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A Phase I/II Trial of Concurrent Chemohormonal Therapy Using Enzalutamide (MDV-3100) and Cabazitaxel in Patients with Metastatic Castration Resistant Prostate Cancer

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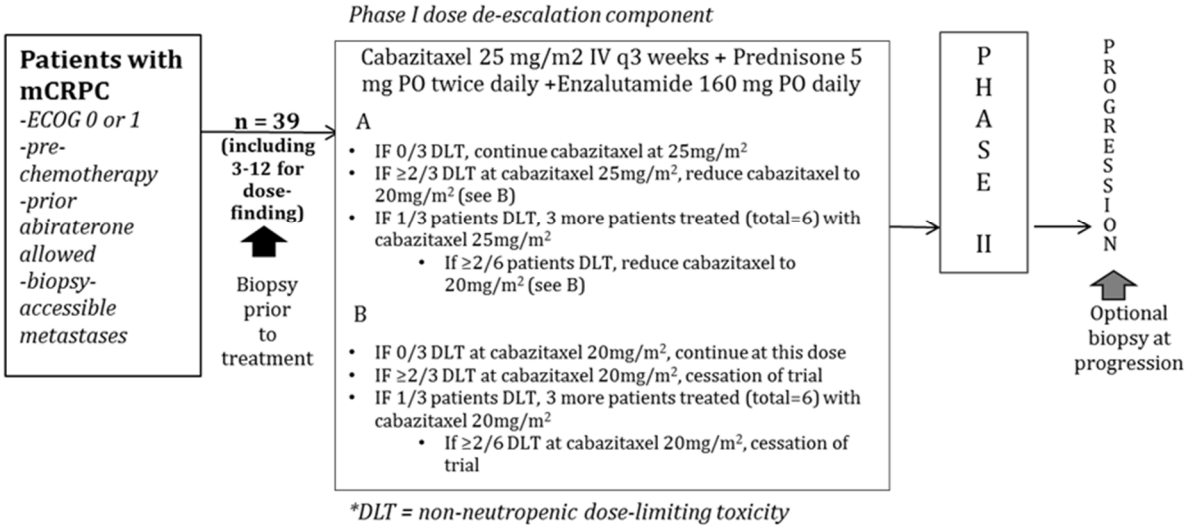
SCHEMA

STUDY SCHEMA:



We propose a single-arm Phase II study design with a Phase I dose de-escalation component to identify safe dosing of concurrent cabazitaxel (with prednisone) and enzalutamide. All safety data will be reviewed by the Principal Investigators and an independent data safety monitoring committee at Oregon Health & Science University.

Toxicity requiring therapy discontinuation or dose reduction will be the event of interest (a pragmatic endpoint that measures the viability of a regimen) in the Phase I portion. If ≥2 such events are reported in the initial 6 patients, the dose of cabazitaxel will be reduced by 20% to 20 mg/m^2 IV q3 weeks thereafter. There will not be dose reductions for enzalutamide. The endpoint for the Phase II portion is percent of patients whose PSAs decrease by ≥90%.

A total of 39 study subjects will be treated as part of this study, including the first 3-12 subjects in the dose-finding component.
To understand the biological effects of the treatment, and to evaluate for potential prognostic biomarkers, we will collect correlative biospecimens. Metastatic tumor biopsies will be obtained prior to first treatment. Sites where prior radiation has been administered for metastatic disease will be avoided. Patients will be offered the option of a second biopsy at the time of progression. If they consent, all attempts will be made to biopsy the same lesion as was sampled for the first biopsy. Blood will also be collected pre- and post-treatment for evaluation of circulating tumor cells and other circulating markers, such as microRNAs.

Serum PSA will be checked on day 1 of each cycle. Restaging CT and bone scans will be performed every 12 weeks ±7 days.

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1. OBJECTIVES

1.1. Primary Objectives

- To determine the safety and tolerability of combination treatment with enzalutamide and cabazitaxel (as determined by percent dose limiting toxicities (DLT), where DLT < 17% is consistent with it being a tolerable combination).
- To determine the efficacy of treatment with the hormonal agent enzalutamide and the chemotherapy cabazitaxel in combination in men with metastatic CRPC (as determined by percent of patients achieving ≥90% PSA declines following initiation of treatment). There will be a subgroup analysis according to prior abiraterone exposure.

1.2. Secondary Objectives

The secondary objective will be to further define the anticancer effect and safety profile of the combination of enzalutamide and cabazitaxel.

- Collect toxicity data (description of adverse events)
- Determine PSA response (percent of patients who achieve ≥50% PSA decline and ≥30% PSA decline)
- Examine PK data of cabazitaxel to characterize enzalutamide and cabazitaxel pharmacokinetic blood levels
- Determine tumor response by RECIST 1.1 for measurable disease and Prostate Cancer Working Group 2 criteria for non-measurable (bone) disease
- Determine overall survival

1.3 Exploratory Objectives

There are still many unknowns regarding molecular determinants of response and resistance to cabazitaxel and enzalutamide. We will attempt to better define them using the following techniques and markers.

- To determine baseline (and at progression) biological tumor characteristics to evaluate for possible biomarkers indicative or predictive of response.
  - Apoptosis by cleaved caspase 3
  - Androgen signaling axis (including but not limited to: androgen receptor expression, androgen receptor splice variants, and intratumoral androgen levels)
  - Glucocorticoid receptor
- To collect circulating tumor cells (CTCs) and determine the degree to which tumor characteristics (delineated above) are shared by the CTCs.
- To collect plasma and serum pre-treatment and at progression for assessment of circulating microRNAs and other circulating markers.
- To collect buffy coat to evaluate for steroid transporters.

2. BACKGROUND

2.1 *Study Disease*

Metastatic, castration resistant prostate cancer (mCRPC) is prostate cancer that no longer responds to castration alone, either surgically or chemically, and which has spread to organs outside of the prostate as seen on an imaging study, such as bone scan or CT scan. It is also the final disease state in prostate cancer and invariably fatal. There are several new agents that prolong survival in mCRPC, but none that cure it. The benefit of using these agents in combination, rather than sequentially, is unknown. We seek to better

understand the effect of combining enzalutamide and cabazitaxel. If it looks especially promising, this will lead to a phase III study examining the combination of these agents versus sequential use.

2.2 ***Study Agents***

Recently the CHAARTED study results were released. This study showed that the combination of androgen suppression therapy and docetaxel in treatment naïve metastatic prostate cancer prolonged survival relative to androgen suppression therapy alone. This is one example of how combining therapies may be effective.

Cabazitaxel is a cytotoxic chemotherapeutic currently FDA-approved for metastatic CRPC after prior treatment with docetaxel chemotherapy. The Phase III TROPIC trial showed efficacy in metastatic CRPC with a 2.4 month survival benefit over mitoxantrone in the post-docetaxel line setting.[1]
The approved dose is 25 mg/m^2 IV every 3 weeks. A known toxicity of cabazitaxel is myelosuppression, including neutropenia, and it is frequently given with growth factor support, i.e. G-CSF or GM-CSF. However, cabazitaxel is considered safe and effective.

Enzalutamide is a hormonal agent that is also FDA-approved for metastatic CRPC after prior docetaxel chemotherapy. It acts as a specific inhibitor of the androgen receptor at multiple steps in the androgen-signaling pathway.[2] In preclinical studies, enzalutamide exerts anti-proliferative activity on prostate cancer cells that exhibit amplification of the androgen receptor. The Phase III AFFIRM study confirms that enzalutamide improves median survival in post-docetaxel metastatic CRPC patients by 4.8 months.[3] In addition, there is a randomized, phase III clinical trial that evaluated its efficacy in the pre-chemotherapy setting (PREVAIL).Treatment with enzalutamide resulted in a 30% reduction in the risk of death (HR 0.7) and an 81% reduction in the risk of radiographic disease progression or death (HR 0.19). Both of these differences were unambiguously statistically significant. Complete results will be presented at an upcoming scientific meeting. Enzalutamide is not recommended in patients with a risk of seizure because seizure was observed in the phase I study.[2] In AFFIRM, which excluded patients with a history of seizure there was a <1% rate of seizure. In retrospect, those who did have a seizure had underlying conditions that should have excluded them from the study (brain metastatic disease) or they were treated with drugs that lowered the seizure threshold (intravenous lidocaine).

2.3 Other Agents.

Prednisone is an oral corticosteroid given with cabazitaxel for its anticancer effect. Once the final cycle of cabazitaxel is completed, the prednisone can be tapered off. One suggested regimen would be to decrease it from 5 mg twice daily to 5 mg once daily for 2 weeks and then off.

Growth factor support (G-CSF or GM-CSF) minimizes neutropenia after (and induced by) chemotherapy.
Both of these agents will be used in conjunction with cabazitaxel and enzalutamide.

2.4 **Rationale**

Castration resistant prostate cancer is the final disease state and an invariably fatal form of prostate cancer. While great strides have been made in developing new agents for

metastatic CRPC, response rates and duration have remained modest, and men ultimately succumb to their disease. In the past three years, five additional agents that extend survival have been approved for this disease. These agents include an immunotherapy (sipuleucel-T), a second-line chemotherapeutic agent (cabazitaxel), a radiopharmaceutical (radium-223) and two hormonally active agents (abiraterone and enzalutamide). Thus, the management of advanced prostate cancer has been both enhanced and complicated by the rapid emergence of at least five new agents that can lengthen survival: enzalutamide, abiraterone, sipuleucel-T, cabazitaxel, radium-223.

Historically, combined chemo-hormonal therapy has not improved outcomes for patients with prostate cancer, but earlier trials were hindered by lack of efficacious chemotherapy and weaker hormonal agents. In this study, we aim to determine if potential synergistic effects between two newer and more effective agents can be identified and exploited for therapeutic effect, and to obtain correlative biological information that may offer predictive and response value.

3. PATIENT SELECTION

3.1 Inclusion Criteria

3.1.1 Men 18 years or older with metastatic CRPC

3.1.2 Willing to provide a tumor sample via biopsy from a metastatic site of disease to be collected at screening if safe and feasible per discretion of treating investigator. Adequate archival metastatic tissue can be used, if available, in lieu of baseline biopsy if done when patient had CRPC. Patients without a site amenable to biopsy and lack of archival tissue may still join the study.

3.1.3 Evidence of prostate cancer progression by any of the following criteria: radiographic or PSA criteria, or symptomatic progression related to prostate cancer. (See section 9.1.2 for details.)

3.1.3 Castrate testosterone levels (<50 ng/dL) achieved by orchiectomy or maintenance on a LHRH agonist or antagonist.

3.1.4 Histologic confirmation of original prostate cancer diagnosis per institutional standard. Life expectancy of greater than 6 months.

3.1.5 ECOG performance status of 0 or 1.

3.1.6 Patients must have normal organ and marrow function as defined below:

- leukocytes $\geq$3,000/mm^3
- absolute neutrophil count $\geq$1,500/mm^3
- platelets $\geq$100,000/mm^3
- total bilirubin within normal institutional limits (or <2X the upper limit of normal in those with Gilbert's disease)
- AST(SGOT)/ALT(SGPT) $\leq$1.5 X institutional upper limit of normal
- creatinine less than the institutional

upper limit of normal

- creatinine clearance* ≥45 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal

*Web link to be used to estimate glomerular filtration rate (GFR) using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula.**http://www.qxmd.com/calculate-online/nephrology/ckd-epi-egfr**

3.1.7 Subject agrees to use a double barrier method of birth control during the course of study treatment period with enzalutamide and/or cabazitaxel treatment and for at least 3 months after the study is discontinued.

- A double-barrier method of contraception involves the use of a condom in combination with 1 of the following: contraceptive sponge, diaphragm, or cervical ring with spermicidal gel or foam.
- Subject who has had a vasectomy at least 6 months prior to starting study treatment period and those whose female sexual partner(s) are more than 55 years of age and postmenopausal for at least 2 years or surgically sterile (tubal ligation, hysterectomy, or bilateral oophorectomy) agree to use at least a condom.

3.1.8 Ability to understand, and the willingness to sign, a written informed consent document, as well as comply with study requirements.

3.1.9 Must have appropriate wash out (> 6 half-lives) of androgen receptor antagonists, 5α reductase inhibitors or ketoconazole prior to the start of cycle 1. If the agent is not in the table below, the washout should be 2 weeks.

Drug	Approximate Half-Life	Washout Period Required
Bicalutamide	6 days	36 days
Flutamide	6 hours	36 hours
Nilutamide	4 days	24 days
Finasteride	8 hours	48 hours
Aminoglutethamide	15 hours	4 days
Ketoconazole	8 hours	48 hours

3.2 Exclusion Criteria

3.2.1 Prior chemotherapy for mCRPC prostate cancer. Chemotherapy given neoadjuvantly, adjuvantly, or for hormone sensitive metastatic disease is permitted as long as the cancer did not progress on chemotherapy AND >6 months have elapsed.

3.2.2 Patients may not have received any other investigational agents within the last 14 days at the time of treatment start.

3.2.3 Patients may not have received enzalutamide or ARN-509 (another androgen receptor antagonist) in the past.

3.2.4 Patients may not have received cabazitaxel in the past.

3.2.5 Subject has clinical signs suggestive of high or imminent risks for pathological fracture, spinal cord compression and/or cauda equina syndrome.

3.2.6 History of severe hypersensitivity reaction (≥grade 3) to docetaxel, polysorbate 80 containing drugs, or any of the capsule components of enzalutamide, including Labrasol, butylated hydroxyanisole, and butylated hydroxytoluene.

3.2.7 Concurrent or planned treatment with strong inhibitors or strong inducers of cytochrome P450 3A4/5. (A one-week wash-out period is necessary for patients who are already on these treatments, see Appendices C and D.)

3.2.8 Uncontrolled, intercurrent illness including, but not limited to, ongoing or active infection, uncontrolled diabetes, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.9 Subject has a history of seizure or any condition that may predispose to seizure including, but not limited to, underlying brain injury, stroke in the past 6 months, primary brain tumors, brain metastases, prior seizures.

3.2.11 Subject has a history of unexplained loss of consciousness or transient ischemic attack within 12 months of treatment start.

3.2.12 Subject is unwilling to stop using herbal supplements that can affect the PSA, such as saw palmetto or PC-SPES.

3.2.13 Subject has another active malignancy other than non-melanomatous skin cancer (unless it is metastatic) or superficial bladder cancer.

3.2.14 Must not have a gastrointestinal condition that would interfere with absorption.

3.2.15 Subjects may not be on other therapies that affect hormone levels, such as estrogens, testosterones, ketoconazole during this study. However, megestrol for hot flashes is permitted.

4. TREATMENT PLAN

4.1 Agent Administration

Treatment will be administered on an outpatient basis. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy. Supportive treatments, such as zolendronic acid or denosumab, may be continued if the subject is on them at the time of study entry.

4.1.1 ***Study Agents***

During treatment with cabazitaxel + enzalutamide, one cycle is 21 days.

During treatment with enzalutamide monotherapy (after 6-10 cycles of cabazitaxel)

one cycle is 28 days.

Cabazitaxel 25 mg/m^2 IV every 21 days. This study has a dose de-escalation portion, so the dose may be decreased to cabazitaxel 20 mg/m^2 IV every 21 days in the Phase I portion if it proves too toxic in combination with enzalutamide. In the event that the combination of cabazitaxel 20 mg/m^2 IV with enzalutamide 160 mg is too toxic in the phase I portion, the study will be terminated.

