

Title: A Phase 2 Study of Docetaxel plus Apalutamide in Castration-Resistant Prostate Cancer Patients Post Abiraterone Acetate

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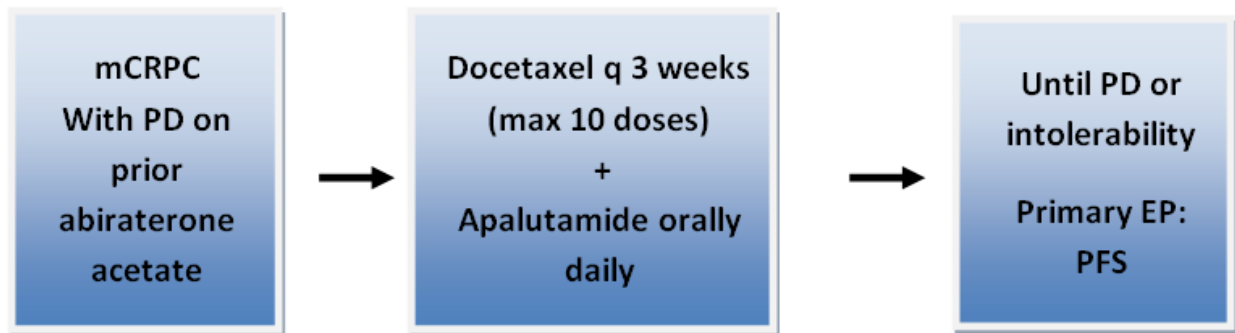
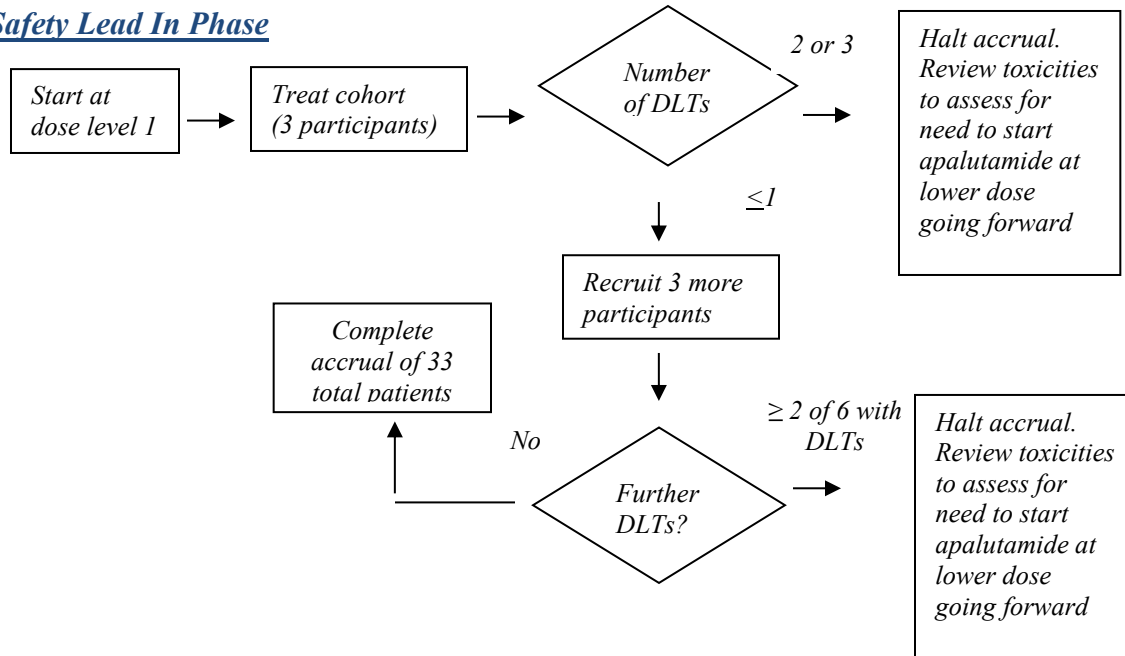
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SCHEMA

Safety Lead In Phase



*Cycle: 21 days +/- 3 days.

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1. OBJECTIVES

1.1 Study Design

A single arm, open label phase 2 design will evaluate the combination of docetaxel with apalutamide (ARN-509). Up to 33 patients with metastatic castration-resistant prostate cancer (CRPC) will be enrolled. A 6-patient safety lead in phase will be undertaken prior to open enrollment. If 0 to 1 of 6 patients have no dose limiting toxicities (DLTs) as defined in Section 6.1, the study will open to full enrollment. With 30 evaluable patients, there is a 90% power to detect a significant improvement in median progression-free survival (PFS) from 4 months (anticipated with docetaxel alone post abiraterone acetate) to 6.5 months with the combination.

1.2 Primary Objectives

To evaluate progression-free survival on the combination of docetaxel plus apalutamide

1.3 Secondary Objectives

To assess the following outcomes with the combination of docetaxel plus apalutamide:

- Safety
- Tolerability
- Dose-limiting toxicities in the safety lead in group
- Evaluate the effect of apalutamide on docetaxel pharmacokinetics
- Radiologic time to progression (rTTP)
- Time to disease progression
- Time to prostate-specific antigen (PSA) progression (TTPP)
- Time to treatment failure (progression plus intolerability)
- Objective response rate
- PSA (biochemical) response
- Percent change in PSA from baseline
- Overall survival (OS)

1.4 Exploratory Objectives

- To assess for changes in efficacy (e.g., PFS, PSA response, OS) in patients based on presence or absence of variants of the androgen receptor (AR) as assessed by ctDNA in plasma and mRNA by qtPCR in whole blood.

2. BACKGROUND

2.1 Study Disease(s)

Castration-resistant prostate cancer is a fatal disease from which nearly 30,000 men die annually in the United States.¹ Docetaxel has long been the backbone of treatment after initial resistance to androgen deprivation therapy with a median OS of 18 months.² More recently, docetaxel was

proven to increase OS when given in combination with androgen deprivation therapy (ADT) at the time of diagnosis of hormone-sensitive metastatic prostate cancer, eliciting a greater than 12 month OS benefit compared to ADT alone (CHAARTED).³ The last several years have witnessed significant improvements in our treatment armamentarium for CRPC with the introduction of the next generation biosynthesis inhibitor abiraterone acetate and the androgen antagonist enzalutamide. Both agents significantly increase progression-free survival (PFS), PSA response rates, and overall survival in the chemotherapy naïve and post-chemotherapy settings.⁴⁻⁷ This efficacy underscores the ongoing dependence on the androgen receptor (AR) pathway despite resistance to the first line hormonal blockade.

In the US, almost all CRPC patients will receive abiraterone acetate, enzalutamide, and docetaxel at some point during their disease course. Given the easy oral administration and tolerability the second line hormonal maneuvers are often prescribed prior to docetaxel. Several retrospective series have reported the efficacy results of either abiraterone acetate administered after enzalutamide or enzalutamide given after abiraterone acetate and have shown only modest PSA and PFS results, when compared to the results leading to approval of either drug. In patients who received abiraterone acetate after enzalutamide, PSA responses ranged from 4-8% and PFS from 2.7 to 3.9 months.^{8,9} In patients who received enzalutamide after abiraterone acetate, PSA responses ranged from 21-28%, and in one study, median PFS was around 3.0 months.^{10,11} In patients treated with both prior docetaxel and abiraterone acetate, median time on enzalutamide was 3.2 months with 18% having a PSA response $\geq 50\%$.¹² Pertinent to this study, several studies have retrospectively analyzed the response to docetaxel after abiraterone acetate, with PSA declines $\geq 50\%$ in 26-63%, median time to PSA progression of 4.1-4.6 months, median PFS 3.7-5.1 months, and median OS of 11.7 -12.5 months just over a year.¹³⁻¹⁸ No abiraterone acetate-refractory patients responded to docetaxel.

Reasons for these lower responses in the third and fourth line setting are likely the transition to a more androgen autonomous disease state and various resistance mechanisms. To investigate this, we should consider the recent results of the ECOG led trial, E3805, which showed that docetaxel given at the time of starting ADT for metastatic hormone-sensitive prostate cancer (HSPC) improved overall survival by 13 months from 44 to 57 months.³ Moreover, for patients with a pre-specified definition of high volume disease, the overall survival was further increased from 32 months to 49 months. It is unknown why docetaxel deployed when the prostate cancer is hormone sensitive improves overall survival to such a dramatic degree. Preclinical and clinical experience has documented minimal activity of taxane therapy without ADT.^{19,20}

On the other hand, the observations from the preclinical work²¹ and E3805 showing marked activity of ADT with taxane therapy at time of starting ADT suggests concurrent AR inhibition may modulate the expression of AR regulated genes, which in turn enhances docetaxel sensitivity. One well characterized mechanism of docetaxel resistance in prostate cancer cells is up-regulation of transporters which protect the cancer cell by facilitating efflux of docetaxel from the cells. Notable preclinical reports include the finding that the ATP-binding cassette (ABC) transporter family, ABCB1, was one of the top up-regulated genes in a taxane resistant variant of C4-2B²². Knockdown of ABCB1 by shRNA re-sensitized the cells to docetaxel treatment. Others have implicated another ABC transporter, BCRP/ABCG2, after they observed that expression of Pim-1L and BCRP are upregulated in mitoxantrone and docetaxel-resistant

prostate cancer cell lines²³. Furthermore, knocking-down Pim-1L blocked multimer formation of endogenous BCRP and also re-sensitized the resistant cells to docetaxel. The ATP-cassette binding protein 4 (ABCC4) is another transporter implicated in prostate cancer resistance to docetaxel preclinically²⁴. The docetaxel-resistant MLL cells had higher levels of ABCC4 than the docetaxel sensitive PC3 cells, which had no detectable ABCC4 expression and inhibition of ABCC4 resulted in MLL cells becoming sensitive to docetaxel. Based on our RNA Seq data of the prostate cancer cell lines we have noted ABCC4 was induced by the androgen, dihydrotestosterone (DHT) by more than 2 fold in LNCaP while in LAPC4 we observed androgen induced up-regulation of other ABC transporters, ABCC11, ABCC1 and ABCA5. The latter adds plausibility to the notion that AR inhibition could decrease the levels and function of these transporters in metastatic HSPC and be the basis of the enhanced activity of docetaxel when given in conjunction with ADT in metastatic HSPC.

Another line of evidence suggesting transporters may impact docetaxel activity in prostate cancer is germline variants of these efflux genes are associated with improved overall survival when patients are treated with docetaxel in CRPC. Specifically, although the mechanism is unclear, SNPs in ABCB1 and ABCG2 have been shown to be associated with improved overall survival in men with CRPC treated with docetaxel.^{25,26}

AR splice variants such as AR-V7 may play a role in such resistant states. AR-V7 is an AR isoform that lacks the ligand binding domain to which abiraterone and enzalutamide bind. Patients with this isoform have a constitutively active AR leading to resistance.²⁷ Recent work published by Antonarakis et al demonstrated that patients with the AR-V7 isoform measured in their circulating tumor cells (CTCs) had resistance to enzalutamide and abiraterone.²⁷ No AR-V7 positive patients achieved a PSA response to either agent compared to 53% and 68% of AR-V7 negative patients respectively. Similar significantly improved outcomes were seen in PSA-PFS, radiologic PFS, and OS in AR-V7 negative patients compared to those whose CTCs expressed the positive variant.

Another line of evidence linking AR activation with docetaxel activity is the observation that the ARv7 splice variant, which lacks the hinge region of the AR does not co-sediment with microtubules or coprecipitate with the dynein motor protein. This was associated with the ARv7-expressing LuCap23.1 tumor xenograft being docetaxel resistant²⁸. In contrast, the microtubule-interacting splice variant ARv567 is sensitive to taxane-induced microtubule stabilization and the ARv567-expressing LuCap86.2 tumor xenografts are sensitive to docetaxel. This body of work suggests the interactions between docetaxel, androgen receptor and microtubule proteins are inter-related and impact the ability to kill prostate cancer cells. As such the findings of concurrent ADT and docetaxel having a profound effect in E3805 may be due to more pronounced blockade of AR transportation to nucleus secondary to ADT leading to ligand depletion and docetaxel blocking AR transportation. As such, hormone sensitive metastatic prostate cancer cells may be more reliant on microtubule mediated trafficking of AR. It is also recognized that cancer cell resistance to taxanes can be seen with microtubule mutations decreasing affinity for taxanes, which results in less cytotoxicity^{29,30}. The potential for the AR-docetaxel-microtubule interaction observations being associated with outcomes will be explored as part of the exploratory studies detailed below.

To support the tenet that AR activation can impact the cytotoxicity of docetaxel we can draw from recent work, which has elucidated biological insights as to how AR modulation enhances another cytotoxic, radiation. Specifically, ADT plus radiation improves cancer control and overall survival when administered to patients with localized disease compared to either alone³¹⁻³³. Recent preclinical insights have shown that AR regulated DNA repair genes are decreased with AR blockade and that this reduction enhanced radiation sensitivity^{34,35}.

This body of work adds plausibility that AR modulation may alter genes and enhance activity of another cytotoxic agent such as docetaxel. These findings could be relevant to decreasing AR signaling with ARN509 plus ADT in the CRPC and hormone sensitive metastatic prostate cancer setting.^{34,35}

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2.3 Rationale

To combat potential resistance mechanisms of chemoresistance and AR autonomous clones in patients with metastatic CRPC who have received prior abiraterone, we propose to study the combination of docetaxel and apalutamide. Because both agents are metabolized (substrates) of CYP3A4 and apalutamide may also be an inducer of CYP3A4, we will perform a safety lead in phase with a pharmacokinetic evaluation of the two agents.

2.4 Correlative Studies Background

Preclinical and clinical studies have shown AR targeted therapies are less effective if the AR is mutated. For example, enzalutamide was less effective if ARv7 was present in CTCs or if mutations in AR DNA were seen in ctDNA from plasma. An alternative strategy to assess the presence of AR splice variants is with qtPCR of whole blood. As such, we will assess the efficacy of docetaxel with apalutamide by assessing PFS, PSA response and OS in patients with and without evidence of variants of the AR as assessed by ctDNA in plasma and mRNA by qtPCR in whole blood. We anticipate the use of a cytotoxic chemotherapy in combination with AR targeting will address clones both responsive to AR inhibition and not responsive to AR inhibition and that the efficacy outcomes will be better for the combination in patients with variants of the AR receptor treated with the combination than with enzalutamide alone or docetaxel alone. We will also assess whether the combination is associated with greater efficacy in the patients without aberrations in the AR than when treated with docetaxel or enzalutamide alone.

3. PARTICIPANT SELECTION

All screening assessments must be performed within 30 days prior to the date of registration.

