Clinical Trial of a Rapidly Cycling, Non-Cross Reactive Regimen of Approved Therapeutic Agents to Treat Prostate Cancer

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Prostate Cancer Intensive, Non-Cross Reactive Therapy (PRINT) for CRPC

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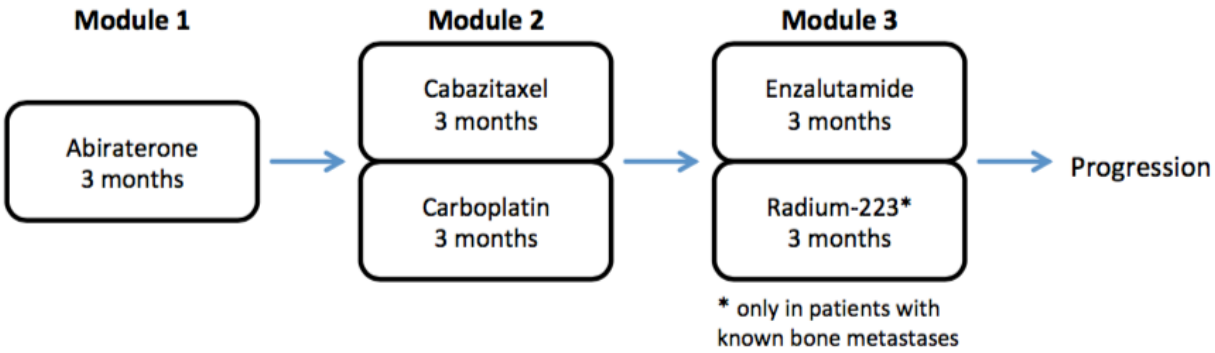
Synopsis

Title:

- Prostate Cancer Intensive, Non-Cross Reactive Therapy (PRINT) for CRPC

Study Schema:



Objective:

- To evaluate the clinical benefit of using a rapidly cycling, non-cross reactive regimen of FDA-approved prostate cancer therapeutic agents in treatment-naïve CRPC patients.

Study Design:

- Investigator initiated study
- Single arm, prospective, open-label, non-randomized phase II clinical trial
- Enrollment at integrated Mount Sinai Health System
- Anticipated number of patients to be screened: 60
- Enrollment period: 3 years
- Follow up period: 2 years

Primary Endpoint:

- Time to disease progression, either PSA or radiographic, after completion of all treatment modules

Secondary Endpoints:

- Overall survival
- PSA response rate with each treatment module
- Alkaline phosphatase levels
- Safety

Exploratory Endpoint:

- Correlation of a peripheral whole blood RNA signature with different treatment modalities and clinical outcome
- Changes to AR-V7 expression in CTCs with different treatment modalities and correlation with clinical outcome

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Inclusion Criteria:

- Histologically or cytologically confirmed adenocarcinoma of the prostate
- Metastatic castrate resistant prostate cancer, defined by progressive disease based on either rising PSA, new bone metastases, or progression of measurable disease on imaging, according to PCWG2 guidelines, despite androgen deprivation therapy
- Ongoing androgen deprivation therapy with a GnRH analogue, GnRH antagonist, or bilateral orchiectomy
- ECOG performance status 0–1
- Serum testosterone level < 50 ng/dL
- Absolute neutrophil count > 1,500/µL, platelet count > 100,000/µL, and hemoglobin > 9 g/dL
- Creatinine < 2 mg/dL
- Total bilirubin < 1.5 times the upper limit of normal, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≤ 1.5 times the upper limit of normal

Exclusion Criteria:

- History of uncontrolled seizure disorder
- Clinically significant cardiovascular disease including:
    - Myocardial infarction or uncontrolled angina within 6 months
    - Congestive heart failure New York Heart Association (NYHA) class 3 or 4, or patients with history of congestive heart failure NYHA class 3 or 4 in the past
    - Uncontrolled hypertension as indicated by a resting systolic blood pressure > 170 mmHg or diastolic blood pressure > 105 mmHg at the screening visit
- Have used or plan to use from 30 days prior to enrollment through the end of the study medication known to lower the seizure threshold or prolong the QT interval
- Major surgery within 4 weeks of enrollment
- Radiation therapy within 4 weeks of enrollment
- Prior use of abiraterone acetate, enzalutamide, docetaxel, cabazitaxel, carboplatin, or radium-223 for the treatment of castration-resistant disease
    - Prior docetaxel use in the hormone-sensitive disease setting is allowed, but must be completed ≥ 4 weeks prior to enrollment
    - Prior sipuleucel-T use is allowed, but must be completed ≥ 4 weeks prior to enrollment
    - Concurrent use of zolendronic acid or denosumab is allowed on study

Statistical Design:

- A sample size of 33 patients that complete all three treatment modules of the study regimen will provide 90% power for a one-sided test at the 5% level to detect an increase in median time to disease progression, either PSA or radiographic, from 3 months to 5 months. We will plan to screen 60 patients (treat 40 patients) to account for any potential patient dropout, defined as anyone who does not complete all three treatment modules.

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List of Abbreviations

ADT	Androgen Deprivation Therapy
AE	Adverse Event
ASCO	American Society of Clinical Oncology
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
CRPC	Castration Resistant Prostate Cancer
CT C/A/P	Computed Tomography Scan of Chest, Abdomen, and Pelvis
CTC	Circulating Tumor Cell
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator Brochure
IND	Investigational New Drug
IRB	Institutional Review Board
LDH	Lactate Dehydrogenase
mCRPC	Metastatic Castration Resistant Prostate Cancer
MRI	Magnetic Resonance Imaging
NIST	National Institute of Standard and Technology
PFS	Progression Free Survival
PHI	Protected Health Information
PI	Principal Investigator
PSA	Prostate Specific Antigen
RECIST	Response Evaluation Criteria in Solid Tumors
rPFS	Radiographic Progression Free Survival
RSI	Reported Safety Information
SRM	Standard Reference Material
TTP	Time to Progression

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1. Study Summary

1.1 Background

Multiple new FDA approved therapies with different mechanisms of action are available for treatment of castration-resistant prostate cancer.

Prostate cancer is the second most commonly diagnosed cancer, and the most common cause of cancer death in US males. First line treatment of metastatic prostate cancer with androgen deprivation therapy (ADT) is effective in the majority of men, by significantly decreasing serum PSA levels and improving disease symptoms, but is not curative. The disease eventually progresses despite ADT and becomes castration-resistant prostate cancer (CRPC). Recent advances in understanding of prostate cancer biology and the androgen signaling axis has led to the development of multiple novel agents for treatment options for CRPC, each with its own distinct mechanism of action. There are at least 4 different classes of treatment recently FDA-approved for metastatic CRPC: androgen signaling inhibitors (abiraterone, enzalutamide), cytotoxic chemotherapy (cabazitaxel), immunotherapy (sipuleucel-T), and bone targeted therapy (radium-223). Individually, each agent has demonstrated efficacy and survival benefits in randomized, phase III clinical trials [1-7].

The standard approach is to use one treatment until resistance develops, then change to a different treatment.

While optimal timing and sequence of these new treatments are still the subject of clinical investigation, the standard treatment approach so far has been to continue with a single treatment agent until resistance develops, at which point the patient is switched to a different treatment.