- Premedication with an antihistamine (dexchlorpheniramine 5 mg or diphenhydramine 25 mg), a corticosteroid (dexamethasone 8 mg or equivalent), and H2 antagonist (ranitidine 50 mg) given 30 minutes before the cabazitaxel or per institutional standard of care.
- Subjects will also receive prednisone 5 mg PO twice daily with cabazitaxel or per institutional standard of care.

Enzalutamide 160 mg PO once daily.

- A minimum of 6 subjects will participate in the PK portion of this study. They will begin taking enzalutamide on day 2 of cycle 1 and continue taking it daily for the rest of cycle 1. On day 1 of cycle 2, they will not take their enzalutamide until they are instructed to take it in the infusion unit when they receive their cabazitaxel. However, on all other days, these patients will take their enzalutamide at home.
- All subjects who are not part of the PK portion of this study will take their enzalutamide at home starting on day 1 of cycle 1 and continuing every day of all subsequent cycles. Enzalutamide may be taken with or without food, but should be taken either with food or without food consistently.

4.2 Supportive Care Guidelines

Subcutaneous G-CSF or GM-CSF is mandated for each cycle as a safety precaution, and should be given 24-48 hours after each cabazitaxel dose. Brand of G-CSF or GM-CSF will be up to the treating physician.

4.3 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment with cabazitaxel may continue for 6-10 cycles, or until one of the following criteria applies:

- Disease progression (see 9.1.2),
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Subject decides to withdraw from the study, or
- General or specific changes in the subject's condition render the patient

unacceptable for further treatment in the judgment of the investigator.

The enzalutamide may be continued after the 6-10 cycles of cabazitaxel are given and may be discontinued for one of the events outlined above.

5. DOSING DELAYS/DOSE MODIFICATIONS

5.1 *Study Agents*

There will not be dose reductions for enzalutamide.

Cabazitaxel may be dose reduced for a subject who experiences the toxicities outlined in section 6.2.1. It is important to note that the dose will only be reduced to 20 mg/m^2. If further dose reductions are required, the subject will be removed from the study.

Also, DLTs identified in the first two cycles of treatment of the Phase I portion of the study will inform the dose of cabazitaxel in the phase II portion of the study. The same toxicities in the phase II portion of the study will only affect the dose of that individual subject. In the case that 8 or more patients in the Phase II portion of the study experience DLTs, the study will be stopped early (see section 11.6).

5.2 Other Agents

Prednisone may be discontinued for the onset or exacerbation of diabetes mellitus, hypertension, gastrointestinal ulceration or bleeding, severe neurological side effects, or other serious adverse events that the Investigator considers to be a contraindication to continuing steroids. Prednisone may be reinstituted with the resolution of the adverse event at the discretion of the Investigator. The reason for altering the dose or discontinuing prednisone should be documented on the CRF. Prednisone may also be tapered off after the final cycle of cabazitaxel in all patients.

Bisphosphonate or Denosumab Usage
Subjects who are on a bisphosphonate or denosumab should be on a steady dose for at least four weeks prior to day 1 of the study. Zoledronic acid and denosumab can be added after cycle 2.

6. AGENT FORMULATION AND PROCUREMENT

6.1 **Agent Accountability**

The Investigator, or a responsible party designated by the Investigator, must maintain a careful record of the inventory and disposition of the study agent.

6.2 *Study Agents:*

6.2.1 *Cabazitaxel*

Availability: Cabazitaxel is supplied to investigators by Sanofi for study purposes.

Product description:
Cabazitaxel is supplied for parenteral administration as a sterile, non-pyrogenic non-aqueous solution contained in a 15 mL clear glass vial closed with a rubber closure. The closure is crimped to the vial with an aluminum cap covered with a light green plastic flip-off cap. The solution is clear and yellowish to brownish-yellow. Each vial contains 60 mg of cabazitaxel, expressed on anhydrous and solvent-free basis, per 1.5 mL of solution.

The fill volume has been established to include an overfill [i.e., 1.5 mL (nominal volume) + 0.33 mL]. This overfill was determined to ensure that a 10 mg/mL (corresponding to 60 mg/mL) concentration is obtained in the premix and that 60 mg dose can be extracted. This must be done with the entire contents [i.e., 4.5 mL (nominal volume) + 1.17 mL) of the solvent for dilution for cabazitaxel.

Solvent vial:

The solvent used for the preparation of the premix is a sterile, non-pyrogenic solution containing a 13 % w/w ratio of ethanol 95 % in water for injection. This solution is contained in a 15 mL clear type I glass vial closed with a rubber closure. The closure is crimped to the vial with either an aluminum cap covered with a light grey plastic flip-off cap or a gold-color aluminum cap covered with a colorless plastic flip off cap. The solution is a clear colorless liquid.

Each vial is overfilled to ensure that a 10 mg/mL concentration is obtained in the Premix and that 60 mg dose can be extracted. [i.e., 4.5 mL (nominal volume) + 1.17 mL]

Excipients:

Polysorbate 80 from vegetable origin, for the drug product vial.
Water for injection and ethanol for the solvent vial.

Storage conditions:

Vials should be stored according to their labeling and kept in their kit until use.

Solution preparation
Cabazitaxel drug products should be administered only by intravenous route.
It is supplied as a kit containing one single-use vial of cabazitaxel concentrate for solution for infusion and one single vial of solvent for dilution. The administration of the product requires two dilutions prior to administration.

This pharmaceutical dosage form is a concentrate for solution for infusion and must be diluted before administration. First the dosage form is diluted with the solvent supplied

(preparation of the “cabazitaxel premix solution”). Then this premix solution must be diluted in an infusion vehicle (preparation of the “cabazitaxel infusion solution”). Each cabazitaxel vial and each corresponding solvent vial are overfilled to ensure that a 60 mg dose can be withdrawn after the preparation of the premix.

- **Preparation of cabazitaxel premix solution under aseptic conditions:**

Use one solvent vial per each vial of cabazitaxel concentrate.
Withdraw, under aseptic conditions, the **entire** contents of the solvent vial and inject it into the corresponding vial of cabazitaxel concentrate. **Gently** mix the reconstituted solution by repeated inversions for at least 45 seconds until obtaining clear and homogenous solution. **Do not shake**. Let the premix solution stand for a few minutes at room temperature to allow foam to dissipate. The solution is homogeneous and contains no visible particulate matter. It is normal for foam to persist after this time period.

In order to compensate for liquid loss during preparation and to ensure that the cabazitaxel initial diluted solution (premix) can be prepared at the concentration of 10 mg/mL and that a nominal volume of at least 6 mL can be withdrawn from the premix vial, the cabazitaxel 60 mg/1.5 mL concentrate vials are filled with a 22% overfill (total fill volume 1.83 mL) and the diluent vials with a 26% overfill (total fill volume 5.67 mL).

The concentration of 10 mg/mL in the premix [60mg/1.5 mL (concentrate) + 4.5 mL (diluent)] can be calculated as follows taking into account the overfilling: 73.2mg/ 1.83 ml (22 % overfill concentrate) + 5.49 mL (overfill diluent *) = 10 mg/mL

Thus, the preparation obtained ensures a minimal extractable volume of the premix solution of 6 mL corresponding to a concentration of 10 mg/mL of cabazitaxel corresponding to 60mg/6 mL.

- **Preparation of cabazitaxel infusion solution under aseptic conditions:**

WARNING: Since foam is normally present, the required dose must be accurately adjusted using a graduated syringe.

Withdraw, under aseptic conditions, the volume of the premix solution containing 10 mg/mL of cabazitaxel that corresponds to the required dose (mg) and inject the required premix volume into a 125 to 500 mL infusion container (either 5 % glucose solution for injection or 0.9 % sodium chloride solution for injection). Mix the content of the infusion container manually by gently inverting the bag or bottle. The concentration of the infusion should be between 0.10 mg/mL and 0.26 mg/mL (based on Maximum Tolerated Dose of 30 mg/m² and a Body Surface Area of 2.1 m²).

- **Infusion conditions:**

The recommended infusion duration is one hour. The infusion solution should be used within 8 hours at ambient temperature (including the one hour infusion time) or within a total of 24 hours if refrigerated (including the one hour infusion time).The infusion solution should be administered at room temperature under normal lighting conditions.

- **Do not use PVC infusion containers for cabazitaxel preparation and administration.**
- **Do not use polyurethane infusion sets for cabazitaxel preparation and administration.**

Glass bottles could also be used.

Use an in-line filter of 0.22 µm nominal pore size (also referred to as 0.2 µm) during cabazitaxel administration.

➢ **Shelf life:**

Cabazitaxel premix solution

Premix solution should be used immediately after preparation and within 1 hour at ambient temperature.

Cabazitaxel infusion solution

The infusion solution is stable for 8 hours at ambient conditions (including the 1 hour infusion time) or a total of 24 hours if refrigerated, from preparation to end of infusion.

➢ **Recommendation for the safe handling:**

Cabazitaxel is an antineoplastic agent and, like other potentially toxic compounds, caution should be exercised in handling and preparing cabazitaxel solutions. The use of gloves is recommended. If cabazitaxel concentrate, premix solution or infusion solution should come into contact with skin, wash immediately and thoroughly with soap and water. If cabazitaxel concentrate, premix solution, or infusion solution should come into contact with mucous membranes, wash immediately and thoroughly with water.

Dosing Regimen:

On Day 1 of each cycle, patients will receive cabazitaxel at a dose of 25 mg/m², administered by IV route in 1 hour, unless the Phase I portion identifies the 20 mg/m^2 dose as the safe dose.

Cycle length for cabazitaxel is 21 days. New cycles of therapy may not begin until Absolute Neutrophil Count (ANC) ≥1500/mm^3, platelet count ≥75,000/mm^3, and non-hematologic toxicities (except alopecia) have recovered to baseline. A maximum of 3 weeks delay is allowed between 2 treatment cycles. Patients should come off treatment if treatment delay is more than 3 weeks.

At least 30 minutes prior to each administration of cabazitaxel, patients will be administered IV premedication including:

- An antihistamine (dexchlorpheniramine 5 mg, diphenhydramine 25 mg, or equivalent). In case of IV antihistamine other than promethazine is not being available, local practice should be followed.

- Corticosteroid (dexamethasone 8 mg or equivalent)
- H2 antagonist (ranitidine or equivalent).
- Antiemetic prophylaxis is recommended and can be given orally or intravenously if necessary.

Primary prophylaxis with Granulocyte Colony-Stimulating Factor (G-CSF) or GM-CSF will be given to all patients.

Dose modifications and dose delay: See Section 5.

Expected adverse events:

Hematological toxicity

The dose of cabazitaxel will be modified in case of hematologic toxicity. Dose modifications are summarized in Table1

Table 1 - Dose modifications for hematological toxicity

Toxicity	Grade 2	Grade 3	Grade 4
Neutropenia	If not recovered on D21, delay** next infusion until recovery to grade ≤1 (ANC ≥1,500cells/mm^3). - 1st episode: No dose reduction required. - 2nd episode; reduce by 1 dose level	No dose reduction if isolated and duration ≤7 days. If duration more than 7 days or not recovered on D21 Delay** next infusion until ANC ≥1,500cells/mm^{3}and: - 1st episode: reduce the dose. - 2nd episode: withdraw from study treatment.	
Febrile neutopenia or neutopenic infection	Not applicable	Delay** next infusion until recovery and ANC ≥1,500cells/mm^{3}and: - 1st episode: reduce the dose, see Section 5. - 2nd episode: withdraw from study treatment	
Thrombocytopenia	Delay** next infusion until recovery to grade ≤1 (platelets ≥75,000/mm^3). No dose reduction required.	Delay** infusion until platelets ≥75,000/mm^3. If grade 3 without delay, no dose reduction required. If grade 4 with or without delay, or grade 3 with delay - 1st episode: Reduce dose by 1 dose level. - 2nd episode: Withdraw from study treatment in case of recurrence	

** maximum of 3 weeks delay, otherwise the subject will come off study

Blood counts will be performed in case of fever or infection. Cabazitaxel should not be given to patients with neutrophil counts <1,500 cells/mm^3.

Deaths due to sepsis following severe neutropenia have been reported in patients treated with cabazitaxel. Neutropenic complications should be managed promptly with antibiotic support. Infections concomitant with grade 3-4 neutropenia should be reported with the term “neutropenic infection” in the eCRF.

No dose modification will be made for anemia; patients will be supported appropriately by the treating physician (the investigator can refer to ASCO guidelines).

Allergy (Anaphylactic and Hypersensitivity reactions)

Hypersensitivity reactions that occur despite premedication are very likely to occur within a few minutes of start of the first or second infusion of cabazitaxel. Therefore, during at least the first 10 minutes of the first and second infusions, careful evaluation of general sense of well-being, blood pressure and heart rate will be performed so that immediate intervention can occur.

Facilities equipment and medications (i.e., antihistamine, corticosteroids, aminophylline and epinephrine) for resuscitation must be immediately available. If a reaction occurs, the medically indicated treatment for a given symptom will be instituted (e.g., epinephrine in case of anaphylactic shock, aminophylline in case of bronchospasm, etc). In addition, it is recommended to take the measures listed below:

Mild: localized cutaneous reaction, such as: pruritus, flushing, rash.	○ Consider decreasing the rate of infusion until recovery of symptoms, stay at bedside ○ Complete cabazitaxel infusion at the initial planned rate.
Moderate: Generalized pruritus, more severe flushing or rash, mild dyspnea, hypotension with systolic B.P. >80 mmHg	○ Stop cabazitaxel infusion ○ Give IV diphenhydramine 50 mg and/or IV dexamethasone 10 mg ○ Once all signs and/or symptoms of hypersensitivity reaction disappear, cabazitaxel may be reinfused within 24 hours from the interruption, if medically appropriate, and whenever possible. ○ Re-administer premedication regimen as described in Section 8.6 when cabazitaxel is reinfused more than 3 hours after the interruption ○ Administer cabazitaxel over 2 hours for all subsequent infusions
Severe: bronchospasm, generalized urticaria, hypotension with systolic B.P. ≤80 mmHg, angioedema.	○ Stop cabazitaxel infusion ○ Give IV diphenhydramine 50 mg and/or IV dexamethasone 10 mg ○ Add epinephrine** or bronchodilators and/or IV plasma expanders if indicated ○ Hospitalize if needed ○ Withdraw patient from study; no further exposure to cabazitaxel.

Anaphylaxis(Grade 4 reaction)	Withdraw treatment (DLT)

Nausea/Vomiting

A prophylactic anti-emetic treatment should be given to the patients during all cycles. The use of prochlorperazine is recommended. More aggressive anti-emetic prophylaxis (i.e., ondansetron, etc.) should be given to the patient who has experienced grade ≥3 nausea/vomiting in a preceding cycle. If, despite the appropriate medication, grade ≥3 nausea/vomiting still occur, reduce the dose of cabazitaxel. If, despite dose reduction and prophylaxis, nausea/vomiting still occur at grade ≥3, the patient should be withdrawn from treatment with cabazitaxel. This is considered a DLT.

Stomatitis

If grade 3 stomatitis occurs, cabazitaxel should be withheld until resolution to grade ≤1. Treatment may then be resumed, but the dose of cabazitaxel should be reduced for all subsequent doses. In case of grade 4 stomatitis, the patient will be withdrawn from treatment with cabazitaxel. This is considered a DLT.

Diarrhea

No prophylactic treatment for diarrhea is recommended in Cycle 1. However, following the first episode of diarrhea, the patient should be treated with rehydration or antidiarrheal medications as needed. In case of grade ≥ 3 diarrhea or persisting diarrhea despite appropriate medication, fluid and electrolytes replacement, delay treatment until improvement or resolution, then reduce the dose. If despite dose reduction, diarrhea still occurs at grade ≥3, the patient will be withdrawn from treatment with cabazitaxel. If grade ≥3 diarrhea persists despite adequate antidiarrheal treatment, it is considered a DLT.