3.1 Inclusion Criteria

- Histologically confirmed adenocarcinoma of the prostate
- Castration-resistant prostate cancer requires the following criteria:
 - A castrate level of testosterone (< 50ng/dL)
 - Prostate cancer progression on or since last treatment as documented by PSA rise or bone progression according to PCWG2³⁹ or soft tissue radiographic progression according to RECIST criteria Version 1.1

- If on anti-androgen, will need to show no PSA decline after at least a 6-week withdrawal period from the last dose of bicalutamide or nilutamide or 4 weeks from last flutamide dose
- Will require a 2-week washout period from last dose of ketoconazole, abiraterone acetate or radiation
- Treatment with abiraterone acetate for CRPC in the past is required. It does not need to be the last treatment prior to enrollment.
- There is no limit to number of prior therapies
- Metastatic disease by bone scan or other nodal or visceral lesions on CT or MRI
- Age \geq 18 years
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (See Appendix A)
- Adequate organ function as evaluated by the following laboratory criteria:
 - Hemoglobin \geq 9g/dL; no transfusions and erythropoietin supplementation permitted within the last 3 months
 - Absolute neutrophil count (ANC) \geq 1500/ μ L
 - Platelet count \geq 100 x 10⁹/L
 - Total bilirubin \leq upper limit of normal (ULN) (Note: In subjects with Gilbert's syndrome, if total bilirubin is $>$ ULN, measure direct and indirect bilirubin and if direct bilirubin is \leq ULN, subject may be eligible)
 - AST and ALT $<$ 2.5 x ULN or $<$ 5x the ULN if liver metastasis
 - Serum creatinine $<$ 2.0 \times ULN or creatinine clearance $>$ 30cc/min
 - Serum albumin \geq 3.0 g/dL
 - Serum potassium \geq 3.5 mmol/L (if $<$ 3.5, can be repleted and reassess for eligibility as long as stable off potassium supplementation for $>$ 48 hrs)
- Ability to swallow the study drug as a whole tablet
- The effects of apalutamide and docetaxel on the developing human fetus are unknown. For this reason and because chemotherapeutic agents are known to be teratogenic, men must agree to use adequate contraception. Specifically, they must agree to use a condom (even men with vasectomies) and another effective method of birth control if he is having sex with a woman of childbearing potential or agree to use a condom if he is having sex with a woman who is pregnant while on study drug and for 3 months following the last dose of study drug. They must also agree not to donate sperm during the study and for 3 months after receiving the last dose of study drug.
- Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

- Pathology consistent with majority of specimen having small cell carcinoma of the prostate (prostate cancer with neuroendocrine features is acceptable).
- Prior treatment with enzalutamide for CPRC; non-CRPC use is allowed (e.g., neoadjuvant, combined with radiation for localized disease and didn't progress while on it in those settings)
- Prior treatment with docetaxel chemotherapy in the castration-resistant setting. Prior treatment with docetaxel in either the neoadjuvant or adjuvant setting or for hormone

sensitive disease (e.g., CHAARTED population) is allowed, as long as therapy was completed > 12 months prior to study registration

- Presence of untreated brain metastasis
- Seizure or known condition that may pre-dispose to seizure (including but not limited to prior stroke or transient ischemic attack within 1 year prior to first dose, brain arteriovenous malformation; or intracranial masses such as schwannomas and meningiomas that are causing edema or mass effect). *Loss of consciousness within 12 months may be permitted upon discussion with study PI.*
- Medications known to lower the seizure threshold (see list under prohibited medications, Appendix C) must be discontinued or substituted prior to study treatment initiation.
- Current, recent (within 4 weeks of the first dose of this study), or planned participation in an experimental drug study with an experimental agent.
- Persistent grade > 1 (NCI CTCAE v4.0) AEs due to investigational drugs that were administered more than 14 days before registration.
- Radiation within 2 weeks prior to registration.
- Peripheral neuropathy \geq Grade 2.
- Current evidence of any of the following:
 - Uncontrolled hypertension despite addition or adjustment of antihypertensive regimen
 - Gastrointestinal disorder affecting absorption
 - Active infection (e.g., human immunodeficiency virus [HIV] or viral hepatitis) or other medical condition that would make prednisone/prednisolone (corticosteroid) use contraindicated
- Uncontrolled intercurrent illness including, but not limited to, severe or unstable angina, myocardial infarction, symptomatic congestive heart failure (defined as New York Heart Association Grade II or greater), arterial or venous thromboembolic events (e.g., pulmonary embolism), or clinically significant ventricular arrhythmias, significant vascular disease (e.g. aortic aneurysm, aortic dissection), or symptomatic peripheral vascular disease within 6 months prior to registration.
- Psychiatric illness/social situations that would limit compliance with study requirements.
- Any condition that in the opinion of the investigator, would preclude participation in this study
- History of allergic reactions or severe hypersensitivity reactions to drugs formulated with polysorbate 80 or antisense oligonucleotides.
- History of allergic reactions attributed to compounds of similar chemical or biologic composition to apalutamide or docetaxel
- Participants receiving any medications or substances that are strong inhibitors or inducers of CYP3A4 are ineligible. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated list such as <http://medicine.iupui.edu/clinpharm/ddis/table.aspx>; medical reference texts such as the Physicians' Desk Reference may also provide this information. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product.
- Inability to comply with study and/or follow-up procedures

3.3 Inclusion of Women and Minorities

Men of all races and ethnic groups are eligible for this trial.

Women are not eligible for this trial as they do not have prostates and as such do not get prostate cancer.

4. REGISTRATION PROCEDURES

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

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

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

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Registration cancellations must be made in OnCore as soon as possible.

4.2 Registration Process for DF/HCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

5. TREATMENT PLAN

5.1 Treatment Regimen

Apalutamide will be taken orally once daily. Apalutamide dosing will start on Cycle 1 Day 2 for the PK cohort and on Cycle 1 Day 1 for the rest of the patients. Docetaxel will be administered every 3 weeks intravenously in the infusion center of each site for a maximum of 10 cycles.

Quantities of apalutamide have been predetermined at the start of the study. On average, patients may receive up to two years' worth of treatment. The amount of time on therapy is subject to change and any patients wishing to continue past two years should discuss with their treating physician and overall PI. A treatment cycle is defined as 21 consecutive days. Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

Of note, if 2 or more patients of the first 6 experience a dose limiting toxicity (DLT), the dosing of the study drugs will be reviewed and the protocol amended as necessary.

Table 1: Treatment Regimen

Regimen Description					
<i>Agent</i>	<i>Premedications; Precautions</i>	<i>Dose</i>	<i>Route</i>	<i>Schedule</i>	<i>Cycle Length</i>
Apalutamide	Take with food consistently at approximately the same time each morning.	Starting dose of 240mg (four 60mg tablets)	Orally	Daily	21 days (3 weeks) (+/- 3 days)
Docetaxel	Premedicate with corticosteroids per institutional guidelines	75mg/m ² in 250 cc NS	IV over 1 hr +/- 10 min	Day 1 of each cycle; for up to 10 cycles max	
Prednisone	Refer to the package insert	5mg tablet	Orally Can be dose reduced after cycle 1 per standard of care (SOC).	Twice daily (may hold on days receiving steroid premeds for chemo)	

The participant will be requested to maintain a medication diary of each dose of medication. The medication diary should be completed by the participant each cycle and returned to study staff.

5.2 Laboratory Studies

5.2.1 Pre-Treatment Criteria for C1D1. Subsequent Day 1 dosing criteria should follow section 6 guidelines:

C1D1 labs should meet the following criteria prior to treatment:

- Hemoglobin \geq 9g/dL: no transfusions and erythropoietin supplementation permitted within the last 3 months
 - ANC \geq 1500/ μ L
 - Platelet count \geq 100 x 10⁹/L
 - Total bilirubin \leq ULN (Note: In subjects with Gilbert's syndrome, if total bilirubin is > ULN, measure direct and indirect bilirubin and if direct bilirubin is \leq ULN, subject may be eligible)
 - AST and ALT < 2.5 x ULN or < 5x the ULN if liver metastasis
 - Serum creatinine < 2.0 \times ULN or creatinine clearance > 30cc/min
- If screening labs have been done within 72 hrs of C1D1, they may be used in lieu of

repeat C1D1 labs.

- Day 1 labs must be reviewed by study staff prior to treatment to ensure they meet criteria as detailed in Section 6
- For cycle 2 and onward, if assessments due on day 1 of the cycle are completed within 72 hours prior to day 1 treatment, they do not need to be repeated (unless a toxicity or assessment parameter needs to be re-assessed in order to meet criteria to treat)

5.2.2 Serial thyroid function monitoring

- Thyroid function tests to include thyroid stimulating hormone (TSH), total T3 and free T4 should be evaluated at screening. The TSH should subsequently be evaluated throughout the study (with T3 and T4 done only if TSH is abnormal). These labs do not need to be reviewed prior to dosing on D1 and subsequent cycles, but once results have returned, the subsequent dosing should be adjusted as needed per the dosing modification guidelines in section 6.
 - Screening: TSH, total T3, free T4
 - Day 1 of each cycle for the first 4 cycles: TSH; only if abnormal at prior assessment: total T3 and free T4. Once T3 and FT4 normalize, they do not need to continue to be checked unless TSH becomes abnormal again
 - Every 12 weeks starting after Cycle 5: TSH; only if abnormal at prior assessment: total T3 and free T4. Once T3 and FT4 normalize, they do not need to continue to be checked unless TSH becomes abnormal again

5.3 Agent Administration

5.3.1 Apalutamide

- Apalutamide will be given at a fixed dose of 240 mg orally daily: four 60 mg tablets taken all at once.
- The drug should be taken with food at the same time each day within 30 minutes after a meal for consistency. It will be advised that patients both on the PK cohort and in the non-PK cohort take apalutamide with food.
- **In the PK cohort, the first dose of apalutamide in cycle 1 will be given on day 2 after the 24 hour PK sample has been collected. On day 1 of cycle 2, the dose of apalutamide should be taken after the pretreatment PK sample is collected, coincident with starting the docetaxel infusion.**
- **For the non-PK cohort, the first dose of apalutamide will start on cycle 1, day 1 or day 2 if logistical issues with scheduling. The drug should be taken at approximately the same time each day.**
- The drug should not be crushed, dissolved, or chewed.
- A drug diary will be supplied
- A missed dose should be taken as soon it is remembered. If twelve or more hours have lapsed since a missed dose, participants should not take the missed dose; rather the

participant should resume dosing at the next scheduled dose. Participants should not double up or take more than one dose of apalutamide per day.

- Vomited doses should not be made up.
- Caregiver Precautions - Pregnant women and women of childbearing potential should not handle apalutamide without protection, e.g. gloves. No need to wear gloves or use extraordinary caution when cleaning up vomited or fecal matter.

5.3.2 **Docetaxel**

5.3.2.1 Steroid pre-medication

All participants should be premedicated with corticosteroids per institutional standards in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions. Refer to institutional standards for recommendations on premedication prior to docetaxel chemotherapy. Additional premedications (e.g.: antihistamines) may be administered as needed per institutional standards.

5.3.2.2 Docetaxel plus prednisone

Intravenous docetaxel plus oral prednisone will be administered according to the Docetaxel package insert or institutional standards for advanced prostate cancer. Docetaxel will be administered by a constant-rate intravenous (IV) infusion over 1 hour on Day 1 of each cycle of the Treatment Period.

Prednisone (5 mg) will be taken orally twice daily on days 1-21 of each cycle. On the days the patient receives steroid premedication for chemotherapy, prednisone may be held. However, prednisone dose **can be modified as needed per standard of care or physician preference after cycle 1.**

Dose reductions or delays with docetaxel should be determined according to section 6 and at the discretion of the Investigator.

Prednisone may be tapered and discontinued after completion of docetaxel chemotherapy per investigator discretion.

If docetaxel is discontinued, patients may still be eligible to receive apalutamide. This continuation should be discussed with the PI.

5.3.3 **GnRH agonist or antagonist**

Patients will be maintained on their existing GnRH agonist or antagonist and schedule unless they were intolerant or have been surgically castrated

5.3.4 Order of Administration – No specific order of administration is required

5.4 General Concomitant Medication and Supportive Care Guidelines

5.4.1 Seizure risk

As a class effect, AR antagonists have been associated with seizures due to an off-target mechanism of action (gamma amino butyric acid chloride channel [GABA_A] inhibition). Drugs known to lower the seizure threshold or cause seizures are prohibited and a representative list is included below:

- Atypical antipsychotics (e.g. clozapine, olanzapine, risperidone, ziprasidone)
- Bupropion
- Lithium
- Meperidine and pethidine
- Phenothiazine antipsychotics (e.g., chlorpromazine, mesoridazine, thioridazine)
- Tricyclic antidepressants (e.g., amitriptyline, desipramine, doxepin, imipramine, maprotiline, mirtazapine)
- Prochlorperazine maleate (Compazine) should be avoided given potential interactions with apalutamide due to seizure risk.

See Appendix C for a representative list.

5.4.2 Potential CYP450 isoenzyme interactions

Because there is a potential for interaction of apalutamide with other concomitantly administered drugs through the cytochrome P450 system, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Overall PI Dr. Harshman should be alerted if the participant is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes.

Apalutamide is metabolized primarily by human CYP3A4, thus co-administration with strong inhibitors or inducers of CYP3A4 should be avoided as much as possible. Apalutamide may also induce CYP3A4; therefore, caution should be taken when administered in conjunction with CYP3A4 substrates that have a narrow therapeutic index. Docetaxel is a CYP3A4 substrate. *In vitro* studies have shown that the metabolism of docetaxel may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by cytochrome P450 3A4.

Examples of the strong CYP3A4 inhibitors and inducers that should be avoided if possible (some allowances per PI discretion) and alternatives used include the following:

- **Co-administration with any of these strong CYP3A4 inhibitors may increase apalutamide plasma concentrations and potentially lead to increased toxicity.**

- Itraconazole, clarithromycin, erythromycin, diltiazem, verapamil, delavirdine, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole, grapefruit juice (or grapefruits), ketoconazole, dexamethasone (with the exception of dexamethasone given as premedication for docetaxel)
- **Co-administration with any of these strong CYP3A4 inducers decrease apalutamide plasma concentrations and may lead to decreased efficacy.**
- Phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital, efavirenz, tipranavir, St. John's wort

5.4.3 Anticoagulation

- The potential for drug-drug interaction between apalutamide and warfarin (e.g., Coumadin) is unknown at present. If a subject is taking warfarin, re-assess PT (prothrombin time)/international normalized ratio (INR) as clinically indicated and adjust the dose of warfarin accordingly.
- Patients on stable doses of other anticoagulants such as lovenox or fondaparinux are permitted if they have been on it for >6 months.

5.4.4 Supportive care medications

- Drugs needed for supportive care such as anti-emetics are permitted
- Steroids for nausea: prednisone is permitted **but dexamethasone** is not due to its CYP3A interaction, which may increase the levels of apalutamide. Dexamethasone is permitted as a docetaxel premedication.
- We do not anticipate patients will require growth factors but if they are on them prior to trial for other reasons and meet other eligibility criteria they will be permitted. Growth factors may be started during treatment if clinically indicated.
- Bone strengthening agents such as denosumab and zoledronic acid are permitted.

5.5 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

Patients will be discontinued from the study drug but continued to be followed for toxicity if:

- They have evidence of **confirmed** progressive disease as defined by new bone metastases, progression of existing osseous disease (i.e., appearance of 2 or more new lesions by PCWG2 criteria), new visceral metastases as defined by traditional RECIST 1.1 criteria,⁴⁰ or symptomatic disease. New visceral metastases and symptomatic disease do not require confirmatory scans. Per PCGW2 bone progression, confirmatory scans are only required if progression on first restaging scans.