The emerging concept of tumor heterogeneity, both between different prostate cancer patients and within a single tumor, argues that a “one size fits all” sequential, single-agent approach to cancer treatment ultimately will have limited success. Inherent genetic instability from rapidly dividing malignant cells can lead to substantial tumor heterogeneity [8], and along with it, varied amounts of genetic dysregulation and varied patterns of anti-neoplastic resistance [9]. A single agent treatment may succeed in effecting a response on the majority of malignant cells, but may select for more resilient subpopulations, eventually leading to drug resistance and treatment failure. New first-in-class therapeutics that exhibit anti-tumor activity even in the face of multi-drug resistance are in development, but eventually these will likely breed resistance as well.

Combining drugs is a classic oncologic paradigm, but dose limiting toxicities can be significant.

Combination drug therapy has been a paradigmatic approach not only to improve response to treatment, but also to avoid therapeutic resistance. The probability of the disease simultaneous developing resistance towards multiple agents is far less than that towards a single agent alone. This concept has parallels in treatment of infectious disease, where the simultaneous use of multiple antibacterial or antiretroviral agents has long been the standard for treatment of tuberculosis and HIV, respectively. Multiple regimens of combination chemotherapy are already in routine use in both the hematologic and solid tumor malignancies, with significant rates of cures in diseases such as Hodgkin lymphoma and testicular cancer.

Treating prostate cancer simultaneously with multiple agents from each class of therapy (androgen signaling inhibitors, cytotoxic chemotherapy, immunotherapy, bone-targeted therapy) would cause significantly increased side effects. While it may be more justifiable to treat with a regimen that has more side effects when the intent is curative, regimens meant to control or palliate a malignancy over longer periods of time need to strike a fine balance between toxicity, efficacy, and quality of life.

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Overlapping toxicities of non-cross reactive treatment drugs and their supportive regimens would make delivering each drug at its respective optimal therapeutic dosing and schedule a difficult task, and would limit therapeutic impact.

New drug deployment strategies are needed to address this issue. Metastatic CRPC patients offer a unique opportunity to establish an optimal sequence of treatment as this has not yet been accomplished with these many recently approved agents.

Rapid cycling of therapy allows targeting of different cell populations, switching to non-cross reactive therapies before development of resistance and the potential to increase long term disease control. One solution to minimize toxicity and mimic the benefits of multidrug combination treatment is to rapidly cycle therapies, maintaining the end goal of exposing the disease to multiple agents in a relatively short duration of time. This is a concept already in clinical use, and hard-wired into some standard-of-care chemotherapy regimens, particularly in the treatment of aggressive hematologic malignancies. Hyper-CVAD, used in the treatment of acute lymphocytic leukemia (ALL) [10] and Burkitt lymphoma [11], and the Stanford V regimen, used in advanced bulky Hodgkin lymphoma [12], are two examples of complex regimens that require alternating cycles of different drug combinations. They rely on the differential timing and delivery of different drugs to be able to preserve dose intensity of each individual agent, without being overwhelming by toxicities.

Understanding that metastatic prostate cancer is a heterogeneous disease [13-15], both intrapersonally and between patients, the cycling of treatment would allow for the targeting of different cell populations. By switching between non-cross reactive therapies, the selective pressure exerted by any one therapeutic agent's intermittent use is limited [16], allowing resistance rates to stabilize or decrease in its absence. The rationale underlying this strategy is that drug resistance evolution is related to the duration of drug exposure, and that a gain of drug resistance comes with a biological fitness cost. This is a concept also seen in infectious diseases; the higher the fitness cost, the more rapidly the resistance frequency fades in a disease population once the selective pressure is removed, as the nonresistant cells outcompete the resistant cells [17]. In this way, the same agent can be reintroduced at a later time with its efficacy intact, sustaining drug sensitivity and long term disease response.

1.2 Research Proposal/Rationale

This phase II clinical trial will explore the efficacy of rapidly cycling non-cross reactive treatment therapies in the treatment of patients with newly diagnosed mCRPC. The primary hypothesis is that the best chance of eliminating or controlling disease is when the cancer is treatment naïve, and has not yet developed therapeutic resistance. By finding an optimal drug deployment strategy of already approved and available treatments for mCRPC, we believe we can more effectively treat an intrinsically heterogeneous disease, delay/prevent drug resistance, as well as minimize treatment toxicity.

All of the treatment agents selected have well-defined individual toxicity profiles from large phase III trials, but there is limited clinical data about the toxicity profiles of these drugs in combinations. While each agent is generally well tolerated, toxicities remain a significant concern given the older age of the typical mCRPC patient, the comorbid conditions common to this patient population, as well as those borne from previous chronic androgen deprivation therapy.

Each drug in the proposed treatment regimen will be used at their FDA-approved dosing and indication, with the exception of cabazitaxel, which will be used prior to disease demonstration of docetaxel failure,

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and in combination with carboplatin (discussed below). The proposed sequencing is rationally designed, and based on each drug's distinct mechanisms of action as well as their toxicity profiles.

Our rapidly-cycling treatment regimen contains three, separate, consecutive treatment modules, each lasting 3 months: 1. Abiraterone; 2. Cabazitaxel + Carboplatin; 3. Enzalutamide + Radium-223. Therapeutic agents are delivered as non-cross reactive combinations, in order to achieve optimal therapeutic dosing at each cycle and decrease possibility of significant adverse effects.

Utilizing PCWG2 guidelines to define progression of disease by PSA levels, a patient must have been on treatment for at least 12 weeks, which coincides with the duration of one of our treatment modules. As designed into our trial, CT and bone scans will be obtained every 12 weeks, making the earliest possible determination of radiographic disease progression also 12 weeks. The design of the treatment schedule is such that the treatment modality will be changed regardless of the type of response observed at the end of each module. For patients progressing on a previous treatment module, they are already pre-planned to transition to a different treatment agent, which is in line with standard of care management of mCRPC. In this way, we anticipate minimal patient dropout from a disease progression standpoint.

Sipuleucel-T will not be given as part of the treatment protocol, but prior sipuleucel-T use will be allowed for participants of this clinical trial. We will track its use in our cohort of patients. The rationale for allowing previous administration of sipuleucel-T is based on the understanding that immunotherapy requires time to build host immune sensitivity, and likely works best on low disease burden [18]. As sipuleucel-T is approved for use only in the asymptomatic or minimally symptomatic stages of disease, this would grant patients the opportunity to receive a treatment that has shown overall survival benefit in large, randomized phase III clinical trial. It would also allow patients to receive it at a time before they have had any significant corticosteroid exposure, which the majority of other CRPC treatments require, as it may blunt immunologic effects of dendritic cell vaccines.

In keeping with standard of care, concurrent zolendronic acid or denosumab use will be allowed on study, we will track its use in our cohort of patients

Controlling the androgen signaling axis remains key in CRPC, but there exists heterogeneity in response and progression to drugs which target this pathway in prostate cancer. A comprehensive approach to targeting the androgen signaling axis via androgen synthesis inhibition and androgen receptor blockade will be undertaken with abiraterone and enzalutamide. Both therapeutic agents have been approved by the FDA for treatment of mCRPC in both the pre-chemotherapy and post-chemotherapy space based on their merits in prolonging time to PSA progression and PFS in chemotherapy-naïve patients [3, 19], and OS benefits in the chemotherapy-refractory patients [2, 4].

