daily for 7 days). <p>Patients will be pretreated with dexamethasone 4 mg p.o. b.i.d. 24 hours pre- docetaxel, day of docetaxel administration, and 24 hours post-docetaxel. Ondansetron 8 mg p.o. and diphenhydramine 25 mg i.v. 30 minutes prior to docetaxel infusion.</p>

	<p>Maintenance hydrocortisone (20 mg morning and 10 mg afternoon) will be administered daily throughout chemotherapy to counteract potential ketoconazole-induced adrenal complications. To increase absorption, 250 mg of vitamin C is coadministered with ketoconazole.</p> <ul style="list-style-type: none"> • Androgen Deprivation Therapy Patients will be treated with degarelix for 4 months starting week 1. <table border="1" data-bbox="521 537 1425 1222"> <thead> <tr> <th colspan="2">Agent</th> <th colspan="6">Dose and Schedule</th> </tr> </thead> <tbody> <tr> <td colspan="2"><u>Chemotherapy</u></td> <td colspan="6">8-week cycle of chemotherapy</td> </tr> <tr> <td colspan="2">Doxorubicin (ADRIA)</td> <td colspan="6">20 mg/m² CIV over 24 h on days 1, 15, 29</td> </tr> <tr> <td colspan="2">Ketoconazole (KETO)</td> <td colspan="6">400 mg p.o. t.i.d. on days 1-7, 15-21, 29-35</td> </tr> <tr> <td colspan="2">Docetaxel (TAXOT)</td> <td colspan="6">35 mg/m² IVPB on days 8, 22, 36</td> </tr> <tr> <td colspan="2">Estramustine (EMCYT)</td> <td colspan="6">280 mg p.o. t.i.d on days 8-14, 22-28, 36-42</td> </tr> <tr> <td colspan="2">Hydrocortisone</td> <td colspan="6">20 mg p.o. a.m. & 10 mg p.o. p.m. EVERY DAY</td> </tr> <tr> <td colspan="2">No cytotoxic therapy</td> <td colspan="6">Days 43-56 (hydrocortisone continues)</td> </tr> <tr> <th>Week</th> <th>ADRIA KETO ADT</th> <th>TAXOT EMCYT ADT</th> <th>ADRIA KETO ADT</th> <th>TAXOT EMCYT ADT</th> <th>ADRIA KETO</th> <th>TAXOT EMCYT</th> <th>i.v. (weekly) p.o. (3 times daily)</th> </tr> <tr> <td></td> <td>1↓</td> <td>2↓</td> <td>3↓</td> <td>4↓</td> <td>5↓</td> <td>6↓</td> <td></td> </tr> <tr> <td colspan="8">Weeks 7-8: rest</td> </tr> </tbody> </table>	Agent		Dose and Schedule						<u>Chemotherapy</u>		8-week cycle of chemotherapy						Doxorubicin (ADRIA)		20 mg/m ² CIV over 24 h on days 1, 15, 29						Ketoconazole (KETO)		400 mg p.o. t.i.d. on days 1-7, 15-21, 29-35						Docetaxel (TAXOT)		35 mg/m ² IVPB on days 8, 22, 36						Estramustine (EMCYT)		280 mg p.o. t.i.d on days 8-14, 22-28, 36-42						Hydrocortisone		20 mg p.o. a.m. & 10 mg p.o. p.m. EVERY DAY						No cytotoxic therapy		Days 43-56 (hydrocortisone continues)						Week	ADRIA KETO ADT	TAXOT EMCYT ADT	ADRIA KETO ADT	TAXOT EMCYT ADT	ADRIA KETO	TAXOT EMCYT	i.v. (weekly) p.o. (3 times daily)		1↓	2↓	3↓	4↓	5↓	6↓		Weeks 7-8: rest							
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1.0 INTRODUCTION

1.1 Prostate Cancer

More than one-third of patients with non-metastatic prostate cancer who undergo radical prostatectomy eventually relapse with distant disease.¹⁻³ Certain predictors have been identified to help delineate those patients with locally advanced prostate cancer who have a high risk of regional or distant metastases following radical prostatectomy. These predictors are: serum PSA ≥ 10 ng/mL, Gleason scores of 7(4+3) or ≥ 8 , and clinical stage T3 or T4.⁴ Extracapsular extension, seminal vesicle involvement, neurovascular bundle involvement, lymph node positivity, and positive surgical margins also are associated with radical prostatectomy failure.⁵⁻⁸

Locally advanced and metastatic prostate cancer is treated with systemic therapy, the standard of which is chemotherapy and ADT. We have established the regimen to be used in this study in two previously published studies. In one retrospective analysis,⁹ we examined the records of 31 men presenting with locally advanced or metastatic castration-resistant prostate cancer. These patients were treated with two 8-week cycles of chemotherapy consisting of doxorubicin, ketoconazole, docetaxel, and estramustine along with ADT during and after chemotherapy. At 1 year of follow-up, PSA levels among these patients had decreased by 99%, and their median time to progression was >34 months.

Based on the intriguing data from that retrospective study, we conducted a phase 2, prospective trial of the same regimen in a similar patient population.¹⁰ We found similarly encouraging results in that group of 45 patients. Median progression-free survival was 23.4 months, medial overall survival was 53.7 months, and nearly 50% of patients had an objective response rate. These two studies formed the basis for our current standard-of-care systemic therapy for patients with locally advanced or metastatic castration-resistant prostate cancer.