- They have evidence of compromised organ function or performance status
- Unacceptable adverse event(s) or toxicity
- General or specific changes in the participant's condition render the participant unacceptable or unsafe for further treatment in the judgment of the treating investigator
- Patient requests to withdraw from study therapy
- If apalutamide is discontinued per the protocol, per investigator or patient request, the patient will be withdrawn from the study. They may continue to receive docetaxel as it is standard of care.
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen, documentation, or comply with study requirements
- Clinical need for concomitant or ancillary therapy that is not permitted in the study
- Unrelated intercurrent illness that, in the judgment of the investigator, will affect assessments of clinical status to a significant degree

It is the right and duty of the investigator to interrupt the treatment of any patient whose health or well-being may be threatened by continuation in this study.

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

An ODQ Treatment Ended/Off Study Form will be filled out when a participant is removed from protocol therapy. This form can be found on the ODQ website or obtained from the ODQ registration staff.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI Lauren C. Harshman MD at 617-632-4524.

5.6 Duration of Follow Up

Participants will be followed for adverse events for 30 days after cessation of protocol therapy or until death, whichever occurs first. Participants removed from protocol therapy for unacceptable adverse event(s) greater than grade 2 deemed related to the study drug will be followed until resolution to a grade <2 or until stabilization (as determined by the investigator) of an irreversible adverse event.

After the 30-day post study drug period is complete, patients will be followed approximately every 3-6 months for up to 36 months (from the patient's last treatment on study) for progression and survival data, either by clinic visit if they are still being treated at the study center or by phone, medical record, referring or subsequent treating physician, or publicly available records such as the Social Security Death Index (SSDI) if the patient cannot be reached by phone or in person.

5.7 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Lost to follow-up

- Withdrawal of consent for data submission
- Death
- 36 months from the patient's last treatment on study

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF).

For Decentralized Subject Registrations, the research team updates the relevant Off Treatment/Off Study information in OnCore.

6. DOSING DELAYS/DOSE MODIFICATIONS

6.1 Toxicity Management

Good clinical practice with supportive care measures and the dose modifications as listed below will be instituted. Toxicity will be graded according to CTCAE grading version 4. Investigators are encouraged to institute preemptive supportive care and patient education (e.g. anti-diarrheals, anti-emetics, anti-hypertensive agents) at early signs of toxicities emerging to prevent grade 2 and 3 occurrence).

All clinically important abnormal laboratory tests occurring during the study will be repeated at appropriate intervals until they return either to baseline or to a level deemed acceptable by the investigator and study monitor, or until a diagnosis is made that explains them. **The criteria for determining whether an abnormal laboratory test result should be reported as an adverse event are as follows:**

1. Test result is associated with accompanying symptoms, and/or
2. Test result requires additional diagnostic testing or medical/surgical intervention (merely repeating an abnormal test, in the absence of any of the above conditions, does not meet criteria for reporting and an AE), and/or
3. Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment or other therapy, and/or
4. Test result leads to any of the outcomes included in the definition of a serious adverse event, and/or
5. Test result is considered to be an adverse event by the investigator or sponsor

Any abnormal test result that is determined to be an error **does not** require reporting as an adverse event, even if it did meet one of the above conditions except for condition #4 (e.g., hyperkalemia due to hemolysis). Hypocalcemia or hyponatremia that correct to normal or a lesser grade when accounted for hypoalbuminemia and hyperglycemia should be counted as the grade based on the corrected level. Clinically significant laboratory results must be recorded on the patient's Adverse Event CRF.

6.2 General Guidelines for Dose Modifications and Delays for apalutamide and docetaxel

Dose delays and modifications will be made as indicated in the following tables. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

If toxicity occurs, the appropriate treatment will be used to ameliorate signs and symptoms including antiemetics for nausea and vomiting, anti-diarrheals for diarrhea and anti-pyretics and anti-histamines for drug fever before toxicity grade is determined.

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

A decision to modify one or both agents will be based on investigator judgment.

Subjects will be monitored continuously for AEs throughout the study and for 30 days after the last dose of study treatment, and for any serious adverse event assessed as related to study treatment or study procedures, even if the SAE occurs more than 30 days after the last dose of study treatment. Subjects will be instructed to notify their physician immediately of any and all AEs. Subjects experiencing one or more AEs due to the study treatment may require a dosing delay or reduction(s) in their dose in order to continue with study treatment. Assessment of causality (chronology and confounding factors such as disease, concomitant medications, diagnostic tests, and previous experience with the study treatment) should be conducted by the principal investigators when possible, before a decision is made to modify the dose or to hold dosing temporarily. As a general approach, it is suggested that all AEs be managed with supportive care when possible at the earliest signs of toxicity to avoid dose interruptions and reductions if possible.

The criteria presented in this section for dose modifications and delays are meant as general guidelines for both study drugs:

1. As a general approach, it is suggested that all AEs be managed with supportive care when possible at the earliest signs of toxicity. Should this be ineffective, a dose delay or dose reduction may be considered to avoid worsening toxicity. Please refer to relevant sections for the dose reduction levels for study treatment.
2. If a subject develops unacceptable toxicity as defined here that is determined to be related to study treatment, and if supportive care measures and/or a dose reduction of the responsible agent fail to lessen the toxicity to acceptable levels, study treatment of one or both agents should be withheld until resolution and then restarted or discontinued as per the protocol.
3. Dose reduce the drug thought to be the offending agent and modify plan based on re-challenge with lower dose.

The following will define DLTs for the first cycle (i.e. first 3 weeks of therapy) and are examples of unacceptable toxicity that should guide dose adjustment after cycle 1:

- Intolerable Grade 2 toxicity (except alopecia) that cannot be adequately managed with supportive care and/or a dose reduction
- Intolerable rash of any grade that cannot be adequately managed with supportive care and/or a dose reduction
- Any Grade 3 or Grade 4 toxicity despite optimal management that poses a significant clinical risk (including nausea, vomiting, diarrhea, hypertension)
- Concurrent elevation of ALT/AST > 3x ULN with total bilirubin > 2x ULN unless due to biliary obstruction or other etiology other than study medications
- Grade 4 thrombocytopenia or anemia > 7 days (transfusions permitted)
- Grade 4 neutropenia > 7 days duration
- Grade \geq 3 neutropenic fever ($> 38.3^{\circ}\text{C}$ single temperature or sustained temperature $\geq 38^{\circ}\text{C}$ for more than one hour)
- Grade \geq 3 neutropenia with documented infection
- Seizure of any grade

Dose modifications or delays may occur in the setting of lower grade toxicity than defined above if the investigator believes that it is in the interest of the subject's safety and does not meet criteria for a DLT.

- If a study drug is withheld for a treatment-related toxicity, re-initiation of study treatment cannot occur until toxicity decreases to \leq Grade 1 or baseline value.
- The minimum dose of study treatment is detailed in the dose reduction tables.
- If the subject recovers from his or her toxicities (per the criteria above) to Grade \leq 1 or to the baseline value (or lower) within 42 days, and the toxicity was deemed related to study treatment, then study treatment may be restarted at a reduced dose (see relevant sections for schedule/magnitude of dose reduction). Subjects receiving the lowest dose of study treatment may be restarted at the same dose at the discretion of the investigator with pre-emptive supportive care, unless it was a DLT event. If the toxicity was unrelated to study treatment, then study treatment may be restarted with no change in dose. The 42-day maximum hold applies to either study drug.
- Dose interruptions for reason(s) other than toxicity, such as surgical procedures, may be allowed with PI approval.
- If study treatment is interrupted, held, or skipped, the subject should be instructed **not** to make up the withheld doses, and **the planned safety and tumor assessment schedule are to be maintained.**
- Dose reductions will be by organ system as detailed below. Unless otherwise specified in the table below, the maximal amount of time allowed for recovery is 42 days. The guidance below is listed based on potential responsible agent. **Investigators can adapt which agent to adjust based on clinical context of patient and must document the rationale for the decision.**

Dose delays for reason(s) other than AEs related to the study drugs, such as surgical procedures with no anticancer therapy intent, may be allowed with study chair approval. The acceptable length of interruption will be determined by the investigator and study chair after assessing the risk benefit analysis.

If a patient shows evidence of progression during a dose interruption, therapy can be restarted if the investigator considers patient was benefiting from therapy prior to therapy being held or was too early to determine.

If a participant experiences several adverse events and there are conflicting recommendations, the investigator should use the recommended dose adjustment that reduces the dose to the lowest level.

No intra-participant dose escalation or re-escalation is permitted.

If one study drug is held or discontinued for toxicity, the other agent may still be given or restarted if they meet treatment criteria.

6.2.1 In general, toxicities attributed to apalutamide, follow this modification.

Table 2: Dose Modifications for Apalutamide Toxicities

Dose Level	Apalutamide
Starting dose	240mg daily
1 st dose reduction	180mg daily
2 nd dose reduction	120mg daily

Table 3: Dose Modification Guidance for Apalutamide Toxicities

Toxicity	Dose of apalutamide (assuming 240 mg/day dosing)
Grade 1 or 2	No change
≥ Grade 3 or higher	Hold until Grade 1 or baseline, resume at full dose
First Recurrence* ≥ Grade 3	Hold until Grade 1 or baseline, resume at 180 mg (3 tablets)
Second Recurrence ≥ Grade 3	Hold until Grade 1 or baseline, resume at 120 mg (2 tablets)
Third Recurrence ≥ Grade 3	Discontinue
First occurrence of seizure of any grade or Grade ≥ 3 neurotoxicity**	Discontinue both apalutamide and docetaxel

*Recurrences refer to the same type of grade 3 event—i.e., grade 3 anemia and grade 3 thrombocytopenia are different types of events

**For peripheral neuropathy, refer to docetaxel dose modifications below as that is unlikely to be due to apalutamide.

Rash

Dose modifications for rash are allowed only for apalutamide and are summarized in below table (Table 4).

If the skin rash has any component of desquamation, mucosal involvement, or pustules, stop dosing with apalutamide, refer to dermatologist for evaluation, and a skin biopsy is recommended (in addition to the interventions listed in below Table). If the skin rash is Grade 3 or higher, asking the subject to consent to documentation by a photograph and further evaluation by a dermatologist should also be considered.

Table 4: Apalutamide Dose Modification Guidance for Rash

Severity	Intervention
Grade 1	<ul style="list-style-type: none"> • Continue apalutamide at current dose • Initiate dermatological treatment^a <ul style="list-style-type: none"> ○ Topical steroid cream AND ○ Oral Antihistamines • Monitor for change in severity^a
Grade 2 (or symptomatic Grade 1)^b	<ul style="list-style-type: none"> • Hold apalutamide for up to 28 days • Initiate dermatological treatment^a <ul style="list-style-type: none"> ○ Topical steroid cream AND ○ Oral Antihistamines • Monitor for change in severity^a <ul style="list-style-type: none"> ○ If rash or related symptoms improve, reinstate apalutamide when rash is Grade≤1. Consider dose reduction at a 1 dose level reduction^c.
Grade ≥3^d	<ul style="list-style-type: none"> • Hold apalutamide for up to 28 days • Initiate dermatological treatment^a <ul style="list-style-type: none"> ○ Topical steroid cream AND ○ Oral Antihistamines AND ○ Consider short course of oral steroids • Reassess after 2 weeks (by site staff), and if the rash is the same or has worsened, initiate oral steroids (if not already done) and refer the subject to a dermatologist <ul style="list-style-type: none"> ○ Reinitiate apalutamide at a 1 dose level reduction^e when rash is Grade ≤1. ○ If the dose reduction will lead to a dose less than 120mg, the study drug must be stopped (discontinued) • If after 28 days, rash has not resolved to Grade≤1, contact Janssen to discuss further management and possible discontinuation of study drug.

Note: Rash may be graded differently according to the type of rash and associated symptoms. For example, maculo-papular rash is graded by body surface area covered and not severity of the rash. Please consult NCI-CTCAE Version 4.03 for specific grading criteria for other types of rash.

a Obtain bacterial/viral cultures if infection is suspected

- b** Subject presents with other rash related symptoms such as pruritus, stinging, or burning
- c** 1 dose level reduction = 60mg (1 apalutamide tablet)
- d** If there is blistering or mucosal involvement, stop apalutamide dosing immediately and contact Janssen
- e** If a subject previously started oral corticosteroids, continue for at least 1 week after resumption of reduced dose of apalutamide. If the proposed total oral steroid use will exceed 28 days, contact Janssen.

6.2.2 In general toxicities attributed to docetaxel, follow this modification.

Table 5: Dose Modification Schedule for Docetaxel Toxicities

Dose Level	<i>Docetaxel</i>
Starting dose	<i>75mg/m² IV every 3 weeks</i>
1 st dose reduction	<i>60mg/m² IV every 3 weeks</i>
2 nd dose reduction	<i>55mg/m² IV every 3 weeks</i>

*No dose less than 55mg/m² will be given; patients will be discontinued from trial.

- Docetaxel may be given within a 3-day window (+/-3 days of Day1 of each cycle). If held for toxicity on Day 1, can reassess within that 3 days and give if meets treatment criteria. If cannot be given within that window from protocol scheduled time point, skip dose until day 1 of next cycle. Day 1 of subsequent cycles will not change if docetaxel is delayed.
- No more than two dose reductions of docetaxel should be allowed for any patient. If a patient who has had 2 dose reductions has toxicities requiring further dose reductions, then docetaxel should be stopped and they should be treated with androgen deprivation and **apalutamide alone**.
- Dose adjustments are to be made according to the system showing the greatest degree of toxicity.
- If the dose level is reduced due to toxicity, then it will not be re-escalated in subsequent cycles.

Dose Modifications for Myelosuppression

- **All hematologic toxicities will be considered related to docetaxel and not apalutamide**
- Dose modifications are to be made based on the granulocyte and/or platelet count drawn prior to planned treatment (can be done the day prior to planned dose):

Table 6: Dose Modifications for Myelosuppression

Docetaxel	Absolute neutrophils/mm³ Day 1 of each cycle	Platelet/mm³ Day 1 of each cycle
No change	≥ 1,500 AND	≥ 100,000
Hold	< 1,500 OR	< 100,000

NOTE: If a dose reduction is made, maintain the lower dose for all subsequent cycles

- A need for three dose reductions will require that the patient discontinue

docetaxel and continue on androgen blockade alone.

- The planned day 1 dose can be delayed for three days to recheck counts and give within the 3-day window if the patient meets the criteria above.
- If the patient experiences febrile neutropenia or ≥ 7 days with a neutrophil count < 500 cells/mm³, the dose should be reduced by one dose level and the patient can be retreated once the neutrophil count has recovered to $\geq 1,500$ /mm³ and platelet count has recovered to $\geq 100,000$ /mm³. The fever must have resolved and if an infection is identified, it must be adequately treated and have clinically resolved before restarting therapy. If prior bacteremia, blood cultures must be negative on recheck. Patient can continue with docetaxel while on antibiotics if no medication interactions found.
 - NOTE: Labs do not need to be re-checked to reassess absolute neutrophil count within 7-days; if absolute neutrophil count is incidentally found to remain <500 cells/mm³ for ≥ 7 days, the docetaxel dose will need to be reduced subsequently.
- Use of growth factors is not required as the dose and schedule does not meet ASCO guidelines. If, however, the investigator considers it in patient's best interest, growth factors can be used per investigator discretion.
- Patients should not be retreated with subsequent cycles of docetaxel until neutrophils recover to a level ≥ 1500 cells/mm³ and platelets recover to a level $\geq 100,000$ cells/mm³. If the previous cycle was held due to absolute neutrophil count $<1,500$ cells/mm³ or platelet count $<100,000$ cells/mm³, docetaxel may be resumed at full dose, or with a dose reduction, at the treating investigator's discretion, and rationale should be documented. (See above for specific requirements for patients who experience febrile neutropenia or absolute neutrophil count <500 cells/mm³ for ≥ 7 days.)

