TITLE: A PHASE II TRIAL OF ANDROGEN DEPRIVATION, DOCETAXEL AND ENZALUTAMIDE IN PATIENTS WITH METASTATIC HORMONE SENSITIVE PROSTATE CANCER.

LAY TITLE: ANDROGEN DEPRIVATION, DOCETAXEL AND ENZALUTAMIDE IN ADVANCED HORMONE SENSITIVE PROSTATE CANCER

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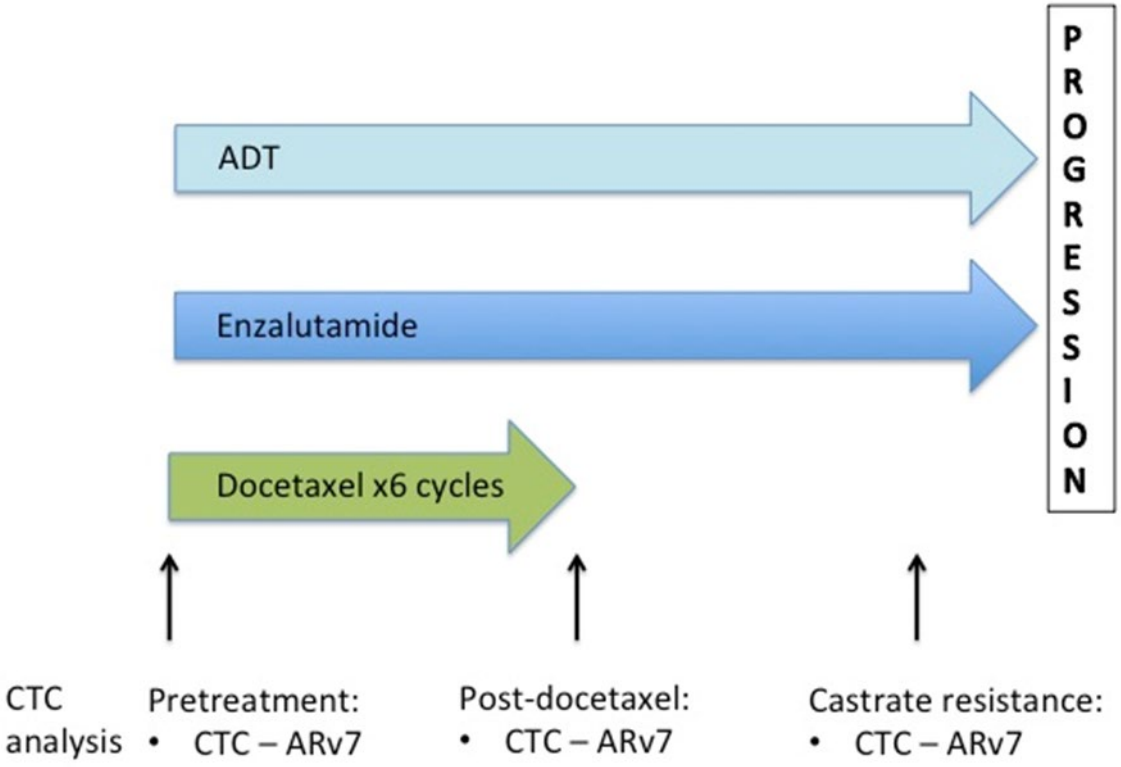
Schema


ADT
Enzalutamide
Docetaxel x6 cycles
PROGRESSION
CTC analysis
Pretreatment:
• CTC – ARv7
Post-docetaxel:
• CTC – ARv7
Castrate resistance:
• CTC – ARv7

LIST OF ABBREVIATIONS

ADT	Androgen deprivation therapy
AE	Adverse event
ALT	Alanine transaminase
AST	Aspartate transaminase
AR	Androgen receptor
ARV7	Androgen receptor splice variant 7
BUN	Blood urea nitrogen
CBCD	Complete blood count with differential
CMP	Complete metabolic profile
CT	Computed tomography
CTC	Circulating tumor cell
CTCAE	Common terminology criteria for adverse events
CTMS	Clinical trial management system
DNA	Deoxyribonucleic acid
DSMC	Data and safety monitoring committee
ECOG	Eastern Cooperative Oncology Group
ECRF	Electronic case report form
FN	Febrile neutropenia
IB	Investigator brochure
IDS	Investigational drug Services
IRB	Institutional review board
LCI	Levine Cancer Institute
LHRH	Luteinizing hormone-releasing hormone
MCRPC	Metastatic castrate resistant prostate cancer
OS	Overall survival
PCWG2	Prostate cancer working group 2
PD	Progressive disease
PRES	Posterior reversible encephalopathy syndrome
PSA	Prostate specific antigen
RECIST	Response evaluation criteria in solid tumors
RPFS	Radiographic progression free survival
SAE	Serious adverse event
SAR	Suspected adverse reaction
SPFS	Serologic Progression Free Survival
UAP	Unanticipated problem
ULN	Upper limit of normal

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1. Objectives

1.1 Primary Objective

To assess the 52-week prostate specific antigen (PSA) complete response rate in subjects with metastatic hormone sensitive prostate cancer treated with the combination of androgen deprivation therapy (ADT), docetaxel and enzalutamide.

1.2 Secondary Objectives

To assess PSA and radiographic response rates, time to castrate resistance, serologic progression-free survival (sPFS), radiographic progression free-survival (rPFS), time to treatment failure, overall survival (OS) and the safety and toxicity profile of this regimen.

1.3 Exploratory Objectives

To assess and correlate baseline circulating tumor cell levels and androgen receptor splice variant 7 (ARv7) protein expression with primary and secondary objectives.

2. Background and Rationale

2.1 Prostate Cancer

Prostate cancer is the most common malignancy in men with over twenty seven thousand deaths anticipated in the United States in 2015.[1] Management of patients with advanced disease remains focused on improving tumor related morbidity and mortality, as no curative therapies currently exist. The role of androgen signaling in this disease has long been recognized and underlies current treatment strategies.[2] Although inhibition of the androgen axis through suppression of testosterone levels induces high initial response rates in men with metastatic disease, overall survival remains generally poor and cancer related morbidity is common, underscoring the need for more effective therapies.[3]

Until recently, men with metastatic prostate cancer were initially managed with primary ADT alone, though seminal results of two large randomized trials have recently demonstrated a marked survival improvement and delay in the development of castrate resistance by the addition of docetaxel.[4,5] Results from a large cooperative group study reported by Sweeney et al. demonstrated that the addition of docetaxel to ADT in the treatment naïve setting improved overall survival by 13.6 months ($p<0.001$) and delayed the time to castrate resistance from 11.7

months to 20.2 months (p<0.001). Although the improvement in overall survival was more pronounced in the men with "high volume" metastatic disease, the benefit was statistically significant for the entire study population. The PSA complete response rate (<0.2 ng/mL) at 12 months was also improved in the chemohormonal therapy arm (27.7% vs 16.8%, p<0.001).[4] Preliminary results from another large randomized trial comparing the addition of docetaxel to ADT alone in men with metastatic disease show similar findings with an OS improvement noted in the chemohormonal therapy arm,[5] thus providing confirmation that docetaxel provides marked synergistic benefit when combined with ADT in men with metastatic castrate sensitive prostate cancer.

On the basis of these trials, the use of chemohormonal therapy has become the standard of care in fit patients presenting with metastatic disease. Although the survival improvement gained by the addition of docetaxel to ADT represents an important advancement in the field, median survival for this population remains less than five years,[4] particularly in patients with high volume disease, highlighting the need for more effective therapeutic strategies.

2.2 Enzalutamide and Prostate Cancer

In the metastatic setting, resistance to androgen suppression inevitably develops due in part to tumor cell upregulation of the androgen receptor (AR) and persistence of intratumoral androgens.[6,7]

Enzalutamide is a potent androgen receptor inhibitor that binds the AR ligand binding domain, impairing nuclear translocation and DNA binding.[8] In patients with metastatic castrate resistant prostate cancer (mCRPC), enzalutamide improves overall survival in the pre-[9] and post-docetaxel[10] settings, which underscores the critical role of continued AR signaling despite castrate androgen levels.

Enzalutamide has also been studied in less advanced clinical settings. In a small pilot study of patients with treatment naïve prostate cancer and non-castrate androgen levels, enzalutamide monotherapy led to a PSA decline of at least 80% after six months of therapy in 93% of patients.[11] It is therefore anticipated that more stringent blockade of the androgen axis using the non-cross resistant mechanisms of action of enzalutamide in combination with primary ADT may improve clinical outcomes in men with hormone sensitive metastatic disease and is the subject of ongoing clinical trials (NCT02446405, NCT02058706).

In patients with mCRPC, both enzalutamide[9,10] and docetaxel[12] improve survival as single agents when given with ADT. In preclinical prostate cancer models, enzalutamide inhibits the drug efflux pump ABCB1 and

restores sensitivity to docetaxel, suggesting potential clinical synergy with the combination of these two agents.[13] In humans, the combination of enzalutamide and docetaxel has been studied in the phase I setting and appears safe at standard doses. Of note, enzalutamide induces CYP3A4, which is responsible for the metabolism of docetaxel; however, docetaxel pharmacokinetics do not appear to be significantly impacted by the addition of enzalutamide.[14] Further study of the efficacy of this combination at standard doses is ongoing in the castrate resistant setting (NCT02453009).

2.3 Biomarkers in Advanced Prostate Cancer

2.3.1 Circulating Tumor Cells

Available biomarkers to guide therapeutic decisions in patients with metastatic prostate cancer are limited. Enumeration of circulating tumor cells (CTCs) from the peripheral blood of metastatic prostate cancer patients has demonstrated prognostic value in the castrate resistant and castrate sensitive settings.[15-17] Although early studies are based on a platform utilizing an immunoaffinity cell capture methodology, comparison of immunoaffinity versus size filtration-based CTC enrichment suggests that immunoaffinity-based strategies may be less sensitive and lack the ability to capture cytokeratin negative CTCs or CTC clusters, which may have additional prognostic value.[18,19] Despite the established prognostic value in patients with advanced prostate cancer, how best to utilize CTC enumeration in the clinical setting remains poorly defined as an established role for prediction of treatment response is lacking.