While no directly comparative studies have been performed, both abiraterone and enzalutamide showed in their respective randomized trials to have comparable median time to PSA progression (11.1 months and 11.2 months) in the pre-chemotherapy setting. Optimal sequencing of the two AR-pathway targeting agents have been the subject of controversy, especially as there are likely overlapping mechanisms of resistance between abiraterone and enzalutamide [20-23]. Small studies looking at the efficacy of one agent following the other in direct sequence suggest that the percentage of men who have a >50% PSA response from the later agent are higher in those who received abiraterone first and enzalutamide second [20-24]. The role of glucocorticoid receptors as a potential mechanism of enzalutamide resistance [25] also lends consideration for sequencing abiraterone earlier given its

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requirement for concurrent prednisone. With this data in mind, we have sequenced abiraterone to be given first in the rapidly cycling regimen, to be followed by enzalutamide at a slightly later time.

Sequencing a second androgen pathway inhibitor following failure of a previous one is not strongly supported because of likely overlapping mechanisms of resistance. Earlier studies raise the possibility of cross-resistance between AR-directed agents and taxanes [26], specifically the decreased efficacy of docetaxel in abiraterone-refractory mCRPC [27]. Mechanistically, it's hypothesized that taxanes disrupt microtubule function, which is essential not only in cellular division, but also in androgen receptor nuclear trafficking [28]. More recent data suggests that taxanes exhibit their significant antineoplastic effects through AR-pathway independent pathways as well, with second generation agents such as cabazitaxel retaining efficacy even in the enzalutamide-refractory setting [29]. In keeping with our underlying principle to cycle treatments with different mechanisms of action in order to avoid development of resistance, the cytotoxic chemotherapy module is juxtaposed between the abiraterone and enzalutamide modules.

Though structurally similar, recent in vitro data finds that cabazitaxel suppresses microtubule dynamic instability more strongly than docetaxel, is taken up into cells significantly faster, and is retained in cells longer, likely explaining the potency of cabazitaxel in docetaxel-resistant tumors [30]. Given that this trial is designed to thwart resistance development, this drives the decision to move cabazitaxel into a position of front-line therapy. A phase III randomized trial is currently underway to compare cabazitaxel/prednisone vs. docetaxel/prednisone in the chemotherapy-naïve CRPC population (NCT01308567).

Platinum agents have long been studied in prostate cancer and may play a stronger role in treatment of prostate cancer with neuroendocrine or aggressive features. Androgen-independent neuroendocrine cells, which are classically platinum-sensitive, are thought to be selected for by prolonged courses of androgen deprivation [31]. Recent studies have shown that the addition of carboplatin to docetaxel is well tolerated and demonstrates significant activity both in the first-line and the docetaxel-refractory disease setting [32-34].

While the combination of cabazitaxel and carboplatin have not yet been extensively studied, side effect profiles between docetaxel and cabazitaxel are similar given their similar mechanisms of action, making it a suitable and reasonable substitute for docetaxel. A phase I study of the cabazitaxel and carboplatin combination finds it to be safe and have significant antitumor activity [35], with its key dose-limiting toxicity of neutropenia able to be abrogated with the addition of pegfilgrastim. Recently reported at ASCO 2015, a multi-institutional randomized phase II study comparing cabazitaxel vs. cabazitaxel plus carboplatin demonstrated improved PFS and response rates with the addition of carboplatin to cabazitaxel in men with mCRPC that have failed at least one line of prior therapy [36].

Radium-223 dichloride has a modest toxicity profile, and is not anticipated to have significant interactions or overlapping toxicities with enzalutamide. It will only be given to patients with bone metastases demonstrated on imaging in accordance with its well-delineated mechanism of action. The presence of visceral metastases will not discount the use of radium-223, as it will be paired with enzalutamide.

Radium-223 will not be offered in combination with abiraterone as part of this study, due to a recent safety analysis leading to the unblinding of a randomized trial evaluating abiraterone with or without radium (NCT02043678). Interim data suggests an increased treatment emergent fractures, worse

symptomatic skeletal events-free survival, and more total deaths in the abiraterone plus radium-223 treatment arm.

As CRPC is a heterogeneous disease with varied prognosis, biomarker development has been a field of great clinical interest and active development. Tracking changes in prostate cancer over time is challenging due to the need for rebiopsy in order to obtain fresh tissue. Blood-based biomarker assays are far less invasive and easier to incorporate into clinical practice.

Peripheral blood cell gene expression is altered by interactions with its environment, including neoplastic tissue. The transcriptional profiling of whole blood has the potential to capture underlying biological and immunological processes that drive prostate cancer, and can yield crucial prognostic information in men with CRPC. We previously developed a six-gene RNA signature (consisting of ABL2, SEMA4D, ITGAL, C1QA, TIMP1, and CKDN1A) with prognostic significance for survival, demonstrating the ability to stratify men with CRPC into low-risk and high-risk groups [37]. The effect of different classes of therapeutic agents on this six gene signature, as well as its correlation with clinical outcome, is the subject of further study.

A potential mechanism by which CRPC gains resistance to AR-directed agents is via constitutively active androgen receptor variants (AR-V). AR-Vs have been shown to be expressed in hormone-sensitive prostate cancer cells, but at significantly lower levels as compared to castration-resistant disease [38]. Recent data associates patients with AR-V7 expression in circulating tumor cells (CTCs) with worse treatment response to AR-target agents [39], suggesting AR-V7 as a predictive biomarker for resistance. More studies are needed to validate AR-V7 as a predictive biomarker, as well as to better understand changes to its expression associated with different therapeutic agents and clinical outcome.

The design of this trial will expose patients to multiple different types of therapy and have a significant interval of follow up, so it presents a prime opportunity to evaluate the predictive potentials of the six-gene signature and AR-V7 expression. We also plan to bank additional blood specimens for future correlative science studies.

2. Study Objectives

To our knowledge, no study has evaluated the use of rapidly cycling, non-cross reactive therapies for the treatment of mCRPC. Our hypothesis is that the identification of optimal combinations and sequencing of rapidly cycling non-cross reactive therapies can help prevent or delay the development of therapeutic drug resistance, and can be safely tolerated.

2.1 Primary Objective

The primary objective of the study is:

- To evaluate time to disease progression, as determined by either PSA or radiographic progression, after completion of all modules of the rapidly-cycling, non-cross reactive regimen in patients with mCRPC.

2.2 Secondary Objectives

The secondary objectives are:

- To evaluate overall survival
- To assess PSA response rate with each treatment module
- To assess changes to alkaline phosphatase levels
- To assess safety of the rapidly-cycling, non-cross reactive regimen

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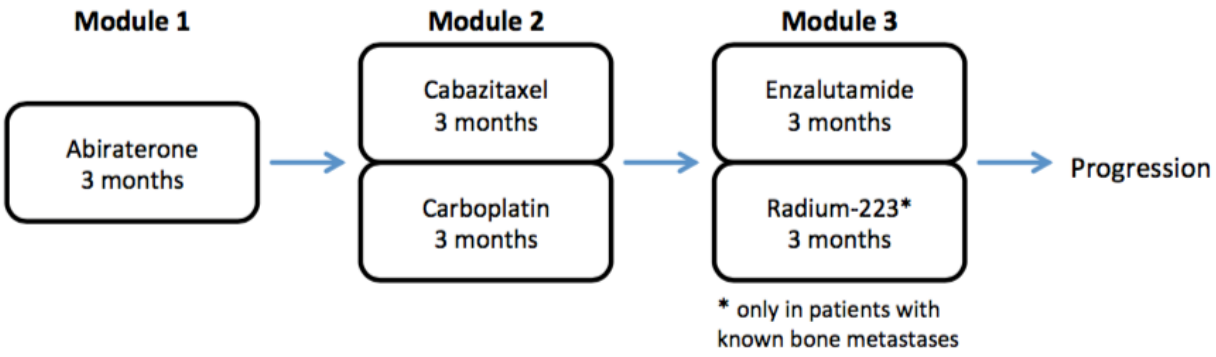
2.3 Exploratory Objectives

The exploratory objective are:

- To evaluate the correlation of a peripheral whole-blood RNA signature with clinical outcome measures during and after treatment.
- To evaluate changes to AR-V7 expression in CTCs with different treatment modalities and clinical outcomes.