Neoadjuvant systemic therapy has been shown to improve disease-specific survival and reduce recurrences in several cancers, including breast,¹¹ bladder,¹² and colon.¹³ It is generally thought that neoadjuvant systemic therapy decreases local tumor burden and eradicates micrometastatic disease, leading to improved outcome for patients. In those with prostate cancer who undergo local therapy (radical prostatectomy) alone, recurrence rates of 30%-50% have been documented; failure of radical prostatectomy is believed to be the result of residual disease at the primary site and occult metastatic disease.

Previous neoadjuvant hormonal therapy using 5-alpha reductase inhibitors or GnRH analogs has been successfully used to reduce PSA and tumor volumes in patients with prostate cancer; however, this approach has not been shown to improve disease-free or overall survival.¹⁴⁻¹⁶

Based on the observed benefits of docetaxel chemotherapy in patients with metastatic prostate cancer, several studies have examined the role of taxane-based chemotherapy in the neoadjuvant setting for high-risk prostate cancers. Phase II studies using docetaxel as a single agent have demonstrated biochemical and histologic effects of reducing PSA and down-staging tumor volume.^{17,18} There has been some success with chemo-hormonal therapy, in which taxane-based chemotherapy is used in combination with androgen deprivation therapy with GnRH agonists, but complete pathologic response has been rare.¹⁹ Other studies have evaluated docetaxel in combination with other agents with anti-androgen activity, including estramustine and ketoconazole. These regimens also have demonstrated biochemical and some pathologic response, but no complete responses (pCRs) were observed.^{20,21}

Abiraterone has been shown to lower serum testosterone and DHT to <1 ng/dL and has improved survival in patients with advanced prostate cancer.²² A Phase II study was conducted to evaluate abiraterone plus leuprolide acetate administered in the neoadjuvant setting in patients with localized high-risk prostate cancer. In this study, the effect of leuprolide alone on intra-prostatic testosterone/DHT was compared with leuprolide plus abiraterone. Secondary endpoints were PSA, pathological complete response, near pathological complete response ($\leq 0.2 \text{ cm}^3$ of residual tumor), and safety. Fifty-eight men were treated; 27 received leuprolide and 29 received leuprolide plus abiraterone. Twenty-five percent (14/56) of patients had a complete response or near complete response. Grade 3 adverse events included elevated AST/ALT (5/58, 9%) and hypokalemia (3/58, 5%). Neoadjuvant androgen deprivation therapy in combination with abiraterone was well-tolerated. Declines in PSA were high and achieved earlier when abiraterone was given alongside leuprolide vs. leuprolide alone. Complete response rate were higher for 24 weeks of abiraterone (34%) vs. 12 weeks of abiraterone (15%). The authors concluded that aggressive androgen deprivation therapy as neoadjuvant/adjuvant therapy for patients with localized high-risk prostate cancer needed to be further evaluated.

Further studies have continued to bolster the support for the combination of ADT and chemotherapy in the neoadjuvant setting for high-risk, locally advanced prostate cancer. A small study in Japan²³ found that all patients were eligible for radical prostatectomy after their neoadjuvant treatment, 77.8% of whom remained disease-free after 18 months of follow-up. A larger, NIH-funded, multicenter trial in the United States²⁴ enrolled almost 800 men presenting with metastatic prostate cancer and administered neoadjuvant docetaxel with ADT. The three-year survival rate in men receiving the neoadjuvant chemotherapy was 69.0%, compared with 52.5% in men who received ADT alone. These encouraging results underscore the need to determine optimal regimens for administering neoadjuvant chemotherapy for the treatment of high-risk, locally advanced prostate cancer.

1.2 Rationale

Thirty to fifty percent of patients with localized high-risk prostate cancer who undergo radical prostatectomy eventually relapse with distant disease. Clinical trials suggest that neoadjuvant treatment in this patient population is promising, but additional approaches are warranted.

We previously conducted a retrospective analysis of combined neoadjuvant ADT and chemotherapy. Records for 20 patients were assessed for pathological parameters comparing the diagnostic biopsy to the surgical specimen for changes in Gleason grade, proliferation and apoptosis to evaluate for complete pathological response and near complete pathological response ($\leq 0.2 \text{ cm}^3$ of residual tumor). We also assessed the efficacy of therapy prior to prostatectomy based on PSA response and the volume and profusion of the prostate utilizing multiparametric prostate magnetic resonance imaging (mpMRI). The retrospective review indicated that the combination of ADT and chemotherapy in the neoadjuvant setting demonstrated pathologic benefit and PSA regression in all patients with minimal reversible treatment-related adverse events.

Here we will conduct a prospective clinical trial of neoadjuvant ADT and chemotherapy in patients with localized high-risk prostate cancer prior to radical prostatectomy.

2.0 STUDY OBJECTIVES

2.1 Primary Objective

- To assess rates of complete pathologic response or near-complete pathologic response of androgen deprivation therapy (ADT) plus chemotherapy prior to radical prostatectomy in prostate patients presenting with localized high-risk prostate cancer.

2.2 Secondary Objective

- To assess the efficacy of therapy prior to prostatectomy based on:
 - Prostate-specific antigen (PSA) response
 - Circulating tumor cell (CTC) response
 - Volume and perfusion of the prostate utilizing multiparametric prostate magnetic resonance imaging (mpMRI)
- To assess the safety of preoperative administration of ADT and chemotherapy
- To assess the surgical morbidity following therapy with ADT and chemotherapy

2.3 Tertiary Objective

- To assess the effect of ADT and chemotherapy administered in the neoadjuvant setting on the natural disease history of patients with locally advanced prostate cancer who undergo radical prostatectomy

3.0 INVESTIGATIONAL PLAN

3.1 Study Design

This study is a single-arm, prospective clinical trial of neoadjuvant ADT and chemotherapy in patients with locally-advanced, high-risk prostate cancer who are eligible for radical prostatectomy.