2.3.2 Androgen Receptor Splice Variant 7

Although second generation AR antagonists improve the outcome of patients with mCRPC, resistance to these agents inevitably develops. Recently described AR genomic aberrations including mutations[20] and mRNA splice variants[21,22] appear to play a critical role mediating resistance to agents such as enzalutamide. Androgen receptor splice variant 7 (ARv7) is a mRNA splice variant lacking the canonical ligand binding domain and is frequently detected in patients with mCRPC.[22]

Antonarakis et al. elegantly demonstrated that patients with detectable ARv7 in CTCs do not respond as well to enzalutamide or abiraterone,[23] suggesting this may be a key mechanism of resistance for AR targeted therapies. However, ARv7 expression does not appear predictive for taxane resistance[24,25] and may actually decline following taxane-based therapy.[26] These observations raise the possibility that chemotherapy may potentially sensitize patients to AR targeted agents when ARv7

expression emerges. Whether concurrent taxane-based therapy with second generation AR targeted therapies influences the timing and expression level of the ARv7 aberration is unknown and warrants further investigation.

2.4 Rationale for Proposed Study

Two large randomized trials have recently shown that the addition of docetaxel to ADT in men with metastatic treatment naïve prostate cancer significantly improves patient survival and clinical outcomes and has become the standard of care in appropriately fit patients. Docetaxel also improves survival in the castrate resistant setting; however, the magnitude of synergism between docetaxel and ADT is clearly greater in the androgen dependent tumor setting.

In patients with more advanced mCRPC, the AR antagonist enzalutamide also improves survival. The combination of enzalutamide and docetaxel may enhance antitumoral efficacy over monotherapy with either agent based on preclinical observations that enzalutamide may potentially enhance the cytotoxic effect of docetaxel through inhibition of the ABCB1 drug efflux pump. Furthermore, docetaxel may eradicate tumor clones with ARv7 splice variant expression and prolong sensitivity to enzalutamide. This combination is currently being studied in patients with mCRPC, though whether this regimen improves outcomes in the hormone sensitive setting is unknown. It is therefore hypothesized that the addition of enzalutamide to the standard combination of ADT and docetaxel may be well tolerated and demonstrate improved antitumoral efficacy compared to ADT and docetaxel alone in patients with metastatic castrate sensitive prostate cancer. Enumeration of CTCs and detection of ARv7 expression may also predict clinical outcomes in this setting.

3. Overall Study Design and Plan

This is a single center, single arm, phase II trial designed to evaluate the 52-week PSA complete response rate in subjects with metastatic hormone sensitive prostate cancer treated with ADT, docetaxel and enzalutamide.

Patients with metastatic (M1) adenocarcinoma of the prostate who are previously untreated or have received ADT for 16 weeks or less without development of castrate resistance will be eligible. Subjects will be stratified by the presence of high or low volume disease, as defined in Section 5.2. Based on a total of 39 subjects, the study will restrict enrollment to 13 subjects with low volume disease and 26 subjects with high volume disease in an effort to enroll a subject population similar to a

contemporary control study, which serves as the basis for the present study.[4]

Subjects will receive continuous androgen deprivation for the study duration to maintain castrate androgen levels. Additionally, all subjects will receive docetaxel 75mg/m2 IV over 1 hour every 21 days for a maximum of 6 cycles and enzalutamide 160mg orally with or without food daily until the development of clinical or radiographic progression utilizing RECIST 1.1 and PCWG2 criteria.[27] Subjects who develop serologic progression only will be encouraged to remain on study therapy until radiographic or clinical progression.

Disease response rates will be assessed serologically by measuring serum prostate specific antigen (PSA) every 3 weeks during docetaxel therapy followed by every 8 weeks once docetaxel is completed. After the development of castrate resistance as determined by PSA progression using PCWG2 criteria, serum PSA will be monitored every 28 days until the end of study treatment. Radiographic imaging will include chest imaging, a computed tomography scan of the abdomen and pelvis, and radionuclide bone scan at baseline, at the development of castrate resistance, and every 12 weeks following castrate resistance until the end of study treatment.

The primary endpoint of this study will be 52-week PSA complete response rate, which will be assessed against a contemporary historical control rate for the combination of ADT and docetaxel alone in the metastatic hormone naïve setting.[4]

The study will be conducted at all participating sites across North and South Carolina within the Levine Cancer Institute network. Enrollment is anticipated to be completed in approximately 24 months.

4. Subject Selection

Following informed consent and registration, subjects will undergo study eligibility screening. Each of the criteria in the following section must be met for a subject to be eligible for study participation.

4.1 Inclusion Criteria

1. Histologically or cytologically confirmed adenocarcinoma of the prostate without evidence of small cell carcinoma or greater than 50% neuroendocrine differentiation. Metastatic disease must be present including soft tissue, and/or bone metastases OR non-regional lymph node involvement prior to study enrollment. If the subject has regional lymph node involvement, there must be at

least one additional site of disease including visceral, non-regional nodal or skeletal metastases.

2. ADT with surgical castration with bilateral orchiectomy or medical castration with LHRH agonist or LHRH antagonist therapy may have been initiated no greater than 112 days (16 weeks) prior to enrollment date. Subjects who initiated ADT prior to consent, are not eligible if PSA has risen ≥ 25% and ≥ 2 ng/ml above nadir value since initiation of ADT prior to consent.
3. At least one PSA level of ≥ 5 ng/ml within 90 days prior to consent.
4. Prior ADT for non-metastatic disease with LHRH agonist or LHRH antagonist therapy in the neoadjuvant/adjuvant setting is permitted if:
    a. Total duration of therapy did not exceed 36 months
    b. 6 months have elapsed since completion of therapy prior to consent.
    c. Serum testosterone > 50 ng/dl within 28 days prior to re-initiation of ADT for metastatic disease.
    d. Prior ADT for non-metastatic disease must have accompanied definitive local therapy for curative intent.
5. Age ≥ 18 years.
6. ECOG performance status 0-2.
7. Adequate liver function: AST and ALT ≤1.5x upper limit of normal, total bilirubin ≤ 1x upper limit of normal.
8. Adequate bone marrow function: Platelets ≥100,000 cells/mm3, Hemoglobin ≥ 8.0g/dL and ANC ≥ 1,500 cells/$mm^{3.}$
9. Adequate renal function with a creatinine clearance (based on Cockcroft-Gault formula) ≥ 30 mL/min.
10. Ability to understand and the willingness to sign a written informed consent document.
11. Able to swallow and retain oral medication.

4.2 Exclusion Criteria

1. Personal history of seizure.
2. Personal history of conditions that may predispose to seizure activity including cortical cerebrovascular accident or brain trauma.
3. Known central nervous system metastases, including involvement of brain parenchyma and leptomeninges.
4. Personal history of any condition that may impair absorption of enzalutamide.
5. Prior or current therapy with ketoconazole, abiraterone, enzalutamide, apalutamide (ARN-509, JNJ-56021927), darolutamide (ODM-201, BAY1841788) or cytotoxic chemotherapy such as docetaxel, cabazitaxel, cyclophosphamide.

6. Prior therapy with bicalutamide, nilutamide or flutamide within 14 days of enrollment.
7. Within 28 days of major surgery and/or lack of recovery from prior surgical procedure or 14 days of palliative radiation prior to enrollment.
8. Prior or current therapy with an investigational agent for metastatic prostate cancer.
9. Known hypersensitivity to drugs formulated with polysorbate 80.
10. Personal history of posterior reversible encephalopathy syndrome.
11. CTCAE version 4.0 grade 2-4 peripheral sensory neuropathy.
12. Human immunodeficiency virus infection or active hepatitis B or C infection.
13. Uncontrolled and current illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements in the opinion of the Investigator.
14. Presence of any of the following within the previous 3 months prior to enrollment: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, congestive heart failure, or cerebrovascular accident including transient ischemic attack.
15. History of an additional active malignancy within 12 months prior to the date of consent (except non-melanoma skin cancer).
16. Current use of strong CYP2C8 inhibitors, CYP3A4 inducers or CYP3A4, CYP2C9 or CYP2C19 substrates with a narrow therapeutic range as listed in Section 7.2.1.
17. Any condition that requires the use of prednisone > 10mg daily, or equivalent daily glucocorticoid dose, for greater than 14 days.

5. Investigational Plan

5.1 Milestone Date Definitions

Registration Date: the date subject signs study consent.

Enrollment (On Study) Date: the date of initiation of docetaxel and enzalutamide treatment.

Treatment Discontinuation Date: the date the Investigator decides to discontinue the subject from enzalutamide treatment (see Section 5.5).

Castrate Resistance Date: the date of serologic progression as defined in Section 11.1.1 or radiographic progression as defined in Section 11.2, whichever occurs first.

5.2 Registration and Enrollment

Potentially eligible and interested patients will be presented with the study consent and complete the treatment eligibility checks. A Study ID number will then be sequentially assigned by the Sponsor. The Study ID will be a four digit number, where 1001 will be the Study ID assigned to the first registered subject**.** Those confirmed eligible subjects will be enrolled on the date of initiation of docetaxel and enzalutamide treatment. Registration will also be documented in the subject research chart.

Note: A subject who, for any reason (e.g. failure to satisfy the selection criteria or withdraws consent), terminates participation in the study before receiving first dose of study treatment is regarded as a "screen failure". All screen failures will be tracked.

Subjects will be stratified by the presence of high or low volume disease, as defined below:

High volume: presence of visceral metastases or 4 or more bone lesions detectable by radionuclide bone scan with 1 or more outside of the pelvis and vertebral bodies.

Low volume: absence of visceral metastases and up to 3 bone lesions or 4 or more bone lesions detectable by radionuclide bone scan with no lesions outside of the pelvis and vertebral bodies.

Based on a total of 39 subjects, the study will restrict enrollment to 13 subjects with low volume disease and 26 subjects with high volume disease.

5.3 Pre-treatment Screening Period

No protocol-related assessments may be performed prior to obtaining written informed consent. Subjects will be counseled regarding risk of teratogenicity and the need to use contraception throughout the course of the study and for 90 days after completion of enzalutamide administration.

5.3.1 Clinical Assessments

- **Demographics and Medical History**

  A complete medical history should be obtained, including documentation of any clinically significant pre-existing

condition. Medical history is to be completed within 28 days prior to the first dose of study medication.

- **Prostate Cancer History**

  Whether a subject presented with metastatic disease at the diagnosis of prostate cancer or a prior history of local prostate cancer and associated treatment should be documented. In subjects who presented with metastatic disease at diagnosis, a Gleason score should be documented from a diagnostic biopsy if possible.