3. Study Design/Schema



3.1 General Design

This is a prospective open-label non-randomized phase II clinical trial of rapidly cycling non-cross reactive prostate cancer treatments in patients with treatment-naïve metastatic CRPC. Treatments will include enzalutamide, cabazitaxel, carboplatin, abiraterone, and radium-223. Radium-223 will only be given to patients with known bone metastases. Expected duration of subject participation is 24 months.

3.2 Primary Study Endpoint

The primary clinical endpoint of this study is the time to disease progression after completion of all 3 modules of the rapidly-cycling study regimen. Disease progression is determined by either PSA or radiographic progression, whichever occurs first. Only disease progression that occur after the completion of all treatment modules will be counted.

3.2.1 PSA Progression

PSA progression is as defined by PCWG2 criteria [40]. Baseline PSA will be defined as the serum PSA level measured following completion of the third treatment module.

PSA changes will be reported globally using a waterfall plot for each module. In patients who have a decline in PSA value from baseline, progression is defined by:

- An increase in PSA by 25% above the nadir, AND
- An increase in PSA by a minimum of 2 ng/ml, or an increase in PSA to the pre-treatment PSA value, AND
- Confirmation by a second PSA at least 3 weeks apart, AND
- Occur following at least 12 weeks of therapy, AND
- There is no objective evidence of disease response.

In patients whose PSA value from baseline has not declined from baseline, progression is defined by:

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- An increase in PSA by 25% above either the pre-treatment level, or the nadir PSA level (whichever is lowest), AND
- An increase in PSA by a minimum of 2 ng/ml, AND
- Confirmation by a second PSA at least 3 weeks apart, AND
- Occur following at least 12 weeks of therapy, AND
- There is no objective evidence of disease response.

3.2.2 Radiographic Progression

Radiographic progression will be evaluated by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria, with definitions of CR, PR, SD, and PD for target and non-target lesions as defined below. Baseline imaging defined as the CT and bone scan obtained following completion of the third treatment module.

Lesions are categorized as either measurable or non-measurable based on the criteria below. 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 6 weeks before the beginning of the treatment. Tumor lesions that are situated in a previously irradiated area will not be considered measurable. 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

Guidelines for Evaluation of Measurable Disease

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.

Categorization of Radiologic Lesions

Measurable Disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) with a minimum size of 10 mm by CT scan (CT scan slice thickness no greater than 5 mm) and 20 mm by conventional techniques (X-ray). All tumor measurements will be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes:

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

Non-Measurable Disease

All other lesions, including small lesions (longest diameter <10 mm on CT or pathological lymph nodes > 10 to <15 mm in short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

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Special considerations
Bone lesions:
• Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
• Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
• Blastic bone lesions are non-measurable.

Target Lesions
All measurable lesions up to a maximum of 5 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 diameters (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 objective tumor response.

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.

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

Partial Response (PR): At least a 30% decrease in the sum of the 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. The sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.

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

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

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 two 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 Principal Investigator.

Outcomes Based on Radionuclide Bone Scans
The subjectivity in interpreting serial changes in radionuclide bone scan is well recognized. The primary outcome will be whether the scan is stable or improved vs. worse or progression. Changes in intensity will not be used as an outcome measure.

Stable/Improved: A stable or improved classification requires that no new lesions appear or that new pain has not developed in an area that was previously visualized.

Progression: Two or more new lesions not consistent with tumor flare, confirmed on a second bone scan ≥ 6 weeks later that shows ≥ 1 additional new lesion.

3.3 Secondary Study Endpoints
Secondary end points include evaluation of overall survival, PSA response to each treatment module, alkaline phosphatase response to each module, and safety.

3.3.1 Overall Survival
Overall survival will be defined as the time of study entry to death from any cause.

3.3.2 PSA Response
PSA response rates to the overall regimen as well as to each individual treatment module will be evaluated. For the purposes of calculating PSA response for the overall regimen, baseline PSA level will be defined as the PSA drawn at day 0. For calculating PSA response for individual treatment modules, baseline PSA will be defined as the PSA drawn at the beginning of that treatment module. Patients who do not tolerate at least 12 weeks of therapy will not be evaluable for PSA response.

Patients with a 50% PSA decline from their baseline PSA level will be considered responders, provided objective tumor measurements are stable or also demonstrate response. Patients with a 25% PSA increase from their baseline PSA will be considered nonresponders. Patients that do not meet criteria for responder or nonresponder, will be considered to have stable disease.

3.3.3 Alkaline Phosphatase Levels
Serum alkaline phosphatase levels will be monitored throughout the rapidly-cycling treatment regimen. Changes to alkaline phosphatase levels will be assessed at the end of each individual treatment module, upon completion of the rapidly-cycling treatment regimen, and at time of disease progression. Although alkaline phosphatase is a relatively nonspecific biomarker, the dominant source of alkaline phosphatase in patients with bone metastases is likely from the bone, and may reflect volume of bony metastatic disease and rate of bone turnover.

3.3.4 Safety
Throughout the study, safety and tolerability of the rapidly cycling non-cross reactive multi-drug treatment regimen will be assessed by the recording of adverse events, monitoring of vital signs and physical examinations, safety laboratory evaluations, and 12-lead ECG.

3.4 Exploratory Endpoints

We will evaluate whether there are prognostic or predictive implications associated with changes in the whole blood six-gene RNA signature score with each treatment module, clinical response to treatment, and overall clinical outcome.

AR-V7 expression in CTCs will be evaluated serially throughout the treatment period and post-treatment observation period for a subset of the study patients. Changes to AR-V7 expression will be monitored with each treatment module, clinical response to treatment, overall clinical outcome, and at time of disease progression.

Additional blood specimens will be banked for future correlative science studies.

4. Study Design

This single-arm phase II study will enroll patients over a 36 month period from the Mount Sinai Health System. We anticipate the enrollment of 2-3 patients per month to the clinical trial. Patients will be followed for at least 24 months following the last patient's entry.