Other GI toxicity

Gastrointestinal (GI) haemorrhage and perforation, ileus, colitis, including fatal outcome, have been reported in patients treated with cabazitaxel. Caution is advised with treatment of patients most at risk of developing gastrointestinal complications: those with neutropenia, the elderly, concomitant use of NSAIDs, anti-platelet therapy or anti-coagulants, and patients with prior history of pelvic radiotherapy, gastrointestinal disease, such as ulceration and GI bleeding. Symptoms such as abdominal pain and tenderness, fever, persistent constipation, diarrhea, with or without neutropenia, may be early manifestations of serious gastrointestinal toxicity and should be evaluated and treated promptly. Cabazitaxel treatment discontinuation may be necessary.

Hematuria

An imbalance in the incidence of hematuria was observed in the Phase III study in second line mCRPC (EFC6193). More hematuria was reported in cabazitaxel arm versus mitoxantrone arm (62 patients/16.7% versus 14 patients/3.8%). In cabazitaxel arm, no clear possible explanation such as local infection/obstruction/progression, or anticoagulation/aspirin therapy, or thrombocytopenia was found for 21 patients.

Therefore, in case of hematuria with no clear possible explanation every effort should be undertaken to document the cause (e.g., urine cultures, urinary tract ultrasound, and if no cause identified cystoscopy with or without biopsy).

Kidney function

- Consider nephrologist advice in case of creatinine increase by at least 2 x ULN from baseline value or eGFR (according to CKD-EPI formula) decrease by 50%. Cabazitaxel or enzalutamide would only be held for a calculated creatinine clearance less than 45 ml/min. Web link to be used to estimate glomerular filtration rate (GFR) using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula. **http://www.qxmd.com/calculate-online/nephrology/ckd-epi-egfr**. This is not considered a DLT.
- Recommend IV hydration for CT scan with contrast in case of eGFR< 60 ml/min and to provide some examples of hydration protocol in Appendices (see Appendix E).
- In case of renal function impairment, make every effort to identify the cause and report the cause as an adverse event. The existing renal function should be considered in the grading of the event. If no cause is identified (no diagnostic), report eGFR decrease as an adverse event.
- Creatinine and eGFR should be assessed until recovery or stabilization.

Liver toxicity

In case of increase of SGOT(AST) and/or SGPT(ALT) >2.5 x ULN or bilirubin to >ULN, delay cabazitaxel treatment for up to 2 weeks until SGOT(AST) and/or SGPT(ALT) returned to ≤2.5 x ULN and bilirubin to ≤ULN. If the subject was treated with 25 mg/m2, resume treatment at the reduced dose of cabazitaxel 20mg/m2. If the subject was receiving the 20mg/m2 dose of cabazitaxel, he will be removed from the study.

Peripheral neuropathy

Dose modification should be performed as follows:

- Grade ≤1: No change
- Grade 2: Retreat with reduced dose
- Grade 3: Patient will be withdrawn from treatment with cabazitaxel, and it is considered a DLT.

Other Toxic Effects

For ≥ grade 3 toxicities except fatigue, local reaction, fluid retention, anemia and other toxicities that merely are uncomfortable but do not cause serious morbidity to patients, chemotherapy should be held for a maximum of 3 weeks from the planned date of reinfusion until resolution to ≤ grade 1, then reinstituted, if medically appropriate. A dose reduction of subsequent doses will be left to the investigator's judgment. These patients will be withdrawn from study treatment if >1 dose reductions are needed. Any measures such as frozen gloves or socks or scalp cooling cap to prevent nail toxicity or alopecia are left to the investigator's judgment.

Concomitant Medication

Concurrent treatment with strong inhibitors and strong inducers of cytochrome P450 3A4 is not permitted. For patients who were receiving treatment with such agents, a 2-week washout period is required prior to cycle 1 day 1. Concurrent participation in another clinical trial or treatment with any other anti-cancer therapy is also not permitted. The Investigator may prescribe any other concomitant medications as

deemed necessary. The Investigator should look in Appendix E to see if the patient is on drugs metabolized by CYP 2C19, 2C8, 2C9 or 3A4. If this is the case, and the patient is on a drug with a narrow therapeutic index (shown in the table in bold), then the patient will need careful observation on the study.

Adverse event relationship to treatment
Investigators are required to assess if there is a reasonable causal relationship with the study drug/treatment regimen administered for each reported AE. “Reasonable causal relationship” means that, in the Investigators best clinical judgment, there are facts/evidence or arguments to suggest a causal relationship. Possible answers are ‘Yes’ or ‘No'.

All Serious Adverse Events (SAEs) must be transmitted within 1 working day of the Investigator’s awareness or identification of the event. They need to be transmitted to PCCTC and Oregon Health & Science University. The PCCTC SAE Report form will be used for reporting (see appendix K).

6.2.2 Enzalutamide (formerly known as MDV3100)

Availability: Agent Provided by Medivation/Astellas until the final patient is off of study drug.

Product description: Enzalutamide is a white to off white solid. It is insoluble in water and no salts are formed from ~ pH 2 to 10. Enzalutamide drug product is formulated in a Labrasol solution containing antioxidants (butylated hydroxytoluene and butylated hydroxyanisole) and filled into gelatin capsules. Capsules are filled to contain 40 mg of active pharmaceutical ingredient and are provided in high-density polyethylene bottles with child-resistant induction seal closure.

Packaging and Labeling
All medication used in this study will be prepared, packaged, and labeled under the responsibility of a qualified person at Astellas US Technologies, Inc. (AUST) in accordance with AUST Standard Operating Procedures (SOPs), Good Manufacturing Practice (GMP) guidelines, ICH GCP guidelines, and applicable local laws/regulations.

Information presented on the label for investigational product will comply with applicable local regulations.

Site pharmacist or medically qualified staff will dispense the study treatment to each subject in accordance with this protocol.

Solution preparation: Not applicable.

Storage requirements: Enzalutamide should be stored in a secure location with limited access at 77°F (25°C), with excursions permitted to 59°F to 86°F (15°C to 30°C). Bottles will be labeled with the study protocol number, medication or bottle number, contents, directions for use, storage directions, clinical trial statement, and the sponsor. Subjects will be instructed to store study drug at room temperature out of the reach of children.

Route of administration: Oral; four tablets comprise one dose.

Study Drug Handling
Current ICH GCP Guidelines require the investigator to ensure that study drug deliveries from the sponsor are received by a responsible person (e.g. pharmacist), and that

- such deliveries are recorded
- study drug is handled and stored safely and properly
- study drug is only dispensed to study subjects in accordance with the protocol
- any unused study drug is returned to the sponsor or standard procedures for the alternative disposition of unused study drug are followed

Drug inventory and accountability records for the study drugs will be kept by the investigator/pharmacist/designee. Study drug accountability throughout the study must be documented. The following guidelines are therefore pertinent:

- The investigator agrees not to supply study drugs to any persons except the subjects in this study.
- The investigator/pharmacist/designee will keep the study drugs in a pharmacy or other locked and secure storage facility under controlled storage conditions, accessible only to those authorized by the investigator to dispense these test drugs.
- Inventory and to record the results of this inventory on the Drug Accountability. A study drug inventory will be maintained by the investigator/pharmacist/designee. The inventory will include details of material received and a clear record of when they were dispensed and to which subject.
- At the conclusion or termination of this study, the investigator/pharmacist/designee agrees to conduct a final drug supply record. It must be possible to reconcile delivery records with those of used and returned medication. Any discrepancies must be accounted for. Appropriate forms of deliveries and returns must be signed by the person responsible.
- Used or unused study drug may be destroyed at the study center according to standard institutional procedures after drug accountability has been conducted by the Sponsor or representative, only if agreed upon by the Sponsor. A copy of the standard institutional procedure for destroying investigational drugs will be provided to the Sponsor or designee upon request. Unused study drug not destroyed at the site must be returned to the Sponsor or designee at the end of the study or upon expiration.

Expected adverse events:
Enzalutamide was examined in a Phase III placebo-controlled study in 1199 men with metastatic CRPC previously treated with docetaxel chemotherapy. It was generally well tolerated.

Adverse events in men treated with enzalutamide 160 mg by mouth daily with an incidence of at least 5% and by at least 2% greater than those who received placebo are summarized below.

- fatigue (33.6% v 29.1%)
- diarrhea (21.4% v 17.5%)
- hot flash (20.3% v 10.3%)

- musculoskeletal pain (13.6% v 10.0%)
- headache (11.6% v 5.5%)
- insomnia (8.6% v 6.0%)
- anxiety (6.4% vs. 4.0%)
- hypertension (6.1% v 2.8%)
- nasopharyngitis (5.1% v 3.0%)

Adverse events reported less than 5% but may be associated with enzalutamide after careful assessment of the adverse events include the following.

- falls (4.0% vs.1.3%)
- dry skin (3.6% vs. 1.3%)
- pruritus (3.5% vs. 1.3%)

A greater proportion of patients in the enzalutamide-treated group (4.1% vs. 1.8%) reporting the following adverse event terms: memory impairment, cognitive disorder, amnesia, disturbance of attention, and dementia. In addition, event terms related to hallucination (visual hallucination, tactile hallucination, hallucination) were reported more frequently in the enzalutamide-treated group (1.6% vs. 0.3%).

Serious events that occurred at a ≥0.5% absolute difference in event frequency and more frequently in the enzalutamide arm than the placebo arm included spinal cord compression (6.0% vs. 3.8%), bone pain (1.5% vs. 1.0%), metastatic pain (1.5% vs. 0.8%), pathological fracture (1.5% vs. 0.5%), urinary tract infection (0.9% vs. 0.3%), and cauda equina syndrome (0.8% vs. 0.0%).

Seizure is a known potential toxicity of enzalutamide. In vitro studies have shown that MDV3100 and its metabolite M2 bind to the GABA-gated chloride channel with IC_{50} values of 1.2 µg/mL and 3.3 µg/mL, respectively and in a cell-based assay inhibit the channel's activity with IC_{50}values of 1.4 µg/mL and 1.07 µg/mL, respectively. Some compounds that inhibit the GABA gated chloride channel are associated with seizures [Foster, 2011].

In the first clinical study of enzalutamide (S-3100-1-01), a dose-escalation study in men with castration-resistant prostate cancer with and without prior exposure to chemotherapy, the following doses were evaluated: 30, 60, 150, 240, 360, 480 (as 240 mg twice per day [BID]), and 600 (as 300 mg BID) mg/day. Three patients were reported to have dose-limiting toxicities of seizure, one each at doses of 360, 480, and 600 mg/day. The results of this study led to the selection of the clinical dose of MDV3100 of 160 mg/day.

As of the database cut-off date for the respective unblinded or open-label studies reported in the Investigator's Brochure, 7 patients out of a total of 1100 patients (0.6%) exposed to enzalutamide at a dose of 160 mg/day have reported a seizure during the enzalutamide treatment emergent adverse event reporting period. These include one patient each in studies 9785-CL-0007 and 9785-CL-0321, and 5 patients in the CRPC2 study. Two additional patients have been identified by the Sponsor to have experienced adverse events that may have been seizures, including one case reported by the Investigator as syncope (CRPC2) and the other reported as a transient ischemic attack with an abnormal electroencephalogram (CRPC-MDA-1). As of the data cut-off date, treatment with enzalutamide at a daily dose of 160 mg is associated with a 0.6-0.8% risk of seizure in men with late-stage castration-resistant prostate cancer. Taking into account information from

ongoing blinded studies and events occurring after the database cut-off date, the range for seizure risk is unchanged. No seizures have been reported in the blinded placebo-controlled Phase 3 study MDV3100-03 (PREVAIL) with over 1300 patients enrolled (randomized 1:1 to enzalutamide 160 mg/day or placebo). One additional patient in the CRPC2 study has been reported to have had a seizure after the safety data cut-off date, and one additional patient in an ongoing blinded study (9785-CL-0222) has also reported a seizure.

6.3 *Commercial Agents*

Prednisone
Prednisone is a corticosteroid given twice daily in this trial during cabazitaxel treatment. It is commercially available. There is no preparation required. The patients will receive a prescription for this agent, which they will fill at their outpatient pharmacy. We will provide information on it to the patient within the consent form. They will also receive written information with their prescription. It should be stored away from heat, light, and moisture at room temperature.

Expected adverse events:
Prednisone should be administered with fluids and food to decrease the risk of gastrointestinal complications. Prednisone can exacerbate diabetes mellitus, hypertension, and chronic and acute infections. Prednisone can mask symptoms of infections.

Other toxicities include:
a. Cardiovascular: fluid retention (common), hypertension, congestive heart failure
b. Gastrointestinal (GI): pain and/or ulcerations anywhere in the GI tract (common), weight gain (common), increased thirst, pancreatitis (rare)
c. Infections: increased risk of acute and chronic infections (common)
d. Metabolic: diabetes mellitus, fluid and electrolyte disturbances
e. Musculoskeletal: weakness (common), decrease in muscle mass (common), osteoporosis
f. Neurological: mood swings (common), depression, insomnia (common), dizziness, headache, confusion (rare), excitement (rare), psychosis (rare), seizures (rare)
g. Ophthalmological: visual changes
h. Urological: increased frequency of urination

G-CSF or GM-CSF
G-CSF and GM-CSF are commercially available growth factors (brand per institution). Must be given 24-48 hours after the cabazitaxel for each cycle. Dose, ingredients and packaging will be different according to the brand. Refer to the package insert for this information as well as “standard” preparation instructions.

Expected adverse events:
G-CSF: Common side effects include headache, loss of appetite, irritation at injection site, fluid retention, flu like symptoms, bone pain, diarrhea and/or constipation. Occasional side effects include rash, fever, hair loss, dizziness, weakness, indigestion, sore throat, fatigue, liver function abnormalities, and/or splenomegaly.

GM-CSF: Common side effects with GM-CSF are lightheadedness, flushing, tachycardia and hypotension with the first dose; diarrhea; local reaction at the injection site (redness,

swelling, tenderness); weakness and fatigue. Some may have mild flu-like syndrome (fever, headache, generalized aches and pains) or swelling in the hands or feet. Rarely (<1%), there may be a “capillary leak syndrome” or blood clots.

7. CORRELATIVE/SPECIAL STUDIES

7.1 Correlative Studies

Tumor Biopsies
Metastatic tumor biopsies will be obtained prior to first treatment, unless not safe and feasible. Sites where prior radiation has been administered for metastatic disease will be avoided. Soft tissue sites are preferred over bone sites. Patients will be offered the option of a second biopsy at the time of progression. If they consent, all attempts will be made to biopsy the same lesion as was sampled for the first biopsy. See Appendices F-I for details on specimen handling.

The correlative science and biopsy endpoints will be considered exploratory and will therefore be described without formal statistical hypotheses. However, they are a critical piece of this trial and will provide important hypothesis-generating biological evidence that can be further studied and validated in later trials.