Patients will undergo a screening period. Those who are deemed eligible will be entered into the study. A total of 24 patients will be enrolled in this study and, in the absence of prohibitive toxicity, will receive 4 monthly treatments with ADT and 2 cycles chemotherapy prior to prostatectomy.

Patients will be treated with 4 monthly injections of degarelix along with two 8-week cycles of chemotherapy. Each cycle of chemotherapy will consist of 6 weeks of chemotherapy and 2 weeks of rest.

Patients will receive two 8-week cycles of chemotherapy (6 weeks of chemotherapy followed by 2 weeks of rest). In weeks 1, 3, and 5, patients will receive doxorubicin (20 mg/m² as a 24-hour intravenous infusion on day 1 of each applicable week) and ketoconazole (400 mg orally 3 times daily for 7 days); in weeks 2, 4, and 6, patients will receive docetaxel (35 mg/m² intravenously on day 1 of each applicable week) and estramustine (280 mg orally 3 times daily for 7 days).

Patients will be pretreated with dexamethasone 4 mg p.o. b.i.d. 24 hours pre- docetaxel, day of docetaxel administration, and 24 hours post-docetaxel. Ondansetron 8 mg p.o. and diphenhydramine 25 mg i.v. 30 minutes prior to docetaxel infusion.

Maintenance hydrocortisone (20 mg morning and 10 mg afternoon) will be administered daily throughout chemotherapy to counteract potential ketoconazole-induced adrenal complications.

Since all of the drugs in this trial are standard of care, there may be instances when subjects will receive their treatment at other infusion centers as well as their standard blood draws due to insurance network provider determinations, cost, etc. Dr. Amato will work closely with referring physicians and infusion centers. The lab results and clinic/infusion notes will be obtained and reviewed by Dr. Amato. All subjects will still come to the cancer center for restaging study visits.

The primary objective of the study is to evaluate the biologic activity of ADT and chemotherapy administered in the neoadjuvant setting prior to radical prostatectomy. Tissue collected for disease diagnosis, Gleason score, proliferation and apoptotic index will be measured. After 4 months of ADT and 2 cycles of chemotherapy, the patient will undergo radical prostatectomy and these same parameters will be assessed on the surgical specimen. It is anticipated that ADT and chemotherapy will bring about pathologic or near pathology complete responses.

The safety of ADT and chemotherapy in this patient population will be assessed based on the incidence, severity, duration, causality, seriousness and type of adverse events (AEs) and changes in the patient's physical examinations, vital signs, and clinical laboratory results. The severity of adverse events and abnormal laboratory findings will be assessed according to the NCI CTCAE V4.03.

The effect of ADT and chemotherapy on PSA and CTC levels will be assessed at 8-week intervals after beginning treatment for the first 4 months.

The volume and perfusion of the prostate will be assessed by multiparametric prostate magnetic resonance imaging (mpMRI) before beginning treatment with ADT and chemotherapy. The effect of ADT and chemotherapy on volume and perfusion will be assessed after 2 cycles of chemotherapy.

3.2 Duration of Study

It is anticipated that all patients will be enrolled within 12 months of study initiation. With 4 months of ADT treatment, 2 cycles of chemotherapy, and surgery performed at Week 18-20, it is anticipated that active participation in the study will conclude within 18 months of study initiation. Long-term indirect follow-up to assess patient outcome by chart review will continue for up to 10 years.

4.0 PATIENT POPULATION AND SELECTION

Patients who meet all eligibility criteria, are able and willing to participate in the study, and who provide written informed consent to participate will be enrolled.

4.1 Inclusion Criteria

Patients must meet all of the inclusion criteria to participate in this study:

- 4.1.1** Pathologic confirmation of prostatic adenocarcinoma without evidence of regional and/or distant metastasis
- 4.1.2** Negative bone scan and CT of chest and abdomen within 6 weeks of first treatment
- 4.1.3** Candidate for radical prostatectomy (i.e., disease confined to the prostate) and ECOG performance status <2 (Appendix 2)

- 4.1.4 Adequate bone marrow function, defined as absolute peripheral granulocyte count >1500 and platelet count >100,000 cells/mm³
- 4.1.5 Clinical stage T1c or T2a with high-grade disease (Gleason 8-10) on initial biopsy, clinical stage T2b-T2c with Gleason grade 7 (4+3), or clinical stage T3
- 4.1.6 Most recent liver function tests performed within 7 days prior to the first infusion of treatment indicate adequate hepatic function per the following criteria:
 - Albumin \geq 2.8 g/dL
 - AST and ALT \leq 5 x ULN for the lab
 - Total bilirubin < 2 mg/dL
- 4.1.7 Most recent renal function tests performed within 7 days prior to the first dose of study therapy indicate adequate renal function per the following criteria:
 - Serum creatinine \leq 1.5 x ULN for the lab
- 4.1.8 Use of anticoagulants is limited to local use only (for control of central line patency). Most recent coagulation studies performed within 2 weeks prior to the first dose of study therapy indicate an acceptable coagulation profile per the following criteria and no history of substantial non-iatrogenic bleeding diatheses:
 - INR \leq 1.5
 - aPTT \leq 1.5 x ULN for the lab
- 4.1.9 Age \geq 18 years
- 4.1.10 Written, informed consent to participate in this study.