  In subjects with a prior history of local prostate cancer, the following information should be documented: Gleason score from original diagnostic biopsy and/or surgical specimen, type of prior local therapy, and duration of prior ADT used in the curative setting if applicable.

- **Physical Examination**

  Evaluation by body system, height (at screening only), weight, and body surface area (BSA) should be documented. Vital signs will be recorded and should include temperature, pulse rate, blood pressure, respiratory rate, and oxygen saturation. ECOG performance status should be documented at baseline.

- **Concomitant Medications**

  Any medications taken up to 14 calendar days prior to signing of the informed consent will be considered a concomitant medication. Dose, route, frequency, administration and start/stop dates will be documented. Concomitant medications include but are not limited to over the counter medications, supplements, and vitamins.
  Date and dose of administration of all prior LHRH agonist or antagonist agents and anti-androgens (bicalutamide, nilutamide, flutamide) will be documented.

- **Symptoms and Toxicities**

  Baseline adverse events at the time of first dose of study treatment will be documented.

5.3.2 Radiologic Assessments

The following tests are required prior to enrollment:

- Computed tomography (CT) scan of the abdomen and pelvis. The use of intravenous contrast is recommended though not required.
- Radionuclide bone scan.
- CT scan of the chest with or without intravenous contrast or chest x-ray (CT preferred).

5.3.3 Laboratory Assessments

The following tests are required prior to enrollment:

- Complete blood count with differential (CBCD)
- Complete metabolic panel (CMP) (including sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, albumin, total protein, total bilirubin, AST, ALT, alkaline phosphatase)
- Serum Testosterone
- PSA

For subjects who initiated ADT prior to study registration, maximum pre-ADT (defined as the maximum PSA associated with the diagnosis of metastatic disease) and all post-ADT PSA values and dates of measurement will be documented.

5.4 Treatment Period

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 8. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the subject's malignancy.

Subjects will receive treatment as described in Section 7.

5.4.1 Treatment Assessments

5.4.1.1 Docetaxel Treatment Phase

The docetaxel treatment phase will consist of the time from the Enrollment date until the Castrate Sensitive Enzalutamide Treatment Phase. The required clinical assessments include:

- Physical exam
- Documentation of symptoms and toxicities
- Documentation of concomitant medications
- Laboratory assessments include a CBCD, CMP and PSA

- Specimen for CTC analysis will be collected on the Enrollment date (i.e. C1D1) only

Radiologic assessments are not required during this phase.

During this phase, subjects who develop a rising PSA value ≥ 25% and ≥ 2 ng/ml above nadir value since initiation of ADT across two consecutive increasing values obtained (as defined in Section 11.1.1), must have a serum testosterone level checked within 14 days of the second consecutive rising PSA value. If castration (serum testosterone ≤ 50 ng/dl) is confirmed, docetaxel should be discontinued, and the subject will transition to the Castrate Resistant Treatment phase per Section 5.4.1.3. If serum testosterone > 50 ng/dl, the subject may remain on study pending approval from the Sponsor-Investigator. Serum testosterone should be repeated in 21 days (+/- 7 days), and the subject should be withdrawn from the study if serum testosterone remains > 50 ng/dl at the subsequent assessment.

5.4.1.2 Castrate Sensitive Enzalutamide Treatment Phase

The Castrate Sensitive Enzalutamide Treatment Phase will consist of the time 28 days (+/- 3 days) from the docetaxel treatment discontinuation date until the castrate resistance date as defined in Section 5.1.

The required clinical assessments include:

- Physical exam
- Documentation of symptoms and toxicities
- Documentation of concomitant medications
- Laboratory assessments to include a CBCD, CMP and PSA
- A specimen for CTC analysis will be collected on the first date of this phase

Additional laboratory visits to obtain a <u>PSA only</u> should be performed 26 and 52 weeks (+/- 1 week) <u>from the enrollment date</u> if subject has not developed castrate resistance as defined in Section 5.1 prior to this date.

Radiologic assessments are not required during this phase.

5.4.1.3 Castrate Resistant Treatment Phase

The Castrate Resistant Treatment Phase will consist of the time from the castrate resistance date as defined in Section 5.1 until the end of all study treatment.

The required clinical assessments include:

- Physical exam
- Documentation of symptoms and toxicities
- Documentation of concomitant medications
- Serum testosterone
- Laboratory assessments to include CBCD, CMP and PSA
- A specimen for CTC analysis will be collected on the first date of this phase
- Radiologic assessments consist of the studies obtained at screening and should be obtained within 28 days of the castrate resistant date and at the frequency defined in the Study Calendar (Section 6.2) including:
    - Computed tomography (CT) scan of the abdomen and pelvis. The use of intravenous contrast is recommended though not required.
    - Radionuclide bone scan
    - CT scan of the chest with or without intravenous contrast or chest x ray. The same chest imaging modality used at screening should be used throughout the duration of the study.

If radionuclide bone scan shows the development of two or more new lesions, a confirmatory bone scan must be performed a minimum of 6 weeks later and show development of two additional new lesions to be considered radiographic progression per Section 11.2.

5.5 Treatment Discontinuation

Study treatment will continue until one of the following criteria applies:

- Evidence of progressive disease as defined per treatment phase below:
    - Docetaxel: Evidence of confirmed serologic progression per Section 11.1.1. Subjects will discontinue docetaxel but remain on study treatment and move into the Castrate Resistant Treatment Phase.
    - Enzalutamide: Evidence of radiographic or clinical progressive disease per Section 11.2. Investigators are encouraged to continue enzalutamide after serologic progression until the development of radiographic or clinical progression as defined in Section 11.2
- Unacceptable toxicity

- Withdrawal of consent for treatment only
- Deterioration of ECOG performance status to 4.
- Use of illicit drugs or other substances that may, in the opinion of the Investigator, have a reasonable chance of contributing to toxicity or otherwise skewing trial result.
- Severe allergic reaction to docetaxel or enzalutamide (Grade 3 or 4 hypersensitivity reaction). Subjects with Grade 3 or 4 hypersensitivity to docetaxel will remain on study treatment and move into the Castrate Sensitive Enzalutamide Treatment Phase.
- Development of an additional malignancy.
- Any other reason, at the Investigator's discretion with prospective notification of the Sponsor Investigator (e.g. non-compliance with study treatment or procedures, development of an intercurrent illness which would significantly affect assessments of clinical status and trial endpoints).
- Enzalutamide is held for greater than 21 days (for any reason)

Note: In the event the criteria for the final analysis are met, and there are subjects who have not yet been discontinued from study treatment, they will continue to receive therapy beyond the date the criteria for the study final analysis are met and until one of the above criteria applies.

5.6 End of Treatment Period

Every subject will undergo an end-of-treatment evaluation at the time it is determined that he is no longer eligible to receive both docetaxel and enzalutamide per Section 5.5. If enzalutamide is held at the Investigator's discretion for greater than 21 days, subject withdrawal from study treatment is required.

End of treatment evaluations will include:

- Physical examination
- Documentation of symptoms and toxicities
- Documentation of concomitant medications
- Laboratory evaluation to include a CBCD, CMP, and PSA if these laboratory studies have not been obtained within the prior 14 days

5.7 Follow up Period

Subjects will be tracked for at least 30 days following cessation of study treatment to monitor for adverse events, serious adverse reactions, and any other unanticipated problems. If the end of treatment visit occurs prior to 30 days from last dose of study treatment, subjects will be

contacted by telephone on day 31 or next business day if possible for monitoring; no later than by day 50.

If the subject cannot be contacted following three attempted telephone calls over a period of 10 business days, subject will be contacted in writing. Following this period, subjects will be contacted every 6 months +/- 30 days from treatment discontinuation by telephone, in writing, or during clinic visits after treatment discontinuation for collection of follow-up data until death, lost to follow-up, withdrawal, or until the criteria defined for the final analysis are met (Section 12.4.1). Note: in the event the criteria for the final analysis are met, and there are subjects who have not yet been discontinued from study treatment, subjects in follow-up will continue to be followed until all subjects have discontinued study treatment (see Section 7.4) and completed the required 30 day safety monitoring period (see above). Follow-up clinical information may also be obtained through chart reviews or other data sources (e.g. death registries). Lost to follow-up is defined as four consecutive unsuccessful documented attempts (telephone and written) to contact the subject.

All subjects, regardless of when they discontinue treatment, will be followed per standard of care procedures until all treatment-related toxicities have resolved, returned to baseline, stabilized, or are deemed irreversible.

5.8 Off Study

Subjects will be considered off-study when the following criteria are met:

- Death
- Lost to follow-up (as defined in Section 5.7).
- Consent withdrawal
- Withdrawn from study participation by the Investigator

Off-study subjects will not receive study treatment or participate in any study procedures, including data collection. Subjects may also be withdrawn from study treatment at the Investigator's discretion per Section 5.5. though continue to participate in study procedures and data collection if subject does not withdraw consent for study participation.

Any subject who goes off study will remain under medical supervision until discharge or transfer is medically acceptable.

In all cases, the reason for study withdrawal must be documented in the subject's medical records and/or research chart and in the CTMS. Withdrawn subjects are considered to be off-study.

Details for the premature termination of the study as a whole (or components thereof [e.g. investigational sites, treatment arms, dose steps]) are provided in Section 14.2.