Dose Modification for Hepatic Dysfunction

- ALT and bilirubin will be evaluated prior to each Day 1
- Patients who develop abnormal liver function tests for any reason while on the study will have the following dose reductions:

Table 7: Dose Modifications for Abnormal Liver Function			
Bilirubin		ALT/ SGPT	Action
$> \text{ULN}^*$	or	$> 5 \text{ x ULN}$	Hold ≤ 3 weeks. If recovered**, reduce docetaxel dose by one dose level. If not, discontinue docetaxel.
$\leq \text{ULN}^*$	and	$> 3 \text{ x ULN}$	Reduce docetaxel by one dose level

* For patients with Gilbert's Syndrome, hold if the bilirubin level is > 1.5 x its baseline

value

** Recovery is $< 3 \times$ ULN for ALT/SGPT and WNL for bilirubin. For patients with Gilbert's Syndrome, recovery is defined as a bilirubin level $< 1.5 \times$ its baseline value. Dose modifications are based on ALT/ SGPT alone due to the lack of specificity of AST/SGOT.

Stomatitis

- If stomatitis \geq grade 2 is present on day 1 of any cycle, docetaxel should be held until stomatitis has resolved.
- If Grade 3/4 stomatitis occurs at any time, the dose of docetaxel will be reduced one dose level for all subsequent doses.
- If a second Grade 3/4 stomatitis event occurs, docetaxel will be reduced one more dose level.
- If a third Grade 3/4 stomatitis event occurs, the patient will be taken off study.

Peripheral Neuropathy

- If \geq Grade 3, the patient will discontinue docetaxel.
- If Grade 2, the docetaxel will be held and the patient should be retreated upon recovery to a \leq Grade 1 toxicity with a dose reduction of docetaxel by one level.
- If Grade 2 or greater neurotoxicity persists for more than 3 weeks, the patient will discontinue docetaxel. Peripheral neuropathy is unlikely to be secondary to apalutamide and thus it may be continued if patient was receiving clinical benefit.

Infusion or Hypersensitivity Reactions for Docetaxel

- Infusion reactions (including fever, chills, diarrhea, rash, urticaria, erythema, pruritus, bronchospasm, hypotension, and anaphylaxis) can occur with docetaxel.
- In the event of an infusion reaction, follow the Institutional Guidelines and/or the recommendations shown in the tables below, based on the grade of the reaction.
- To identify the grade of a reaction, refer to the list below adapted from the General Disorders and Administration Site Conditions section of the NCI CTCAE Version 4.0:

Table 8: Dose Modification and Management for Infusion or Hypersensitivity Reactions for Docetaxel

Infusion Reaction	Definition	Management/Next Dose for Docetaxel
\leq Grade 1	Mild transient reaction; infusion interruption not indicated	Interruption or intervention not indicated. Slow the rate of infusion of the drug until resolution of symptoms, then resume at the planned infusion rate.
Grade 2	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids indicated for \leq	Interrupt the infusion. Follow institutional guidelines or give steroids (e.g., solumedrol 40 mg IV), diphenhydramine 50 mg IV, and/or an H2

Infusion Reaction	Definition	Management/Next Dose for Docetaxel
	24 hours).	blocker (e.g. Ranitidine 50 mg IV) after consultation with the attendant physician. Resume after recovery of symptoms at a slower rate, and then increase incrementally toward the initial rate. If the reaction reoccurs, stop the infusion and do not administer the remaining volume.
Grade 3	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae Note: any infusion that is interrupted and not resumed within the visit will be considered a Grade 3 reaction.	Stop the infusion. Treat the participant as per grade 2 reaction above. Remove the participant from docetaxel therapy or consider desensitization after allergy consult review.
Grade 4	Life-threatening consequences; urgent intervention indicated. ICU level care (e.g., vasopressor support)	Stop the infusion. Treat the participant as per grade 2 reaction above. Remove the participant from docetaxel therapy.

Diarrhea

- If patients experience significant diarrhea (>3 loose stools/24hrs over baseline), they should be treated prophylactically in subsequent cycles with loperamide or diphenoxylate.
- If patient experiences >grade 2 diarrhea despite prophylaxis, docetaxel should be reduced one dose level.
- If patients experience > grade 2 diarrhea despite 36 hrs of prophylaxis AND dose reduction, they should discontinue docetaxel.
- Maximal prophylactic treatment includes (e.g., loperamide, diphenoxylate hydrochloride with atropine, octreotide)

Fluid Retention

- There are no dose reductions for fluid retention. Participants should be treated with salt restrictions and diuretics. More aggressive therapy depends on the clinical situation. In severe situations, the Investigator, with the participant, should determine if it is in the participant's best interest to continue or discontinue study treatment.

Other Toxic Effects possibly related to docetaxel:

- If toxicities \leq Grade 2, manage the subject symptomatically if possible, and retreat without dose reduction.
- If toxicities \geq Grade 3 and clinically significant (not mentioned above), docetaxel should be withheld (**except for anemia as patients can be transfused**) until resolution to \leq Grade 1 or baseline and patients treated with a one dose level reduction.

Delay of Therapy:

- If docetaxel has to be delayed for more than 42 days from planned day of dosing because of any docetaxel-related toxicity, then docetaxel should be stopped **and the patient should be continued on treatment with androgen deprivation therapy plus apalutamide as long as no contra-indications/toxicities due to apalutamide prohibit further dosing.**

6.2.3 Dose Modification Tables for Specific Adverse Events:

- Any **seizure** is considered a DLT and the patient will be discontinued from both study medications
 - Unless clearly due to another source or to one of the study agents (e.g., only occurs night/week of docetaxel or only occurs 3rd week of cycle when only on apalutamide), can consider nausea, vomiting, and diarrhea as ‘related’ to both docetaxel and apalutamide as they are known toxicities of both agents. Dose reduce both agents per table below if unable to tease out which agent is the source as it is likely that both may contribute to the toxicity.

Table 9: Dose Modification and Management for Nausea, Vomiting, or Diarrhea

Nausea, Vomiting or Diarrhea	Management	Next Dose
\leq Grade 1	No holding/change required	No change in dose
Grade 2	No holding/change required. Maximize supportive care.	Resume at same dose level
Grade 3	Hold* until $<$ Grade 2	Resume at one dose level lower, if indicated and per MD discretion**
Grade 4	Off protocol therapy	Off protocol therapy
*Participants requiring a delay of $>$ 42 days should go off protocol therapy.		
**Participants requiring a greater number of dose reductions than allowed per Section 6.2.1 should go off protocol therapy.		
Recommended management: Nausea/vomiting: antiemetics per recommendations in section 5.4 given possible interactions		
Diarrhea: Loperamide antidiarrheal therapy Dosage schedule recommendations: 4 mg at first onset, followed by 2 mg with each loose movement until diarrhea-free for 12 hours (maximum dosage: 16 mg/24 hours) Adjunct anti-diarrheal therapy is permitted and should be recorded when used.		

Event	Action
Grade 1	Continue current dose level
Grade 2	Continue current dose level
Grade 3	Discontinue for up to 42 days until the event is \leq Grade 1 or baseline. Administer at one dose level lower for subsequent cycles, unless further dose reduction is required.
Grade 4	Discontinue for up to 42 days until the event is \leq Grade 1 or baseline. Discuss the event with the PI prior to restarting. If the investigators agree, then administer at one dose level lower for subsequent cycles, unless further dose reduction is required.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Sections 7.1 and 7.2) and the characteristics of an observed AE (Section 7.4) will determine whether the event requires expedited reporting **in addition** to routine reporting.

■ [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

7.2 Expected Adverse Event List for Docetaxel

The most serious adverse reactions from docetaxel are (taken from the package insert):

- Toxic Deaths
- Hepatotoxicity
- Neutropenia
- Hypersensitivity
- Fluid Retention

The most common adverse reactions across all docetaxel indications are infections, neutropenia, anemia, febrile neutropenia, hypersensitivity, thrombocytopenia, neuropathy, dysgeusia, dyspnea, constipation, anorexia, nail disorders, fluid retention, asthenia, pain, nausea, diarrhea, vomiting, mucositis, alopecia, skin reactions, and myalgia. Incidence varies depending on the indication.

The following data are based on the experience of 332 patients, who were treated with docetaxel 75 mg/m² every 3 weeks in combination with prednisone 5 mg orally twice daily (see Table 12).

Table 12: Clinically Important Treatment Emergent Adverse Reactions (Regardless of Relationship) in Patients with Prostate Cancer who Received Docetaxel in Combination with Prednisone (TAX327)

Adverse Reaction	TAXOTERE 75 mg/m ² every 3 weeks + prednisone 5 mg twice daily n=332 %		Mitoxantrone 12 mg/m ² every 3 weeks + prednisone 5 mg twice daily n=335 %	
	Any	Grade 3/4	Any	Grade 3/4
Anemia	67	5	58	2
Neutropenia	41	32	48	22
Thrombocytopenia	3	1	8	1
Febrile neutropenia	3	N/A	2	N/A
Infection	32	6	20	4
Epistaxis	6	0	2	0
Allergic Reactions	8	1	1	0
Fluid Retention*	24	1	5	0
Weight Gain*	8	0	3	0
Peripheral Edema*	18	0	2	0
Neuropathy Sensory	30	2	7	0
Neuropathy Motor	7	2	3	1
Rash/Desquamation	6	0	3	1
Alopecia	65	N/A	13	N/A
Nail Changes	30	0	8	0

	TAXOTERE 75 mg/m² every 3 weeks + prednisone 5 mg twice daily n=332 %		Mitoxantrone 12 mg/m² every 3 weeks + prednisone 5 mg twice daily n=335 %	
Adverse Reaction	Any	Grade 3/4	Any	Grade 3/4
Nausea	41	3	36	2
Diarrhea	32	2	10	1
Stomatitis/Pharyngitis	20	1	8	0
Taste Disturbance	18	0	7	0
Vomiting	17	2	14	2
Anorexia	17	1	14	0
Cough	12	0	8	0
Dyspnea	15	3	9	1
Cardiac left ventricular function	10	0	22	1
Fatigue	53	5	35	5
Myalgia	15	0	13	1
Tearing	10	1	2	0
Arthralgia	8	1	5	1

*Related to treatment

- Neutropenia (<2000 neutrophils/mm³) occurs in virtually all patients given 60 mg/m² to 100 mg/m² of docetaxel and grade 4 neutropenia (<500 cells/mm³) occurs in 85% of patients given 100 mg/m² and 75% of patients given 60 mg/m². Frequent monitoring of blood counts is, therefore, essential so that dose can be adjusted. Docetaxel should not be administered to patients with neutrophils <1500 cells/mm³.
- Febrile neutropenia occurred in about 12% of patients given 100 mg/m² but was very uncommon in patients given 60 mg/m². Hematologic responses, febrile reactions and infections, and rates of septic death for different regimens are dose related.
- Patients should be observed closely for hypersensitivity reactions, especially during the first and second infusions. Severe hypersensitivity reactions characterized by generalized rash/erythema, hypotension and/or bronchospasm, or very rarely fatal anaphylaxis, have been reported in patients premedicated with 3 days of corticosteroids. Severe hypersensitivity reactions require immediate discontinuation of the docetaxel infusion and aggressive therapy. Patients with a history of severe hypersensitivity reactions should not be rechallenged with docetaxel.
- Hypersensitivity reactions may occur within a few minutes following initiation of a

docetaxel infusion. If minor reactions such as flushing or localized skin reactions occur, interruption of therapy is not required. All patients should be premedicated with a corticosteroid prior to the initiation of the infusion of docetaxel per institutional standards.

- Severe fluid retention has been reported following docetaxel therapy. Patients should be premedicated with oral corticosteroids prior to each docetaxel administration to reduce the incidence and severity of fluid retention
- Patients with pre-existing effusions should be closely monitored from the first dose for the possible exacerbation of the effusions.
- When fluid retention occurs, peripheral edema usually starts in the lower extremities and may become generalized with a median weight gain of 2 kg.
- Treatment-related acute myeloid leukemia (AML) or myelodysplasia has occurred in patients given anthracyclines and/or cyclophosphamide
- Localized erythema of the extremities with edema followed by desquamation has been observed.
- In case of severe skin toxicity, an adjustment in dosage is recommended. The discontinuation rate due to skin toxicity was 1.6% (15/965) for metastatic breast cancer patients. Among 92 breast cancer patients premedicated with 3-day corticosteroids, there were no cases of severe skin toxicity reported and no patient discontinued docetaxel due to skin toxicity.
- Severe neurosensory symptoms (*e.g.* paresthesia, dysesthesia, pain) were observed in 5.5% (53/965) of metastatic breast cancer patients, and resulted in treatment discontinuation in 6.1%.
- Patients who experienced neurotoxicity in clinical trials and for whom follow-up information on the complete resolution of the event was available had spontaneous reversal of symptoms with a median of 9 weeks from onset (range: 0 to 106 weeks).
- Severe peripheral motor neuropathy mainly manifested as distal extremity weakness occurred in 4.4% (42/965).
- Severe asthenia has been reported in 14.9% (144/965) of metastatic breast cancer patients but has led to treatment discontinuation in only 1.8%.
- Symptoms of fatigue and weakness may last a few days up to several weeks and may be associated with deterioration of performance status in patients with progressive disease.

Post-marketing experiences across all indications: (from PI)

The following adverse reactions have been identified from clinical trials and/or post-marketing surveillance. Because they are reported from a population of unknown size, precise estimates of frequency cannot be made.

Body as a whole: diffuse pain, chest pain, radiation recall phenomenon.

Cardiovascular: atrial fibrillation, deep vein thrombosis, ECG abnormalities, thrombophlebitis, pulmonary embolism, syncope, tachycardia, myocardial infarction.

Cutaneous: very rare cases of cutaneous lupus erythematosus and rare cases of bullous eruptions such as erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, and Scleroderma-like changes usually preceded by peripheral lymphedema. In some cases, multiple factors may have contributed to the development of these effects. Severe hand and foot syndrome has been reported.

Gastrointestinal: abdominal pain, anorexia, constipation, duodenal ulcer, esophagitis, gastrointestinal hemorrhage, gastrointestinal perforation, ischemic colitis, colitis, intestinal obstruction, ileus, neutropenic enterocolitis and dehydration as a consequence to gastrointestinal events have been reported.

Hematologic: bleeding episodes. Disseminated intravascular coagulation (DIC), often in association with sepsis or multiorgan failure, has been reported. Cases of acute myeloid leukemia and myelodysplastic syndrome have been reported in association with docetaxel when used in combination with other chemotherapy agents and/or radiotherapy.