4.2 Exclusion Criteria

Subjects meeting any of the exclusion criteria at baseline will be excluded from study participation:

- 4.2.1 Prostatic adenocarcinoma with neuroendocrine differentiation or small cell features
- 4.2.2 Surgical resection or major surgery within 4 weeks or stereotactic biopsy within 1 week of first ADT and chemotherapy treatment
- 4.2.3 Previous or current hormonal treatment, chemotherapy, radiation therapy, immunotherapy, or investigational drug for the patient's prostatic adenocarcinoma
- 4.2.4 Unable to tolerate multiparametric MRI or is contraindicated
- 4.2.5 Patients not appropriate surgical candidates for radical prostatectomy based on the evaluation of coexisting medical diseases and competing causes of death
- 4.2.6 Severe or uncontrolled medical disease, including uncontrolled cardiac, hepatic, renal, or neurologic/psychiatric disorder
- 4.2.7 Severe gastrointestinal bleeding within 12 weeks of treatment with ADT and chemotherapy
- 4.2.8 Positive for HIV or chronic hepatitis B or hepatitis C infection
- 4.2.9 Congestive heart failure New York Heart Association (NYHA) class 3 or 4, or history of congestive heart failure NYHA class 3 or 4, unless a 2D echocardiogram or multi-gated acquisition scan performed within 3 months of enrollment demonstrates a left ventricular ejection fraction >45%.

- 4.2.10** Another primary malignancy that has not been in remission for at least 2 years. Non-melanoma skin cancer or intraepithelial carcinoma of the cervix is allowed.
- 4.2.11** Use of herbal products that may decrease PSA levels (e.g., saw palmetto) or systemic corticosteroids greater than the equivalent of 10 mg of prednisone per day within 4 weeks of screening laboratory studies.
- 4.2.12** Any other condition, including concurrent medical condition, social circumstance or drug dependency, which in the opinion of the investigator could compromise patient safety and/or compliance with study requirements

4.3 Removal of Patient from Study

A patient may be removed from the study for a variety of reasons, including:

- Progressive disease
- Patient becomes ineligible for radical prostatectomy
- Initiation of nonstudy treatment for prostate carcinoma
- Patient withdraws consent to continue in the trial
- Patient develops an adverse event or intercurrent condition that precludes further participation or requires a prohibited treatment
- The investigator withdraws the subject in the subject's best interest
- The subject is lost to follow-up (defined as inability to contact the subject on at least 2 separate occasions over a period of 4 weeks)
- Administrative reasons (the patient is unable to return to the site, moves away from the investigational site, other social reasons)

Patients who withdraw in the absence of progressive disease will be followed for disease progression, recurrence after prostatectomy, and survival.

4.4 Patient Replacement

If a patient completes at least 1 cycle of chemotherapy with 2 doses of ADT and has to undergo prostatectomy operation early (rather than at weeks 18-20 after 2 cycles of chemotherapy), that patient will be considered evaluable for the primary objective. Otherwise, the patient will be replaced in the study.

5.0 TREATMENT

5.1 Description of ADT

Patients will be treated with degarelix every 28 days for 4 months.

5.2 Description of Chemotherapy

Patients will receive two 8-week cycles of chemotherapy (6 weeks of chemotherapy followed by 2 weeks of rest). In weeks 1, 3, and 5, patients will receive doxorubicin (20 mg/m² as a 24-hour intravenous infusion on day 1 of each applicable week) and ketoconazole (400 mg orally 3 times daily for 7 days); in weeks 2, 4, and 6, patients will

receive docetaxel (35 mg/m² intravenously on day 1 of each applicable week) and estramustine (280 mg orally 3 times daily for 7 days).

Patients will be pretreated with dexamethasone 4 mg p.o. b.i.d. 24 hours pre- docetaxel, day of docetaxel administration, and 24 hours post-docetaxel. Ondansetron 8 mg p.o. and diphenhydramine 25 mg i.v. 30 minutes prior to docetaxel infusion.

Maintenance hydrocortisone (20 mg morning and 10 mg afternoon) will be administered daily throughout chemotherapy to counteract potential ketoconazole-induced adrenal complications. To increase absorption, 250 mg of vitamin C is coadministered with ketoconazole.

5.3 Concomitant Medications and Therapies

5.3.1 Permitted Medications

All intercurrent medical conditions and adverse events should be treated in accordance with community standards of medical care. Any changes in documented, permitted concomitant medications being taken at the beginning of the clinical trial or permitted concomitant medications added during the time the patient is participating in this study must be recorded.

5.3.2 Prohibited Medications

Any other anti-cancer therapy, including radiotherapy and other investigational agents, are prohibited during the study.

5.3.3 End of Treatment

Patients may remain on study for two 8-week cycles or until any of the following:

- Progressive disease
- Initiation of treatment with an alternative therapy
- Patient withdraws consent to continue in the trial
- Patient develops an adverse event or intercurrent condition that precludes further participation or requires a prohibited treatment
- The investigator withdraws the subject in the subject's best interest
- The subject is lost to follow-up

6.0 STUDY ASSESSMENTS

All study assessments, including safety and response assessments, are described in Appendix 3 and summarized by type of study visit in the following pages. All visit dates and procedures are relative to Day 1, defined as the first day of treatment infusion, of each cycle.