4.1 Eligibility

4.1.1 Inclusion Criteria

Patients must meet the following inclusion criteria:

- Histologically or cytologically confirmed adenocarcinoma of the prostate
- Metastatic castrate resistant prostate cancer, defined by progressive disease based on either rising PSA, new bone metastases, or progression of measurable disease on imaging, according to PCWG2 guidelines, despite androgen deprivation therapy
- Ongoing androgen deprivation therapy with a GnRH analogue, GnRH antagonist, or bilateral orchiectomy
- ECOG performance status 0–1
- Serum testosterone level < 50 ng/dL
- Absolute neutrophil count > 1,500/µL, platelet count > 100,000/µL, and hemoglobin > 9 g/dL
- Creatinine < 2 mg/dL
- Total bilirubin < 1.5 times the upper limit of normal, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≤ 1.5 times the upper limit of normal

4.1.2 Exclusion Criteria

Patients must not meet any of the following exclusion criteria:

- History of uncontrolled seizure disorder
- Clinically significant cardiovascular disease including:
    - Myocardial infarction or uncontrolled angina within 6 months
    - Congestive heart failure New York Heart Association (NYHA) class 3 or 4, or patients with history of congestive heart failure NYHA class 3 or 4 in the past
    - Uncontrolled hypertension as indicated by a resting systolic blood pressure > 170 mmHg or diastolic blood pressure > 105 mmHg at the screening visit
- Have used or plan to use from 30 days prior to enrollment through the end of the study medication known to lower the seizure threshold or prolong the QT interval
- Major surgery within 4 weeks of enrollment

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- Radiation therapy within 4 weeks of enrollment
- Prior use of abiraterone acetate, enzalutamide, docetaxel, cabazitaxel, carboplatin, or radium-223 for the treatment of castration-resistant disease.
    - Prior docetaxel use in the hormone-sensitive disease setting is allowed, but must be completed ≥ 4 weeks prior to enrollment
    - Prior sipuleucel-T use is allowed, but must be completed ≥ 4 weeks prior to enrollment
    - Concurrent use of zolendronic acid or denosumab is allowed on study

4.2 Pretreatment Evaluation

All patients must sign a written informed consent form before study specific screening procedures are performed. Informed consents may be obtained up to 30 days prior to day 1 of treatment. Screening procedures to evaluate patient eligibility for the study will be conducted within 8 weeks prior to day 1. The pretreatment evaluation includes a complete medical history and physical examination. Baseline studies include complete blood count (CBC) with differential, comprehensive metabolic panel (CMP), lactate dehydrogenase (LDH), PSA, and testosterone panel. Baseline EKG, bone scan, and CT chest/abdomen/pelvis will also be performed up to 8 weeks prior to Day 1 of treatment.

If baseline CT and bone scan are without radiographic evidence of metastatic disease, but metastatic disease is demonstrated on newer imaging modalities that are more sensitive and specific for prostate cancer, such as F18-fluciclovine PET scan or Ga68-PSMA PET scan, these patients will be considered eligible for the study.

If the patient meets eligibility, they will return on Day 1 to be initiated on the first treatment module of the clinical trial.

5. Drug Dosing and Rationale

The proposed dosing for abiraterone, cabazitaxel, enzalutamide, and radium-223 are that which the FDA has approved them for. Each of these agents has been studied in individual large, multi-center phase III trials in men with mCRPC, and have demonstrated benefits in OS, and either PFS or TTP [1-4, 6]. As per FDA approved indication, radium-223 will only be given to patients with known bone metastases demonstrated on radiographic imaging. Abiraterone acetate must be taken on an empty stomach (one hour before or two hours after food) as systemic exposure of abiraterone acetate is increased by 5- and 10-fold when administered with a low- and high-fat meals, respectively, as compared to overnight fasting.

The combination of cabazitaxel and carboplatin is not a standard treatment regimen for mCRPC, but is under active investigation. A phase I study presented at GU ASCO 2014 finds the combination of cabazitaxel, dosed at 25 mg/m2 (FDA approved dosing), and carboplatin, at AUC 4, to be safe and have significant antitumor activity. The use of supportive pegfilgastim mitigates neutropenia, which is the key dose-limiting toxicity of cabazitaxel [35]. Premedication, consisting of a single intravenous dose of an antihistamine, histamine H2-antagonist (except cimetidine), and corticosteroids (dexamethasone 12 mg or equivalent), should be administered 30 minutes or more before cabazitaxel. Antiemetic prophylaxis can be given at the physician's discretion. Recent phase III study, PROSELICA, shows noninferiority of 20 mg/m2 dosing as compared to 25 mg/m2 dosing, leading to this study adopting the lower dose in order to limit myelosuppression [41]. To enhance efficacy, cabazitaxel will be administered before carboplatin [42].

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Each treatment module will last 12 weeks. Oral agents will be started on day 1 of each module and be continued at home on a daily basis until day 72. For intravenous treatments, aa total of 4 cycles are planned for cabazitaxel and carboplatin, and a total of 3 doses of radium-223 in patients with known bone metastases.
Study visits and intravenous treatments should adhere as closely to the schedule as possible, but a deviation from schedule of ± 5 days will be allowed. Reasonable deviations from schedule will also be made for holidays and religious observances.

The table below lists each therapeutic agent, dosing, and associated supportive regimens.

Treatment Module	Therapeutic Agent	Dosing	Supportive Regimen
1	Abiraterone	1000 mg PO once daily one hour before or two hours after food	Prednisone 5 mg PO BID
2	Cabazitaxel	20 mg/m2 IV on D1, every 3 weeks	Prednisone 5 mg PO BID; Pegfilgastim 6 mg SQ, 24-72 hours after completion of each cabazitaxel cycle; Antiemetics as needed
	Carboplatin	AUC 4 IV on D1, every 3 weeks	None
3	Enzalutamide	160 mg PO once daily	None
	Radium-223	50 kBq/kg IV on D1, every 4 weeks (55 KBq after implementation of NIST update)	None

	Module 1 (12 weeks)**			**Module 2** (12 weeks)**								**Module 3** (12 weeks)**		
	D1	**D29**	**D57**	**D1**	**D2**	**D22**	**D23**	**D43**	**D44**	**D64**	**D65**	**D1**	**D29**	**D57**
Abiraterone	daily													
Prednisone	daily													
Cabazitaxel				x		x		x		x				
Carboplatin				x		x		x		x				
Pegfilgrastim					x		x		x		x			
Prednisone				daily										
Enzalutamide												daily		
Radium-223*												x	x	x

* only in patients with known bone metastases

** deviation from schedule of ± 5 days allowed for study visits and IV therapies

5.1 Anticipated Risks

The adverse effect profiles of each therapeutic agent in the proposed treatment regimen have been well

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studied in large clinical trials. The Reported Safety Information (RSI) for expectedness of adverse events for this study are detailed by each drug's respective package insert.

Concurrent participation in another clinical trial or treatment with any other anti-cancer therapy is not permitted. The Investigator may prescribe any other concomitant medications as deemed necessary.

Abiraterone
Abiraterone is generally well tolerated, as demonstrated by two large phase III trials, in both the pre- and post-chemotherapy settings [2, 3]. Compared to placebo, abiraterone has a notably higher incidence of adverse effects associated with mineralocorticoid excess due to CYP17 blockade: fluid retention/edema, hypokalemia, and hypertension. These side effects are generally grade 1 or 2, and are mitigated by the addition of low dose prednisone. Cardiac disorders and LFT abnormalities also occur at a slightly higher incidence with abiraterone than with placebo, although without significant increases in fatal cardiac or hepatic events. Hepatotoxicity consists primarily of a reversible elevation in aminotransferase levels. The most common side effects observed with abiraterone are fatigue, back pain, nausea, constipation, bone pain, and arthralgia, and are primarily grade 1 or 2. Dose modification/interruption or treatment discontinuation of abiraterone due to adverse effects was similar to that of placebo in both phase III trials.

Radium-223
As radium-223 is a highly targeted radioisotope with short range effects, adverse effects to normal tissue and myelosuppression is minimized. Overall incidence of adverse events of all grades, and those graded III or IV, were lower in the radium-223 arm as compared to the placebo arm in the phase III trial that got it approved [6]. Notable grade 3 and 4 adverse events associated with radium-223 include disease progression, bone pain, anemia, and spinal cord compression. No differences in the frequency of hematologic toxicities were observed between the radium and placebo arms. One instance of grade 5 thrombocytopenia occurred during the trial that is considered possibly due to radium-223.