6. Study Calendars

6.1 Docetaxel and Castrate Sensitive Enzalutamide Treatment Phases

Required Procedures	**Screening**	**Docetaxel Treatment Phase[a]**				**Castrate Sensitive Enzalutamide Treatment Phase[b]**			
		Cycle 1		**Cycles 2-6**		**Cycle 1[c]**	**Cycles ≥ 2**		
	Within 28 days prior to enrollment date	**Day 1[o]**	**Day 2**	**Day 1** (+/- 3 days)	**Day 2**	**Day 1**	**Day 1** (+/- 7 days)	**Week 26** (+/- 7 days)	**Week 52** (+/- 7 days)
Informed Consent	X								
Demographics	X								
Medical and Treatment History	X								
Symptoms and Toxicities	X	X		X		X	X		
Concomitant Medications	X	X		X		X	X		
Physical Exam[l]	X	X		X		X	X		
Radiology and Tumor Measurements	X[d]								
Laboratory Tests	X[e]	X[f]		X[f]		X[f]	X[f]		
PSA[n]	X	X		X		X	X	X[g]	X[g]
Docetaxel Administration[h]		X		X					
Enzalutamide Administration[i]		X	X	X	X	X	X		
Myeloid Growth Factor Administation[j]			X		X				
Medical or Surgical Castration	May have been initiated no greater than 16 weeks prior to enrollment date; continuously throughout treatment period [k]								
Circulating Tumor Cell Blood Collection[m]		X				X			

a. Docetaxel Treatment Phase cycle length = 21 days.

b. Castrate Sensitive Enzalutamide Treatment Phase cycle length = 56 days (8 weeks).
c. Castrate Sensitive Enzalutamide Treatment Phase cycle 1 day 1 should occur 28 days (+/- 3 days) from the last date of docetaxel administration.
d. Including a CT of the abdomen and pelvis (the use of IV contrast is recommended although not required), radionuclide bone scan and chest imaging (Chest x-ray or CT Chest with or without IV contrast (CT preferred). Required within 70 days prior to enrollment.
e. Including: CBC with differential, CMP, serum testosterone.
f. Including: CBC with differential, CMP. Laboratory assessment may occur up to 3 days prior to Day 1 of each cycle.
g. An additional laboratory visit to obtain a PSA only should be performed at 26 and 52 weeks (+/- 1 week) from the date of study enrollment if subject has not demonstrated progression as defined in Section 11 prior to this date.
h. Every 21 days (+/- 3 days) for a total of up to 6 cycles.
i. Enzalutamide administration should be continuous throughout the study period.
j. Pegfilgrastim or equivalent may be used at the Investigator's discretion. Administer on Day 2 (or up to+ 4 days from Day 2). Refer to Section 7.1.2.3 for guidelines regarding long acting prophylactic myeloid growth factor use.
k. Surgical castration with bilateral orchiectomy prior to study enrollment or medical castration with continuous use of a LHRH agonist or antagonist is required throughout the study period. Surgical castration or initiation of LHRH agonist/antagonist therapy must not have occurred greater than 16 weeks prior to enrollment date.
l. Including evaluation by body system, height (at screening only), weight, BSA calculation and ECOG performance status. Vital signs should include temperature, pulse rate, blood pressure, respiratory rate and oxygen saturation. Perform within 3 days prior to Day 1 of each cycle.
m. Whole blood samples (10 ml) in Streck cell-free DNA preservative tubes should be collected up to 3 days prior to Cycle 1 Day 1 and after completion of docetaxel
n. Perform at screening and within 3 days prior to Day 1 of each cycle
o. C1D1 pre-treatment procedures do not need to be repeated if the screening procedures were performed within 7 days prior to C1D1

6.2 Castrate Resistant Treatment Phase and End of Treatment

Required Procedures	Castrate Resistant Treatment Phase[p]		End of Treatment	
	Cycle 1	Cycle ≥ 2	End of Treatment	Follow-up
	Day 1[q]	Day 1 (+/- 3 days)	Within 30 days after the last dose of study medication unless otherwise specified	Every 6 months +/- 30 days after End of Treatment visit until criteria in Section 5.7 are met
Symptoms and Toxicities	X	X	X[r]	
Concomitant Medications	X	X	X[r]	
Physical Exam[aa]	X	X	X[r]	
Radiology and Tumor Measurements[s]	X	Every 12 weeks (+/- 7 days) until radiographic progression		X[z]
Laboratory Tests	X[t]	X[u]	X[v,r]	
Enzalutamide Administration[w]	X	X		
Medical or Surgical Castration	Continuously throughout treatment period[x]			
Circulating Tumor Cell Collection	X[y]			
Survival Analysis	X			

p. Castrate Resistant Treatment Phase cycle length = 28 days.
q. Castrate Resistant Treatment Phase cycle 1 day 1 defined by within 28 days of the castrate resistance date (see Section 5.1 for castrate resistance date definition).
r. If not obtained within 14 days of the End of Treatment Visit.
s. Including a CT of the abdomen and pelvis (the use of IV contrast is recommended although not required), radionuclide bone scan and chest imaging (Chest x-ray or CT Chest with or without IV contrast) (CT Chest preferred). Imaging should occur within 28 days of the castrate resistance date and every 12 weeks from Castrate Resistant Treatment Phase C1D1 (+/- 7 days) thereafter until radiographic progression.
If bone scan shows the development of 2 or more new lesions, a confirmatory bone scan must be performed a minimum of 6 weeks

later and show development of 2 additional new lesions to be considered radiographic progression per Section 11.2.2.

t. Serum testosterone only.
u. Including CBC with differential, CMP, PSA. Laboratory assessment may occur up to 3 days prior to Day 1 of each cycle.
v. Including CBC with differential, CMP, PSA if not obtained within 14 days.
w. Enzalutamide administration should be continuous throughout the study period and should be discontinued at the time of study completion.
x. Surgical castration with bilateral orchiectomy prior to study enrollment or medical castration with continuous use of a LHRH agonist or antagonist is required throughout the study period.
y. Whole blood samples should be collected (10 ml) in Streck cell-free DNA preservative tubes. Collect up to 3 days prior to Cycle 1 day 1
z. For subjects who discontinue study treatment and who have not yet had disease progression or started new anti-cancer therapy, every effort should be made to continue radiographic disease assessments at a frequency as determined by the Investigator
aa. Including evaluation by body system, weight, and ECOG performance status. Vital signs should include temperature, pulse rate, blood pressure, respiratory rate and oxygen saturation. Perform within 3 days of Day 1 of each cycle.

7. Study Treatment

7.1 Treatment

No investigational or commercial agents or therapies other than enzalutamide, docetaxel and ADT may be administered with the intent to treat the subject's malignancy. The study drugs will be exclusively used for the investigation specified in this protocol.

7.1.1 Androgen Deprivation Therapy

ADT with surgical castration (bilateral orchiectomy) or medical castration with LHRH agonist or LHRH antagonist therapy for metastatic disease may have been initiated no greater than 112 days (16 weeks) prior to the enrollment date. Subjects who have not initiated ADT prior to enrollment must begin ADT on C1D1. ADT should be administered continuously for the study duration in subjects who have not undergone surgical castration.

Prior combined androgen blockade therapy with anti-androgens other than enzalutamide (bicalutamide, nilutamide or flutamide) to permit tumor flare with initiation of LHRH agonist therapy is permitted; however, anti-androgen agents must have been discontinued at least 14 days prior to subject enrollment date.

The agents used for medical androgen deprivation therapy are commercially available and will be sourced locally. Refer to the individual agent's current Prescribing Information for further details on available formulations, preparation, administration and storage conditions.

7.1.2 Docetaxel

7.1.2.1 Premedication

Premedication is required to lower the risk of infusion related anaphylactoid reactions to docetaxel. Dexamethasone 8mg orally should be administered approximately 12 and 3 hours prior to docetaxel infusion. Additionally, dexamethasone 8mg should be administered orally or intravenously approximately 1 hour prior to docetaxel infusion. Antihistamine premedications may be used at the Investigator's discretion.

The use of concurrent daily prednisone with docetaxel is not permitted due to potential CYP3A4-mediated drug interactions with enzalutamide.

7.1.2.2 Dosage and Administration

Starting on the day of the enrollment visit, docetaxel should be administered intravenously over one hour at a dose of 75 mg/m^2 on day 1 every 21 days for up to six cycles during the Docetaxel Treatment Phase as defined in Section 5.4.1.1. Potential adverse events and dose modifications are described in Section 8.

Docetaxel is commercially available and will be sourced locally. Refer to current Prescribing Information for further details on available formulations, preparation and storage conditions

7.1.2.3 Myeloid Growth Factor Support

The incidence of neutropenic fever with the use of ADT and docetaxel is approximately 6-12%.[4,5] Prophylactic myeloid growth factor support may be used at the Investigator's discretion. If a subject experiences febrile neutropenia (FN), prophylactic myeloid growth

factor support is recommended with remaining docetaxel cycles. The incidence of FN with the study regimen will be continuously monitored during conduct of the study. If the incidence of FN exceeds the predetermined threshold defined in Section 12.4.4.3, the use of prophylactic myeloid growth factors will be required for subsequent enrolled subjects.

7.1.3 Enzalutamide

7.1.3.1 Dosage and Administration

Enzalutamide will be started on the day of the enrollment visit, concurrent with administration of the first docetaxel cycle. Enzalutamide is administered orally at 160mg once daily. Subjects will swallow four 40mg enzalutamide tablets whole with or without food at approximately the same time each day. Tablets should not be broken, chewed or crushed.

If a dose is missed, subject should take it as soon as possible unless the next dose is due within 12 hours. If vomiting occurs after taking a dose of study drug, an extra dose should not be taken. The subject should take the next dose at the regular time.

Treatment will be administered orally on an outpatient basis. Potential adverse events and dose modifications are described in Section 8.

Treatment monitoring during the Docetaxel Treatment Phase is defined in Section 5.4.1.1.

Treatment monitoring during the Castrate Sensitive Enzalutamide Treatment Phase is defined in Section 5.4.1.2.

Treatment monitoring during the Castrate Resistant Treatment Phase is defined in Section 5.4.1.3.

7.1.3.2 Drug Supply

Enzalutamide tablets for oral administration are formulated as yellow, round, film-coated tablets embossed with E 40. Enzalutamide will be supplied by Astellas. To request enzalutamide from Astellas, the requesting pharmacy will use the drug order forms available on the Astellas Portal. Drug inventory levels should be able to provide subjects with enzalutamide for up to eight weeks while waiting for additional ordered supplies.

The requesting pharmacy will receive enzalutamide 40mg tablets in study drug bottles containing 120 tablets each. The study drug bottles will have a label affixed containing study identification, product identification and quantity of tablets. Once the drug has been received, it must be kept in a secure, dry location. Study drug must be stored in its original study drug bottle at room temperature 20° to 25°C (68° to 77°F). Temperature excursions between 15° to 30°C (59° to 86°F) are permitted.

Study drug bottles dispensed to subjects will be labeled as an investigational treatment and subjects will be instructed to comply with the following directions:

- Store tablets in the original study drug bottle.
- Take tablets at the same time once daily, with or without food.
- Swallow tablets whole.
- If a dose is missed, it should be taken as soon as possible. Unless it is close to the next dose (within 12 hours), in which case the normal dose should be taken at the usual time.
- If vomiting occurs after taking a dose, an additional dose should not be taken. The next dose should be taken when due.
- Men should use adequate contraceptive methods (per Section 8.1) while taking study medication and for at least 90 days after completing therapy.