6.1 Screening Assessments (-7 to -1)

- Collection of written informed consent
- Medical history
- Concomitant medications assessment
- Physical examination, vital signs, height, weight
- Performance status assessment
- Testosterone

- Hematology
- Serum chemistry
- Coagulation panel
- Urinalysis
- ECG, echocardiogram
- Disease assessment (DRE, bone scan, CT of chest and abdomen, mpMRI of the pelvis)
- Collection of tissue for laboratory studies
- Collection of blood for PSA and CTCs
- Adverse Events assessment

6.2 For each cycle: Days 1, 8, 15, 22, 29, 36 (± 1) of Chemotherapy Administration

- Interim physical examination
- Vital signs, weight
- Hematology and serum chemistry, if not performed in previous 72 hours
- Concomitant medications assessment
- Adverse events assessment
- Administration of treatment, including pre-medications, post-infusion observation period

6.3 Days 1, 29, 57, 85 (± 1) of Androgen-Deprivation Therapy Administration

- Interim physical examination
- Vital signs, weight
- Hematology and serum chemistry, if not performed in previous 7 days
- Testosterone
- Concomitant medications assessment
- Adverse events assessment

6.4 End of 2 ADT Treatments and First Cycle of Chemotherapy Visit

- Interim physical examination
- Vital signs
- Performance Status assessment
- Hematology and serum chemistry
- Testosterone
- Urinalysis and coagulation panel
- Disease assessment (mpMRI)
- Concomitant medications assessment
- Adverse events assessment
- Collection of blood for PSA, CTCs

6.5 Completion of ADT and Chemotherapy Visit

- Physical examination
- Vital signs
- Performance Status assessment
- Hematology and serum chemistry
- Testosterone
- Urinalysis and coagulation panel
- Disease assessment (mpMRI)

- Concomitant medications assessment
- Adverse events assessment
- Collection of blood for PSA, CTCs

6.6 Pathologic Assessment Associated with Radical Prostatectomy (Day 133 ± 7 days)

- Collection of blood for PSA, CTCs
- Collection of prostatectomy tissue for pathologic assessment

6.7 Long-Term Follow-Up

PSA and CTCs will be assessed every 3 months for the first 2 years after the completion of the therapy program. PSA will be assessed every 6 months for the following 3 years and annually thereafter. Other follow-up measurements include mpMRI and bone scans at yearly intervals beginning when PSA elevation (>0.3 ng/mL) is detected or earlier if clinically indicated, documentation of recurrence and survival. When applicable, follow-up may be assessed by medical record review, telephone call or review of the Social Security Index.

7.0 TOXICITY CRITERIA ALTERATION OF THERAPY

Ketoconazole/ estramustine dose level

Dose Level	Tablet/capsule
0	2 tablets t.i.d
-1	1 tablet t.i.d

If >1 dose level reduction is required, patient will be removed from the study.

Doxorubicin dose level

Dose Level	Dose (mg/m ²)
0	20
-1	15

If >1 dose level reduction is required, patient will be removed from the study.

Docetaxel dose level

Dose Level	Dose (mg/m ²)
0	35
-1	30
-2	25

If >2 dose level reductions are required, patient will be removed from the study.

Previous studies on the use of this regimen, including our retrospective analysis,⁹ have indicated no combinatorial effects of the regimen and only minimal, reversible adverse events during treatment. However, patients will be questioned about unexpected adverse events during clinic visits.

7.1 Hematologic Toxicity

Patients must have an absolute granulocyte (neutrophil) count (ANC) >1,000 and platelet count >75,000 in order to receive doxorubicin or docetaxel. If these counts are not obtained, treatment should be withheld for 1 week and counts rechecked. Filgrastim can be administered as needed to increase ANC counts. When counts have recovered, treatment should resume with the drug that was due when therapy was suspended (i.e., docetaxel and doxorubicin will continue to

alternate). Weeks 7 and 8 will be “rest” weeks no matter how many doses of chemotherapy were actually delivered in weeks 1-6.

If >1 week is required for cell counts recover, treatment will be resumed with doxorubicin at 15 mg/m² and docetaxel at 30 mg/m² (i.e., 25% reduction). This 25% dose reduction should also apply if a patient has a second or third treatment delay. If therapy is delayed >3 times or >3 weeks are required for cell count recovery, chemotherapy will be discontinued and the patient will proceed directly to androgen deprivation.

7.2 Specific Non-Hematologic Toxicities

- Patients unable to tolerate ketoconazole due to GI upset should be offered sucralfate, 1 g p.o. q.i.d., observing the convention of taking it 1 hour before or 2 hours after a dose of ketoconazole. If that is not helpful, ketoconazole should be reduced by 50% to 200 mg p.o. t.i.d. If patients still cannot tolerate ketoconazole, it will be discontinued. Such patients may continue with the rest of the regimen at the discretion of the treating physician.
- Patients with transaminases >4 × ULN should discontinue ketoconazole/estramustine until the transaminases are <2 × ULN. Ketoconazole may be restarted at 200 mg p.o. t.i.d. at the discretion of the treating physician, with weekly liver enzyme monitoring.
- Patients developing a deep venous thrombosis or pulmonary embolism will have estramustine discontinued. They may continue on the remainder of the regimen at the discretion of the treating physician.
- Patients who have myocardial infarction or stroke will have all chemotherapy discontinued and proceed to androgen deprivation.
- After starting an antiandrogen, patients experiencing an increase in hepatic enzymes to >4 × ULN will have the agent withdrawn for a month. If the patients had been on flutamide, it is suggested that bicalutamide or nilutamide be substituted. Patients unable to tolerate an alternative anti-androgen will be maintained on testicular suppression only.
- Other hepatotoxicities:
 - If a grade 1 increase in AST, ALT, or bilirubin occurs (e.g., increase in AST or ALT from ULN to 2.5× ULN or increase in total bilirubin from ULN to 1.5× ULN), the frequency of liver function test monitoring should be increased if the Investigator judges that the laboratory abnormalities are potentially related to study medication. No study treatment dose reduction is required.
 - If a grade 2 increase in AST, ALT, or bilirubin occurs (e.g., AST or ALT to >2.5-5× ULN or total bilirubin to 1.5-3× ULN), the frequency of liver function test monitoring should be increased to at least once per week if the Investigator judges that the laboratory abnormalities are potentially related to study medication. No study treatment dose reduction is required.
 - If a grade 3 increase in AST, ALT, or bilirubin occurs (e.g., AST or ALT to >5× ULN or total bilirubin to >3× ULN), hold study medication and all other concomitant medications that are potentially hepatotoxic. Frequent laboratory evaluations (at least once per week) should be conducted until liver function results return to baseline value or grade 1. Liver enzymes should be measured immediately, regardless of when the next study visit or monitoring interval is scheduled.