Cabazitaxel
In phase III study [1], cabazitaxel commonly caused hematological toxicities, of which the most common grade 3 or higher adverse events were neutropenia, leukopenia, and anemia. Common grade 3 or higher non-hematologic toxicities include diarrhea, fatigue, and asthenia. The diarrhea was expectantly managed. Peripheral neuropathy, a notable side effect of the taxane class, was present in 14% of patients in the cabazitaxel arm, although was uncommon (1%) as a grade 3 or higher adverse event.

The combination of cabazitaxel and carboplatin have been demonstrated to be safe when given concurrently; its key dose-limiting toxicity of neutropenia abrogated with the administration of prophylactic pegfilgrastim [35], which this trial incorporates. Notable grade 3-4 adverse events of the cabazitaxel/carboplatin combination reported by a recent randomized phase II study were mainly hematologic: neutropenia (15%), anemia (10%), thrombocytopenia (8%), and fatigue (10%). Febrile neutropenia was a rare occurrence (2%) [36].

Carboplatin
Carboplatin is a well studied agent and used in multiple chemotherapy combinations. Dosing is calculated by the target AUC using the Calvert formula: total dose (in milligrams) = Target AUC x (GFR + 25). For GFR that is estimated instead of measured, the FDA recommends capping GFR at a maximum of 125 mL/min to avoid potential toxicities. Its most notable adverse effects are hematologic: moderate incidence of grade 3/4 anemia (21%), leukopenia (15-26%), neutropenia (16-21%), and

thrombocytopenia (25-35%). Myelosuppression is dose dependent and is often the dose limiting toxicity. Other commonly reported adverse effects of carboplatin include pain, nausea, vomiting, weakness, hypersensitivity/allergic reactions, electrolyte disturbances (hyponatremia, hypomagnesemia, hypocalcemia, hypokalemia), decreased creatinine clearance, and LFT abnormalities. Carboplatin has limited nephrotoxic and ototoxic potential.

Enzalutamide
Enzalutamide, when used prior to chemotherapy exposure, was shown to have a good tolerability profile in PREVAIL [19], having similar rates of grade 3 or higher adverse events as compared to placebo (43% vs. 37%). Adverse events that occurred slightly more often with enzalutamide include fatigue (36% vs. 26%), back pain (27% vs. 22%), constipation (22% vs. 17%), and arthralgia (20% vs. 16%), although the majority of these are grade 1 or 2 in severity. Seizure was reported in 2 patients in the PREVAIL study, with one in each the treatment and placebo arms.

5.2 Adverse Events
An adverse event or experience is defined as any symptom, sign, illness, or untoward experience (including a clinically significant laboratory finding classified as grade ≥ 3 by the National Cancer Institute's Common Terminology Criteria for Adverse Events [CTCAE]) that develops or worsens during the course of the study, whether or not the event is considered related to study drug, and should be recorded only after the first dose of study drug is taken. Serious adverse events are recorded from the time the informed consent form is signed.

5.2.1 Definitions
Serious adverse event (SAE): any untoward medical occurrence that at any dose:

- 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., 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.

5.3 Management of Study Drug Events and Drug Dosing Modifications
The Reported Safety Information (RSI) for expectedness of adverse events for this study are detailed by each drug's respective package insert.

Concurrent participation in another clinical trial or treatment with any other anti-cancer therapy is not permitted. The Investigator may prescribe any other concomitant medications as deemed necessary.

5.3.1 Abiraterone
For a grade 3 or higher adverse event associated with abiraterone, a maximum of 2 dosage reductions will be allowed. At each dose reduction, the total dose will be decreased by 250 mg. Specific AE's and their management strategies are specified below. Any return to protocol dose level after dose reduction must follow documentation of AE resolution and a discussion with the Primary Investigator.

Adverse Event	Action	Further Action and/or Maintenance
Hypokalemia ≥ Grade 3	• Hold abiraterone and initiate IV K+ and cardiac monitoring.	• Reinitiating abiraterone at either full or reduced dosage requires discussion with Primary Investigator.
Hypertension ≥ Grade 3	• Hold abiraterone, blood pressure management with antihypertensives. • Once resolved to ≤ Grade 1, reinitiate abiraterone at full dose.	• If toxicity recurs, hold abiraterone until resolved to ≤ Grade 1, and reinitiate at reduced dose of 750 mg daily. • If toxicity recurs despite first dose reduction, hold abiraterone until resolved to ≤ Grade 1, and reinitiate at a further reduced dose of 500 mg daily. • If toxicity recurs despite second dose reduction and optimal hypertension management, discontinue abiraterone.
Edema ≥ Grade 3	• Hold abiraterone, medical management of edema, consider eplerenone. • Once resolved to ≤Grade 1, reinitiate abiraterone at full dose.	• If toxicity recurs, hold abiraterone until resolved to ≤ Grade 1, and reinitiate at reduced dose of 750 mg daily. • If toxicity recurs despite first dose reduction, hold abiraterone until resolved to ≤ Grade 1, and reinitiate at a further reduced dose of 500 mg daily. • If toxicity recurs despite second dose reduction and optimal hypertension management, discontinue abiraterone.
LFT abnormalities ≥ Grade 3	• Hold abiraterone, once resolved to ≤ Grade 1, reinitiate abiraterone at reduced dose of 750 mg daily.	• If toxicity recurs, hold abiraterone until resolved to ≤ Grade 1, and reinitiate at a further reduced dose

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		of 500 mg daily. • If toxicity recurs despite second dose reduction and discontinuation of other potentially hepatotoxic medications, discontinue abiraterone.
All other AE's related to abiraterone ≥ Grade 3	• Hold abiraterone, once resolved to ≤ Grade 2, reinitiate abiraterone at reduced dose of 750 mg daily.	• If toxicity recurs, hold abiraterone until resolved to ≤ Grade 2, then reinitiate treatment at a further reduced dose of 500 mg daily. • If toxicity recurs despite second dose reduction, discontinue abiraterone.

Avoid concomitant strong CYP3A4 inducers during abiraterone acetate treatment. If a strong CYP3A4 inducer must be co-administered, increase abiraterone acetate dosing frequency to twice a day only during the co-administration period (e.g., from 1000 mg once daily to 1000 mg twice a day). If co-administration of the strong inducer is discontinued, abiraterone acetate should be returned to the dose and frequency used prior to initiation of the strong CYP3A4 inducer.

5.3.2 Radium-223

Radium-223 dose level adjustments are not permitted. Radium-223 dichloride, 50 kBq/kg body weight, will be administered as a bolus intravenous (IV) injection (up to 1 minute) at intervals of every 4 weeks for up to 6 cycles (55kBq/kg body weight after implementation of the NIST update).

Every effort will be made to administer radium-223 according to schedule.

Adverse Event	Action	Further Action and/or Maintenance
Neutropenia ≥ Grade 3	• Hold radium-223, if resolved to ≤ Grade 2 within 14 days, resume radium-223 at its full dosing.	• If neutropenia persists for >14 days, discontinue radium-223.
Thrombocytopenia ≥ Grade 3	• Hold radium-223, if resolved to ≤ Grade 2 within 14 days, resume radium-223 at its full dosing.	• If thrombocytopenia persists for >14 days, discontinue radium-223.
Anemia ≥ Grade 3	• Hold radium-223, if resolved to ≤ Grade 2 within 14 days, resume radium-223 at its full dosing. • pRBC transfusion permitted between drug administrations.	• If anemia persists for >14 days despite supportive transfusions, discontinue radium-223.
All other AE's related to radium-223 ≥ Grade 3	• Hold radium-223, if resolved to ≤ Grade 2, resume radium-223 at its full dosing.	• If toxicity recurs, discontinue radium-223.