Optional tumor biopsy at progression: During treatment, tumors change at a DNA level, and these changes can be reflected in their phenotype. The pre- and post-treatment biopsies will be interrogated to see if there are changes in the androgen signaling access and glucocorticoid receptor. If there are changes between the first and second biopsy, we will be able to hypothesize about how resistance may have arisen and how we might target cancers better in the future. This is optional, but encouraged.

i. Baseline tumor biopsy (and optional tumor biopsy at progression) to assess cytotoxic effects and androgen axis. Biopsies will be obtained with imaging-guidance and undergo pathology review at the participating site to ensure presence of tumor. For PCR-based assays (AR expression, splice variants), we estimate a minimum of ~3,000-5,000 cells would be needed. For each core, the participating site will perform H&E to determine presence of tumor. All cores with presence of tumor will be prioritized for analysis as per below:

- **Core #1 (FFPE):** IHC staining for expression of AR, PTEN, glucocorticoid receptor; add caspase-3 for apoptosis at biopsies taken at progression (not baseline). Please see Appendix G for FFPE processing and shipping details.
  Core #2, 4, 6 (Frozen): Evaluate AR copy number, AR splice variants, SLCO transport genes[5], and CYP17 lyase levels by RT-PCR[6]. Also measure testosterone, dihydrotestosterone and DHEA levels by mass spectroscopy. Finally, measure TMPRSS2-ERG by FISH.

  Please see Appendix I for fresh frozen biopsy tissue processing and shipping details.

  Core #3, 5 (FFPE): Next Generation Sequencing on Ion Torrent (using a Solid Tumor Panel). Please see Appendix G for FFPE processing and shipping details.
  - This will require minimum 10% of tumor.

- We will try to enrich for tumor selection by performing methyl green staining (in order to only remove tumor cells). However, in instances where we cannot easily separate tumor from normal, then we need at least 10% of the biopsy to consist of tumor.

ii.Evaluation of circulating blood markers. To be drawn at baseline and progression.

- Evaluate prostate cancer-associated miRNAs[7], cell-free tumor DNA, and host genetic factors from plasma or serum prior to treatment and at end of treatment (time of resistance). See Appendix J.
  - 7.5-10 mls of blood (i.e. 1 red top serum tube)
  - 7.5-10 mls of blood (i.e. 1 purple top EDTA tube)
  - 7.5-10 mls of blood (i.e. 1 tan/black top Streck Cell-Free DNA BCT tube)
  - Buffy coat (no extra tube required; can be taken off of purple top tube)

iii.Molecular characterization of circulating tumor cells

- Enumerate circulating tumor cells (CTCs)[8,9] (Drawn at baseline and progression)
- Interrogate molecular features of CTCs:
  - CTCs will be isolated using an immunodensity cell isolation system (Stem Cell Technologies, Vancouver, BC). The assay is optimized for enrichment of CTCs by the negative depletion of WBCs and RBCs. 15-20 mls of blood (i.e. 2 purple-top EDTA tubes with 7.5-10 mls) will be needed for the proposed CTC analysis. If the samples cannot be shipped the same day as the collection, use CellSave tubes instead of EDTA tubes. See Appendix H.

7.2 Pharmacokinetic Studies

Cabazitaxel: Patient evaluations will be performed to assess the pharmacokinetic parameters of cabazitaxel with and without concomitant enzalutamide treatment for a minimum of 6 subjects. Serial post-cabazitaxel whole blood samples (2 mL) will be collected at time points during Cycle 1 and Cycle 2 (after 21 days of enzalutamide) to measure post-infusion plasma concentrations of cabazitaxel. Samples will be drawn pre-cabazitaxel infusion shortly before the start of the infusion (Cycle 2 only), and after the start of the 1-hour cabazitaxel infusion at 0.5-hour, 1-hour (coinciding with the end of the infusion), 1.5-hour, 2-hour, 4-hour, 8-hour and 24-hour time points. See Appendix J.

8. STUDY PROCEDURES AND SCHEDULE OF EVENTS

8.1 Subject Registration (Local and Multicenter)

Written informed consent will be obtained from all patients participating in this trial, as stated in the Informed Consent section of the Code of Federal Regulations, Title 21, Part 50. If a patient's signature cannot be obtained, the investigator must ensure that the informed consent is signed by the patients legally authorized representative. Documentation of the consent process and a copy of the signed consent shall be maintained in the patient's medical record.

The PCCTC will manage subject registration on behalf of OHSU through Caisis EDC, the PCCTC Clinical Data Management System (CDMS). To initiate enrollment, the investigator

will verify eligibility according to all inclusion and exclusion criteria. All eligible subjects must be centrally registered through PCCTC. To complete the registration process, the study site must email the signed completed study-specific eligibility checklist, all source documents verifying eligibility, any supporting documents, and the signed informed consent to PCCTC at pcctc@mskcc.org. Once the enrollment packet is received and reviewed at PCCTC and if eligibility is confirmed, the subject will be enrolled in PCCTC Caisis EDC.

Each site must maintain a log of all subjects who sign informed consents. The log must also document an explanation for exclusion due to screen failure. Subjects who are enrolled on study will be assigned a site and protocol specific subject number. Participating sites are required to retain, in a confidential manner, sufficient information on each subject so that the subject may be contacted should the need arise. Sub-sites should submit their logs to OHSU monthly.

8.2 Baseline Screening

Baseline screening evaluations are to be conducted within 4 weeks prior to start of protocol therapy. Scans must be done within 4 weeks prior to the start of therapy.

- A biopsy should be performed at this time, if safe and feasible. The preferred site of the biopsy is unradiated soft tissue. Unradiated bone is the second choice.
- Screening labs include:
  - CBC with differential: white blood cells count (WBC), red blood cell count (RBC), hemoglobin (HGB), hematocrit (HCT), mean corpuscular volume (MCV), , platelet count (UNVPLT), neutrophils (NEUTP), lymphocytes (LYMP), monocytes (MONP), eosinophils (EOSP), basophils (BASOP).
  - Chemistry Panel (sodium (NA), potassium (K), chloride (CL), bicarbonate (CO2), blood urea nitrogen (BUN), creatinine (CREAT), glucose (GLU), calcium (CA), ,
  - Liver Function Tests (aspartate transaminase (AST), alanine transaminase (ALT), total protein (TP), albumin (ALB), total bilirubin (TBILI), alkaline phosphatase (ALK)
  - LDH
  - PSA
  - Testosterone (TEST)
- Radiographic examinations include: CT scan chest/abdomen/pelvis with contrast (preferred) or MRI chest/abdomen/pelvis and nuclear medicine bone scan.
- EKG
- Review of past medical history
- Physical exam
- Medications
- Height and weight
- Collection of circulating blood markers
- Collection of circulating tumor cells

8.3 Phase I Details

An initial 3-12 study subjects will be treated with cabazitaxel at 25 mg/m^2 on day 1 and enzalutamide 160 mg daily every 21 days (starting on day 2 of cycle 1 for those in the PK

studies or day 1 of cycle 1 for all others). These subjects will be permitted to continue on cabazitaxel and enzalutamide until progression and will be included in the final analysis of efficacy. Depending on the number of DLTs in these initial patients, we may move on to the Phase II portion of the study or study cabazitaxel at 20 mg/m^2 with enzalutamide 160 mg per day. See below for details.

The rationale for starting at current FDA approved doses of both agents with a dose de-escalation design is below:

The product label for cabazitaxel (JEVTANA USPI) states the following: "Though no formal drug interaction trials have been conducted for JEVTANA, the concomitant administration of strong CYP3A inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital) is expected to decrease cabazitaxel concentrations. Therefore, co-administration with strong CYP3A inducers should be avoided."

The product label for enzalutamide (XTANDI USPI) states the following: "Enzalutamide is a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer in humans. At steady state, XTANDI reduced the plasma exposure to midazolam (CYP3A4 substrate), warfarin (CYP2C9 substrate), and omeprazole (CYP2C19 substrate). Concomitant use of XTANDI with narrow therapeutic index drugs that are metabolized by CYP3A4 (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus and tacrolimus), CYP2C9 (e.g., phenytoin, warfarin) and CYP2C19 (e.g., S-mephenytoin) should be avoided, as enzalutamide may decrease their exposure."

Based on these labels, concomitant use of enzalutamide with **cabazitaxel could theoretically lead to decreased exposure to cabazitaxel.**

In addition, the Phase I enzalutamide-docetaxel study was presented at GU ASCO 2013. In 22 patients, it was shown that enzalutamide did not have significant effects on the PK of docetaxel and that the toxicity profile of docetaxel was not altered.[10]

In the phase I portion, DLT will be assessed during the first 2 cycles of treatment. Further dosing with cabazitaxel will be determined by the review committee consisting of participating investigators and an independent review committee using the following measures (standard 3+3 design):

- If 0 of the first 3 patients experience a DLT, we will cease the dose finding part of the trial and continue with the cabazitaxel 25 mg/m^2 dose for the entire trial.
- If ≥2 of the first 3 patients experience a DLT, cabazitaxel will be reduced 20% to 20 mg/m^2 thereafter.
- If 1 of the first 3 patients experiences a DLT, 3 additional patients will be treated (total of 6) with cabazitaxel 25 mg/m^2.
    - If ≥2 of 6 patients experience DLT, cabazitaxel will be reduced 20% to 20 mg/m^2 thereafter for the rest of the trial.
- If we need to use the dose-reduced cabazitaxel (20 mg /m^2), we will review the side effects of the next 3-6 subjects for DLTs during the first two cycles. If there are no DLTs, we will move forward with the trial. If there is ≥2 DLT, we will terminate the study. If there is 1 DLT, we will examine the next 3 subjects. If there are any other DLTs, we will terminate the study. If not, we will move forward with the study.

- No lower dose levels will be tested. If the combination of full dose enzalutamide and cabazitaxel 20 mg/m^2 proves intolerable, we will conclude that the two drugs cannot be combined safely and the study would not continue further.

Treatment will continue at the determined concurrent dosing on a 21-day cycle for 6-10 cycles of cabazitaxel and enzalutamide. Patients may then continue enzalutamide monotherapy on a 28-day cycle until progression or limiting toxicity.

Definition of DLT in the phase I portion of this study.
Toxicity will be evaluated according to the NCI CTCAE, Version 4.0.
These criteria are available online. See Appendix B.

DLT will be defined as any of the following events that are considered by the investigator to be related to therapy with cabazitaxel in combination with enzalutamide.

1. Grade 3 neutropenia associated with coincident fever (where fever is defined as an oral temperature ≥ 38.5 degrees Celsius)
2. Grade ≥3 neutropenia that lasts >7 days or has not recovered by day 1 of the next cycle
3. Grade 3-4 thrombocytopenia with clinically significant bleeding
4. Delay in the initiation of the subsequent cycle of therapy by more than 21 days due to treatment-related toxicity
5. Grade ≥3 nausea and vomiting despite optimal antiemetic therapy (5-hydroxytryptamine 3 (5-HT3) serotonin receptor antagonist
6. Grade ≥3 diarrhea despite optimal supportive therapy with loperamide
7. Grade ≥3 stomatitis
8. Grade ≥4 anaphylaxis
9. Grade ≥3 neuropathy
10. Seizure

Although DLTs may occur at any point during treatment, only DLTs occurring during cycles 1 and 2 of treatment during the phase I portion of this study will necessarily influence decisions regarding dose de-escalation. DLTs in cycle 3 and beyond will not influence dose decisions. Patients experiencing DLTs during cycles 1 or 2 of the phase I portion of the study may continue on the study providing they are deriving clinical benefit and will have their dose of cabazitaxel decreased no more than one level.

Patients will be monitored during all cycles of therapy for treatment-related toxicities. AEs that require dose reductions after the first two cycles will not be considered DLTs.

8.4 Study Visits (Day 1 of each cycle, +/- 3 days)

For all participants' weeks 1-30, the following will be performed every 3 weeks during treatment with cabazitaxel (first 10 cycles):

- Physical exam
- Concomitant medications
- CBC with differential:
  - During the first cycle, the CBC with differential will be completed weekly.
- Chemistry panel
- Liver function tests
- LDH (collected for the first 10 cycles only)
- PSA

- Assessment of adverse events

For all participants in the PK portion (3-12 possible participants, minimum 6):
All of the above, plus **PK** measurements:

- Serial post-cabazitaxel whole blood samples (2 mL) will be collected at the following time points during Cycle 1: after the start of the 1-hour cabazitaxel infusion at 0.5-hour +/- 5 minutes, 1-hour (coinciding with the end of the infusion) +/- 15 minutes, 1.5-hour +/- 15 minutes, 2-hour +/- 15 minutes, 4-hour +/- 15 minutes, 8-hour +/- 15 minutes and 24- hour +/- 60 minutes time points (prior to initiation of enzalutamide).
- At Cycle 2, serial blood samples will be drawn pre-cabazitaxel infusion shortly before the start of the infusion, after the start of the 1-hour cabazitaxel infusion at 0.5-hour +/- 5 minutes, 1- hour (coinciding with the end of the infusion) +/- 15 minutes, 1.5-hour +/- 15 minutes, 2-hour +/- 15 minutes, 4-hour +/- 15 minutes, 8-hour +/- 15 minutes and 24- hour time points +/- 60 minutes.
- Note that for all subjects in the PK portion, enzalutamide starts on day 2 of cycle 1.

For all participants in the phase I portion (3-12 possible participants):

- Assessment of dose limiting toxicities at each cycle in the DLT period.

For all participants weeks 30+, the following will be performed every 4 weeks (±3 days):

- Physical exam
- Concomitant medications
- CBC with differential
- Chemistry panel
- Liver function tests
- PSA
- Assessment of adverse events

For all participants weeks 1 until end of study:

- Imaging studies every 12 weeks (± 7 days) (CT scan chest/abdomen/pelvis with contrast (preferred) or MRI chest/abdomen/pelvis and nuclear medicine bone scan)
- Toxicities and adverse experiences will be assessed at each visit using the NCI Common Toxicity Criteria for Adverse Events v4.0 (CTCAE, see appendix B).

8.5 Follow-up

End of Study Visit (28 (±7) days after last dose for safety follow up for monitoring toxicity for study drug)

- Physical exam
- CBC with differential
- Chemistry panel
- Liver function tests
- PSA
- Collection of circulating blood markers
- Circulating tumor cells
- Optional tumor biopsy
- Phone calls every 6 months for up to 5 years after study to assess survival.