- If study treatment resumption is considered for subjects who have experienced grade 3 increases in AST, ALT, or bilirubin, and the Medical Monitor agrees, resume study treatment with the first dose level reduction when grade 3 toxicities resolve to grade 1 or baseline.
- If grade ≥ 3 increases in AST, ALT, or bilirubin recur after the first dose reduction, hold study medication and all other concomitant medications that are potentially hepatotoxic. Frequent laboratory evaluations should be conducted (at least once per week) until liver function results return to baseline value or grade 1. Liver enzymes should be measured immediately, regardless of when the next study visit or monitoring interval is scheduled.
- If study treatment resumption is considered for patients who have experienced grade 3 increases in AST, ALT, or bilirubin with the first dose reduction and the Medical Monitor agrees, resume study treatment with the second dose level reduction (see table) when AST, ALT, or bilirubin returns to baseline value or grade 1.
- If grade 4 increases in AST, ALT, or bilirubin occur (e.g., AST or ALT to $>20\times$ ULN or total bilirubin to $>10\times$ ULN), patients must discontinue study treatment immediately and will not be re-challenged. They should be followed until resolution of abnormal liver function tests.
- Doxorubicin is extensively metabolized in the liver and eliminated primarily in bile. Up to 40% of an administered dose is eliminated through the bile duct. Very small amounts of drug are eliminated through the urinary system. Doxorubicin is well tolerated. Common side effects include alopecia (92%), nausea ($>10\%$) and vomiting (34%-37%), myelosuppression, cardiomyopathy, and secondary malignancies. It is unclear which mechanisms play the biggest role in the cytotoxicity. However, it is clear that free radical formation, as a result of reactions with metal catalysts (e.g. iron, copper) and hydrogen peroxide is responsible for the cumulative cardiac toxicity seen with doxorubicin. Although commonly seen at total doses in excess of 500 mg/m², it is clear that some patients have clinically significant cardiac dysfunction at substantially lower doses.
- Docetaxel-associated neuropathy is usually mild and predominantly sensory. In most cases symptoms resolve after treatment discontinuation, but the toxicity can be severe and dose limiting, with symptoms that persist (and may even worsen) long after the last dose has been administered. Symptoms of neuropathy include paresthesia (skin sensation such as burning, prickling, itching, or tingling, with no apparent physical cause), weakness, feeling of heaviness in hands and feet, numbness and loss of ankle and knee jerk. These symptoms often result in clumsiness, loss of dexterity and unsteadiness of gait, and can be both painful and disabling. Peripheral neuropathy is most commonly prevented by dose reduction. Whether the incidence of neuropathy is reduced by corticosteroid use remains unproven. There is also some anecdotal evidence that vitamin B6 may help to guard against neuropathy, and published preliminary evidence that glutathione may be protective. These measures require further study. There are no evidence-based management strategies for docetaxel-induced neuropathy

7.3 Other Non-Hematologic Toxicities

NCI standard toxicity criteria are included as Appendix A. Any grade 3 or 4 toxicity should be reported promptly to the Principal Investigator, and therapy should be held. Since such events are anticipated to be distinctly uncommon, dosage adjustment will be determined on an individual basis.

8.0 METHODOLOGY AND STATISTICAL CONSIDERATIONS

8.1 Study Populations

The Safety population will consist of all subjects who have received at least one cycle of ADT and chemotherapy.

The Evaluable population will consist of all subjects who received at least two cycles of ADT and chemotherapy and underwent radical prostatectomy.

Safety analyses will be performed in the Safety population. Other objectives will be assessed in the Evaluable population.

8.2 Primary Objective

- To assess rates of complete pathologic response or near-complete pathologic response of androgen deprivation therapy (ADT) plus chemotherapy prior to radical prostatectomy in prostate patients presenting with localized high-risk prostate cancer.

8.2.1 Power and Sample Size for Primary Objective

This is a single-arm study with pathologic complete response (CR) and near-complete response (PR) as the primary efficacy end point. Using the one-step Fleming design, while considering a response rate <25% not sufficient to warrant further research, 24 patients were needed to assure with 90% power and a type I error of 0.05 that if the response rate is $\geq 40\%$ this regimen can be recommended for further investigation. Therefore, a CR and PR among ≥ 10 of the 24 patients would indicate that this regimen merits further study. Patients with CR will be compared with those with PR and examined for differences in patient, tumor, and laboratory factors. Fisher's exact test or chi-square test will be used to compare categorical variables, and Student's *t* test or the Wilcoxon two-sample test will be used to compare continuous variables. Significance is set at $P \leq 0.05$.