Hypersensitivity: rare cases of anaphylactic shock have been reported. Very rarely these cases resulted in a fatal outcome in patients who received premedication.

Hepatic: rare cases of hepatitis, sometimes fatal primarily in patients with pre-existing liver disorders, have been reported.

Neurologic: confusion, rare cases of seizures or transient loss of consciousness have been observed, sometimes appearing during the infusion of the drug.

Ophthalmologic: conjunctivitis, lacrimation or lacrimation with or without conjunctivitis. Excessive tearing which may be attributable to lacrimal duct obstruction has been reported. Rare cases of transient visual disturbances (flashes, flashing lights, scotomata) typically occurring during drug infusion and in association with hypersensitivity reactions have been reported. These were reversible upon discontinuation of the infusion.

Hearing: rare cases of ototoxicity, hearing disorders and/or hearing loss have been reported, including cases associated with other ototoxic drugs.

Respiratory: dyspnea, acute pulmonary edema, acute respiratory distress syndrome, interstitial pneumonia. Pulmonary fibrosis has been rarely reported. Rare cases of radiation pneumonitis have been reported in patients receiving concomitant radiotherapy.

Renal: renal insufficiency and renal failure have been reported. The majority of these cases were associated with concomitant nephrotoxic drugs.

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7.11 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.
- **For expedited reporting purposes only:**
 - AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information, which is provided.
- **Attribution of the AE:**
 - Definite – The AE *is clearly related* to the study treatment.
 - Probable – The AE *is likely related* to the study treatment.
 - Possible – The AE *may be related* to the study treatment.
 - Unlikely – The AE *is doubtfully related* to the study treatment.
 - Unrelated – The AE *is clearly NOT related* to the study treatment.

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7.13 Expedited Adverse Event Reporting

Investigators **must** report to the Overall PI Dr. Harshman any serious adverse event (SAE) that occurs **after the initial dose of study treatment**, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form.

Investigative sites within DF/HCC will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

7.14 Expedited Reporting to the Food and Drug Administration (FDA)

The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Overall PI will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA. Please refer to 21 CFR § 600.80 for guidance.

7.15 Expedited Reporting to Hospital Risk Management

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

7.16 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must also be reported in routine study data submissions.**

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8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or other agents administered in this study can be found in Sections 7.1 and 7.2.

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8.1.2 Form

The tablet formulation of apalutamide will be used in this study. The apalutamide drug substance is an almost white to slightly brown powder. The tablet formulation of apalutamide is an immediate release oral tablet containing 60-mg of drug substance, with a non-functional green film coat. Each 60-mg tablet contains the following inactive ingredients: hydroxypropyl methylcellulose acetate succinate (HPMC-AS), colloidal anhydrous silica, croscarmellose sodium, microcrystalline cellulose, silicified microcrystalline cellulose, and magnesium stearate. Commercially available Opadry® coating powder is used for the film coating, which is comprised of polyvinyl alcohol (partially hydrolyzed), titanium dioxide, polyethylene glycol, talc, and colorants iron oxide yellow and iron oxide black (E172).

8.1.3 Storage and Stability

Apalutamide tablets (60-mg) are packaged in 120-count, 160 cc high-density polyethylene (HDPE) bottles with child-resistant closure (CRC) and include desiccant. For clinical formulation-specific and batch-specific storage instructions, see the packaging labels. At the clinical site and at the patient's home, the study drug should be stored at room temperature and protected from heat and should not be frozen. Participants should be advised to keep all medications out of the reach and out of sight of children.

8.1.4 Compatibility

N/A

8.1.5 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

Study treatment must only be dispensed by a Pharmacist or medically qualified staff. Study treatment is to be dispensed only to participants enrolled in this study. Once the study treatment is prepared for a participant, it can only be administered to that participant.

Pregnant women and females of childbearing potential should use gloves as a precautionary measure.

8.1.6 Availability

Apalutamide will be distributed to the Dana-Farber Cancer Institute pharmacy by Janssen. The Dana-Farber Cancer Institute Pharmacy will distribute study drug to participating Dana-Farber/Harvard Cancer Center sites. Apalutamide will be provided free of charge for this study.

8.1.7 Preparation

No preparation is required. The apalutamide tablets will come fully constituted.

8.1.8 Administration

- Apalutamide will be administered orally.
- The drug should be taken with food at the same time each day within 30 minutes after the meal for consistency. It will be advised that patients both on the PK cohort and in the non-PK cohort take apalutamide with food.
- The drug should not be crushed, dissolved, or chewed.
- Missed doses should be skipped if less than 12 hours until next planned dose.
- Vomited doses should not be made up.

8.1.9 Ordering

Apalutamide will be ordered from Janssen or their designee. A drug order form as well as instructions on how to order study drug will be distributed to study site prior to site activation.

8.1.10 Accountability

Accountability for study drug is the responsibility of the investigator.

The study site must maintain accurate records demonstrating dates and amount of study drug received, to whom dispensed (participant by participant accounting), and accounts of any study drug accidentally or deliberately destroyed. At the end of the study, reconciliation must be made between the amount of study drug supplied, dispensed, and subsequently destroyed.

At the time of delivery of study drug to the site, the investigator, designee, or Pharmacist (where appropriate) will confirm that the supplies for the study have been received. This following information will be confirmed: lot numbers, quantities shipped/delivered, and date of receipt.

8.1.11 Destruction and Return

Drug will be destroyed at the site at the end of the study. Destruction will be documented in the site's drug accountability records.

8.2 Docetaxel⁴¹

Please see the prescribing information.

8.2.1 Description

Docetaxel is an antineoplastic agent belonging to the taxoid family. It is prepared by semisynthesis beginning with a precursor extracted from the renewable needle biomass of yew plants. The chemical name for docetaxel is (2R,3S)-N-carboxy-3-phenylisoserine, N-*tert*-butyl ester, 13-ester with 5 β -20-epoxy-1,2 α ,4,7 β ,10 β ,13 α -hexahydroxytax-11-en-9-one 4-

acetate 2-benzoate, trihydrate.

Mechanism of Action:

Docetaxel is an antineoplastic agent that acts by disrupting the microtubular network in cells that is essential for mitotic and interphase cellular functions. Docetaxel binds to free tubulin and promotes the assembly of tubulin into stable microtubules while simultaneously inhibiting their disassembly. This leads to the production of microtubule bundles without normal function and to the stabilization of microtubules, which results in the inhibition of mitosis in cells. Docetaxel's binding to microtubules does not alter the number of protofilaments in the bound microtubules, a feature which differs from most spindle poisons currently in clinical use.

8.2.2 Form

Docetaxel Injection Concentrate is supplied in glass vials as non-aqueous, clear, viscous, colorless to pale yellow solution at 20mg/mL concentration. Docetaxel injection concentrate is sterile, non-pyrogenic, and is available in single-dose vials as 20 mg/mL or 80mg/4mL.

One vial formulation (Injection Concentrate)

Docetaxel injection concentrate (20mg/mL) requires no prior dilution with a diluent and is ready to add to the infusion solution. Docetaxel injection concentrate should be inspected visually for particulate matter or discoloration prior to preparation. If the injection concentrate is not clear or appears to have precipitation, then it should be discarded.

8.2.3 Storage and Stability

Store vials at 25°C (77°F); excursions permitted to 15°C to 30°C (36°F and 77°F). Retain in the original package to protect from bright light.

Docetaxel final dilution for infusion, if stored between 2°C and 25°C (36°F and 77°F) is stable for 4 hours. Docetaxel final dilution for infusion (in 0.9% Sodium Chloride solution), diluted to a final concentration of 0.3mg/ml to 0.74mg/ml, should be used within 4 hours (including the 1 hour intravenous administration).

8.2.4 Compatibility

Contact of the docetaxel injection concentrate with plasticized PVC equipment or devices used to prepare solutions for infusion is not recommended. In order to minimize patient exposure to the plasticizer DEHP (di-2-ethylhexyl phthalate), which may be leached from PVC infusion bags or sets, the final docetaxel dilution for infusion should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

8.2.5 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

Study treatment must only be dispensed by a Pharmacist or medically qualified staff. Study treatment is to be dispensed only to participants enrolled in this study. Once the study treatment is prepared for a participant, it can only be administered to that participant.

Docetaxel is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised when handling and preparing docetaxel solutions. The use of gloves is recommended.

If docetaxel injection concentrate or final dilution for infusion should come into contact with the skin, immediately and thoroughly wash with soap and water. If docetaxel injection concentrate or final dilution for infusion should come into contact with mucosa, immediately and thoroughly wash with water.

8.2.6 Availability

Docetaxel is commercially available.

8.2.7 Preparation

Docetaxel may be prepared according to institutional standards or package insert.

For one vial preparation:

1. Docetaxel vials should be stored at room temperature, 25°C (77°F), and protected from light.
2. Aseptically withdraw the required amount of docetaxel injection concentrate (20 mg/mL) with a calibrated syringe and inject into a 250-mL infusion bag of either 0.9% Sodium Chloride solution to produce a final concentration of 0.3 to 0.74 mg/mL.
If a dose greater than 200 mg of docetaxel is required, use a larger volume of the infusion vehicle so that a concentration of 0.74 mg/mL docetaxel is not exceeded.
2. Thoroughly mix the infusion by manual rotation.
3. Attach non-PVC tubing with a 0.22-micron filter attached
3. As with all parenteral products, docetaxel should be inspected visually for particulate matter or discoloration prior to administration whenever the solution and container permit. If the docetaxel injection concentrate or final dilution for intravenous infusion is not clear or appears to have precipitation, these should be discarded.

8.2.8 Administration

The final docetaxel dilution for infusion should be administered intravenously as a 1-hour infusion (+/- 10 min) under ambient room temperature and lighting conditions. Docetaxel may be administered according to institutional standards or package insert.

8.2.9 Ordering

Docetaxel will not be provided by the sponsor. Commercial supply will be used.

8.2.10 Accountability

Accountability for study treatment is the responsibility of the investigator.

The study site must maintain accurate records demonstrating dates and amount of study treatment received, to whom dispensed (participant by participant accounting), and accounts of any study treatment accidentally or deliberately destroyed. At the end of the study, reconciliation must be made between the amount of study treatment supplied, dispensed, and subsequently destroyed.

8.2.11 Destruction and Return

N/A for IV agent.

8.3 Prednisone

8.3.1 Description

Prednisone is a corticosteroid

8.3.2 Form

Prednisone 5-mg tablets are small, white tablets.

8.3.3 Storage and Stability

Prednisone will be prescribed and prescriptions may be filled at a pharmacy chosen by the participant.

8.3.4 Compatibility

We do not anticipate any excess toxicity combining prednisone with the study medications.

8.3.5 Handling

There are no specific instructions for handling prednisone.

8.3.6 Availability

Prednisone is commercially available.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Pharmacokinetic Studies (Supko Laboratory)

9.1.1 Rationale

Pharmacokinetic sampling will be performed in the first 12 patients enrolled in the clinical trial at Dana-Farber Cancer Institute to evaluate the possible effect of daily oral administration of apalutamide on the pharmacokinetics of docetaxel. The initial daily dose of apalutamide given in cycle 1 will be withheld until just after the 24-hour sample is collected on day 2. Serial blood

samples will be collected according to the same schedule on days 1-2 of cycles 1 and 2. The concentration of docetaxel will be determined in all plasma samples. Determining the drug concentration in a sample obtained 24 hours after dosing, *just prior to taking the next daily dose of apalutamide*, is absolutely necessary to properly define the plasma profile for a single dosing interval. Alterations in the pharmacokinetic behavior of docetaxel will be evaluated by comparing the mean pharmacokinetic parameters estimated from the plasma concentration-time profiles defined for the doses given on day 1 of cycles 1 and 2.

The sampling schedule has been devised to accommodate treatment on an outpatient basis. **Patients are to be instructed to take apalutamide, at approximately the same time every day within 30 minutes after a meal/food, at a time that will allow the patient to arrive at the clinic to obtain a pharmacokinetic sample before dosing and to remain for an additional 8 hours.** The actual sampling schedule and procedures that are to be used to establish times, collect samples, and process specimens for storage and shipment prior to analysis are described below.

9.1.2 Collection of Specimens

Place a large gauge peripheral catheter (e.g., 19- or 20-gauge angiocath straight set with T-connector, or similar IV access device) within a vein in the arm of the patient for the collection of pharmacokinetic blood samples on day 1 of cycles 1 and 2. Patency of the sampling catheter should be maintained between blood draws using either a heparin lock (e.g., 10 U/mL in normal saline) or a slow drip of Normal Saline for Injection, USP (e.g., 10 mL/h). Blood may be obtained directly by venipuncture on days when only a single pharmacokinetic sample is scheduled for collection. When sampling through the peripheral catheter, begin to clear the catheter approximately 1 min before the specified sample time by withdrawing the lock solution and approximately 0.5 mL of blood into a syringe. Remove and properly dispose the syringe used to clear the catheter.

A battery-powered digital timer/stopwatch programmed to operate continuously as a 24-hour clock must be used to accurately monitor the drug administration and sample collection times. The same timer must be allowed to run without interruption until the last pharmacokinetic blood specimen has been obtained from the subject. Timer readings will be noted at the precise time that the two drugs are taken on days when the patient is in the clinic and at the beginning and ending times of the blood sample collection intervals. Readings of the digital timer must be directly recorded on a copy of the Pharmacokinetic Data Form for this study. Computer files for printing the Pharmacokinetic Data Form and sample collection and storage tube labels will be prepared by the DF/HCC Cancer Pharmacology Core and distributed by e-mail to clinical research staff each study site.

Samples are to be collected in a plastic lavender stoppered Vacutainer 4.0 mL plasma collection tube with spray-coated K₂EDTA (Becton-Dickinson, cat. no. 367844). Blood samples will be obtained on day 1 of cycles 1 and 2 just before starting the docetaxel infusion (within 15-minutes pre-dose), at the midpoint of the infusion (30 minutes +/- 5 minutes) and at the end of the infusion (60 minutes +/- 5 minutes.) Post-dose samples will be obtained at 30 minutes (+/- 5 minutes), 1.0 hour (+/- 10 minutes), 1.5 hours (+/- 10 minutes), 2.0 hours (+/- 10 minutes), 4.0 hours (+/- 15 minutes), 6.0 hours (+/- 15 minutes), and 8.0 hours (+/- 15 minutes) after completion of the infusion. On day 2 a sample will be collected at 24.0 hours (+/- 1 hour) after start of the infusion.

The dose of apalutamide on day 1 of cycle 2 should be taken after the pretreatment sample is collected coincident with starting the docetaxel infusion. It is also very important that the patient is aware that the morning dose of apalutamide on day 2 of cycle 1 and cycle 2 must not be taken before arriving at the clinic and the 24-hour pharmacokinetic sample has been collected.