8.6 Early Termination (Termination from the study other than progression of disease)

Voluntary subject withdrawal

Investigator’s decision that is in the patient’s best interest to withdrawal
Noncompliance
Significant protocol violation
For any reason, at the Sponsor or Investigator discretion

8.7 Schedule of Events

	Pre-Study	Wk 1 C1	Wk 4 C2	Wk 7 C3	Wk 10 C4	Wk 13 C5	Wk 16 C6	Wk 19 C7	Wk 22 C8	Wk 25 C9	Wk 28 C10	Change to 4-Week Cycles	End of Study[f]	Off Study (Every 6 months)[d]
Window (days)		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		
Cabazitaxel, day 1		A	A	A	A	A	A	A	A	A	A			
Enzalutamide, days 1-21		B[e]	B	B	B	B	B	B	B	B	B	B		
Prednisone, daily		X	X	X	X	X	X	X	X	X	X			
Informed consent	X													
Demographics	X													
Medical history	X													
Concomitant meds	X	X ---------- X												
Physical exam	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	
Height	X													
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	
Performance status	X	X	X	X	X	X	X	X	X	X	X	X	X	
CBC w/diff, plts	X[g]	X	X	X	X	X	X	X	X	X	X	X	X	
Chemistry panel[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	
PSA	X	X	X	X	X	X	X	X	X	X	X	X		
Circulating blood markers	X												X	
Circulating Tumor Cells	X												X	
Testosterone	X													
Pharmacokinetic Studies[h]		X[h]	X[h]											
EKG	X													
Adverse event evaluation (safety)		X ---------- X											X	
Tumor measurements by Radiographic evaluation (CT or MRI Chest/Abd/Pel and Whole body bone scan)	X	Tumor measurements are repeated every 12 weeks (±7 days). Documentation (radiologic) must be provided for subjects removed from study for progressive disease.											X[c]	
Tumor Biopsy[b]	X												X	
Survival assessment														X

A: *Cabazitaxel*: Dose as assigned; given day 1 (+/- 2 working days) of each cycle
B: *Enzalutamide: 160 mg by mouth daily, throughout cycle*
a: Albumin (ALB), alkaline phosphatase (ALK), total bilirubin (TBILI), bicarbonate (CO2), BUN, calcium (CA), chloride (CL), creatinine (CREAT), glucose (GLU), LDH, potassium (K), total protein (TP), (AST), (ALT), sodium (NA). LDH is collected for the first 10 cycles only.
b: Screening biopsy to be performed if safe and feasible. End of study biopsy is optional, but encouraged. See Section 7.1
c: Off-study evaluation. Two bone scans taken 6-12 weeks apart must be used to document progressive disease if the patient is removed from study for this reason in order to account for flare phenomenon. CT scan and MRI progression does not require confirmation
d: For up to 5 years per subject, not study close
e: For the patients in the PK analysis, enzalutamide starts day 2 of cycle 1. For all others, it begins on day 1 of cycle 1.
f: Visit occurs 28 (+/- 7) days after the last dose of study medication.
g: Weekly CBC with differential for cycle 1
h: For patients in the PK portion only (minimum 6). Serial post-cabazitaxel whole blood samples (2 mL) will be collected at Cycle 1 after the start of the 1-hour cabazitaxel infusion at 0.5-hour +/- 5 minutes, 1-hour (coinciding with the end of the infusion) +/- 15 minutes, 1.5-hour+/- 15 minutes, 2-hour +/- 15 minutes, 4-hour +/- 15 minutes, 8-hour +/- 15 minutes and 24-hour +/- 60 minutes time(prior to initiation of enzalutamide). At Cycle 2, samples will be drawn pre-cabazitaxel infusion shortly before the start of the infusion, after the start of the 1-hour cabazitaxel infusion at 0.5-hour +/- 5 minutes, 1-hour +/- 15 minutes (coinciding with the end of the infusion), 1.5-hour +/- 15 minutes, 2-hour +/- 15 minutes, 4-hour +/- 15 minutes, 8-hour +/- 15 minutes and 24-hour +/- 60 minutes time points.

9. MEASUREMENT OF EFFECT

For the purposes of this study, subjects should be reevaluated for PSA response every 3 weeks during the first 28 weeks (during the period of combined treatment with cabazitaxel/prednisone plus enzalutamide). After the first 28 weeks, if a patient continues to do well without disease progression and proceeds to enzalutamide monotherapy, the PSA level will be assessed every 4 weeks. Imaging studies with a bone scan and CT scan will be done at baseline and every 12 weeks during the study. If a CT scan is not possible, an MRI of the chest/abdomen/pelvis can be substituted. The Prostate Cancer Working Group 2 (PCWG2) Guidelines will be used to assess stable disease, response and progression of disease.

9.1. Definitions

9.1.1 PSA Definitions

PSA progression: PSA increase of ≥ 25% and at least 2 ng/mL from baseline or nadir PSA achieved, confirmed by a second measurement at least three weeks later.

PSA nadir: Lowest PSA reached that was confirmed by a second equal or lower measurement.

PSA response: As recommended by the PCWG2 definitions. We will not apply a strict definition for PSA response, but we will report ≥90%, ≥50% and ≥30% levels of individual decline from baseline. The primary endpoint is the proportion of patients with a PSA reduction ≥ **90%**. Waterfall plots will be used to describe PSA changes while on study.

Maximum percentage of PSA reduction in each patient. Percentage of PSA reduction will be defined as [1 - (lowest PSA attained on study)/(PSA at study entry)] x 100. This formula only applies to PSAs that have decreased, and not those that have remained constant, i.e. the same as the baseline measurement.

9.1.2 Definition of Disease Progression

The patient may continue on study treatment as long as the patient has not progressed by **ANY** of the following measures:

- Progression by modified RECIST using PCWG2 criteria for target lymph nodes and/or visceral disease.
- Development of 2 or more new lesions on bone scan.
  (If investigator believes bone scan changes may represent a healing flare, new lesions should be confirmed by repeat bone scan 6-12 weeks later – PCWG2 approach will be used to bone scan assessments).
- Clinical progression, i.e., increasing pain that requires radiation therapy to a bone lesion or the addition or increase in narcotic pain medications.

Time to PSA progression is a secondary endpoint and not alone a reason to come off study. For this, PSA progression is defined as a 25% or more PSA

rise from baseline or nadir, whichever is lower. *(A confirmatory PSA in 3 weeks must be drawn to account for flare responses.)*

9.1.3 Summary of PCWG2 definitions on metastatic disease

- The PCWG2 definitions use modified RECIST.
- Measurable lesions are visceral or extranodal lesions that are ≥1 cm in one direction. Lymph nodes are measurable lesions if they are ≥2 cm in one direction. Tumor in the prostate may also be used as a measurable lesion.
- Non-measurable lesions are those lesions that do not meet the size criteria given above. Other non-measurable lesions are cysts, leptomeningeal disease, ascites, pleural/pericardial effusions and lymphangitis cutis/pulmonis.
- Bone lesions will not be considered measurable lesions. For bone lesions, a minimum of two new lesions must be seen on bone scan to be determined progression of disease. Any lesion on bone scan suspected to be flare or inflammation, another study (such as CT or MRI scan) should be done to document the presence of a new lesion. Bone scan interpretation will follow PCWG2 recommendations.
- All measurable and non-measurable lesions should be measured at Screening and at the defined tumor assessment time points. Extra assessments may be performed, as clinically indicated, if there is a suspicion of progression.

9.1.4 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 with conventional techniques (CT, MRI, x-ray) or as ≥10 mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

9.1.5 Non-measurable disease

All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional techniques or <10 mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

For bone lesions, a minimum of two new lesions must be seen on bone scan to be determined progression of disease. Any lesion on bone scan suspected to be flare or inflammation, another study (such as CT or MRI scan) should be done to document the presence of a new lesion. Bone scan interpretation will follow PCWG2 recommendations.

9.1.6 Target lesions

All measurable lesions up to a maximum of five lesions per organ and 10 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) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

9.1.7 Non-target lesions

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Non-target lesions include measurable lesions that exceed the maximum numbers per organ or total of all involved organs as well as non-measurable lesions. Measurements of these lesions are not required but the presence or absence of each should be noted throughout follow-up.

9.2 Guidelines for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks 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 when both methods have been used to assess the antitumor effect of a treatment.

Conventional CT and MRI. These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

9.3 Response Criteria

9.3.1 Evaluation of target lesions

Complete Response (CR): Disappearance of all target lesions

Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the

baseline sum LD

Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

9.3.2 Evaluation of non-target lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level

Incomplete Response/
Stable Disease (SD): 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

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

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

9.3.3 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 (see section 9.3.1).

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Note:

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having “symptomatic deterioration.” Every effort should be made to document the objective progression, even after discontinuation of treatment.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

9.4 Confirmatory Measurement/Duration of Response

9.4.1 Confirmation

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed at least 4 weeks after the criteria for response are first met.

9.4.2 Duration of overall response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

9.4.3 Duration of Stable Disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

9.5 Progression-Free Survival

Progression-Free survival is defined as the number of weeks from study entry to the time of confirmed progression, which is defined here.

- Progression by RECIST using PCWG2 criteria for target lymph nodes and/or visceral disease.
- Development of 2 or more new lesions on bone scan.
  (If investigator believes bone scan changes may represent a healing flare, new lesions should be confirmed by repeat bone scan 6-12 weeks later – PCWG2 approach will be used to review bone scan assessments).
- Clinical progression, e.g., increasing pain that requires radiation therapy to a bone lesion or the addition or increase in narcotic pain medications.

10 ETHICAL AND REGULATORY REQUIREMENTS

10.1 Protocol Review

The protocol and informed consent form for this study must be reviewed and approved in writing by the OHSU Knight Cancer Institute (CI) Clinical Research Review Committee (CRRC), PCCTC and appropriate Institutional Review Board (IRB) prior to any patient being registered on this study.

10.2 Informed Consent

Written informed consent will be obtained from all patients, or the legally authorized representative of the patient, participating in this trial, as stated in the Informed Consent section of the Code of Federal Regulations, Title 21, Part 50. If a patients signature cannot be obtained, and for all patients under the age of 18, the investigator must ensure that the informed consent is signed by the patients legally authorized representative. Documentation of the consent process and a copy of the signed consent shall be maintained in the patient's medical record. Privacy will be maintained by reviewing patient specific information in a private room. Data will be stored as described in 10.4.

10.3 Changes to Protocol

Any modification of this protocol must be documented in the form of a protocol revision or amendment signed by the Principal Investigator and approved by the CRRC, PCCTC and IRB, before the revision or amendment may be implemented. The only circumstance in which the amendment may be initiated without regulatory approval is for a change necessary to eliminate an apparent and immediate hazard to the patient. In that event, the

investigator must notify the CRRC and IRB in writing within 10 working days after the implementation.

10.4 Maintenance of Records

If the investigator relocates or for any reason withdraws from the study, the study records must be transferred to an agreed upon designee, such as another institution, another investigator, or to OHSU Knight Cancer Institute Clinical Research Management. Records must be maintained according to sponsor or FDA requirements.

Hard copies will be kept in a locked room on a floor that requires a badge to access (Center for Health & Healing, floor 14). Electronic information will be kept on a secured drive. Patient specimens will be stored in the same fashion as hard copies. They will be labeled with an identifier that does not contain protected health information.

10. 5 Safety Evaluation

10.5.1 Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment (ICH E2A).

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

An adverse event will be recorded and followed from treatment administration to 30 days post treatment or resolution.

10.5.2 Expected Adverse Events

Expected adverse events are those that have been previously identified as resulting from administration of the agent. An adverse event can be considered expected when it appears in the current adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk. For Cabazitaxel, Reported Safety Information (RSI) for expectedness of adverse events will be the Investigator Brochure (IB).

10.5.3 Unexpected Adverse Events

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational medicinal product) (ICH E2A).

Contact the Principal Investigator and PCCTC to confirm unexpected adverse events when necessary.

10.5.4 Serious Adverse Event (SAE)

An SAE/ADR as defined in the Code of Federal Regulations (21CFR312.32) is any event that:

- Results in death,
- Is life threatening, (Note: the term “life-threatening” refers to an event/reaction in which the patient was at risk of death at the time of the event/reaction; it does not refer to an event/ reaction which hypothetically might have caused death if it were more severe),
- Requires inpatient hospitalization or results in prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity,
- Is a congenital anomaly/birth defect, or
- Is a medically important event or reaction. Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious, such as important medical events that might not be immediately life-threatening or result in death or hospitalization, but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed in the definition above.

Related Adverse Event, i.e. Adverse Drug Reaction (ADR): There is a reasonable possibility according to the IST/ISS sponsor that the product may have caused the event.

Unexpected Adverse Drug Reaction: An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product). An expected ADR with a fatal outcome should be considered unexpected unless the local/regional product labeling specifically states that the ADR might be associated with a fatal outcome.

10.6 OHSU Safety Reporting

All SAEs will be reported to PCCTC and OHSU Principal Investigator Julie Graff. PCCTC will report SAEs to the OHSU IRB according to the policies, procedures and guidelines posted on the OHSU IRB web site: http://www.ohsu.edu/research/rda/irb/policies.shtml.

SAEs should be reported to PCCTC and Principal Investigator Julie Graff within 24 hours of knowledge via email (pcctc@mskcc.org; graffj@ohsu.edu). The PCCTC SAE Report form (Appendix K) must be completed and emailed to the PCCTC within 5 working days of knowledge of the event. Copies of the report documents will be kept in the study regulatory binder.

SAEs are submitted through OHSU e-IRB and will be reviewed by OHSU Knight Cancer Institute and IRB. Monthly accumulative reports will be generated by PCCTC, reviewed by a DSMC Oncologist and forwarded to the CRRC.

If applicable, PCCTC will report SAEs to the FDA using the PCCTC SAE Report form. When the serious adverse event is reported to the FDA, copies of the PCCTC SAE Report form and supporting materials will be submitted to the OHSU IRB and the OHSU Drug Information Service. A copy of the PCCTC SAE Report form and supporting materials will be kept on file in the study regulatory binder.

10.7 Astellas Safety Reporting

All serious adverse events, as defined above, need to be reported to the PCCTC via email

(pcctc@mskcc.org) and OHSU Principal Investigator, Julie Graff, MD, within 24 hours. She can be reached at 503-220-8262 x 55688; paged through the OHSU operator at 503-494-9000; or, emailed at graffj@ohsu.edu.

PCCTC will report the SAE to Astellas as instructed below.

The SAE documentation, including the PCCTC SAE Report Form and available source records should be emailed or faxed to: Astellas Pharma Global Development – United States

Email: Safety-us@us.astellas.com
Fax number: (847) 317-1241

The following minimum information is required:
• Study number/IIT regulatory identifier
• Subject number, sex and age
• The date of report
• A description of the SAE (event, seriousness of the event)
• Causal relationship to the study drug

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

10.8 Sanofi Safety Reporting

As in the case of the Astellas reporting, Sanofi reporting will be done by the PCCTC. All serious events, as defined above, need to be reported to Sanofi by PCCTC.

The PCCTC must report the following information in English to the Sanofi group entity Pharmacovigilance contact:

1. Routine transmission of:

All Serious Adverse Events (SAEs) and Adverse Events of Special Interest (AESI), if any. These events must be transmitted within 24 hours of the Investigator's awareness or identification of the event.

Results of any relevant complementary exams performed to obtain the final diagnosis of any SAE (e.g., hospital discharge summary, autopsy, consultation) will be made available to Sanofi group entity upon request.

2. Other events or periodic reports (e.g. Development Safety Update Report (DSUR)), submitted to Regulatory Authority must be transmitted at the time of submission.

3. Other significant safety issues or findings in a study pertaining to safety of product must be transmitted within 1 working day to the Sanofi GPE. (e.g., Data Safety Monitoring Board recommendations).

4. The study report of any IST/ISS must contain a section describing safety review and conclusion.

5. The reference safety information to be used by the IST/ISS sponsor for evaluation of expectedness of adverse events shall be the Investigator Brochure.

SANOFI GROUP ENTITY PHARMACOVIGILANCE CONTACT

Fax/email of SAE Reports to Sanofi:

IST/ISS Investigators will notify sanofi via fax or email, attention Sanofi Pharmacovigilance (PV):

Fax: 908-203-7783
E-mail: USPVmailbox@sanofi-aventis.com.