8.3 Secondary Objectives

- To characterize the clinical activity of neoadjuvant ADT and chemotherapy by evaluation of:
 - PSA response
 - CTC response
 - Volume and profusion of the prostate utilizing mpMRI
- To investigate the safety profile of ADT and chemotherapy in patients with localized, high-risk prostate cancer prior to radical prostatectomy
- To assess surgical morbidity after preoperative administration of ADT and chemotherapy

8.3.1 Analysis of Secondary Objectives

With exception of the safety investigations, secondary endpoint analyses will be performed for all patients having received at least 2 cycles of chemotherapy. These studies are essentially exploratory in nature and are not designed to meet statistical significance. Data from these studies will be summarized using descriptive statistics. As necessary, more definitive statistical methods can be applied to evaluate apparent trends. Subgroup analyses will be performed as appropriate.

8.3.2 Safety Assessments

Adverse events, including outcome, severity and relationship to the study treatment, will be listed. Incidence rates of adverse events and the proportion of subjects prematurely withdrawn from the study due to adverse events will be shown. Treatment-emergent adverse events and concomitant medications will be summarized over the entire study period. Treatment-emergent adverse events also will also be summarized by severity and by relatedness to study medication. Serious adverse events (SAE) will be summarized. Reasons for withdrawal from the study will be summarized.

8.4 Tertiary Objectives

- To assess the effect of ADT and chemotherapy administered in the neoadjuvant setting on the natural disease history of patients with locally advanced prostate cancer who undergo radical prostatectomy.

8.4.1 Analysis of Tertiary Objectives

After prostatectomy, patients will undergo routine standard of care per the Investigator's recommendation. Long-term follow-up will consist of chart abstractions and will attempt to collect PSA levels at 9 months, 12 months, every 6 months for 5 years and annually thereafter; CTCs at 9 months and 12 months; mpMRI and bone scans at yearly intervals beginning when PSA elevation (>0.3 ng/mL) is detected or earlier if clinically indicated; documentation of recurrence; documentation of survival.

9.0 SAFETY MONITORING

9.1 Adverse Events

The Investigator is responsible for monitoring the safety of patients who have entered the study. An adverse event (AE) is any untoward medical occurrence in a patient or subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of the investigational product, whether or not related to the investigational product.

Adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events version 4.03. All AEs, including observed or volunteered problems, complaints or symptoms, must be recorded. Investigators must document all AEs occurring during the clinical trial, commencing with the first administration of ADT and chemotherapy. Patients will be instructed to report to the Investigator any AE that they experience. Laboratory data will be collected in this study and analyzed using objective toxicity criteria. Abnormal laboratory values that are determined to be SAEs will be captured. Laboratory value changes from baseline generally will not be recorded as AEs unless they become an SAE and/or DLT. Disease progression is considered an efficacy outcome parameter and not an AE.

Each adverse event should be evaluated to determine:

- duration (start and end dates)
- severity (grade)
- seriousness
- relationship to study agent
- action taken (i.e., none, study agent modification, medical intervention)
- outcome (i.e., resolved without sequelae, resolved with sequelae, ongoing)

All patients experiencing a documented adverse event at least possibly related to the study drug will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline or stabilize;
- there is a satisfactory explanation other than the study drug for the changes observed;
- the patient begins alternative treatment; or
- death.

9.2 Serious Adverse Events (SAE)

A Serious Adverse Event (SAE) is defined in regulatory terminology as any untoward medical occurrence that:

- Results in death
- Is life-threatening (The patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires in-patient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event

Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of "Serious Adverse Event". Examples include: allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

9.3 Adverse Event Reporting

Adverse events that are serious, unexpected, and at least possibly related to study participation will be reported to the Institutional Review Board and the DSMB according to their respective requirements.

9.3.1 Expedited Reporting

The **Principal Investigator** must be notified within 24 hours of learning of any serious adverse events, regardless of attribution, occurring during the study or within 30 days of the last administration of the study drug.

Serious Adverse Events (SAE) that are determined by the PI to be unexpected + related will be submitted to the DSMB within 7 calendar days of the determination by telephone or fax; written report no later than 15 calendar days of the determination. Deaths should be reported to the IRB within 24 hours of investigator knowledge. Any unexpected, serious, related adverse experiences should be reported to the IRB within 7 calendar days of investigator knowledge.

The **IRB** will be notified within 7 calendar days of “any unanticipated problems involving risk to subjects or others” (UPR). Examples include:

- Any adverse event which in the opinion of the PI is both unexpected and related and places patients or others at risk of harm
- Protocol deviation that harmed patients or placed patients in increased risk of harm
- Unanticipated adverse device effect
- A breach of confidentiality
- Change in FDA labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol
- Information that indicates a change to the risks or potential benefits of the research

9.4 Relatedness to Study Drug

The Investigator must attempt to determine if an adverse event or serious adverse event is related to the use of the study drug. This relationship should be described as follows:

Unlikely The event is clearly due to causes distinct from the use of the study drug, such as a documented pre-existing condition, the effect of a concomitant medication, a new condition which, based on the pathophysiology of the condition and the pharmacology of the study drug, would be unlikely to be related to use of the study drug.

Possible The event follows a reasonable temporal sequence from administration of the study drug and the event follows a known response pattern to the study drug *BUT* the event could have been produced by an intercurrent medical condition which, based on the pathophysiology of the condition and the pharmacology of the study drug, would be unlikely to be related to the use of the study drug *OR* the event could be the effect of a concomitant medication.