7.1.3.3 Discontinuation

Criteria for treatment discontinuation is defined in Section 5.5.

If a subject is discontinued from docetaxel treatment prior to completion of six cycles for reasons other than serologic progression of disease or withdrawal of consent for treatment, he may continue enzalutamide at the Investigator's discretion.

Because the interval between serologic (rising PSA) and radiographic progression may be clinically significant,[9] Investigators are encouraged to continue enzalutamide after serologic progression until the development of radiographic or clinical progression as defined in Section 11.2. Once serologic progression is established, treatment monitoring should occur during the Castrate Resistant Treatment Phase as defined in Section 5.4.1.3.

Subjects who discontinue both docetaxel and enzalutamide or require enzalutamide to be held at the Investigator's discretion for greater

than 21 days are considered to be off-treatment and should undergo end of treatment evaluation as defined in Section 5.5.

7.2 Concomitant Therapy

7.2.1 Medications

Anticancer therapy with agents other than enzalutamide, docetaxel and ADT is not permitted. Medication that is considered necessary for the subject's welfare, and which is not expected to interfere with the study treatment, may be given at the discretion of the Investigator.

Enzalutamide is metabolized by CYP2C8 and CYP3A4 in vivo. Specific caution should be taken when considering administration of a concomitant medication that is metabolized by these cytochrome enzymes. Such concomitant medication should be avoided if possible.

Avoid concomitant use of enzalutamide with strong CYP2C8 inhibitors, CYP3A4 inducers or CYP3A4, CYP2C9 or CYP2C19 substrates with a narrow therapeutic range.

Example medications are listed below; however, an updated list may be found at:
http://medicine.iupui.edu/clinpharm/ddis/table.aspx

Strong inhibitors of CYP2C8 include but are not limited to: gemfibrozil.

Strong inducers of CYP3A4 include but are not limited to: carbamazepine, efavirenz, modafinil, nevirapine, oxcarbazepine, phenobarbital, phenytoin, pioglitazone, rifabutin, rifampin, St. John's Wort and troglitazone.

CYP3A4, CYP2C9 or CYP2C19 substrates with a narrow therapeutic range include but are not limited to: alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus and warfarin.

Co-administration with warfarin is permitted if it cannot be avoided; however, subjects are required to conduct additional INR monitoring.

Glucocorticoids may induce CYP3A4. The use of glucocorticoid agents equivalent to prednisone 10mg or greater daily for longer than 14 days is not permitted.

7.2.2 Radiotherapy

The development of a new symptomatic disease site requiring palliative radiotherapy constitutes subjective disease progression as defined in Section 11.2.1.2.2 and requires subject withdrawal from study treatment. Palliative radiotherapy may begin at least one day after enzalutamide treatment is stopped.

7.2.3 Surgery

The impact of enzalutamide on wound healing is not known. If surgical intervention is necessary during study participation, enzalutamide should be stopped 48 hours before surgery and resumed no sooner than 48 hours after surgery.

If surgery is necessary during the Docetaxel Treatment Phase, management of docetaxel-induced cytopenias will be at the Investigator's discretion.

7.3 Treatment Compliance

Enzalutamide will be dispensed to subjects, and the study drug pill bottles returned to LCI Clinical Trials staff or delegate according to LCI standard operating procedures. Study drug bottles will be returned to the dispensing pharmacy. Tablets will be counted by pharmacy staff or delegate and reported to the applicable research designee. The number of tablets taken by the subject per cycle will be determined by these tablet counts.

Subject compliance with the treatment and protocol includes willingness to comply with all aspects of the protocol. Subjects will be asked to return used study drug bottles. Compliance with study treatment will be assessed at the end of each cycle.

At the discretion of the Sponsor-Investigator or the subject's Physician Investigator, a subject may be discontinued from the protocol for non-compliance with study visits or study drug.

7.4 Drug Accountability

Study drug will be stored at the investigational site in accordance with all applicable federal, state and local laws, rules, regulations, product labeling, Good Clinical Practice (GCP) and Good Manufacturing Practices (GMP) requirements and will be inaccessible to unauthorized personnel.

The study bottles will be returned to the pharmacy from which it was dispensed. Pharmacy staff or a delegate will count the number of pills and communicate that to the applicable research designee.

An adequate record of receipt, distribution, and destruction of all study drugs must be kept in the form of a Drug Accountability Form. The Investigator, or responsible party designated by the Investigator, will maintain a careful record of the inventory using the Drug Accountability Form.

7.5 Destruction

At the end of the study, unused supplies of enzalutamide will be destroyed according to LCI IDS Pharmacy policies. Destruction will be documented by the LCI IDS or dispensing pharmacy in the Study Closure Form provided by Astellas certifying that all remaining drug was destroyed.

8. Treatment-Related Adverse Events

Based on prior clinical studies with docetaxel and enzalutamide, the Investigator should anticipate that any of the following AEs could occur with the use of this medication.

The occurrence of AEs and SAEs should prompt immediate notification of the appropriate groups as outlined in Section 10. NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be used for grading treatment related-related adverse events.

8.1 Reproductive Risks

Enzalutamide and docetaxel can cause harm to the developing human fetus. For this reason, men with female partners of reproductive potential must agree to use adequate contraception (e.g., prior surgical sterilization, hormonal or barrier method of birth control; abstinence) prior to study entry, the duration of study participation and for at least 90 days after completion of study treatment.

Women who are pregnant or breast-feeding should not handle enzalutamide.

8.2 Dose Modifications for Androgen Deprivation Therapy

Dose modifications for ADT are not permitted. Subjects must remain on continuous ADT for the duration of study participation.

8.3 Dose Modifications for Docetaxel

8.3.1 Dose Levels

Dose modifications will follow pre-defined dose levels below. Unless otherwise stated below, subjects with Grade 1 or 2 docetaxel-related toxicities should be treated symptomatically and continued at the same docetaxel dose level. For subjects with Grade 3 or 4 docetaxel-related toxicities (other than anemia), docetaxel should be withheld until improvement to grade 0-1 (or baseline if greater than grade 1) and resumed at one dose level reduction. If greater than two dose reductions are required or greater than 21 days is required for resolution of toxicity to less than grade 2, docetaxel should be discontinued. If docetaxel is held for toxicity, enzalutamide and ADT should continue.

Table 1: Docetaxel Dose Levels

Dose Level	Docetaxel
0	75 mg/m^2
-1	65 mg/m^2
-2	55 mg/m^2

8.3.2 Myelosuppression

Dose modifications for neutropenia or thrombocytopenia on day 1 of each docetaxel cycle are listed below.

Table 2: Docetaxel Dose Modification for Hematologic Toxicities

Docetaxel	Granulocytes/mm^3	Platelets/mm^3
No dose adjustment	≥ 1500	≥ 100,000
Reduce one dose level	1000-1499	75,000-99,999
Delay dosing one week and reduce one dose level[a]	< 1000	< 75,000

[a]Delay resumption of docetaxel at one dose level reduction until recovery of granulocyte count ≥ 1500/mm^3 and platelet count ≥ 100,000/mm^3. If docetaxel is held for 3 consecutive weeks due to prolonged neutropenia or thrombocytopenia, discontinue docetaxel and continue ADT and enzalutamide alone. The use of prophylactic myeloid growth factors should be considered according to Section 7.1.2.3.

Dose reductions that are necessary for subjects who receive prophylactic myeloid growth factor support following the prior docetaxel cycle will be permanent.
For subjects who are started on prophylactic myeloid growth factor support following dose reduction for neutropenia, escalation to prior docetaxel dose level is permitted at the Investigator's discretion with subsequent docetaxel cycles if granulocyte count ≥ 1500/mm^3 on day one of the following cycle.

Dose reductions that are necessary for thrombocytopenia will be permanent.

8.3.3 Hepatic Dysfunction

Table 3: Docetaxel Dose Modification for Hepatic Toxicities

Docetaxel	Bilirubin		AST/ALT
Delay dosing one week and reduce one dose level[a]	> ULN	or	> 1.5x ULN with concomitant alkaline phosphatase > 2.5x ULN

[a]Delay resumption of docetaxel at one dose level reduction until recovery of bilirubin to ≤ ULN and/or AST/ALT to ≤ 1.5 times ULN if alkaline phosphatase > 2.5x ULN. If docetaxel is held for 3 consecutive weeks due to prolonged hepatic dysfunction, discontinue docetaxel and continue ADT and enzalutamide alone.

8.3.4 Peripheral Neuropathy

If grade 3-4 peripheral neuropathy occurs, subject should discontinue docetaxel and continue ADT and enzalutamide alone.

If grade 2 peripheral neuropathy occurs, docetaxel should be held until resolution to < grade 2 and resumed at one dose level reduction. If docetaxel is held > 21 days or > 2 dose reductions are required, subject should discontinue docetaxel and continue ADT and enzalutamide alone.

8.4 Dose Modifications for Enzalutamide

8.4.1 Dose Levels

Dose modifications will follow pre-defined dose levels below. Unless otherwise stated below, subjects with Grade 1 or 2 enzalutamide-related toxicities should be treated symptomatically and continued at the same enzalutamide dose level. For subjects with Grade 3 or 4 enzalutamide-related toxicities, enzalutamide should be withheld for one week or until symptoms improve to grade 0-2 and resume at one dose level reduction. If greater than two dose reductions are required or greater than 21 days is required for resolution of toxicity to less than grade 3, enzalutamide should be discontinued. Subjects who discontinue enzalutamide are considered to be off-treatment and should undergo end of treatment evaluation as defined in Section 5.6.

Table 4: Enzalutamide Dose Levels

Dose Level	Enzalutamide
0	160 mg
-1	120 mg
-2	80 mg

8.4.2 Seizures

Enzalutamide should be discontinued in any subject who experiences seizure activity. Subjects who discontinue enzalutamide are considered to be off-treatment and should undergo end of treatment evaluation as defined in Section 5.6.

8.4.3 Posterior Reversible Encephalopathy Syndrome

Posterior Reversible Encephalopathy Syndrome (PRES) is a neurologic disorder that can manifest as headache, confusion, seizure, visual disturbances and lethargy. Diagnosis requires confirmation by brain imaging. Enzalutamide should be discontinued in any subject who is diagnosed with PRES. Subjects who discontinue enzalutamide are considered to be off-treatment and should undergo end of treatment evaluation as defined in Section 5.6.