In the event that either study drug is held at a PK-collection time point, PK collection should be discussed with study PI. In general, PK sampling will be skipped if:

- The docetaxel infusion is not administered (e.g., cycle 2 day 1 infusion held)
- The patient has not completed 5 consecutive days of apalutamide dosing before scheduled PK sampling
- Apalutamide dose is held on the day of scheduled PK sampling

9.1.3 Handling of Specimens

Once collected in a plastic lavender stoppered Vacutainer 4.0 mL plasma collection tube with spray-coated K₂EDTA (Becton-Dickinson, cat. no. 367844). Promptly mix the plasma collection tube by immediately inverting it 8-times gently (i.e. without agitation), then place the tube on wet ice until centrifuged (1,300 x g, 10 min, 4°C) within 15 min after collection. Separate the plasma from the blood cells using a disposable pipette and transfer the plasma into a 4.5 mL self-standing polypropylene cryogenic storage vial with external threads (Fisher Scientific, cat. no. 12-565-291). Affix a pre-printed label, with the protocol number, patient accession number, and sample number onto the cryovial, oriented crosswise toward the upper part of the tube, without overlapping the vial cap. Completely cover the label with polyester protective label tape (Fisher Scientific, cat. no. 11-867B) to prevent the label from detaching from the vial when stored frozen. Place the tube on crushed dry-ice until stored in a freezer maintained at < -70°C.

9.1.4 Shipping of Specimens for PK analysis

Complete sets of samples from one or more patients will be sent by next day delivery to the address listed below. Place the sample tubes in a zip lock plastic bag. Package samples in a seamless styrofoam container. Place the sample bag over at least 3-4 inches of dry ice on the bottom of the container and completely cover with an additional 3-4 inches or more of dry-ice. Seal the styrofoam container within a tight-fitting cardboard shipping box. Insert copies of the Pharmacokinetic Data Form for each set of samples into a separate zip-lock plastic bag placed on top of the styrofoam container before the external shipping box is sealed. Send the samples from Monday to Wednesday by overnight courier for delivery on the following day. Samples should not be shipped on a Thursday or Friday. Notification of the shipment and the courier tracking no. must be made by sending an e-mail to the following: (1) MGHCCPOSPL@partners.org; and (2) jsupko@partners.org. Attach a scanned copy of the Pharmacokinetic Time Record for all samples in the shipment to the email. Please do not attempt to charge shipping costs to Dr. Supko.

Dr. Jeffrey G. Supko
Massachusetts General Hospital
55 Fruit St., GRJ 1025
Boston, MA 02114
Tel: 617-724-1970

9.1.5 Pharmacokinetic Analysis

The concentration of docetaxel and other analytes of interest will be determined by analytical methods based upon reversed-phase high-performance liquid chromatography with tandem mass spectrometry established by the DF/HCC Cancer Pharmacology Core laboratory located at the Massachusetts General Hospital. Validation of the analytical methods and their application to the analysis of study samples will conform to recommendations in the current FDA Guidance for Industry on Bioanalytical Method Validation, May 2001 (<http://www.fda.gov/downloads/Drugs/Guidances/ucm070107.pdf>).

Individual patient plasma concentration-time curves will be analyzed by noncompartmental methods using routines supplied in the WinNonlin Professional Version 4.0.1 software package (Pharsight Corp., Cary, NC). Pharmacokinetic parameters and variables will be calculated according to standard equations. Mean values of pharmacokinetic parameters will be statistically compared using the paired two-tailed t-test of the log-transformed data.

9.2 Blood Collection for PD assays for Biomarker Testing

To be done at the Dana-Farber Cancer Institute

Unused samples will be destroyed at the end of the study and will not be used for future analysis.

9.2.1 cfDNA Plasma

As an exploratory endpoint, plasma will be collected for genomic analysis of circulating free DNA (cfDNA). cfDNA will be collected at baseline, C5D1, and at time of progression or discontinuation of treatment. The cfDNA from each time point will be subjected to low pass whole genome sequencing to assess DNA quality, tumor purity (i.e. the approximate percentage of DNA isolated from peripheral blood originating from tumor rather than normal cells), and copy number profile of tumor DNA. For subjects with cfDNA of adequate quality and purity, we will also perform whole exome sequencing from cfDNA isolated at baseline, at best tumor response, and at progression. The sampling schedule and procedures that are to be used to establish times, collect samples, and process specimens for storage and shipment prior to analysis are described in the lab manual.

- **Time Points**
 - Pre-dose Cycle 1 Day 1 (Note: Whole Blood for Germline DNA needs to only be collected once at pre-dose Cycle 1/Day 1)
 - C5D1
 - At time of progression or discontinuation of treatment
- **Method for analysis:**
 - **Assay Details for ultra low pass whole genome sequencing (ULP-WGS):** Frozen aliquots of plasma will be thawed at room temperature. Cell-free DNA is extracted from 2 mL of plasma and eluted into 60 uL of resuspension

buffer using the Qiagen Circulating DNA kit on the QIA Symphony liquid handling system. Extracted cell-free DNA is frozen at -20 °C until ready for further processing. Quantification of extracted cfDNA and gDNA is performed using the PicoGreen (Life Technologies) assay on a Hamilton STAR-line liquid handling system. Library construction of cell-free DNA is performed using the Kapa HyperPrep kit with custom adapters (IDT). Generally, 5 ng of cfDNA input is used for ultra low-pass whole-genome sequencing (ULP-WGS). A Hamilton STAR-line liquid handling system is used to automate and perform this method. Constructed sequencing libraries are pooled (2 uL of each x 96 per pool) and sequenced using 100bp paired-end runs over 1 x lane on a HiSeq2500 (Illumina) for ULP-WGS.

- The genome is divided into T non-overlapping windows, or bins, of 1Mb. Aligned reads are counted based on overlap within each bin using the tools in HMMcopy Suite (<http://compbio.bccrc.ca/software/hmmcopy/>). The read counts are then normalized to correct for GC-content and mappability biases using HMMcopy R package. This data is used to generate a Hidden Markov Model to derive copy number alterations and Tumor DNA purity using TitanCNA R package v1.9.0 (<https://github.com/gavinha/TitanCNA>) 8. Samples must pass a quality threshold (median absolute deviation score < 0.115) for accurate purity estimate.
- **Assay details for whole exome sequencing:** When possible, 20ng of cfDNA input is used to construct another cfDNA library for WES, which affords greater library complexity and reduced the depth of sequencing required to achieve the desired mean target coverage. Library construction was performed using the Kapa HyperPrep kit with custom adapters (IDT) on a Hamilton STAR-line liquid handling system. Libraries are then quantified using the PicoGreen (Life Technologies) assay on a Hamilton STAR-line liquid handling system and pooled up to 12-plex. Hybrid selection of cfDNA libraries is performed using the Nextera Rapid Capture Exome kit (Illumina) with custom blocking oligos (IDT and Broad Institute). Sequencing to generate 100bp paired-end reads is performed on the Illumina HiSeq2500 in high-output mode with 2-4 libraries per lane. Single nucleotide variants are identified using MuTect16 and cancer cell fractions of these variants are derived using ABSOLUTE.

9.2.2 AR Variant Testing

AR variants will be measured at RNA level by qRT-PCR and by measuring circulating tumor DNA (ctDNA)

- **Time Points**
 - Pre-dose Cycle 1 Day 1
 - C5D1
 - At time of progression or discontinuation of treatment
- **Method for analysis:**
 - Total RNAs sourced from the buffy coat containing normal circulating cells (i.e. PBMC) as well as the circulating tumor cells (CTCs) will be used for ARv7

analysis. Droplet digital polymerase chain reaction (ddPCR) technology will be used.

- DdPCR (QX200, Bio-Rad, Hercules, CA, USA) will be employed in this study. Droplet generation, PCR reactions, and detection will be carried out according to the manufacturer's instruction. Briefly, the reactions will be performed in 20- μ L reaction volume that consists of 10 μ L of 2 \times ddPCR Supermix for probes (No dUTP) (Bio-Rad), 1 μ L of gene-specific primers (900 nM) and probes (250 nM) and 2 μ L of the cDNA sample. Each reaction mix will be converted to droplets with the QX200 droplet generator (Bio-Rad). Droplet-partitioned samples will be transferred to a 96-well plate, sealed and cycled in a C1000 Touch thermal cycler (Bio-Rad) under the following cycling protocol: 95 °C for 10 min, followed by 40 cycles of 94 °C for 30 s, 60 °C for 60 s, and a 10-min incubation at 98 °C. The cycled plates will then be read on a Bio-Rad QX200 droplet reader. At least two negative control wells with no cDNA template will be included in every run. The data analysis will be performed with QuantaSoft droplet reader software v1.7.4 (Bio-Rad). The target mRNA concentrations will be calculated using Poisson statistics and the background will be corrected based on the data of the no template control. Absolute transcript levels will be initially presented as copies per μ L and converted to copies per μ g RNA based on the input amount of RNA.

10. STUDY CALENDAR

All screening assessments must be performed within 30 days prior to the date of registration.

In the event that the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

Assessments must be performed prior to administration of study agents. Study assessments and agents should be administered within ± 3 days of the protocol-specified date, unless otherwise noted.

Table 13: Study Calendar

	Screening ^a	C1D1 _{a, b}	C1D8, C1D15	C2 D1	C2 D15	C3 D1	C4 D1	Cycle 5, Day 1 (week 13)	Cycles 6+, Day 1 ^b	Every 12 weeks	30day Post-study drug follow-up visit (+ 7 days)
Informed consent	X										
Medical and cancer history	X										
Physical exam/Clinic visit^{b, c}	X	X		X		X	X	X	X		X
Vital signs^d	X	X		X		X	X	X	X		X
Weight	X	X		X		X	X	X	X		X
Height	X										
Performance status^e	X	X		X		X	X	X	X		X
CBC with differential^f	X	X	X	X	X	X	X	X	X		X
Complete metabolic panel^g	X	X	X	X	X	X	X	X	X		X
Serum PSA	X			X		X	X	X	X		X
Serum Testosterone	X										X
LDH	X									X	X
PT/PTT or INR	X										
EKG	X										
PK samples^h		X		X							
Blood/plasma for ARv7		X						X			X ^o

and biomarker studiesⁱ											
TSH, Free T4, T3^j	X	X		X		X	X	X		X	
Bone Scan	X							X		X	
MRI or CT chest/abd/pelvis^k	X							X		X	
Docetaxel		X		X		X	X	X	X		
Apalutamide^l	X (daily dosing while on study)										
GnRH agonist/antagonist^m	X										
Concomitant medications	X	X		X		X	X	X	X		X
Adverse events Assessment		X	X* by MD, NP, PA or RN	X	X* by MD, NP, PA, or RN	X	X	X	X		X
Study Drug Diary		X		X		X	X	X	X		
Progression/Survival Follow-upⁿ											X

- ^a All screening assessments must be performed within 30 days prior to the date of registration. If testing is performed within 72 hours of the first dose, screening evaluations may serve as the pre-dose Day 1 visit evaluations. All other visits must be done within +/-3 days and scans +/- 7 days of scheduled event. **If study drugs are held, the assessments and cycle/day numbering should continue according to protocol schedule and will not be adjusted.**
- ^b The physical examination, clinical laboratory tests, and ECOG performance status may be performed up to 72 hours before study drug administration; test results must be available before study drug administration.
- ^c Complete physical examination including neurologic assessment at screening, day 1 of cycle 1. Otherwise, brief disease- and adverse event-focused history and focused physical exam.
- ^d Blood pressure, heart rate, and temperature at screening, day 1 of all cycles, and at post-study drug follow-up visit.
- ^e ECOG Performance status should be assessed
- ^f CBC with differential includes WBC, ANC, hemoglobin, hematocrit, and platelets
- ^g Serum complete metabolic panel includes sodium, potassium, chloride, bicarbonate, BUN/ creatinine, calcium, albumin, and liver function tests (total bilirubin, AST/ALT, alkaline phosphatase)
- ^h Pharmacokinetic (PK) samples will be drawn in the first 12 patients enrolled at Dana-Farber Cancer Institute (more may be added to ensure at least 6 patients with 2 full sets of PK samples C1-C2D2): At each time point, 4mL of whole blood will be collected into an EDTA (lavender top) vacutainer.
 - C1D1: just before starting the docetaxel infusion (within 15-minutes pre-dose), at the

midpoint (30 min +/- 5 min) and end (60 min +/- 5 min) of the infusion; post-dose samples at 30 min (+/- 5 min), 1.0 hour (+/- 10 min), 1.5 h (+/- 10 min), 2.0 h (+/- 10 min), 4.0 h (+/- 15 min), 6.0 h (+/- 15 min), and 8.0 h (+/- 15 min) after completion of the infusion

- C1D2: on day 2 at 24.0 h (+/- 1 h) after start of the docetaxel infusion. Prior to first dose of apalutamide.
- C2D1: just before apalutamide dose and starting the docetaxel infusion (within 15-minutes pre-dose), at the midpoint (30 min +/- 5 min) and end (60 min +/- 5 min) of the infusion; post-dose samples at 30 min (+/- 5 min), 1.0 hour (+/- 10 min), 1.5 h (+/- 10 min), 2.0 h (+/- 10 min), 4.0 h (+/- 15 min), 6.0 h (+/- 15 min), and 8.0 h (+/- 15 min) after completion of the infusion
- C2D2: day 2 at 24.0 h (+/- 1 h) after start of the docetaxel infusion. Prior to dose of apalutamide. The dose of apalutamide should be taken after the pretreatment sample is collected coincident with starting the docetaxel infusion.

i Blood for exploratory biomarker studies. Refer to section 9.2 for further information.

j TSH, total T3, and free T4 should be evaluated at screening. TSH should then be measured on Day 1 of each cycle for the first 4 cycles, and then every 12 weeks starting after Cycle 5, at which point it can be done concomitant with the every 12 week scans. After screening, total T3 and free T4 should be performed only if TSH abnormal at previous assessment, or becomes abnormal. They should be followed until they normalize. These labs do not need to be reviewed prior to dosing on D1 and subsequent cycles, but, once results have returned, the subsequent dosing should be adjusted as needed per the dosing modification guidelines in section 6.

k Radiologic or symptomatic documentation must be provided for subjects who are removed from the study for progressive disease. Contrast CT or MRI scans of the chest/abdomen/pelvis are preferred but if the patient's renal function will not permit contrast, non-contrast imaging will be permitted. Type of imaging should remain consistent throughout the study. If baseline CT chest does not demonstrate prostate cancer, do not need to repeat chest CT on study unless the investigator suspects new findings based on clinical signs/symptoms. NOTE: If bone lesions are present in the chest CT imaging field at baseline, chest CT is to be continued at subsequent assessments.

l The first dose of apalutamide will start on C1D2 for the PK cohort but C1D1 for all others. Apalutamide dose is to be taken in clinic on days when PKs are being collected (e.g., C1D2, C2D1, C2D2; unless PK collection is held per protocol.) For the PK cohort, the dose of apalutamide on C2D1 should be taken after the pretreatment sample is collected, coincident with starting the docetaxel infusion.

m Patients without a history of surgical castration will be maintained on their GnRH agonist or antagonist per their normal schedule unless intolerant

n Follow-up regarding progression and survival every 3-6 months for up to 36 months from end of treatment. This can be performed at a follow-up visit in clinic if they are still being treated at DF/HCC, phone, medical record, referring or subsequent treating physician, or publicly available records such as SSDI.

o At 30 day Post-study drug follow-up visit (+ 7 days) or at visit when drug discontinued for PD.

* Adverse assessments may be performed by MD, NP, PA or RN.