5.3.2.1 NIST Standardization Amendment

The quantification of radium-223 radioactivity in Xofigo (radium-223 dichloride; BAY 88-8223) is based on the primary standardization performed by the US NIST. National Institute of Standards and

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Technology prepares the standard reference material (SRM) using an official dial setting (primary standardization) as published [43]. The NIST SRM is used to calibrate the instruments in production and quality control for both the drug substance and drug product. Additionally, the NIST SRM is used to prepare the NIST traceable Ra-223 reference materials which are then sent to the end-users (e.g., nuclear medicine laboratory physicians or technicians) for dial-setting of their dose calibrators, to allow verification of the patient dose. In 2014, NIST performed a re-assessment of the primary standardization based on preliminary information suggesting a potential discrepancy of approximately 8-10% between the published NIST primary standardization [43] and results obtained by other national metrology institutes (United Kingdom, Germany, Japan). After completion of the re-assessment, NIST reported their findings and had issued a revised NIST SRM in 2015 [44]. The discrepancy in the NIST standardization was determined to be −9.5% between activity values obtained using the old reference standard relative to the new primary standardization. Consequently, the current numerical values need to be corrected by approx. + 10.5%. The current NIST standard for radium-223 dichloride will remain in effect until the FDA has fully approved the regulatory variation submitted for Xofigo and is anticipated in the 2nd quarter of 2016. All sites are expected to begin preparation for the updated NIST standardization and obtain all necessary IRB approvals. Bayer will continue to notify sites about the status of the regulatory approval and the date that the updated NIST standardization is to be implemented. Upon notification, and prior to the implementation, all sites are expected to add a new dial setting to their dose calibrators for the new NIST standardization for radium-223 dichloride, which should be documented on the appropriate study forms. The change in the numerical description of the patient's dose, product strength and labeled vial activity does not impact the safety or efficacy of Xofigo. The change in the NIST radium-223 standard has no impact on subjects; dose subjects are receiving, and will continue to receive. Subjects will receive the same actual dose and volume that was studied in Study 15245 (BC1-06 dosimetry study) and is associated with the proven safety and efficacy of radium-223 dichloride, though the stated nominal radiation dose received is being updated to reflect the new standard.

The change in the numerical description of the patient's dose, product strength and labeled vial activity does not impact the safety or efficacy of Xofigo. The change in the NIST radium-223 standard has no impact on subjects; dose subjects are receiving, and will continue to receive. Subjects will receive the same actual dose and volume that was studied in Study 15245 (BC1-06 dosimetry study) and is associated with the proven safety and efficacy of radium-223 dichloride, though the stated nominal radiation dose received is being updated to reflect the new standard.

5.3.2.2 Dose calibration

Radium-223 dichloride can be measured in a normal dose calibrator instrument. When written approvals for the use of Radium-223 dichloride from the Radiation Protection Agency for the specific center have been received by the sponsor, a vial of Radium-223 dichloride for technical use will be sent to the study center. (A new reference vial will be sent to each center corresponding to the updated NIST reference material). Different clinical study centers possess dose calibrators from various suppliers; thus, the isotope calibration factor may differ from center to center. Consequently, each center must perform the Radium- 223 dichloride dial setting on their relevant dose calibrator(s) (upon notification by Bayer each center is required to update the dial settings to correspond to the new NIST standard). The current dial settings are to remain in effect until Bayer obtains full approval from the FDA for implementation. In preparation for implementation of the new dial setting, the clinical study center will receive a sealed vial labeled NIST standard containing a Radium-223 dichloride solution for calibration only. The vial is identical to the vials used for study treatment. The amount of Radium- 223 dichloride in

the vial will be stated on the label. Instructions for the dial setting, including the calibration log form, will be enclosed with the dispatch of the calibration sample.

All sites will be notified by Bayer when final regulatory approval from the FDA is in place and the updated NIST standardization is to be implemented.

5.3.2.3 Dose calculation

The dosage of Radium-223 dichloride is 50 kBq/kg body weight (55kBq/kg after NIST update). The patient dose is calculated based on date of injection, a decay correction (DK) factor specific to number of days from reference date applied to correct for physical decay of radium-223 , and patient weight. . A table with DK values according to physical decay of the study medication will be provided with every shipment of Radium-223 dichloride. Radium-223 is an alpha particle emitter with a physical $t^{1/2}$ of 11.4 days. The radioactive concentration at the reference date is 1,000 kBq/mL (1,100 kBq/mL after implementation of NIST update).

5.3.3 Cabazitaxel and Carboplatin

To continue treatment, patients should have an absolute neutrophil count ≥1,500 cells/mm^3, platelets ≥75,000 cells/mm^3, and non-hematologic toxicities attributed to the combination of cabazitaxel and carboplatin resolved to ≤ Grade 2. Specific AE's and their management strategies are specified below. The two agents have some overlapping toxicities, and since they are being given in combination, should dose reduction become necessary, we will favor dose reducing carboplatin first over cabazitaxel, as cabazitaxel has demonstrated OS benefit in mCRPC patients. Any return to protocol dose level after dose reduction must follow documentation of AE resolution and discussion with the Primary Investigator.

Every effort will be made to administer the full dose regimen to maximize dose-intensity.
If possible, toxicities should be managed symptomatically. If toxicity occurs, the appropriate treatment will be used to improve signs and symptoms including antiemetics for nausea and vomiting, antidiarrheals for diarrhea, and antipyretics, and/or antihistamines for drug fever.

Dose can be reduced for cabazitaxel when necessary as described in following sections. The dose, which has been reduced for toxicity, must not be re-escalated. Only one dose reductions will be allowed per patient. If a second dose reduction is required per the modifications below, the patient should discontinue study treatment. Treatment may be delayed no more than 2 weeks to allow recovery from acute toxicity. In case of treatment delay greater than 2 weeks, patient should discontinue cabazitaxel.

Blood counts will be performed in case of fever or infection. No dose modification will be made for anemia; patients will be supported appropriately by the treating physician (the investigator can refer to ASCO guidelines). Study treatment 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).