8.4.4 Hypersensitivity

Hypersensitivity reactions, including edema of the face, tongue, or lip have been observed with enzalutamide. Pharyngeal edema has been reported in post-marketing cases. Advise subjects who experience any symptoms of hypersensitivity to temporarily discontinue enzalutamide

and promptly seek medical care. Permanently discontinue enzalutamide for serious hypersensitivity reactions.

8.4.5 Ischemic Heart Disease

In the combined data of previous clinical studies, ischemic heart disease occurred more commonly in patients taking enzalutamide when compared to patients on placebo. Some ischemic events led to death in more patients taking enzalutamide then patients on placebo. Subjects should be monitored for signs and symptoms of ischemic heart disease. Manage cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. Permanently discontinue enzalutamide for Grade 3-4 ischemic heart disease.

8.4.6 Falls and Fractures

Falls and fractures occurred in patients receiving enzalutamide. Evaluate subjects for fracture and fall risk. Monitor and manage subjects at risk for fractures according to established treatment guidelines and consider use of bone-targeted agents.

8.4.7 Embryo-Fetal Toxicity

The safety and efficacy of enzalutamide have not been established in females. Based on animal reproductive studies and mechanism of action, enzalutamide can cause fetal harm and loss of pregnancy when administered to a pregnant female. Advise males with female partners of reproductive potential to use effective contraception during treatment with enzalutamide and for 3 months after the last dose of enzalutamide. Enzalutamide should not be handled by females who are or may become pregnant.

9. Data and Safety Monitoring Plan

Data will be collected in electronic case report forms (eCRFs). Study personnel will be trained on data entry by the sponsor and provided protocol-specific eCRF guidelines.

This protocol will be monitored according to the processes in effect for all LCI investigator-initiated studies and the protocol-specific monitoring plan and will abide by applicable regulations and guidelines (e.g. Good Clinical Practice [GCP]). It is the responsibility of the Sponsor-Investigator to monitor the safety data for this study. The Sponsor-Investigator and other sponsor-level team members will meet regularly to monitor subject consents,

enrollment and retention, safety data, and timeliness/validity/integrity of the data. Documentation of these meetings will be kept with study records. The Sponsor-Investigator will submit reports to the LCI Data and Safety Monitoring Committee according to the institutional Data and Safety Monitoring Plan.

This study will be monitored to ensure the study is conducted in compliance with the study protocol, SOPs of the LCI and Atrium Health Office of Clinical and Translational Research (and/or other participating institutional SOPs), the FDA, and other applicable regulations and guidelines (e.g. GCP).

Investigators and/or their delegated study personnel will be required to be available during the monitoring visits.

9.1 Communication Between Investigational Sites

Investigational sites will be required to report SAEs, protocol and subject level deviations, and any other problem that could affect the validity/integrity of the study data to the Sponsor-Investigator. All investigational sites will record AEs using the eCRFs and report SAEs to the Sponsor. SAEs will be reported within 1 business day of the Investigator learning of the event (immediately if the event is fatal or life-threatening). Protocol deviations should be reported to the Sponsor-Investigator promptly.

10. Safety Data Collection, Recording and Reporting

All subjects who receive at least one dose of study treatment will be evaluable for the safety analysis. All observations pertinent to the safety of the study treatment will be recorded and included in the final report.

Safety variables include the following: AEs and SAEs (whether related to investigational therapy or not), treatment administration, and, in some instances, changes in radiographic images, as ordered per the Investigator's discretion (e.g., for evaluation for pneumonitis). These assessments should be performed according to study protocol except for adverse events, which will be evaluated continuously throughout the study. Safety and tolerability, relationship to treatment and intensity will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. All adverse events (Grades 1 – 5) will be determined by the Investigator and documented in subject study charts.

10.1 Adverse Event Definitions

10.1.1 Unanticipated Problem (UAP) Definition

An UAP is any incidence, experience or outcome that is unexpected, given the information provided in research-related documentation (e.g. Investigator's brochure, protocol, informed consent) and the study population characteristics that is related or possibly related to participation in the research study and places the participant at an increased risk.

10.1.2 Adverse Event (AE) Definition

An adverse event or adverse experience is any untoward medical occurrence in a study subject who is administered a study drug that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of the study drug, whether or not considered related to the study drug. Pre-existing conditions that increase in frequency or severity or change in nature during or as a consequence of use of a drug in human clinical trials are also considered adverse events. Adverse events may also include pre or post-treatment complications that occur as a result of protocol-mandated procedures (e.g., invasive procedures such as biopsies).

Any continuing medical condition or clinically significant laboratory abnormality with an onset date before the first date of study drug administration should be considered pre-existing and should be documented in the subject's medical records and/or in the study chart.

An AE does not include:

- relapse or progression of the underlying malignant disease; however, the associated signs, symptoms, or diagnoses should be recorded as adverse events (e.g., "jaundice" due to new or increasing liver metastases, or "tumor pain" or "bone pain" due to progressive disease);
- medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion). The condition that leads to the procedure is the adverse event;
- situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions);
- overdose of either study drug or concomitant medication without any signs or symptoms unless the subject is hospitalized for observation

Laboratory abnormalities are usually not recorded as adverse events; however, signs and/or symptoms that are associated with laboratory findings requiring study withdrawal, dose modification, or medical intervention (e.g., anemia requiring transfusions or hyperglycemia

requiring treatment) or other abnormal assessments (e.g., ECG, radiographs, vital signs) must be recorded as adverse events if they meet the definition of an adverse event. In addition, laboratory abnormalities marked as clinically significant by the Investigator should also be recorded as adverse events on the eCRF. The Investigator will record the most severe grade of the clinically significant laboratory abnormality and will evaluate its relationship to the study drug and clinical condition if/when a clinically significant laboratory abnormality occurs.

All adverse events (including event name, grade, start/stop date and attribution) will be documented in the medical record and/or research chart.

The Investigator is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for each event for all subjects enrolled on the trial.

10.1.3 Adverse Event Attribution

Descriptions and grading scales listed in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for all AE reporting. Each AE will be assigned an attribution to one of the following categories:

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

For the purposes of statistical analyses, the relationship to study drugs will be further dichotomized into the following categories:

"Not Related": This includes events that are considered *unlikely* or *unrelated* to study drug(s). In the Investigator's opinion, the AE has an etiology other than the study drug(s) (e.g., pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).

"Related": This includes events that are considered *possibly*, *probably*, or *definitely* related to study drug(s). A temporal relationship exists between the event onset and administration of the study drug(s). It cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies. In the case of cessation or reduction of the dose, the event abates or resolves and reappears upon rechallenge. Ineffective study drug treatment should not be considered as causally related in the context of AE reporting.

10.1.4 Adverse Event Reporting

All AEs from the time of enrollment until 30 days after last dose of study treatment (including event name, grade, start/stop date and attribution) will be captured.

10.1.5 Suspected Adverse Reaction (SAR) Definition

A SAR is an adverse event in which there is reasonable possibility that the study drug(s) caused the adverse event as defined by 21 CFR 312.32. The Investigator is responsible for judging whether it is a reasonable possibility that the study drug caused the adverse event.

10.1.6 "Unexpected" Definition

An AE or SAR is to be considered unexpected if the event is not listed in the current version of the Investigator Brochure (IB), package insert or is not listed in the severity or specificity observed. Investigators should refer to the Safety Information section of the current IB and/or prescribing information for docetaxel and/or enzalutamide, including the DCSI (development core safety information), for the expected side effects of docetaxel and/or enzalutamide. As with any agent, there is always the potential for unexpected AEs, including hypersensitivity reactions.

10.1.7 Serious Adverse Event (SAE) Definition

An AE or SAR is to be considered serious if the Investigator deems it as such and the event results in any of the following outcomes:

- Death;
- Life-threatening situation (subject is at immediate risk of death);
- Inpatient hospitalization or prolongation of an existing hospitalization (excluding those for study drug administration, protocol-related procedures, palliative or hospice care, or placement of an indwelling catheter, unless associated with other serious events);
- Persistent or significant disability/incapacity;
- Congenital anomaly/birth defect in the offspring of a subject who received study drug;
- Other: Important medical events that may not result in death, be immediately life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are:

- Intensive treatment in an emergency room or at home for allergic bronchospasm;
- Blood dyscrasias or convulsions that do not result in hospitalization;
- Development of drug dependency or drug abuse.

Planned hospitalizations:
Elective surgeries that have been planned prior to subject enrollment in the study or for conditions existing prior to study enrollment do not need to be captured as SAEs, unless complications occur or the conditions are worse than the subject's baseline. If there are complications, they should be clearly documented.

10.2 Expedited Safety Reporting

10.2.1 Expedited Safety Reporting to the Sponsor-Investigator

SAEs must be reported to the Sponsor-Investigator within 1 business day.

SAEs will be captured from the time of enrollment through 30 days after the date of the last study drug administration. SAEs will be followed until clinical recovery is complete and laboratory tests have returned to baseline, until progression has been stabilized, or until there has been acceptable resolution of the event. This may at times cause the follow-up period for SAEs to be greater than 30 days. The above referenced 30-day time period applies even if the subject is removed from study treatment and begins new anti-cancer therapy during this time period. Similarly, the Sponsor-Investigator is responsible for following the subject during the required follow-up period even if the subject lives elsewhere or has been released from his or her care and is being treated under another provider.

SAEs that are determined to be related to study treatment or study procedures are reportable throughout the duration of the subject's participation (informed consent through off study).

10.2.2 Expedited Safety Reporting to the IRB

All events occurring during the conduct of a protocol and meeting the definition of an UAP or SAE will be reported to the IRB per their reporting requirements.

Protocol deviations that, in the Investigator's judgment, potentially caused harm to participants or others or indicates that the participants or others are at an increased risk of harm, or has adversely impacted data

integrity will be reported promptly to the IRB per IRB reporting requirements.

10.2.3 Expedited Safety Reporting to Astellas

Within 24 hours of awareness of a serious adverse event, whether or not related to the study treatment, the Sponsor-Investigator will submit a completed Medwatch 3500A Form, containing all required information to Astellas by either e-mail or fax.