10.9 Roles and Responsibilities

Sponsor Investigator
The Sponsor Investigator is responsible for performing the following tasks:

- Responsibility for the overall conduct of the study at all participating sites and for monitoring the progress of the study
- Ensuring that the study will be performed in compliance with all applicable local and international laws and regulations including without limitation ICH E6 guidelines for Good Clinical Practice
- Reviewing and ensuring reporting of Serious Adverse Events (SAEs)
- Reviewing data from all participating sites

PCCTC
The PCCTC is responsible for performing the following tasks:

- Ensuring that IRB approval has been obtained at each participating site prior to the first patient registration at that site, and maintaining copies of IRB approvals and required regulatory documents from each site
- Managing subject registration
- Developing and maintaining Clinical Data Management documents and procedures
- CRF development, setup of study database, and subsequent design changes
- Participating in review of content of the CRF against the protocol requirements
- EDC system administration (user/site accounts setup, maintenance and revocation)
- Data review, cleaning, query management and resolution
- Establishing procedures for documentation, reporting and submitting of AE's and SAE's to the PCCTC
- Reviewing Serious Adverse Events (SAEs)
- Ensuring submission of required expedited and periodic reports to the appropriate Health Authority (HA), the Ethics Committee and investigators of each country participating in the IST/ISS (based on applicable regulations)
- Providing any "Dear Investigator Letter" (DIL) for new safety finding received from Sanofi group entity to the investigators and Ethics Committee in each country participating in the study
- Training participating sites on EDC
- Collecting and compiling data from each participating site
- Data reviewing from all participating sites

- Facilitating monitoring visits by securing selected source documents and research records from participating sites for review, or by on-site monitoring at participating sites

Participating Sites
Participating sites are responsible for performing the following tasks:

- Following the protocol as written, the guidelines of Good Clinical Practice (GCP), and applicable Standard Operating Procedures (SOPs)
- Registering all patients with the PCCTC by submitting the eligibility checklist, supporting source documentation, and signed informed consent promptly
- Providing sufficient experienced clinical and administrative staff and adequate facilities and equipment to conduct a collaborative trial according to the protocol
- Maintaining regulatory binders on site and providing copies of all required documents to the PCCTC
- Collecting and submitting data according to the schedule specified by the protocol
- Responding to queries in a timely manner

10.10 OHSU Knight Cancer Institute Data and Safety Monitoring Plan

In addition to complete study and pharmacy files, complete records must be maintained on each patient treated on this protocol. Study specific Electronic Case Report Forms (eCRFs) will document safety and treatment outcomes for safety monitoring and data analysis. All study data will be entered into PCCTC Caisis EDC via standardized eCRFs in accordance with the CDMS study calendar, using single data entry with a secure access account. The Clinical Research Coordinator (CRC) will complete the eCRFs as soon as possible upon completion of the study visit; the Investigator will review and approve the completed eCRFs. OHSU Knight Cancer Institute (CI), CRM shared resource is responsible for ensuring that all member investigators and affiliate investigators conduct clinical research studies in compliance with local IRB standards, FDA regulations and NIH policies. The Data and Safety Monitoring Committee (DSMC) is responsible for conducting Quality Assurance audits on CI approved protocols according to the Data and Safety Monitoring Plan policies and procedures http://ohsucancer.com/crm. PCCTC will generate audit reports and provide to Principal Investigator Julie Graff for submission to the DSMC.

Regularly scheduled registration reports will be generated by the PCCTC to monitor subject accruals and the completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and the extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period, and potential problems will be brought to the attention of the Principal Investigator for discussion and action.

Each site participating in the accrual of participants to this protocol will be monitored by the PCCTC on behalf of the OHSU Knight CI DSMC audit team. Visits will be performed at least once a year, for protocol and regulatory compliance, data verification and source documentation. Newly approved studies may be monitored any time after enrollment. Monitoring visits may be accomplished in one of two ways: (1) sending source documents and research records for selected patients from participating sites to the PCCTC for review, or (2) on-site monitoring of selected patient records at participating sites.

Visits will usually be determined by participant accrual numbers and rate of accrual, but can also be prompted by reported SAEs or request of sponsor investigator.

Monitoring will be conducted at least once shortly after initiation of subject recruitment at a site, annually during the study (or more frequently if indicated based on the approved Monitoring Plan), and at the end or closeout of the trial. The number of subjects reviewed will be determined by available time and the complexity of the protocol.

The visit will include a review of source documentation to evaluate compliance for:

- Informed consent documents and procedures
- Adherence to eligibility criteria
- Protocol defined treatment
- Required baseline, on study and follow-up protocol testing
- IRB documents (submitted amendments, annual continuing review reports, SAEs)
- eCRF completion

All clinical work conducted under this protocol is subject to Good Clinical Practice (GCP) guidelines. This includes inspection of study-related records by the lead site, sponsor, its designee, or health authority representatives at any time.

Audits may be conducted by the lead site at any time and will be facilitated by the PCCTC.

11. STATISTICAL CONSIDERATIONS

11.1 Study Design

This is a Phase I/II clinical trial to determine the dose for cabazitaxel (choose between 25 mg/m2 and 20 mg/m2) when combined with enzalutamide and to assess the treatment effect of the study drugs in men with metastatic CRPC.

The Phase I stage of the study is composed of 3-12 patients. The trial will proceed to Phase II stage at the dose of 25 mg/m2 if 0/3 or 0-1/6 patients receiving 25 mg/m2 had DLT. The dose de-escalation will happen if ≥2/3 or ≥2/6 patients receiving 25 mg/m2 had DLT. The trial will proceed to Phase II stage at the dose of 20 mg/m2 if 0/3 or 1/6 patients receiving 20 mg/m2 had DLT. Otherwise, the trial will not proceed to Phase II stage. Since DLTs within the first 2 cycles are used for dose consideration, those who receive less than 2 cycles, and did not have a DLT, will not be used for dose consideration. The requirement for moving on to the Phase II portion requires adequate evaluable patients. For example, at least 3 evaluable patients (i.e. those who have received at least 2 cycles) are needed if there are no DLTs at full dose prior to moving on to the phase II portion. Efficacy will be assessed for all subjects in the Phase I stage, and those who received the same dosage as was given to patients in phase II stage will be included for efficacy analysis as well.

The Phase II stage will assess both efficacy (reflected by PSA change) and toxicity (reflected by the percentage of patients who had DLT). However, the definition of DLT differs slightly for Phase I stage and Phase II stage (see section 8.3 for more details).

We anticipate a low dropout rate because we have low dropout rates in other studies and have very motivated patients, and we will not replace patients who drop out.

11.2 Primary and Secondary Endpoints

11.2.1 Primary Endpoints:

DLT, as defined in Section 8

PSA response 1, defined as ≥90% PSA decline from baseline. This analysis will be performed when the final patient has PSA progression, where the final patient refers to the final patient to have a PSA progression, not the last patient enrolled.

11.2.2 Secondary Endpoints

Adverse events will be collected continuously

PSA response 2, defined as ≥50% PSA decline from baseline. Will be determined when the primary endpoint is analyzed.

PSA response 3, defined as ≥30% PSA decline from baseline. Will be determined when the primary endpoint is analyzed.

PK measurements

Overall survival

11.3 Analysis Population

Patients with metastatic CRPC. In the phase I portion, only patients receiving 2 or more cycles will be evaluable for DLT. In the phase I and II portions, patients who receive at least one cycle will be evaluable for safety and efficacy outcomes.

11.4 Statistical Analysis Plan

Descriptive statistical analysis will be conducted for all primary and secondary endpoints. The proportion estimate will be reported with 95% confidence interval using exact method. One-sample binomial test will be used to assess whether the proportion of response 1 is significantly different from 0.25. As an exploratory subgroup analysis, the various PSA response rates will be estimated in two subgroups that either received prior abiraterone or had not received prior abiraterone. The median overall survival will be estimated with 95% confidence interval (if available). Kaplan-Meier plot will be used to graphically illustrate the overall survival distribution.

Individual and mean plasma concentration data will be plotted over time for cabazitaxel alone (Day 1, Cycle 1) and for cabazitaxel co-administered with enzalutamide (Day 1, Cycle 2). Non-compartmental PK analysis will be performed on individual concentration-time data to calculate PK parameters, including, but not limited to Cmax, $AUC_{0\text{-tlast}}$, $AUC_{0\text{-}\infty}$, and half-life, for cabazitaxel administered alone or co-administered with enzalutamide. Descriptive statistics will be presented for plasma PK parameters.

11.5 Sample size and Power

As stated in Section 11.1, we expect to include 3-12 patients to the Phase I stage of the study. Based on the dose de-escalation rules specified in the protocol, we could have at least 33 subjects who receive same dosage as determined for phase II stage, if the trial is not stopped early for excessive toxicity. For the efficacy analysis, we take into account existing data on rates of PSA decline in similar patient populations from earlier randomized control trials. Treatment with 160 mg of enzalutamide daily resulted in 24.8% of patients achieving a ≥90% PSA decline in the post-docetaxel setting, as demonstrated in the Phase III AFFIRM

trial.[11] Based on these results, the null hypothesis to be tested is that 25% of patients will achieve a ≥90% reduction in serum PSA, and the alternative assumption is that 50% of patients will achieve at least a 90% reduction in serum PSA. A total of 33 subjects will achieve 82% power using one sample binomial method for a 2-sided alpha of 0.05. That means we will have at least 82% power for efficacy analysis, with higher potential in power depending on the findings in the phase I stage.

11.6 Early Stopping Rule

The trial will be terminated at Phase I stage if none of the two doses of cabazitaxel is determined to be adequately safe (see more details in Section 11.1). However, as the trial may proceed to Phase II stage with only 3-12 patients in the phase I stage, we propose an interim analysis for safety in the middle of Phase II study. The trial will be stopped due to safety consideration if ≥8 patients in the first 20 patients in the Phase II cohort had a DLT as defined in Section 8.3. This stopping rule will ensure that the trial be stopped early at 87% chance if the probability of having DLT is 50%. On the other hand, if the combination of drugs is safe (with chance of DLT = 20%), there is only 3% chance that the trial will be stopped early.

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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

Common Terminology Criteria for Adverse Events v4.0 (CTCAE)

Toxicities and adverse events will be assessed using the NCI Common Toxicity Criteria for Adverse Events v4.0 (CTCAE). Since CTEP has standardized the CTCAE, the NCI does not require the inclusion of the CTCAE within the protocol document. A copy can be downloaded from the CTEP home page http://ctep.cancer.gov/reporting/ctc.html

List of CYP3A Inhibitors

Precipitant	Therapeutic Class	Object (oral)	AUC_{ratio}	PMID or NDA #	Published
Potent CYP3A Inhibitors (yielding substrate $AUC_r > 5$)					
ritonavir	Protease Inhibitors	triazolam	**40.70**	16513448	2006 Mar
indinavir	Protease Inhibitors	vardenafil	**16.25**	NDA # 021400	2003 Aug
ketoconazole	Antifungals	midazolam[1]	**15.90**	8181191	1994 May
troleandomycin	Antibiotics	midazolam	**14.80**	15536460	2004 Dec
itraconazole	Antifungals	midazolam	**10.80**	8181191	1994 May
voriconazole	Antifungals	midazolam	**9.40**	16580904	2006 Apr
saquinavir / RIT	Protease Inhibitors	maraviroc	**9.23**	18333863	2008 Apr
mibefradil	Calcium Channel Blockers	midazolam	**8.86**	14517191	2003 Oct
clarithromycin	Antibiotics	midazolam	**8.39**	16432272	2006 Feb
lopinavir / RIT	Protease Inhibitors	aplaviroc	**7.71**	16934050	2006 Sep
nelfinavir	Protease Inhibitors	simvastatin	**6.07**	11709322	2001 Dec
telithromycin	Antibiotics	midazolam	**6.0**	NDA# 021144	2004
grapefruit juice DS[2]	Food Products	midazolam	**5.95**	12953340	2003 Aug
conivaptan	Diuretics	midazolam	**5.76**	NDA # 021697	2005
nefazodone	Antidepressants	midazolam	**5.44**	14551182	2003 Nov
saquinavir	Protease Inhibitors	midazolam	**5.18**	10430107	1999 Jul

APPENDIX D: LIST OF INDUCERS BY CYP3A ISOENZYMES

Amobarbital
Carbamazepine
Dexamethasone
Efavirenz
Modafinil
Nevirapine
Norethindrone
Oxcarbazepine
Phenobarbital
Phenytoin
Primidone
Rifabulin
Rifampin
Rifampicin
Rifapentin
Ritonavir
Secobarbital
St John's Wort
Troglitazone

Referenced using University of Washington database (May 207)

APPENDIX E: KNOWN SUBSTRATES OF CYP 2C19, 2C8, 2C9, 3A4

Comprehensive list of agents known to be substrates of CYP 2C19

Generic name	Trade name
Amiodarone Hydrochloride	Cordarone, Cordarone IV, Pacerone
Amitriptyline Hydrochloride	Elavil, Vanatrip
Clordiazepoxide/ Amitriptyline	Limbitrol, Limbitrol DS
Aprepitant	Emend
Atomoxetine Hydrochloride	Strattera
Azelastine Hydrochloride	Astelin, Astelin Ready-Spray, Optivar
Bortezomib	Velcade
Bupivacaine Hydrochloride	Marcaine HCl, Marcaine Spinal, Sensorcaine, Sensorcaine-MPF
Carisoprodol	Soma, Vanadom
Cilostazol	Pletal
Citalopram Hydrobromide	Celexa
Clomipramine Hydrochloride	Anafranil
Clozapine	Clozaril, FazaClo
Cyclophosphamide	Cytoxan, Cytoxan Lyophilized, Neosar
Dapsone	Aczone
Desogestrel/ Ethinyl Estradiol	Apri, Cesia, Cyclessa, Desogen, Ortho-Cept, Solia, Velivet, Reclipsen
Dextromethorphan Hydrobromide	Robitussin, Pediacare, Vicks 44 Cough Relief, Creomulsion, Dexalone, Hold DM, Babee Cof Syrup, Benylin Pediatric Formula
Dextromethorphan Hydrobromide/ Guaifenesin/Potassium Guaiacolsulfonate	Humibid DM
Diazepam	Diastat, Diastat Pediatric, Diazepam Intensol, Valium
Diclofenac Potassium	Cataflam
Diclofenac Sodium	Solaraze, Voltaren, Voltaren-XR
Diclofenac Sodium/Misoprostol	Arthrotec
Escitalopram Oxalate	Lexapro
Esomeprazole Magnesium	Nexium
Esomeprazole Sodium	Nexium I.V.
Estradiol	Alora, Climara, Esclim, Estrace, Estraderm, Estrasorb, Estring, EstroGel
Estrogens, conjugated A/synthetic	Cenestin
Estrogens, conjugated Equine	Premarin
Fluoxetine Hydrochloride	Prozac, Prozac Weekly, Sarafem, Rapiflux
Fluoxetine Hydrochloride/Olanzapine	Symbyax

Formoterol Fumarate	Foradil Aerolizer
Budesonide/Formoterol	Symbicort
Fosphenytoin Sodium	Cerebyx
Ibuprofen	Advil, Motrin, A-G Profen, Addaprin, Bufen, Genpril, Haltran, I-Prin
Ifosfamide	Ifex
Imatinib Mesylate	Gleevec
Imipramine Hydrochloride	Tofranil
Imipramine Pamoate	Tofranil-PM
Indomethacin	Indocin, Indocin SR
Lansoprazole	Prevacid, Prevacid I.V., Prevacid SoluTab
Lansoprazole/Naproxen	Prevacid NapraPAC
Meperidine Hydrochloride	Demerol, Meperitab
Mephenytoin	Mesantoin
Mephobarbital	Mebaral
Methadone Hydrochloride	Dolophine, Methadone HCl Intensol, Methadose
Methsuximide	Celontin Kapseals
Hydrochlorothiazide/ Metoprolol Succinate	Dutoprol
Metoprolol Succinate	Toprol-XL
Metoprolol Tartrate	Lopressor
Nelfinavir Mesylate	Viracept
Nicotine	Habitrol, Nicoderm CQ, Nicotrol, Nicotrol
Nicotine Polacrilex	NSCommit, Nicorette, Nicorelief
Nilutamide	Nilandron
Nortriptyline Hydrochloride	Aventyl, Pamelor
Omeprazole	Prilosec, Prilosec OTC
Omeprazole/Sodium Bicarbonate	Zegerid
Pantoprazole Sodium	Protonix
Pentamidine Isethionate	Nebupent, Pentam
Perphenazine	Trilafon
Phenobarbital Sodium	Luminal
Phenytoin	Dilantin, Dilantin Kapseals, Dilantin Infatabs, Dilantin-125, Phenytek
Progesterone	Crinone, Prochieve, Prometrium, Progestasert, Gesterol 50
Atovaquone/Proguanil Hydrochloride	Malarone, Malarone Pediatric
Propofol	Diprivan
Propranolol Hydrochloride	Inderal, Inderal LA, InnoPran XL, Propranolol HCl Intensol
Quinine	Formula Q
Rabeprazole Sodium	Aciphex
Ranitidine Hydrochloride	Zantac, Zantac 150, Zantac 150 Efferdose, Zantac 25, Zantac 300, Zantac 75, Taladine
Sertraline Hydrochloride	Zoloft