Probable The event follows a reasonable temporal sequence from administration of the study drug and the event follows a known response pattern to the study drug *AND* the event cannot have been reasonably explained by an intercurrent medical condition *OR* the event cannot be the effect of a concomitant medication.

Definite The event follows a reasonable temporal sequence from administration of the study drug, the event follows a known response pattern to the study drug and based on the known pharmacology of the study drug, the event is clearly related to the effect of the study drug.

Unknown Based on the evidence available, causality cannot be ascribed.

9.5 Maximum Intensity

The Investigator will evaluate all AEs and SAEs with regard to maximum intensity and relationship to study drug. Maximum intensity should be assigned using one of the severity grades as outlined in the NCI CTCAE v4.03. If the adverse event is not specifically listed in CTCAE v4.03, the following grades will be used:

- Grade 1: mild
- Grade 2: moderate
- Grade 3: severe
- Grade 4: life-threatening or disabling
- Grade 5: death

9.6 Data and Safety Review

Subjects enrolled to the trial will be monitored for adverse events by the Investigator and clinical co-investigators. Safety data will be reviewed after every 5 patients have completed their first cycle by the investigators and the medical monitor. Adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events version 4.03. Toxicity assessments are required prior to study treatment, at the beginning of each treatment cycle, following termination of study treatment, and may be performed at any additional time at the discretion of the treating physician.

To ensure that the protocol and Good Clinical Practices (GCP) are being followed and that study data are accurate, complete and reliable, the trial will be monitored by a Data Safety Monitoring Board (DSMB), Medical Monitor and CRA monitoring as specified in the Data Safety Monitoring Plan (DSMP) for the study and the DSMB's charter.

10.0 STUDY MANAGEMENT

10.1 Ethical Considerations

This study will be conducted in accordance with current Regulatory Authorities regulations, ICH GCP guidelines, the principles of the Declaration of Helsinki, and local ethical and legal requirements.

10.2 Informed Consent

The IRB-approved Informed Consent document (ICD) must be signed by the patient before participation in the study. A signed copy of the ICD must be provided to the patient. If necessary, the ICD will be provided in a certified translation of the local language.

Signed consent forms must remain in each patient's file and must be available for verification by study monitors or authorized regulatory representatives at any time.

10.3 Institutional Review Board (IRB) Approval and Consent

The IRB should approve the consent form and protocol prior to any study-related activities. It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state

regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

10.4 Confidentiality

The information obtained during the conduct of this clinical study is confidential, and disclosure to third parties other than regulatory authorities is prohibited. Processing, evaluation or use of the information will be performed by a health professional for medical purposes and/or by those operating under a duty of confidentiality that is equivalent to that of a health professional.

All investigators and research study personnel who process information from the study must agree to take appropriate measures to prevent unauthorized or unlawful processing or disclosure of data.

10.5 Subject Data Protection

In accordance with the Health Information Portability and Accountability Act (HIPAA), subjects who have provided written informed consent must also sign a subject authorization to release medical information to the study investigator and allow a regulatory authority, or Institutional Review Board access to subject's medical information relevant to the study.

10.6 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB 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.

Government agency regulations and directives require that the study investigator must retain all study documentation pertaining to the conduct of a clinical trial. Study documents should be kept on file until three years after the completion and final study report of this investigational study.

10.7 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator is responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of

proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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Appendix 1: NCI Common Terminology Criteria for Adverse Events, Version 4.03

Version 4.03 of the NCI CTCAE, dated 14 June 2010, may be viewed and/or downloaded by accessing the following website: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

Appendix 2: Assessment of Performance Status

ECOG Performance Status*	Criteria	Karnofsky Score
0	Fully active; able to carry on all pre-disease performance without restriction	90-100%
1	Restricted in physically strenuous activity but ambulatory	70-80%
2	Ambulatory and capable of self-care, but unable to carry out any work activities	50-60%
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours	30-40%
4	Completely disabled	10-20%

* Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

Appendix 3: Schedule of Assessment

Visit Name	Screening	Cycle 1					Cycle 2				Post-Treatment	
	Day -7 to -1	Day 1	Days 8,15,22	Day 29	Day 36	C1D43,50 (REST)	Day 1	Days 8,15,22	Day 29	Day 36	C2 Day 57 ± 2 days	Day 133 ± 7 days
Informed Consent	X											
Comprehensive Physical exam	X										X	
Medical History	X											
Concomitant medication assessment	X	X	X	X	X		X	X	X	X	X	
Adverse events assessment	X	X	X	X	X		X	X	X	X	X	
Vital signs	X	X	X	X	X		X	X	X	X	X	
Height, weight	X	X	X	X	X		X	X	X	X	X	
ECOG performance status	X	X	X	X	X		X	X	X	X	X	
Complete metabolic profile*	X	X	X	X	X		X	X	X	X	X	
Electrolytes*	X	X	X	X	X		X	X	X	X	X	
CBC with diff. platelet count*	X	X	X	X	X		X	X	X	X	X	
PT, INR, PTT	X										X	
Urinalysis	X										X	
PSA	X						X				X	X
Testosterone	X			X			X		X		X	
CTC's	X						X				X	X
Bone Scan	X											
CT Chest and abdomen	X											
mpMRI pelvis	X						X				X	
ECG	X											
Echo	X											
Tissue collection	X(biopsy)											X (surgery)
Interim physical		X	X	X	X		X	X	X	X		
IV Chemotherapy (2 cycles)		X	X	X	X		X	X	X	X		
ADT		X		X			X		X			

* If not performed within the previous 72 hours