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

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

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(s)

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

11. Measurement of Effect

11.1 Serologic Assessment

11.1.1 PSA Response

Serum PSA levels will be assessed as defined in the Study Calendar (Section 6). Subjects will be assigned a PSA response based on the following criteria:

- **Serologic Complete Response** – PSA level less than 0.2 ng/ml for two consecutive measurements at least 3 weeks apart.

- **Serologic Partial Response (50)** – PSA level decline of greater than or equal to 50% reduction of the maximal pre-ADT level for two consecutive measurements at least 3 weeks apart.

- **Serologic Partial Response (90)** – PSA level decline of greater than or equal to 90% reduction of the maximal pre-ADT level for two consecutive measurements at least 3 weeks apart.

- **Serologic Progression** – PSA increase ≥ 25% and ≥ 2 ng/ml above nadir value since initiation of ADT. Once serum PSA has increased above this threshold, an additional PSA measurement should be obtained at least 1 week later, confirming the initial value is above the defined threshold. If the second PSA measurement does not confirm the PSA increase ≥ 25% and ≥ 2 ng/ml above nadir value, then additional PSA values should be obtained at least one week apart until the initial PSA value above this defined threshold is confirmed. The date of the first recorded elevated PSA above the defined threshold will be deemed the date of progression. For subjects without a PSA decline following enrollment, progression will be defined by a PSA increase ≥ 25% and ≥ 2 ng/ml after 12 weeks following enrollment.

11.2 Radiographic Assessment

To evaluate objective response, it is necessary to determine tumor burden at baseline for comparison of subsequent assessments. The same method of assessment and technique should be utilized to define lesions identified at baseline and follow-up imaging.

Soft tissue lesion response and progression will be evaluated in this study using the Response Evaluation Criteria in Solid Tumors (RECIST) guideline version 1.1.[28] Skeletal lesion response and progression will be evaluated in this study using the Prostate Cancer Clinical Trials Working Group 2 (PCWG2) criteria.[27]

Only those subjects who have measurable disease present at baseline and have received at least one dose of study therapy will be considered evaluable for overall response.

11.2.1 RECIST

11.2.1.1 Measurable Disease

At baseline, all soft tissue tumor lesions should be defined as measurable or non-measurable.

Measurable:

- Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded), with a minimum size of 10 mm by CT scan or caliper measurement by clinical exam.
- Malignant lymph nodes must be measured by *shortest diameter*, with a minimum size of 15 mm.
- Lesions growing within a previously irradiated field may be considered measurable if enlargement has occurred following prior radiation treatment.

Non-measurable:

- All other lesions (<10 mm by long axis or malignant lymph nodes < 15 mm by short axis).
- Leptomeningeal disease, ascites, pleural or pericardial effusions.

Note: Bone lesions will not be evaluated per RECIST criteria. Please refer to Section 11.2.2 for evaluation of bone lesions.

11.2.1.2 Response Criteria

11.2.1.2.1 Target Lesions

All lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as *target lesions* and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements.

Pathological lymph nodes, which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan.

A *sum of the diameters* (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the *baseline sum diameters*. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions: All other lesions including pathological lymph nodes should be identified as *non-target lesions* and should also be

followed as 'present', 'absent', or in rare cases 'unequivocal progression'.

11.2.1.2.2 Definitions of Response

Complete Response (CR):

- Target lesion: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
- Non-target lesion: Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10 mm short axis).

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. This means that subjects with CR may not have a total sum of the diameters of 'zero'.

Partial Response (PR):

- Target lesion: At least a 30% decrease in the sum of diameters of target, taking as reference the baseline sum diameters.
- Non-target lesion: Not applicable

Stable Disease (SD):

- Target lesion: Neither sufficient shrinkage to qualify for a partial response, nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameters while on study.
- Non-target lesion: Not applicable.

Progressive Disease:

- Target lesion: At least a 20% increase in the sum of diameters of target lesions, taking as reference the *smallest sum on study* (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (*Note:* the appearance of one or more new lesions is also considered progression).
- Non-target lesion: *Unequivocal progression* (as described in RECIST version 1.1) of existing non-target lesions. (*Note:* the appearance of one or more new lesions is also considered

progression). Skeletal lesion response and progression will be evaluated using the PCWG2 criteria per section 11.2.2.2.

Non-Complete Response / Non-Progressive Disease:

- Target lesion: Not applicable
- Non-target lesion: Persistence of one or more non-target lesion(s)

Table 5: Summary of RECIST 1.1 (Subjects with measurable disease)

Target Lesions	Non-target Lesions	New Lesions	Overall Response	Best Response for this Category also requires
CR	CR	No	CR	Documented at least once ≥ 4 weeks from baseline
CR	Non-CR/Non-PD	No	PR	Documented at least once ≥ 4 weeks from baseline
CR	Not evaluated	No	PR	
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	Documented at least once ≥ 4 weeks from baseline
Not all evaluated	Non-PD	No	NE	N/A
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
CR = Complete Response, PR = Partial Response, SD = Stable Disease, PD = Progressive Disease, and NE = Inevaluable

Table 6: Summary of RECIST 1.1 (Subjects with non-measurable disease only)

Non-target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/Non-PD	No	Non-CR/ Non-PD
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Symptomatic Deterioration

- Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Symptomatic deterioration is *not* a descriptor of an objective response: it is a reason for stopping study therapy. It is

included as part of the criteria for determination of Progression Free Survival. The objective response status of such subjects is to be determined by evaluation of target and non-target disease.

- The development of pain or alternate symptoms requiring palliative radiotherapy constitutes subjective clinical disease progression, and study treatment should be stopped.

11.2.2 Evaluation of Skeletal Lesions

Skeletal lesion response and progression will be evaluated using the PCWG2 criteria.[27] Radionuclide bone scans should be utilized for characterization of skeletal lesions.

11.2.2.1 Baseline Assessment

The anatomic location and number of skeletal lesions detected on baseline radionuclide bone scan should be defined at baseline for subjects with one to three lesions. When four or more bone lesions are identified at baseline, subjects should only be classified as having "four or greater" lesions and whether or not all lesions are confined to the pelvis and vertebral bodies.

11.2.2.2 Definition of Progression

Progression of skeletal disease is defined as the appearance of two or more new lesions on follow up radionuclide bone scan followed by a confirmatory bone scan performed six or more weeks later that shows development of at least two additional new lesions. The date of progression is defined as the date of the first scan showing new bone lesions.

12. Statistical Considerations

12.1 Sample Size

The primary endpoint is 52-week PSA complete response, which will be determined as a binary variable for each subject indicating whether or not the PSA level at 52 weeks (+/- 1 week) is below 0.2 ng/ml. The 12-month PSA complete response rate with ADT plus docetaxel is 27.7%.[4] We estimate that the corresponding lower limit of the 95% confidence interval is 23.4%. Therefore, this design will be used to test the null hypothesis that the 52 week PSA complete response rate (<0.2 ng/mL) for a cohort of subjects treated with study therapy is less than or equal to 25%. Thirty-nine (39) subjects will be enrolled, and if 14 of 39 subjects achieve a 52-week PSA complete response then the null hypothesis will be rejected. The design will provide 90% power with a 1-sided alpha =

0.10 significance level, assuming the true 52-week PSA complete response rate is 45%. An improvement from 25% to 45% in 52-week PSA complete response rate is considered clinically relevant.

12.2 Endpoint Definitions

12.2.1 Serologic

12.2.1.1 52-week PSA Complete Response

52-week PSA Complete Response will be determined for each subject as a binary variable indicating whether or not the subject achieved a PSA complete response (CR) at 52-weeks (+/- 1 week) (52-week window) from enrollment date as determined by PSA response criteria in Section 11.1.1.

In subjects with missed PSA assessments at 52 (+/- 1) weeks:

- If a confirmed CR is achieved and at least one PSA assessment occurs beyond the 52-week window shows serologic complete response (providing the subject did not earlier experience confirmed progressive disease), the subject achieves 52-week PSA Complete Response.
- If confirmed-CR is achieved before the 52-week window and the first assessment after the 52-week window is not a CR, the subject did not achieve a 52-week PSA Complete Response.

12.2.1.2 PSA Response

PSA response will be determined for each subject as a binary variable indicating whether or not the subject achieved a best overall response of serologic CR or PR (50 or 90) as determined by PSA response criteria in Section 11.1.1.

12.2.1.3 Serologic Progression-Free Survival (sPFS)

sPFS is defined as the duration of time from enrollment to the study to first occurrence of either PSA progression or death. Disease progression can be objectively determined as per Section 11.1.1 or progression can be subjective as determined by the Investigator. Evidence for subjective progression must be documented in the medical records. For objective disease progression, the date of progressive disease (PD) is the date of the serologic assessment that identified PSA progressive disease as defined in Section 11.1.1. For

subjective disease progression, the date of PD is the date that the clinician makes the determination of PSA progression. If the subject died without documented disease progression, the date of progression will be the date of death. For surviving subjects who do not have documented disease progression, sPFS will be censored at the date of last serologic assessment. For subjects who receive subsequent anti-cancer therapy prior to documented disease progression, sPFS will be censored at the date of last serologic assessment prior to the commencement of subsequent therapy. Subjects who have an initial sPFS event immediately following 2 or more consecutive missed assessments will be censored at the date of the last assessment prior to those missed assessments. For participants with only one missed assessment, the documented progressive disease status and assessment date will be used.

12.2.1.4 Time to Castrate Resistance

Time to Castrate Resistance is defined as the duration from the date of enrollment to the date of castrate resistance or death from any cause. Date of castrate resistance is defined as the date of serologic progression as defined in Section 11.1.1 or the date of radiographic progression as defined in Section 11.2, whichever occurs first. If the subject died without documented castrate resistance, the date of castrate resistance will be the date of death. For surviving subjects who do not have documented castrate resistance, time to castrate resistance will be censored at the date of last serologic or radiologic assessment, whichever occurs last. Other aspects of the censoring mechanism will be the same as described for sPFS.

12.2.1.5 Time to Treatment Failure

Time to Treatment Failure is defined as the duration from the date of enrollment to the date of discontinuation of all study therapies, or death from any cause (whichever occurs first). For surviving subjects who do not discontinue all study therapies, time to treatment failure will be censored at the date of last study visit. Other aspects of the censoring mechanism will be the same as described for sPFS.

12.2.2 Radiographic

12.2.2.1 Objective Response

Objective response of soft tissue lesions will be determined for each subject as a binary variable indicating whether or not the subject achieved a best overall response of CR or PR of soft

tissue lesions as determined by RECIST in Section 11.2.1.2.2, provided there is an absence of progression of skeletal lesions.