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

Response and progression will be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009] and PCWG2 criteria (see Appendix D). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

For the purposes of this study, participants should be re-evaluated every 12 weeks. When possible, confirmatory scans will also be obtained at least 4-8 weeks following initial documentation of an objective response. The serum PSA level will be measured monthly. **Continuation of study therapy will be encouraged in patients with PSA increases but no evidence of radiographic or symptomatic disease progression or unconfirmed disease progression.** Bone flare phenomenon can occur with antiandrogens.

11.1.1 Definitions

Evaluable for Target Disease response. Only those participants who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for target disease response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Participants who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray or ≥ 10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all considered non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

‘Cystic lesions’ thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same participant, these are preferred for selection as target lesions.

Target lesions. **All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs,** should be identified as **target lesions** and 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. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly should be selected. 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. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. 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 (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow up.

11.1.3 Methods for Evaluation of Disease

All measurements should be taken and recorded in metric notation using a ruler, calipers, or a digital measurement tool. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 30 days before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be

imaged but are assessable by clinical exam.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥ 10 mm in diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray. Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung; however, CT is preferable.

Conventional CT and MRI. This guideline has defined measurability of lesions on CT scan based on the assumption that CT thickness is 5mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size of a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure from CT, MRI may be used instead of CT in selected instances.

Tumor markers. Tumor markers alone cannot be used to assess response, but changes in PSA will be evaluated as a secondary measure of clinical outcome.

Definition of PSA response: A PSA partial response is defined as a $\geq 50\%$ decline from baseline and requires a confirmatory PSA at least 3 weeks or more later. Given that a favorable effect on PSA may be delayed for 12 weeks or more, PSA will be monitored every cycle but treatment will continue through early rises for a minimum of 12 weeks.³⁹

Cytology and Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

FDG-PET. While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- (a) Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- (b) No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- (c) FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

PET-CT. At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data, which may bias an investigator if it is not routinely or serially performed.

11.1.4 Response Criteria

11.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the 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).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

11.1.4.2 Evaluation of Non-Target Lesions

Existing bone metastases may be the only target lesions in some patients. Because bone lesions are notoriously difficult to follow, **‘progression’ in non-target lesions is defined as the appearance of ≥ 2 new lesions, and, for the first reassessment only, a confirmatory scan performed 6 or more weeks later is required that shows a minimum of 2 or more additional new lesions (PCWG2 criteria).**

Other measurable disease will be assessed according to RECIST version 1.1:

Evaluation of Measurable Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of “non-target” lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

Because bone lesions are notoriously difficult to follow, **‘progression’ is defined as the appearance of ≥ 2 new lesions, and, for the first reassessment only, requires a confirmatory scan performed 6 or more weeks later that shows a minimum of 2 or more additional new lesions (PCWG2 criteria).**

11.1.4.3 Evaluation of New Lesions

The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (for example, some ‘new’ bone lesions may be simply healing or flare of pre-existing lesions). However, unless symptomatic or associated with laboratory abnormalities, a lesion identified on a follow-up scan

in an anatomical location that was not scanned at baseline will not be considered new until confirmed with repeat scans ≥ 4 weeks later. If a new lesion is equivocal (because of small size etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

11.1.4.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Table 14: For Participants with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥ 4 wks Confirmation**
CR	Non-CR/Non-PD	No	PR	≥ 4 wks Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥ 4 wks from baseline**
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	
* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion. ** Only for non-randomized trials with response as primary endpoint. As response is not the primary endpoint, this is not required, but encouraged. *** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression. <u>Note:</u> Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as “ <i>symptomatic deterioration.</i> ” Every effort should be made to document the objective progression even after discontinuation of treatment.				

Table 15: For Participants with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD**	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised ** Because bone lesions are notoriously difficult to follow, 'progression' is defined as the appearance of ≥ 2 new lesions, and, for the first reassessment only, requires a confirmatory scan performed 6 or more weeks later that shows a minimum of 2 or more additional new lesions (PCWG2 criteria).		

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

12.1.1 Method

The ODQ will collect, manage, and perform quality checks on the data for this study.

12.1.2 Responsibility for Data Submission

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to the ODQ according to the schedule set by the ODQ.

12.2 Data Safety Monitoring

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

The DSMC will review each protocol up to four times a year or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring with 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a

summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

This is an open-label, single-arm phase 2 study of the combination of docetaxel and apalutamide in patients with metastatic CRPC.

There will be an initial 6 patient safety lead-in phase. The first 3 patients will be accrued to start the initial combination at dose level 1 and then accrual will be halted until all have completed the first cycle (i.e., first 3 weeks of therapy). If less than 2 patients experience a drug related dose-limiting toxicity (DLT) as defined in section 6.1, the next 3 patients will be enrolled. Accrual will be halted again until this next cohort has completed their first cycle and safety assessment. If $<2/6$ patients experience a DLT, the study will open to full accrual. If 2 or more patients experience a DLT, the dosing of the study drugs will be reviewed and protocol amended.

The primary objective is to evaluate the efficacy of the drug combination in terms of progression free survival.

Primary endpoint

Progression free survival (PFS) is defined as the time from treatment initiation until the occurrence of one of the following:

1. A participant was considered to have progressed by bone scan if
 - a. the first bone scan with greater than or equal to (\geq) 2 new lesions compared to baseline was observed in less than ($<$) 12 weeks from study drug initiation and was confirmed by a second bone scan taken ≥ 6 weeks later showing ≥ 2 additional new lesions (a total of ≥ 4 new lesions compared to baseline);
 - b. the first bone scan with ≥ 2 new lesions compared to baseline was observed in ≥ 12 weeks from study drug initiation and the new lesions were verified on the next bone scan ≥ 6 weeks later (a total of ≥ 2 new lesions compared to baseline);
2. Progression of soft tissue lesions measured by computerized tomography (CT) or magnetic resonance imaging (MRI) by RECIST v. 1.1; or
3. Death from any cause.

Patients who have not progressed or died at the time of assessment will be censored at the time of the last date of assessment. In the event that patients demonstrate progression based on soft tissue by RECIST v 1.1, and/or bone scans at differing time points, the earliest date of documented progression will be used to calculate PFS.

Secondary endpoints:

- Safety and tolerability according to NCI CTCAE version 4.0
- Dose-limiting toxicities (DLT) in the safety lead in group
- Pharmacokinetics (C_{max} and AUC) of docetaxel
- Time to disease progression: defined as the time from treatment initiation to objective disease progression by imaging or by worsening symptoms but does not include by PSA rise alone. Death from non-prostate cancer causes are not considered as an event. The date of progression will be determined as described above for PFS. Patients who die for any reason prior to disease progression will be censored at the time of death.
- Time to radiologic progression (rTTP): time from treatment initiation to objective radiologic progression on subsequent screening according to RECIST v.1.1
- Time to PSA progression: time from treatment initiation to first rise $\geq 25\%$ and $>2\text{ng/dL}$ above the nadir that has been confirmed 3 or more weeks later
- Time to Treatment Failure: time from treatment initiation to discontinuation of therapy due to disease progression (not by PSA rise alone), toxicity, or patient withdrawal.
- Overall survival (OS): is defined as the time from trial treatment start to death due to any cause, or censored at date last known alive.
- PSA decline $\geq 50\%$ from baseline at 12 weeks of therapy and which has been confirmed with a second PSA at ≥ 3 weeks later.
- Percent change from baseline in serum PSA³⁹: the percent change from baseline in PSA levels after 12 weeks on study and the maximum percent change (rise or fall) from baseline will be recorded
- Overall Response Rate (ORR): The ORR (%) will be calculated as the number of patients with best objective response via RECIST v 1.1 criteria of CR or PR divided by the number of patients with measurable disease at baseline. The best objective response for a given patient will be based on objective responses determined from data obtained up to: progression, the last evaluable assessment in the absence of progression, or initiation of subsequent anticancer therapy. Patients for whom an objective response cannot be determined or for who the best objective response is ‘not evaluable’ (NE) will be considered non-responders.

13.2 Sample Size, Accrual Rate and Study Duration

The sample size calculations included the following assumptions:

- (1) The distribution of PFS follows an exponential distribution
- (2) The median time to disease progression under standard therapy is about 4 months [observed in multiple series for patients treated with prior enzalutamide after abiraterone for CRPC].¹³⁻¹⁸
- (3) The hypothesis to be tested is based on the median PFS time of H₀: t₀=4 months versus H_a: t₁=6.5 months. The test will be one-sided.

The following table considers a few scenarios with sample size of 30 to achieve at least 90% power.

Table 16

Ho: median PFS (mos.)	Ha: median PFS (mos.)	Number of PFS failures	Type I error (one-sided)	Power (%)
3	5	29	0.1	93
3.5	6	28	0.1	94
4	6.5	28	0.1	90

A sample size of 30 evaluable patients achieves 90% power to detect the difference between the null hypothesis (Ho: 4 months median PFS from historical control or current standard therapy) and the alternative hypothesis (Ha: 6.5 months of median PFS from the combination therapies) at an alpha =0.1 significance level using a one-sided Wald test for the log failure rate parameter, conducted after two-year post-enrollment study duration. Anticipating that 10% of patients will not be evaluable due to possible adjustment in dosing from findings of safety run-in phase, sample size will be augmented to a total of 33 patients.

The accrual is expected to be 3 patients every month for 12 months to complete enrollment with additional follow-up to 2 years for disease progression or survival, the study is expected to last approximately 36 months.

Table 17: Accrual Targets				
Ethnic Category	Sex/Gender			
	Females		Males	Total
Hispanic or Latino	0	+	6	= 6
Not Hispanic or Latino	0	+	27	= 27
Ethnic Category: Total of all subjects	0	+	33	= 33
Racial Category				
American Indian or Alaskan Native	0	+	0	= 0
Asian	0	+	5	= 5
Black or African American	0	+	3	= 3
Native Hawaiian or other Pacific Islander	0	+	0	= 0
White	0	+	25	= 25
Racial Category: Total of all subjects	0	+	33	= 33

13.3 Definition of Study Population/ Stratification Factors

Safety /Evaluable population: All patients receiving at least one dose of docetaxel with apalutamide will be included in analyses unless otherwise specified.

No stratification factors are used in enrolling patients.

13.4 Interim Monitoring Plan of Safety Lead in Phase

There will be an initial 6 patient safety lead-in phase. The first 3 patients will be accrued and then accrual will be halted until all have completed the first cycle. If less than 2 patients experience a drug related dose-limiting toxicity (DLT), the next 3 patients will be enrolled. Accrual will be halted again until this next cohort has completed their first cycle and safety assessment. If <2/6 patients experience a DLT, the study will open to full accrual. If 2 or more patients experience a DLT, the dosing of both study agents will be reviewed and protocol amended.

13.5 Analysis of Primary Endpoints

Progression-free survival (PFS) will be summarized using the product-limit method of Kaplan-Meier. Median times for PFS endpoint will be presented with two-sided 80% confidence intervals estimated using log-log (survival) methodology. If the lower confidence interval (corresponding to a one-sided 90% CI) excludes null hypothesis or historical control of 4 month median PFS, then there is sufficient evidence to indicate the combination therapy improves PFS. Kaplan-Meier estimates of PFS at 6 or 12 months after treatment initiation may also be presented with two-sided 80% confidence intervals.

13.6 Analysis of Secondary Endpoints

Safety and Tolerability: All adverse events recorded during the trial will be summarized for the safety population. The incidence of events that are new or worsening from the time of first dose of treatment will be summarized according to system organ class and/or preferred term, severity (based on CTCAE version 4.0 grade), type of adverse event, and relation to study treatment. Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient and tabulated by primary system organ class, and type of adverse event.

Clinical data will be summarized using descriptive statistics (number of patients, mean, median, standard deviation, minimum and maximum) for continuous variables and using frequency and percentages for discrete variables

Time to event endpoints (e.g., time to radiologic progression, time to treatment failure) will be analyzed using the Kaplan-Meier Method.

PSA response will be assessed according to Prostate Cancer Working Group 2 criteria.

Serum PSA change from baseline: the maximum percent PSA change (rise or fall) from baseline to after 12 weeks on study. It will be summarized using box-whisker plots and waterfall plots for each treatment arm. For patients who discontinue on or before the 12 week assessment or for whom the 12 week assessment is missing, the last observation prior to the week 12 assessment will be utilized. Patients with no post-baseline PSA data will be excluded from the

summaries.

Objective Response Rate: The proportion of patients with ORR (as defined in section 11.1.4.4) will be presented with two-sided 90% confidence interval estimated using exact binomial methods.

Pharmacokinetic (PK) analysis:

The PK parameters of the first 12 patients enrolled at Dana-Farber Cancer Institute will be determined using noncompartmental methods with WinNonLin version 5.2. Maximum blood concentration (C_{max}) and time of maximum blood concentration (t_{max}) will be determined by visual inspection. The area under the blood concentration-time curve (linear trapezoidal rule) will be determined between 0-24 hours (AUC₀₋₂₄). The mean (+/- STDEM) concentration-time profiles of docetaxel will be presented.

Exploratory /Correlative Analysis:

For the subset of patients with AR-V7 expression in CTCs, the association between pre-treatment AR-V7 expression and outcomes will be explored, e.g., the proportion of patients with objective response according to pre-treatment AR-V7 will be summarized with two-sided 90% exact binomial confidence intervals (CI). Kaplan-Meier estimates will be used to assess the distribution of PFS according to baseline AR-V7 expression positivity. Medians of time to event endpoints will be shown with two-sided 90% CIs.

13.7 Safety Considerations

Patients will be monitored throughout treatment and follow-up period for occurrence of adverse events (AE's; acute, delayed, and cumulative) as well as for changes in clinical status, vital signs, and laboratory data. NCI Common Terminology Criteria for Adverse Events (CTCAE, Version 4.0) will be used to grade toxicities.

Safety parameters to be assessed include eligibility assessment, medical history, performance status, vital signs, physical examination, baseline ECG, and the following laboratories: serum PSA, testosterone, CBC with differential, and complete metabolic panel.

13.8 Reporting and Exclusions

13.8.1 Evaluation of Toxicity

All participants who received at least one dose of study treatment will be included in the toxicity assessment. In the safety lead in phase of 6 patients, DLTs will be summarized among all patients evaluable for DLT (i.e., patients are excluded if they stop therapy prior to receiving more than 85% of planned dosing of both agents in first 28 days for reasons other than DLT). Baseline toxicities will not be included/attributed to the study therapy.

13.8.2 Evaluation of the Primary Efficacy Endpoint

The primary endpoint will be based on intent-to-treat population. Specifically, all eligible participants included in the study will be assessed for response/outcome to therapy, even if there are major protocol therapy deviations.

Subanalyses may be performed on the basis of a subset of participants, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses will not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding participants from the analysis should be clearly reported. If applicable to the endpoint, the 95% confidence intervals will be provided.

[REDACTED]

[REDACTED]

APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B INFORMATION ON POSSIBLE DRUG INTERACTIONS

Information on Possible Interactions with Other Agents for Patients and Their Caregivers and Non-Study Healthcare Team

The participant _____ is enrolled on a clinical trial using the experimental agent apalutamide. This clinical trial is sponsored by Dana-Farber Cancer Institute. This form is addressed to the participant, but includes important information for others who care for this participant.