Testosterone	Androderm, Androgel, Striant, Testim, Testro AQ
Thioridazine Hydrochloride	Mellaril
TOLBUTamide	Tol-Tab
Tolterodine Tartrate	Detrol, Detrol LA
Trimethadione	Tridione
Trimipramine Maleate	Surmontil
Valproic acid	Depakene
Venlafaxine Hydrochloride	Effexor, Effexor-XR
Voriconazole	Vfend, Vfend I.V.
Warfarin Sodium	Coumadin, Jantoven
Abacavir Sulfate/Lamivudine/ Zidovudine **Lamivudine/ Zidovudine** **Zidovudine**	Trizivir Combivir Retrovir
Zolpidem Tartrate	Ambien, Ambien CR
Zonisamide	Zonegran

- **Bolded agents are narrow therapeutic index agents due to individual drug therapeutic concentrations or the serious nature of their therapeutic use. Please note that other agents should still be reviewed with the prescribing physician as their therapeutic effect may be diminished in a clinically significant manner.**

Known Substrates of 2C8: Generic name (Brand name): Drugs with a narrow therapeutic index are in BOLD font.
Acenocoumarol (Sintrom)
Amiodarone (Cordarone, Cordarone IV, Pacerone)
Dasabuvir (Exviera)
Paclitaxel (Taxol)
Pioglitazone (Actos)
Repaglinide (Prandin)
Rosiglitazone (Avandia)
Tretinoin (Retin - A, Avita, Renova)

Known Substrates of 2C9: Generic name (Brand name): Drugs with a narrow therapeutic index are in BOLD fold.
Bosentan (Tracleer)
Carvedilol (Coreg)
Celecoxib (Celebrex)
Dapsone (Aczone)
Fluoxetine (Prozac, Prozac Weekly, Sarafem, Rapiflux)
Fluvastatin (Lescol, Lescol XL)
Fosphenytoin (Cerebyx)
Fospropofol (Lusedra)
Glimepiride (Amaryl)
Glipizide (Glucotrol)
Ketamine (Ketalar)
Losartan (Cozaar)
Mestranol (Necon 1/50, Norinyl 1+50, Ortho-Novum 1/50)
Montelukast (Singulair)

Nateglinide (Starlix)
Paclitaxel (Taxol)
Phenytoin (Dilantin)
Propofol (Diprivan)
Sulfadizine (Silvadene)
Sulfamethoxazole (Bactrim, Septra)
Tamoxifen (Nolvadex, Soltamox)
Tolbutamide (Tol-Tab)
Torsemide (Demadex)
Trimethoprim (Bactrim)
Voriconazole (Vfend, Vfend I.V.)
Warfarin (Coumadin, Jantoven)
Zafirlukast (Accolate)

Known Substrates of 3A4: Generic name (Brand name): Drugs with a narrow therapeutic index are in BOLD fold.
Alfentanil (Alfenta, Rapifen)
Alfuzosin (Uroxatral)
Alprazolam (Xanax, Xanax XR, Niravam)
Ambrisentan (Letairis)
Amiodarone (Cordarone, Cordarone IV, Pacerone)
Amlodipine (Norvasc)
Aprepitant (Emend)
Aripiprazole (Abilify)
Armodafinil (Nuvigil)
Atazanavir (Reyataz)
Atorvastatin (Lipitor)
Benzphetamine (Didrex)
Bisoprolol (Zebeta)
Bortezomib (Velcade)
Bosentan (Tracleer)
Bromazepam (Lectopam, Lexotan, Lexilium, Lexaurin, Brazepam, Rekotnil, Bromaze, Somalium, Lexotanil)
Bromocriptine (Cycloset)
Budesonide (Entocort EC, Uceris, Symbicort, Rhinocort Aqua)
Buprenorphine (Butrans, Buprenex)
Buspirone (Buspar)
Busulfan (Myleran, Busulfex)
Carbamazepine (Tegretol, Equetro)
Chlordiazepoxide (Limbitrol, Limbitrol DS)
Chloroquine (Aralen)
Chlorpheniramine (Chlor-Tabs, Aller-Chlor)
Ciclesonide (Alvesco, Omnaris)
Cilostazol (Pletal)
Cisapride (Propulsid)
Citalopram (Celexa)
Clarithromycin (Biaxin)
Clobazam (Onfi)
Clonazepam (Klonopin)
Clorazepate (Tranxene, Novo-Clopate)
Cobicistat (Tybost)

Cocaine
Colchicine (Colcrys)
Conivaptan (Vaprisol)
Cyclophosphamide (Cytoxan, Cytoxan Lyophilized, Neosar)
Cyclosporine (Sandimmune)
Dantrolene (Dantrium)
Dapsone (Aczone)
Darifenacin (Enablex)
Darunavir (Prezista)
Dasantinib (Sprycel)
Delavirdine (Rescriptor)
Dexamethasone (Decadron, Ozurdex, Baycadron)
Dexlansoprazole (Kapidex, Dexilant)
Diazepam (Diastat, Diastat Pediatric, Diazepam Intensol, Valium)
Dihydroergotamine (Migranal)
Diltiazem (Cardizen)
Disopyramide (Norpace, Rythmodan)
Docetaxel (Taxotere)
Doxorubicin (Adriamycin, Doxil)
Efavirenz (Sustiva, Stocrin, Efavir)
Eletriptan (Relpax)
Eplerenone (Inspra)
Ergoloid mesylates (Hydergine)
Ergonazine
Ergotamine (Ergomar)
Erlotinib (Tarceva)
Erythromycin (Ery-tab, Ilotycin, Eryc, Akne-mycin, T-Stat, Ery, Erythra-Derm)
Escitalopram (Lexapro)
Esomeprazole (Nexium)
Estradiol (Alora, Climara, Esclim, Estrace, Estraderm, Estrasorb, Estring, EstroGel)
Estrogens (Apri, Cesia, Cyclessa, Desogen, Cenestin, Ortho-Cept, Premarin Solia, Velivet, Reclipsen)
Estropipate (Ogen)
Eszopiclone (Lunesta)
Ethinyl estradiol (Apri, Reclipsen, Kariva, Azurette, Yaz, Yasmin, Ocella, Gianvi, Beyaz, Safyral Zovia, Demulen, Zovia 1/35, Kelnor 1/35, Nuva ring)
Ethosuximide (Zarontin)
Etoposide (Toposar, VePesid, Etopophos)
Exemestane (Aromasin)
Felbamate (Felbatol)
Felodipine (Plendil)
Fentanyl (Sublimaze, Actiq, Durogesic, Duragesic, Fentora, Matrifen, Haldid, Onsolis, Instanyl, Abstral Lazanda)
Flunisolide (Aerobid, Aerospan, Nasarel, Aerobid-M)
Flurazepam (Dalmane, Dalmadorm)
Flutamide (Eulexin, Flutamin, Cytomid, Chimax, Drogenil)
Fluticasone (Flonase)
Fosamprenavir (Lexiva)
Fosaprepitant (Emend)
Gefitinib (Iressa)
Haloperidol (Haldol)
Ifosfamide (Ifex)

Imatinib (Gleevec)
Indinavir (Crixivan)
Irinotecan (Camptosar)
Isosorbide dinitrate and mononitrate (Monoket)
Isradipine (DynaCirc, Prescal)
Itraconazole (Sporanox, Onmel)
Ixabepilone (Ixempra)
Ketamine (Ketalar)
Ketoconazole (Nizoral, Xolegel, Extina)
Lansoprazole (Prevacid, Prevacid I.V., Prevacid SoluTab)
Lapatinib (Tykerb)
Levonorgestrel (Mirena)
Lidocaine (Xylocaine, Recticare, Solarcaine, Xylocaine-MPF, Anecream)
Lopinavir (component of Kaletra)
Losartan (Cozaar)
Lovastatin (Mevacor)
Marviroc (Selzentry)
Medroxyprogesterone (Depo-Provera, Provera)
Mefloquine (Lariam)
Mestranol (Nelova 1/50 M, Necon 1/50, Ortho-Novum 1/50, Genora 1/50)
Methadone (Dolophine, Methadone HCl Intensol, Methadose)
Methylergonovine (Methergine)
Methylprednisolone (Medrol, A-Methapred, Hybrisil, Depo-Medrol, Solu-Medrol)
Micronazole (Zeasorb, Micatin, Oravig, Monistat-derm, Azolen, Conazol)
Midazolam (Dormicum, Hypnovel, Versed)
Mirtazapine (Avanza, Axit, Mirtaz, Mirtazon, Remeron, Zispin)
Modafinil (Provigil)
Montelukast (Singulair)
Nateglinide (Starlix)
Nefazodone (Dutonin, Nefadar, Serzone)
Nelfinavir (Viracept)
Nevirapine (Viramune)
Nicardipine (Cardene)
Nifedipine (Adalat CC, Procardia)
Nilotinib (Tasigna)
Nimodipine (Nimotop)
Nisoldipine (Sular)
Norethindrone (Aygensin, Jolivette, Miconor, Errin, Heather)
Norgestrel (Cryselle 28, Lo/Ovral-28, Low-Ogestrel, Ogestrel-28)
Omeprazole (Prilosec, Prilosec OTC, Zegerid)
Ondansetron (Zofran, Zuplenz)
Paclitaxel (Taxol, Onxal, Abraxane)
Paricalcitol (Zemplar)
Paritaprevir (found in Viekira Pak)
Pazopanib (Votrient)
Pimozide (Orap)
Primaquine (generic only)
Progesterone (Crinone, Prochieve, Prometrium, Progestasert, Gesterol 50)
Quazepam (Doral, Dormalin)
Quetiapine (Seroquel, Seroquel XR)

Quinidine (Quin-G, Cardioquin, Quinora, Quinidex Extentabs, Quinaglute Dura-Tabs, Quin-Release)
Quinine (Formula Q)
Rabeprazole (Aciphex)
Ranolazine (Ranexa)
Repaglinide (Prandin)
Rifabutin (Mycobutin)
Ritonavir (Norvir)
Salmeterol (Serevent)
Saquinavir (Invirase, Fortovase)
Sibutramine (Meridia)
Sildenafil (Viagra)
Simvastatin (Zocor)
Sirolimus (Rapamune)
Solifenacin (Vesicare)
Spiramycin (Rovamycine)
Sufentanil (**Sufenta**)
Sunitinib (Sutent)
Tacrolimus (Protopic, Hecoria)
Tadalafil (Adcirca, Cialis)
Tamoxifen (Nolvadex, Soltamox)
Tamsulosin (Flomax)
Telithromycin (Ketek)
Temsirolimus (Torisel)
Teniposide (Vumon)
Tetracycline (Acnecycline, Dyabetex, Diabecline, Tetra-abc)
Theophylline (Respbid, Slo-Bid, Theo-24)
Tiagabine (Gabitril)
Ticlopidine (Ticlid)
Tinidazole (Tindamax)
Tipranavir (Aptivus)
Tolterodine (Detrol, Detrol LA)
Toremifene (Fareston)
Tramadol (Ultram, Conzip, Rybix ODT, and Ultram ER)
Trazodone (Oleptro)
Triazolam (Apo-Triazo, Halcion, Hypam, and Trilam)
Trimethoprim (Proloprim, Primsol)
Trimipramine (Surmontil, Rhotrimine, Stangyl)
Vardenafil (Levitra)
Venlafaxine (Effexor, Effexor-XR)
Verapamil (Calan, Verelan, Verelan PM, Isoptin, Covera-HS)
Vinblastine (Alkaban-AQ, Velban)
Vincristine (Oncovin)
Vinorelbine (Navelbine)
Zolpidem (Ambien, Ambien CR)
Zonisamide (Zonegran)
Zopiclone (Zimovane and Imovane)

Appendix F Suggestions of protocols of intra-venous hydration for CT-scan with contrast (1), (2)

Intra-venous hydration at the time of CT-scan with contrast is recommended when creatinine clearance <60 mL/min.

Step 1: identify the population at risk:
- all patients with an eGFR<60 ml/min/1.73 m³,
- especially in diabetic and cardiovascular patients with eGFR<60 ml/min/1.73m².

(PS: eGRF is the estimated GFR from the EPI formula).

Step 2: stop NSAID the day before and the day of the radiocontrast examination and make sure that the patient is well hydrated (eventually diuretics "on hold" and additional fluid intake is advised - if medically possible)

Step 3 (advisable, not obligatory): the day before and the day of the radiocontrast examination, the patient is taking acetylcysteine 600 mg x 2 orally

Step 4: (write down for your radiologist to) use the lowest possible volume of (iso-/low-osmolar) radiocontrast.

Step 5: before the contrast examination IV fluid is started; oral hydration is not sufficient.

A/ Radiocontrast kidney injury prevention with isotonic NaCl 0.9%:

Prehydratation: IV NaCl 0.9% at 1 ml/kg/h during 12h before radiocontrast and during the radiocontrast examination

Posthydratation: continue IV same NaCl 0.9% at 1 ml/kg/h during 12h.

OR

B/ Radiocontrast kidney injury prevention with isotonic NaHCO3:

Prehydratation: prepare IV 850 ml GLU 5% + 150 mEq NaHCO3 and infuse at 3.5 ml/kg/h during 1h before radiocontrast and during the radiocontrast examination.

Posthydratation: IV same preparation 850 ml GLU 5% + 150 mEq NaHCO3 at 1 ml/kg/h during 6h.

OR

C/ Alternative scheme in case of "URGENT - Emergency" radiocontrast administration: IV NaCl 0.9% at 3 ml/kg/h during 1 h before and during the radiocontrast examination; continue IV NaCl 0.9% for 6-12h at 1 ml/kg/h after the radiocontrast examination. (PS: 6 h post only in patients in whom a sustained volume expansion is not possible).

(1) Weisbord S., Palevsky P. Prevention of contrast-induced nephropathy with volume expansion. Clin J Am SocNephrol. 2008;3:273-80.

(2) KDIGO guidelines on contrast media induced AKI (To be published in 2011)

APPENDIX G: FRESH TUMOR BIOPSY IN FORMALIN (to be sent to OHSU)

Supplies and Materials

- Requisition form
- One “Fresh tumor biopsy in formalin” label
- One container of 10% neutral-buffered formalin
- One container of 70% ethanol

Sample Preparation, Collection and Processing

1. Fill out the requisition form.
2. Place the "Fresh tumor biopsy in formalin" label on the 10% neutral-buffered formalin container.
3. Collect the core needle biopsy per institutional procedure. **Cores #1, 3 and 5 to be combined and placed in single container**.
4. Immediately dispense (within one minute of being taken) the core needle biopsy into the container with 20-30 ml of 10% neutral-buffered formalin. The date and time taken must also be recorded so that the total fixation time can be assessed. Please record the date/time of biopsy, total fixation time, biopsy location, and primary tumor details on the requisition form.
5. Allow the biopsy to incubate in the 10% formalin container at room temperature for 16-24 hours.
6. Transfer the biopsy to aliquot with 70% ethanol (20-30 ml) to be stored at room temperature and shipped to the Histopathology Shared Resource of the Knight Cancer Institute/OHSU.