12.2.2.2 Radiographic Progression-Free Survival

rPFS is defined as the duration of time from enrollment to the study to first occurrence of either radiographic progressive disease or death. Disease progression can be objectively determined as soft tissue lesion progression per RECIST in Section 11.2.1.2.2, skeletal lesion progression as defined by PCWG2 criteria in Section 11.2.2.2, or progression can be subjective as determined by the Investigator. Evidence for subjective progression must be documented in the medical records. For objective disease progression, the date of PD is the date of the radiographic assessment that identified radiologic progressive disease. For subjective disease progression, the date of PD is the date that the clinician makes the determination of disease progression. If the subject died without documented disease progression, the date of progression will be the date of death. For surviving subjects who do not have documented disease progression, rPFS will be censored at the date of last radiologic assessment. For subjects who receive subsequent anti-cancer therapy prior to documented disease progression, rPFS will be censored at the date of last radiologic assessment prior to the commencement of subsequent therapy. Subjects who have an initial rPFS event immediately following 2 or more consecutive missed assessments will be censored at the date of the last assessment prior to those missed assessments. For participants with only one missed assessment, the documented progressive disease status and assessment date will be used.

12.2.3 Overall Survival

Overall survival is defined as the duration from enrollment date to the date of death from any cause. Subjects who are alive or lost to follow-up at the time of the analysis will be censored at the last known date they were alive.

12.2.4 Safety Endpoints

Treatment administration

Treatment administration will be collected for each subject in terms of cumulative dose administered, dose intensity, intended dose intensity,

and relative dose intensity. These calculations will be done separately for enzalutamide and docetaxel.

Adverse events

Adverse events will be collected for each subject using NCI CTCAE v. 4.0 criteria. This will be done in terms of treatment-emergent adverse events, defined as follows:

- An AE that occurs after treatment start that was not present at the time of treatment start; OR
- An AE that increases in severity after treatment start if the event was present at the time of treatment start.

SAEs (including deaths while on study treatment) will also be collected for each subject.

12.3 Analysis Populations

Safety and efficacy analyses will be conducted on the population of subjects who begin study treatment. The date of initiation of study treatment will be the enrollment date. Analysis of objective response will be conducted on those subjects in the efficacy population with measurable disease present at baseline. The evaluable population for the primary analysis will include subjects who begin study treatment, do not discontinue enzalutamide prior to the development of castrate resistance for reasons other than can be attributed to study treatment, and are not censored according to the criteria in Section 12.2.1.1. Enrollment will continue until the targeted sample size described in Section 12.1 is achieved for the evaluable population.

12.4 Analysis Methods

12.4.1 Timing of Analysis

The primary analysis will occur after 52-week PSA complete response has been determined for all patients. Updated analyses will be conducted after the overall sPFS or rPFS censoring rate reaches 20% or when all surviving subjects have been on study for at least 3 years, whichever occurs first, or have become lost to follow up or taken off study. A final analysis will be conducted after the overall survival censoring rate reaches 20% or after all surviving subjects have been on study for at least 7 years, whichever occurs first, or have become lost to follow up or taken off study.

12.4.2 Subject Disposition

An accounting of all consenting subjects will be provided at the end of the study. This will include a breakdown of subjects who consented, were treated, discontinued treatment, died, and were lost to follow-up or withdrew consent.

12.4.3 Baseline Subject and Disease Characteristics

A summary of subject demographics and disease-related characteristics will be completed and clinically-significant subject medical history will be assessed.

12.4.4 Efficacy Analysis

12.4.4.1 Primary Analysis

The frequency and proportion of patients experiencing 52-week PSA complete response will be calculated. A corresponding 95% confidence interval will be estimated using the Clopper-Pearson method. A one-sided test for binomial proportions using the rejection regions described in Section 12.1 will be carried out, testing the null hypothesis that the 52-week PSA complete response rate is less than 25%. Based on the design and corresponding sample size calculations described in Section 12.1, if there are at least 14 52-week PSA complete responders the null hypothesis can be rejected.

Logistic regression techniques will be used to correlate 52-week PSA complete response rate to low- versus high-volume disease. This will include multiple regression models incorporating key baseline subject and disease characteristics.

12.4.4.2 Secondary Analyses

The frequencies and proportions of PSA best overall response and radiographic response rate in soft lesions will be calculated. Corresponding 95% confidence intervals will be estimated using the Clopper-Pearson method.

Overall, serologic progression-free survival, radiologic progression-free survival, time to castrate resistance, and time to treatment failure will be analyzed using Kaplan Meier techniques. Medians, 25th, and 75th percentiles will be estimated. Selected landmarks for OS (survival rates for every 6 months from 6 months to 84 months), sPFS (sPFS rates for every 6 months from 6 months to 60 months), rPFS (rPFS rates for every 6 months from 6 months to 84 months), time to castrate resistance, and time to treatment failure will be estimated

form the Kaplan Meier curves. Cox proportional hazards models will be used to correlate OS, sPFS, rPFS, time to castrate resistance, and time to treatment failure to disease volume. This will include multiple regression models incorporating key baseline subjects and disease characteristics.

Safety Analyses

The cumulative dose, dose intensity, and relative dose intensity will be summarized quantitatively. Incident rates for TEAEs, AEs leading to study drug discontinuation, SAEs and deaths while on study therapy will be summarized including Clopper-Pearson 95% confidence intervals. The incidence of TEAEs will be analyzed in term of maximum grade severity experienced for each subject.
It has been reported that the incidence of neutropenic fever with the use of ADT and docetaxel is approximately 6-12%. Prophylactic myeloid growth factor support may be used at the Investigator's discretion. If it becomes evident that the rate of neutropenic fever (in patients who do not receive prophylactic myeloid growth factor) with the addition of enzalutamide treatment convincingly exceeds 0.20, study procedure will mandate the use of prophylactic myeloid growth factor. This rule will hold if the posterior probability of the rate of neutropenic fever exceeding 0.20 is 50% or higher. The prior for this monitoring rule is beta (3,22). This means that our prior assumption regarding the proportion of neutropenic fever in patients not receiving myeloid growth factor is 12% (the high end of estimates of incidence of neutropenic fever with use of ADT and docetaxel), and there is 90% probability that his proportion is between 3.50% and 23.98%. The operating characteristics of the stopping rule are given in the following table and are based on 5000 simulations.

Neutropenic fever events observed	Maximum number of enrolled subjects for mandating myeloid growth factor	Posterior probability: Pr(Risk>0.20|Data)
4	9	0.501
5	13	0.524
6	19	0.503
7	24	0.509
8	29	0.510
9	34	0.502

12.4.4.3 Exploratory Analyses

Cox proportional hazards models and logistic regression will be used to assess the correlations between baseline circulating tumor cell levels and androgen receptor splice variant 7 (Arv7) protein expression with clinical outcomes.

12.5 Interim Analyses

No interim analyses are planned.

13. Biomarker Analysis

13.1 Circulating Tumor Cells

In attempt to identify molecular markers predictive of response to therapy, additional molecular testing will include enumeration of CTCs and characterization of CTC ARv7 protein expression by immunofluorescence at the following time points in each subject:

- Prior to docetaxel
- After completion of docetaxel
- Following development of castrate resistance

14. Study Completion

14.1 Completion

The study will be considered complete when one or more of the following conditions is met:

- All subjects are dead and/or withdrawn from the study.
- All subjects have discontinued from the study.
- The IRB, LCI DSMC, Sponsor-Investigator or Astellas discontinues the study because of safety considerations.
- The Sponsor-Investigator defines an administrative or clinical cut-off date.

14.2 Termination

The study will be terminated when one or more of the following conditions occur:

If risk-benefit ratio becomes unacceptable owing to, for example:

- Safety findings from this study (e.g. SAEs)
- Results of any interim analysis
- Results of parallel clinical studies
- Results of parallel animal studies (e.g. toxicity, teratogenicity, carcinogenicity or reproduction toxicity).
- If the study conduct (e.g. recruitment rate; screen failure rate; withdrawal rate; data quality; protocol compliance) does not suggest a proper completion of the trial within a reasonable time frame.

The Sponsor-Investigator has the right to close the trial at any site and at any time.

For any of the above closures, the following applies:

- Closures should occur only after consultation between involved parties.
- All affected institutions must be informed as applicable according to local law.
- In case of a partial study closure, ongoing subjects, including those in follow-up, must be taken care of in an ethical manner.

Details for individual subject's withdrawal can be found in Section 5.8.3.

14.3 Retention of Records

Essential documentation (e.g. adverse events, records of study drug receipt and dispensation), including all IRB correspondence, will be retained for at least 2 years after the investigation is completed. Documentation will be readily available upon request.

15. Ethical and Legal Issues

15.1 Study Conduct

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Investigator abides by Good Clinical Practice (GCP) guidelines and under the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s).

Documented approval from appropriate agencies (e.g. IRB) will be obtained for all participating centers before start of the study, according to GCP, local laws, regulations and organizations. When necessary, an extension, amendment or renewal of IRB approval must be obtained and forwarded to Astellas.

Strict adherence to all specifications laid down in this protocol is required for all aspects of study conduct. The Investigators may not modify or alter the procedures described in this protocol.

Modifications to the study protocol will not be implemented by the Sponsor-Investigator without discussion and agreement by Astellas. However, the Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to the trial subjects without prior approval from applicable agencies. As soon as possible, the implemented deviation or

change, the reasons for it and if appropriate the proposed protocol amendment should be submitted to the appropriate agencies. Any deviations from the protocol must be explained and documented by the Investigator.

The Sponsor-Investigator is responsible for the conduct of the clinical trial at the sites in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Sponsor-Investigator is responsible for personally overseeing the treatment of all study subjects. The Sponsor-Investigator must assure that all study site personnel, including sub-Investigators and other study staff members, adhere to the study protocol and all applicable regulations and guidelines regarding clinical trials both during and after study completion.

The Sponsor-Investigator will be responsible for assuring that all the required data will be collected and properly documented.

15.2 Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

15.3 Publication

At least thirty (30) days prior to submission for publication, presentation or use, the Sponsor-Investigator must submit any proposal, oral or written to Astellas for review and comment.

The Sponsor-Investigator will ensure that the information regarding the study be publicly available on the internet at www.clinicaltrials.gov.

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