Apalutamide interacts with many drugs that are processed by your liver. Because of this, it is very important to tell your study doctors about all of your medicine before you start this study. It is also very important to tell them if you stop taking any regular medicine, or if you start taking a new medicine while you take part in this study. When you talk about your medicine with your study doctor, include medicine you buy without a prescription at the drug store (over-the-counter remedy), or herbal supplements such as St. John's wort.

Many health care prescribers can write prescriptions. You must also tell your other prescribers (doctors, physicians' assistants or nurse practitioners) that you are taking part in a clinical trial. **Bring this paper with you.** These are the things that you and they need to know:

Apalutamide interacts with (a) certain specific enzyme(s) in your liver.

- The enzyme(s) in question is CYP3A4
- Apalutamide must be used very carefully with other medicines that need these liver enzymes to be effective or to be cleared from your system.
- Other medicines may also affect the activity of the enzyme.
 - Substances that increase the enzyme's activity ("inducers") could reduce the effectiveness of the drug, while substances that decrease the enzyme's activity ("inhibitors") could result in high levels of the active drug, increasing the chance of harmful side effects.
 - Docetaxel is broken down by this enzyme in order to be cleared from your system. Thus, apalutamide may decrease the potency of docetaxel, which could lead to less effectiveness.
 - **Co-administration with any of these strong CYP3A4 inhibitors may increase apalutamide plasma concentrations and potentially lead to increased side effects.**
 - Itraconazole, clarithromycin, erythromycin, diltiazem, verapamil, delavirdine, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole, grapefruit juice (or grapefruits), ketoconazole, dexamethasone
 - **Co-administration with any of these strong CYP3A4 inducers may decrease apalutamide plasma concentrations and may lead to decreased effectiveness.**
 - Phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital, efavirenz, tipranavir, St. John's wort

- You and healthcare providers who prescribe drugs for you must be careful about adding or removing any drug in this category.
- Before you start the study, your study doctor will work with your regular prescriber to switch any medicines that are considered “strong inducers/inhibitors or substrates of **CYP3A4**.”
- Your prescribers should look at this web site <http://medicine.iupui.edu/clinpharm/ddis/table.aspx> or consult a medical reference to see if any medicine they want to prescribe is on a list of drugs to avoid.
- Please be very careful! Over-the-counter drugs have a brand name on the label—it’s usually big and catches your eye. They also have a generic name—it is usually small and located above or below the brand name, and printed in the ingredient list. Find the generic name and determine, with the pharmacist’s help, whether there could be an adverse interaction.
- Be careful:
 - If you take acetaminophen regularly: You should not take more than 4 grams a day if you are an adult or 2.4 grams a day if you are older than 65 years of age. Read labels carefully! Acetaminophen is an ingredient in many medicines for pain, flu, and cold.
 - If you drink grapefruit juice or eat grapefruit: Avoid these until the study is over.
 - If you take herbal medicine regularly: You should not take St. John’s wort while you are taking apalutamide.
 - Unless prescribed by your doctor, do not take dexamethasone with the exception of the day before, day of, and day after docetaxel premedication.

Other medicines can be a problem with your study drugs.

- You should check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.
- Your regular prescriber should check a medical reference or call your study doctor before prescribing any new medicine for you. Your study doctor’s name is:

and he or she can be contacted at

APPENDIX C PROHIBITED MEDICATIONS

Generic Name	Brand Name*
aminophylline	Aminocont; Aminomal; Diaphyllin; Filotempo; Neophyllin; Norphyl; Phyllocontin; Syntophyllin; Tefamin; Truphylline; Xing You Shan;
aminophylline in combination	Asmeton; Cha Xin Na Min; Emergent-Ez; Fufang Dan An Pian; Ke Zhi
amitriptyline	Amirol; Amitrip; Amixide; Deprelieo; Diapatol; Elatrol; cElatrolet; Elavil; Endep; Enovil; Emitrip; Klotriptyl; Laroxyl; Levate; Limbitrol; Limbitryl; Mutabase; Mutabon; Nobritol; Novo-Triptyn; Pertriptyl; Redomex; Saroten; Sarotex; Sedans; Syneudon; Teperin; Triptizol; Triptyl; Tryptizol
amitriptyline in combination	PMS-Levazine
bupropion	Aplenzin; Buproban; Contrave; Elontril; Forfivo; Fortivo XL; Le Fu Ting; Prexaton; Quomem; Voxra; Wellbutrin; Wellbutrin XL; Wellbutrin SR; Yue Ting; Zyban
chlorpromazine	Aminazin; Chlorazin; Hiberna; Klorproman; Largactil; Megaphen; Ormazine; Plegomazin; Solidon; Taroctyl; Thorazine; Vegetamin; Wintermin; Zuledin Note: in Ireland also called “Clonazine” – very easy to confuse with clozapine.
clozapine	Azaleptin; Clopine; Closastene; Clozaril; CloZAPine; Denzapine; Elcrit; Fazacio ODT; Klozapol; Lanolept; Leponex; Lozapine; Nemea; Ozapim; Synthron, Versacloz; Zaponex
desipramine	Deprexan; Norpramin; Nortimil; Pertofrane
doxepin	Adapin; Anten; Aponal; Deptran; Gilex; Li Ke Ning; Quitaxon; Silenor; Sinopin; Sinequan; Zonalon
imipramine	Impril; Melipramin; Mipralin; Norfranil; Novo-Pramine; Persamine; Pertofram; Pyleugan; Talendep; Tofranil; Tolerade
lithium	Arthriselect; Camcolit; Carbolith; Carbolithium; Eskolith; Hypnorex; Li-Liquid; Licarbium; Limas; Liskonum; Litarex; Lithane; Lithicarb; Lithioderm; Lithionit; Lithobid; Liticarb; Litiomal; Lito; Maniprex; Neurolepsin; Plenur; Priadel; Quilonorm; Quilonum; Saniquiet; Sedalite; Teralithe
lithium in combination	Boripharm No 23; Emser Salz; Girheulit HOM; Helidonium-Plus; Heweurat N; rheuma-loges; Rhus Toxicodendron Compose; Rhus-Plus; Ricinus Compose
maprotiline	Cronmolin; Deprilept; Ludiomil; Mapromil; Melodil; Neuomil; Psmion
meperidine/pethidine	Alodan ; Atropine and Demerol; Centralgine ; Demerol ; Dolantin ; Dolantina; Dolantine ; Dolargan; Dolconral; Dolestine ; Dolosal ; Dolsin; Fada; Hospira; Liba; Mepergan ; Meprozone; Mialgin; Opystan; Pethidine ; Petigan Miro ; Psyquil compositum
meperidine/pethidine in combination	Pamergan P100
mesoridazine	Serentil, Mesorin
mirtazapine	Arintapin; Avanza; Axit; Combar; Esprital; Mi Er Ning; Miro; Mirta TAD; Mirtabene; Mirtachem; Mirtadepi; Mirtagamma; Mirtalan; MirtaLich; Mirtamylan; Mirtaron; Mirtaz; Mirtazelon; Mirtazon; Mirtazonal; Mirtel; Mirtin; Mirtor; Mirzaten; Norset; Noxibel; Paidisheng; Psidep; Remergil; Remergon; Remeron; Remirta; Rexer; Yarocen; Zispin
olanzapine	Anzarin, Arenbil; Arkolamyl; Atyzyo; Bloonis; Clingozan; Egolanza; Lansyn; Lanzek; Lazapix; Nolian; Nykob; Olafid; Olanzaran; Olanzep; Olanzin; Olanzine; Olapin; Olasyn; Olazax; Olpinat; Olzapin; Olzin; Ou Lan Ning; Ozilormar; Parnassan; Ranofren; Sanza; Stygapon; Synza; Ximin; Zalasta; Zamil; Zappa; Zapris; Zerpi; Zolafren; Zolaxa; Zonapir; Zopridoxin; Zylap; Zypadhera; Zypine; Zyprexa; Zyprexa Relprew; Zydis

olanzapine in combination	Symbyax
risperidone	Aleptan; Apo-Risperid; Arketin; Calmapride; Diaforin; Doresol; Hunperdal; Jing Ping; Ke Tong; Leptinorm; Lergitec; Orizon; Ozidal; Perdox; Ranperidon; Resdone; Ridal; Ridonex; Rileptid; Ripedon; Risepro; Rispa; Rispaksole; Rispefar; Risphemylan; Rispen; Rispera; Risperanne; Risperdal; Risperdalconsta; Risperdaloro; Risperigamma; Risperon; Rispolept; Rispolux; Rispond; Rispons; Risset; Rixadone; Rorendo; Ryspolit; Si Li Shu; Sizodon; Speridan; Suo Le; Torendo; Zhuo Fei; Zhuo Fu; Ziperid; Zoridal
theophylline	Aerolate; Afonilum; Aminomal; An Fei Lin; Apnecut; Apo-Theo; Asmalix; Asmalon; Bi Chuan; Bronchoparat; Bronchoretard; Cylmin; Diffumal; Elixifilin; Elixophyllin; Etipramid; Euphyllin; Euphyllina; Euphylline; Euphyllong; Frivent; Gan Fei Lin; Nuelin; Protheo; Pulmophylline; Quelesu; ratio-Theo-Bronc; Respicur; Retafyllin; Shi Er Ping; Slo-Bid; Slo-Phyllin; Telbans; Teotard; Terdan; Teromol; Theo-24; Theo-Dur; Theo; Theochron; Theodur; Theofol; Theolair; Theoplus; Theospirex; Theostat ; Theotard; Theotrim; Theovent; Tromphyllin; Unicon; Unicontin; Unifyl; Uniphyl; Uniphyllin Continus; Uniphyllin; UniXan; Xanthium; Xi Fu Li; Yan Er
theophylline in combination	Antong; Baladex; Bi Chuan; Binfolipase; Broncho-Euphyllin; Broncomar; Do-Do ChestEze; Elixophyllin-GG; Elixophyllin-KI; Insanovin; Marax ; Neoasma; Theofol Comp; Theophedrinum-N; Xu Hong; Yi Xi Qing
thioridazine	Detril; Elperil; Melleril; Ridazin; Ridazine; Thiodazine; Thioril; Sonapa
ziprasidone	Geodon; Li Fu Jun An; Pramaxima; Si Bei Ge; Ypsila; Zeldox; Zipwell; Zypsila; Zypsilan

**** Note: this document is intended as an aid in identifying prohibited meds, but due to the global scope of the apalutamide studies may not be all inclusive.**

APPENDIX D PCWG2 CRITERIA

The following eligibility and disease progression criteria were taken from the PCWG2 criteria established by Scher et al. 2008.

Patients with Non-Measurable Disease

A large percentage of men with metastatic prostate cancer have cancer involvement limited to bones, and therefore do not have measurable disease by RECIST v 1.1. These patients are eligible for this study, and will have response to treatment assessed by serial bone scans and serum PSA level.

Eligibility Based on PSA Levels

PSA level that has increased on 2 occasions obtained a minimum of 1 week apart and PSA level ≥ 2 ng/ml (only the screening PSA needs to be ≥ 2 ng/ml; see Figure 2 below for an example).

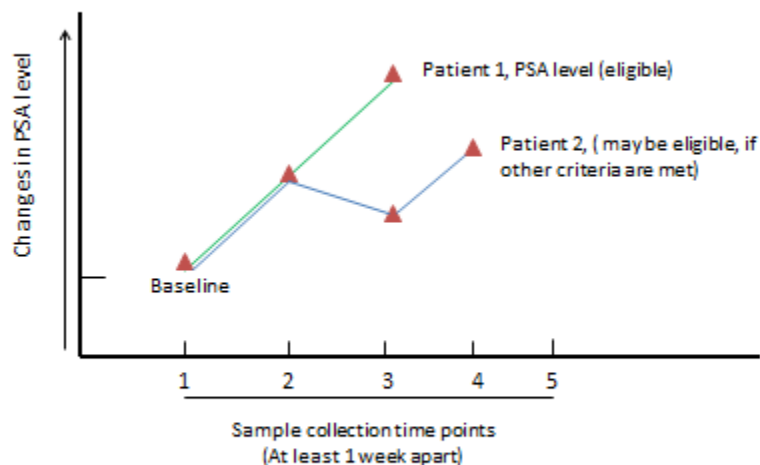


Figure 2 Eligibility based on PSA changes

The baseline value is the last PSA measured before increases are documented and subsequent values are obtained a minimum of 1 week apart. If the PSA at time point 3 is greater than that at time point 2 (2.0 ng/mL or higher), then eligibility has been met (Patient 1 in Figure 2). If the PSA at time point 3 is not greater than at time point 2, but the value at time point 4 is (2.0 ng/mL or higher), then the patient is eligible assuming that other criteria are met (Patient 2 in Figure 2), Bublely et al. 1999).

PCWG2 Criteria (continued)

Details and dates of prior PSA measurements that can be used to estimate PSA doubling times (PSA-DTs) should be recorded. PCWG2 advises estimating a pretreatment PSA-DT if at least three values are available, but does not recommend delaying either treatment or enrollment onto a trial simply to estimate PSA-DT (Arlen et al. 2008).

Eligibility Based on Bone Scan

When the bone scan is the sole indicator of progression, PCWG2 defines progression in bone when at least 2 or more new lesions are seen on bone scan compared with a prior scan for trial entry.

Disease Progression will be defined as follows:

1) Bone Scan and Radiographic Progression

Appearance of 2 or more new lesions on bone scan, and, for the first reassessment only, a confirmatory scan performed 6 or more weeks later that shows a minimum of 2 or more additional new lesions. The date of progression is the date of the first scan that shows the change.

Or

Soft tissue disease progression by modified RECIST v1.1 to report changes in lymph nodes that were ≥ 2 cm in diameter at baseline with additional requirement that progression at first assessment be confirmed by a second scan 6 or more weeks later.

Note that for some treatments, a lesion may increase in size before it decreases.

2) PSA Progression

PSA progression is defined as $\geq 25\%$ increase and ≥ 2 ng/mL increase above the nadir or baseline value for patients who had a PSA decrease on treatment which is confirmed by a second value 3 or more weeks later.

For patients without a decrease on treatment, PSA progression is defined as $\geq 25\%$ and a ≥ 2 ng/mL after 12 weeks.

PSA progressions must be confirmed at the next study visit 4 weeks later. PSA will be collected at screening and on Day 1 of each treatment cycle.

PSA progression alone will **not** be considered diagnostic of disease progression, and will not be used as a reason to discontinue study treatment.

PCWG2 Criteria (continued)

3) Symptomatic Progression

Symptomatic progression is defined as evidence of unequivocal symptomatic or clinical progression defined by at least 1 of the following:

- A marked escalation in cancer-related pain that is assessed by the Investigator to indicate the need for other systemic therapy or palliative radiotherapy. Ignore early changes (≤ 12 weeks) in pain or health-related quality of life in absence of compelling evidence of disease progression. Confirm progression of pain or health-related quality of life ≥ 3 weeks later,
- An immediate need for initiation of new anticancer treatment, surgical or radiological intervention for complications due to tumor progression,
- A marked deterioration in ECOG performance status to Grade 3 or higher, or
- It is felt to be in the best interest of the patient to come off study due to clinical progression

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