   Do not ship on Friday.

Shipping of Formalin-fixed biopsies

Shipping address:

Attn: Joscelyn Zarceno/Jenny Miller
Histopathology Shared Resource
Knight Cancer Institute
Oregon Health and Science University
Marquam Plaza
2525 SW 3rd Ave, Room 235
Portland, OR 97201
Telephone: (503) 494-9631
Fax: (503) 494-9649

APPENDIX H: CIRCULATING TUMOR CELLS (to be sent to OHSU*)

COLLECTION OF BLOOD SAMPLES

At each time point, the blood sample will be drawn in a Rarecyte collection tube. Samples will then be processed as described below, labeled and shipped same day.

Rarecyte Tube (for CTC) Collection
In each tube, at least 7.5 mL of peripheral blood will be collected. It is essential that the tubes are filled completely in order to be processed for CTC. After collection, the tube must be inverted eight times to prevent clotting and then can be stored at ***room temperature***. Rarecyte collection tubes will be provided by OHSU.

**It is essential that both sets of tubes are filled as instructed and shipped at room temperature on the same day.

****Note: DO NOT SPIN OR FREEZE THE TUBES**

SHIPPING OF BLOOD SAMPLES

Shipping reservations must be made to allow delivery within 24 hours, prior to 2:00 PM next day. The blood samples should be **shipped on the same day of the collection** to the Prostate Cancer Program at OHSU for processing.

Do not ship on Friday. Samples must remain at room temperature, do not ship with cold packs.

Shipping address:

Attn: Prostate Program
Knight Cancer Institute
3485 SW Bond Ave
MC: OC14P
Portland, OR 97239
Telephone: (503) 418-3397
Fax: (503) 418-9381

APPENDIX I: PROCEDURE FOR COLLECTION OF FRESH BIOPSY TISSUE (to be sent to FHCRC/UW)

Materials Needed:

MATERIAL	NUMBER/AMT	VENDOR	CAT#
Sterile Tweezers (Forceps)	2	Fisher	84011182
Tissue Tek standard-size Cryomolds	1 PER BIOPSY (Prepare 6 per Procedure; plan to use 5)	Fisher	NC9511236
Tissue Tek OCT	1 bottle	Fisher	14-373-65
Insulated metal bucket	1		
Isopentane or 2-methyl-isobutane	1 liter		
Dry ice	As needed		
Liquid nitrogen (if available)	1 container		
70% alcohol (prep pads)	As needed		
Blue pads and Markers	As needed	Fisher	507105 NC9319816
-80C Freezer			
Sterile saline	1-2 bottles		
Pre-filled specimen container (20ml container) with 10% neutral-buffered formalin (10ml formalin)	1	Dynamic Diagnostics	
1.7 ml Posi-Click tube (Denville)	3	Fisher	C2170
Gloves (non-sterile)	1 box		
Biohazard sharps container	1		

PRE-BIOPSY LABELING

Research staff should communicate with the Interventional Radiology team in advance of the biopsy to ensure that requested specimens are collected according to SOP.

1. Prepare the Posi-click tubes and label 2, 4 and 6. This helps in identifying which biopsy core was taken 2nd, 4th and 6th. Having tubes pre-labeled and ready is preferred.
2. Prepare and label specimen containers for formalin and label 1, 3 and 5.
3. Label tubes and cryomolds with the following information:
   -Biopsy date

-Specimen ID (format: CABENZ--STUDY ID#)
-Biopsy type (core #, Fresh or Frozen)
-Soft tissue or Bone

PREPARATION

Arrive at biopsy collection site at least 15 minutes ahead of scheduled time to allow for sufficient time to set up lab supplies.

Bring the following:

- 2 Sterile tweezers (forceps)
- 8 Tissue Tek standard-size cryomolds
- 1 Bottle Tissue Tek OCT media
- 1 Insulated metal bucket
- Isopentane or 2-methyl-isobutane
- Dry ice
- 70% alcohol (prep pads)
- Blue pads and markers
- 3 pre-chilled 1.7 ml Posi-Click tube (Denville)
- 1 Posi-Click tube holder
- 1 Pre-filled specimen container (20ml container) with 10% neutral-buffered formalin (10ml formalin)
- 2 styrofoam containers

1. Isopentane conducts heat very rapidly and avoids freeze artifacts. Isopentane must be pre-cooled to liquid nitrogen (preferred) or dry-ice temperature.
   -If liquid nitrogen is not available, fill Styrofoam container or ice bucket ¾ full with dry ice. Place steel container with isopentane on the dry ice and allow temperature to equilibrate. Pour 200-400ml of isopentane into a steel container.
   -If isopentane cannot be used due to regulations, dry ice can be used.
   -If using liquid nitrogen: pour liquid nitrogen into an insulated bucket or Styrofoam container that can accommodate both the liquid nitrogen and the steel container. Slowly place (lower) the steel container containing isopentane into the liquid nitrogen and allow the temperature to equilibrate.
2. In a 2nd Styrofoam box with dry ice, place the Posi-click tubes on the ice, preferably in a small Posi-click tube holder (this makes it easier to see the tubes on dry ice). This is to pre-chill the tubes.
3. Place both Styrofoam boxes on a cart for easy transport to the biopsy.

TUMOR NEEDLE BIOPSY COLLECTION

While the biopsy is taking place, record the following information on the requisition form:

- CABENZ—Study ID#
- Needle type, size (gauge and length)
- Specimen #
- Time biopsy snap-frozen on dry ice and/or time biopsy frozen in OCT
  RECORD TIMES USING MILITARY TIME (24-hr designation), e.g., 16:15 to indicate 4:15p

COLLECTION OF BIOPSIES AND FLASH FREEZING

1. Transfer freshly collected needle biopsy with sterile needle or forceps at one end, and touch the opposite end of the biopsy to the 1.7-ml pre-chilled, pre-labeled tube #2. The tissue should immediately attach to the tube, allowing it to be placed into the tube while easily releasing the forceps. This should be done within 15-20 seconds.
2. Place tubes into chilled isopentane or dry ice, each core should be collected into an individual tube. Dispose of needles/forceps into the appropriate biohazard waste container.
3. Repeat for each separate frozen biopsy.

FLASH FREEZING (should be done within 20-30 min of biopsy collection)

1. Add a drop of Tissue Tek OCT medium into the pre-labeled cryomolds
2. Hold and remove the freshly collected frozen core needle biopsy tissue from the tubes with sterile forceps at one end and touch the opposite end of the tissue to the cryomold and push the biopsy to the bottom of the cassette with forceps. Make sure biopsy is as flat as possible using the forceps.
3. Fill cryomold with OCT media, ensuring no air bubbles are present.
4. Place the filled cassette into the chilled isopentane and make sure it is submerged and the cryomold is completely frozen and turns white. This should be done within 15-20 seconds.
5. Once frozen, place cryomold cassettes on dry ice for transport.
6. Repeat procedure for each separate, frozen biopsy.
7. Record time to OCT freeze for each pass.
8. Pour used isopentane back into bottle using a funnel. Do not overfill.

SAMPLE STORAGE AND INVENTORY

1. Transfer cryopreserved biopsy specimens to a -80C freezer. Complete sample storage/location/inventory log and store until shipping.
2. Record time of return to specimen storage in -80C and location of sample.
3. Note any deviations from this protocol.

Samples will be shipped to the University of Washington (see address below):

Univ of Wash
1959 NE Pacific St
HSB I-340
Seattle, WA 98195
Attn: Lori Kollath

APPENDIX J: PROCEDURE FOR COLLECTION AND PROCESSING OF CIRCULATING BLOOD MARKERS (to be sent to FHCRC/UW)

All sample collection tubes must be stored at room temperature prior to use.

MATERIAL	NUMBER/AMOUNT	VENDOR	CAT#
Red top tube (serum)	1	BD	BD REF 366430
Purple top plasma tube (EDTA)	1	BD	BD REF 366643
Streck tube	1	Streck.com	218962
Cryovials for transfer of samples from EDTA, serum, Streck tubes		Per site	Per site
Disposable transfer pipets		Per site	Per site
Sample ID labels for EDTA, serum, Streck and cryovials		Labels will be sent out	Label will be sent out

PREPARATION

1. Label red top tube, EDTA and Streck tubes with appropriate sample ID labels
2. Check expiration date on all tubes
3. Prepare subject for venipuncture
4. Draw red top first, then EDTA tube and Streck tube.
5. Gently invert red tube, EDTA and Streck tubes 8-10 times and place EDTA tube on ice or at 4C. For the Streck tube, leave at room temperature (between 6 and 37 degrees Celsius).

SERUM PROCESSING (red top). Must be performed within 4 hours of draw

1. Centrifuge 15 minutes at 1600xg force, 4C.
2. Use sterile pipette, place equal volume serum into each of 2 mL microfuge tubes
3. Place pre-printed ID labels on microtubes as quickly as possible.
4. Immediately place microtubes into a freezer box at -80C for eventual shipment.

PLASMA/BUFFY COAT PROCESSING (purple top). Must be performed within 4 hours of draw

1. EDTA plasma is obtained from whole blood collected in purple top vacutainer tubes containing EDTA. Ensure a full 10 ml draw.
2. Invert tubes 8-10 times after draw.
3. Centrifuge sample for 15 minutes at 1600xg force, 4C.
4. Using sterile pipette, place equal volume of plasma into each of 2 microfuge tubes. Remove plasma slowly and carefully, so as not to disrupt the layer of white blood cells (leave at least 0.5 cm residual plasma).
5. Immediately place microtubes into a freezer box at -80C for eventual shipment.
6. Buffy coat is removed from the purple top EDTA tube after the plasma aliquots are removed.
7. Use a transfer pipet to harvest the buffy coat by removing the buffy/white layer between the plasma and the cell pellet. Place into a freezer vial with screw cap and O-rings.
8. Red cell pellet can be discarded.

9. Immediately place vials into a freezer box at -80C for eventual shipment.

Samples will be shipped to the University of Washington (see address below):

Univ of Wash
1959 NE Pacific St
HSB I-340
Seattle, WA 98195
Attn: Lori Kollath

APPENDIX K: Procedures for Collection & Processing of PK specimens

Blood samples will be collected in heparinized tubes (lithium heparinate).

The samples will be centrifuged within 30 min at approximately 3,000 RPMs for 15 min.

The plasma will be removed, placed into polypropylene tubes, labeled, frozen, and stored at −20 °C until analysis.

Studies will be done by Covance. (2202 Ellis Road, Durham, NC 27703 c/o Chris Barringer). However, OHSU will batch the samples and send them to Covance.

Samples will be shipped to the Prostate Cancer Program at OHSU and batched prior to shipping to Covance.

Prostate Program
3485 SW Bond Ave
MC: OC14P
Portland, OR 97239

APPENDIX L: PCCTC SAE Report Form

SERIOUS ADVERSE EVENT REPORTING FORM

*Event # Click here to enter text.

*Protocol Title

*PCCTC Protocol # Click here to enter text. *Site Protocol # Click here to enter text.

*Site Name Click here to enter text.

*Date of Report Click here to enter a date. *Reported By Click here to enter text.

☐ Initial Report ☐ Follow-up Report *Date of Original Report Click here to enter a date.

SUBJECT INFORMATION

*Subject Identifier (Study ID) Click here to enter text. *Age at Time of Event Click here to enter text.

*Sex ☒ Male Weight Click here to enter text. ☐ lb ☐ kg

SERIOUS ADVERSE EVENT

*CTCAE Term Click here to enter text.

*Start Date Click here to enter a date. *End Date Click here to enter a date. OR ☐ ongoing

*Grade Click here to enter text.

*Type (check all that apply)

☐ Death Click here to enter a date. ☐ Disability or Permanent Damage

☐ Life-threatening ☐ Congenital Anomaly/Birth Defect

☐ Hospitalization ☐ Other Medically Important Condition

*Event Description

*Outcome

☐ Recovered/Resolved ☐ Not Recovered/Not Resolved ☐ Fatal

☐ Recovering/Resolving ☐ Recovered/Resolved sequelae ☐ Unknown

RELEVANT TESTS/LABORATORY DATA

Date mm/dd/yyyy	**Test**	**Result**	**Unit**	**Notes**

Click here to enter a date.				
Click here to enter a				

date.				
Click here to enter a date.				

OTHER RELEVANT HISTORY

Disease/surgical procedure/etc.	Start Date mm/dd/yyyy	Continuing Y/N/U	End Date mm/dd/yyyy	Comments
	Click here to enter a date.		Click here to enter a date.	
	Click here to enter a date.		Click here to enter a date.	
	Click here to enter a date.		Click here to enter a date.	

SUSPECT PRODUCT(S)

*Name	Relationship to Study Treatment	Action Taken	Dose	Frequency	Route	Start Date mm/dd/yyyy	Last Date Prior to SAE mm/dd/yyyy
	☐Unrelated ☐Unlikely ☐Possibly ☐Probably ☐Definite	☐Drug withdrawn ☐Dose reduced ☐Dose Increased ☐Dose not changed ☐Unknown ☐Not applicable				Click here to enter a date.	Click here to enter a date.
	☐Unrelated ☐Unlikely ☐Possibly ☐Probably ☐Definite	☐Drug withdrawn ☐Dose reduced ☐Dose Increased ☐Dose not changed ☐Unknown ☐Not applicable				Click here to enter a date.	Click here to enter a date.
	☐Unrelated ☐Unlikely ☐Possibly ☐Probably ☐Definite	☐Drug withdrawn ☐Dose reduced ☐Dose Increased ☐Dose not changed ☐Unknown ☐Not applicable				Click here to enter a date.	Click here to enter a date.

CONCOMITTANT MEDICAL PRODUCT(S)

Name	Start Date mm/dd/yyyy	Last Date Prior to SAE mm/dd/yyyy
	Click here to enter a date.	Click here to enter a date.
	Click here to enter a date.	Click here to enter a date.
	Click here to enter a date.	Click here to enter a date.

INVESTIGATOR NAME AND SIGNATURE

*Investigator Name Click here to enter text.

*Investigator Signature _____

*Date Signed Click here to enter a date.

mm/dd/yy

APPENDIX M: Storage and Disposition of data and specimens

During the study, data and specimens will be maintained by the study staff. Specimens will be stored in the program clinical research office, in either a locked room or locked cabinet, on an access restricted floor. Study data will be maintained on access protected, OHSU network servers. Only staff and investigators who are listed as approved study staff with the IRB will be able to access specimens or data. When samples are transferred to testing locations outside of the main storage location, a chain of custody form will be used to document the transfer. If there is sample remaining after the analysis, it will be either transferred back to the principal investigator or destroyed. Either action will be documented.

Samples will be coded with a study subject ID and collection date. The investigators and primary study staff will have access to the key to the code, which will not contain PHI.

Upon completion of the planned analyses in this protocol, all data and remaining specimens will be transferred into the repository, "Master Protocol for Cancer Research Specimen Bank and Database (OHSU IRB 2816). At that time, repository practices will be followed for access restriction, sample requests, and release of data or specimens.

Describe how and where data/specimens will be stored and describe the final disposition of the data/specimens. Include:

- The location of data/specimens, who will have access to the data/specimens, and how access will be controlled.
- Method of coding data/specimens, if applicable. Include a process to protect/maintain the key to the code and limit access to the key. Coding data does not make it anon
- Plans for final disposition of the data/specimens, including release to a repository (either as part of this protocol or into another protocol) or plan to destroy at the end of study.
- Describe the process and requirements for requesting and releasing data/specimens.