Adverse Event	Action	Further Action and/or Maintenance

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Neutropenia Grade 2	• Hold cabazitaxel and carboplatin until ANC ≥ 1,500 cells/mm3, then reinitiate treatment with cabazitaxel at full dose and carboplatin reduced by 20% based on AUC.	• If toxicity recurs, hold until ANC ≥ 1,500 cells/mm^3, then reinitiate treatment with the same carboplatin dose reduction, and cabazitaxel at reduced dose of 15 mg/m^2. • If toxicity recurs despite cabazitaxel and carboplatin dose reductions and pegfilgrastim prophylaxis, discontinue treatment.
Neutropenia ≥ Grade 3	• Hold cabazitaxel and carboplatin until ANC ≥ 1,500 cells/mm^3, then reinitiate treatment with cabazitaxel at 15 mg/m^2 and carboplatin reduced by 20% based on AUC.	• If toxicity recurs despite cabazitaxel and carboplatin dose reductions and pegfilgrastim prophylaxis, discontinue treatment.
Febrile Neutropenia or Neutropenic Infection ≥ Grade 3	• Hold cabazitaxel and carboplatin until ANC ≥ 1,500 cells/mm^3, then reinitiate treatment with cabazitaxel at 15 mg/m^2 and carboplatin reduced by 20% based on AUC.	• If toxicity recurs despite cabazitaxel and carboplatin dose reductions and pegfilgrastim prophylaxis, discontinue treatment.
Anemia	• No dose modification will be made for anemia • Patients will be supported appropriately by the treating physician (the investigator can refer to ASCO guidelines).	
Thrombocytopenia Grade 2	• Hold cabazitaxel and carboplatin until recovery to grade ≤ 1 (platelets ≥ 75,000 cells/mm^3), then reinitiate treatment with cabazitaxel at full dose and carboplatin reduced by 20% based on AUC.	
Thrombocytopenia Grade 3	• Hold cabazitaxel and carboplatin until platelets ≥ 75,000 cells/$mm^{3:}$ o If no delay, then reinitiate treatment with cabazitaxel at full dose and carboplatin reduced by 20% based on AUC. o If delay, then reinitiate treatment with cabazitaxel at 15 mg/m2 and carboplatin reduced by 20% based on AUC.	• If toxicity recurs without cabazitaxel dose reduction, then reinitiate treatment with the same carboplatin dose reduction, and cabazitaxel at reduced dose of 15 mg/m^2. • If toxicity recurs despite cabazitaxel and carboplatin dose reductions, discontinue treatment.
Thrombocytopenia Grade 4	• Hold cabazitaxel and carboplatin until platelets ≥ 75,000 cells/mm^3, then reinitiate treatment with cabazitaxel at 15 mg/m2 and carboplatin	• If toxicity recurs despite cabazitaxel and carboplatin dose reductions, discontinue treatment.

	reduced by 20% based on AUC.	
Diarrhea ≥ Grade 3	• Hold cabazitaxel and carboplatin until resolved to ≤ Grade 2, then reinitiate treatment with cabazitaxel at reduced dose of 15 mg/m^2 and carboplatin reduced by 20% based on AUC	• If toxicity recurs despite cabazitaxel and carboplatin dose reduction and symptomatic support, discontinue treatment.
Hepatic Impairment	• Mild impairment (total bilirubin >1 to ≤1.5 x ULN or AST >1.5 x ULN), keep cabazitaxel at 20 mg/m2. • Moderate impairment (total bilirubin >1.5 to ≤3.0 x ULN and AST = any), reduce cabazitaxel to 15 mg/m2 • Severe impairment (total bilirubin >3.0 x ULN), cabazitaxel is contraindicated in patients with severe hepatic impairment.	
Other AE's* related to cabazitaxel and carboplatin ≥ Grade 3	• Hold cabazitaxel and carboplatin until resolved to ≤ Grade 1, then reinitiate treatment with dose reduction left to the investigator's judgment.	• If requires >1 dose reduction of cabazitaxel or >1 dose reduction of carboplatin, discontinue treatment.

***except fatigue, local reaction, fluid retention, anemia and other toxicities that merely are uncomfortable but do not cause serious morbidity to patients.

5.3.3.1 Specific to Cabazitaxel

Concomitant Medications

Avoid concomitant strong CYP3A4 inhibitors during cabazitaxel treatment. If a strong CYP3A4 inhibitor must be co-administered, decrease cabazitaxel dose by 25%. If co-administration of the strong CYP3A4 inhibitor is discontinued, cabazitaxel should be returned to the dose used prior to initiation of the strong CYP3A4 inhibitor.

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 of the second infusion of cabazitaxel. Therefore, during the 1st and the 2nd infusions, careful evaluation of general sense of well being and of blood pressure and heart rate will be performed for at least the first 10 minutes, so that immediate intervention would occur in response to symptoms of an untoward reaction.

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

Mild: localized cutaneous reaction, such as:	• Consider decreasing the rate of infusion until

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pruritus, flushing, rash.	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 when cabazitaxel is reinfused more than 3 hours after the interruptionAdminister 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 • 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 when cabazitaxel is reinfused more than 3 hours after the interruption • Administer cabazitaxel over 2 hours for all subsequent infusions • If a severe reaction recurs, patient will go off protocol therapy
Anaphylaxis (Grade 4 reaction)	• Withdraw treatment

Nausea/Vomiting

A prophylactic anti-emetic treatment should be given to the patients in all cycles. The use of metoclopramide 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.

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.

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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. In addition, in prior studies conducted in metastatic breast cancer, a total of 6 patients (2 in the ARD6191 and 4 in the TCD6945) experienced cystitis without local infection including 5 hemorrhagic cystitis (3 cystitis were documented with biopsy). 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).

Neurological toxicity
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

Other Toxic Effects
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.

5.3.4 Enzalutamide
For any grade 3 or higher adverse event related to enzalutamide, enzalutamide should be withheld until symptoms improve to Grade 2 or lower toxicity. A maximum of 2 dosage reductions will be allowed.

Adverse Event	Action	Further Action and/or Maintenance
Any AE related to enzalutamide ≥ Grade 3	• Hold enzalutamide until symptoms improve to ≤ Grade 2, then reinitiate at reduced dose of 120 mg daily.	• If toxicity recurs, hold until symptoms improve to ≤ Grade 2, then reinitiate at 80 mg daily. • If toxicity recurs again, then discontinue enzalutamide.

Concomitant use of strong CYP2C8 inhibitors should be avoided if possible. If patients must be co-administered a strong CYP2C8 inhibitor, reduce enzalutamide to 80 mg once daily. If co-administration of the strong inhibitor is discontinued, enzalutamide should be returned to the dose used prior to initiation of the strong CYP2C8 inhibitor.

Concomitant use of strong CYP3A4 inducers should be avoided if possible. If patients must be co-administered a strong CYP3A4 inducer, increase enzalutamide from 160 mg to 240 mg once daily. If co-administration of the strong CYP3A4 inducer is discontinued, enzalutamide should be returned to the dose used prior to initiation of the strong CYP3A4 inducer.

5.3.5 Prednisone
For any grade 3 or higher adverse event related to prednisone, prednisone should be withheld until symptoms improve to Grade 2 or lower toxicity. A maximum of 1 dosage reduction will be allowed.

Adverse Event	Action	Further Action and/or Maintenance
Any AE related to prednisone ≥ Grade 3	• Hold prednisone until symptoms improve to ≤ Grade 2, then reinitiate at reduced dose of 5 mg daily.	• If toxicity recurs, then discontinue prednisone.

5.4 Pharmacovigilance Specifications

5.4.1 Sanofi - Obligations and Responsibilities of the IST/ISS Sponsor

The IST/ISS sponsor warrants 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 Practices.

- The IST/ISS sponsor shall be responsible for the respect of all obligations required by applicable local and international laws and regulations.
- The sponsor shall be responsible for 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).
- The IST/ISS sponsor is responsible for 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.
- 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'.
- The sponsor must report the following information in English to the Sanofi group entity Pharmacovigilance contact:
    1. Routine transmission of:
        a. All Serious Adverse Events (SAEs) and Adverse Events of Special Interest (AESI), if any. These events must be transmitted within 24 hours of awareness of the Investigator's awareness or identification of the event.
        b. 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 24 hours of awareness. (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 of cabazitaxel shall be the Investigator's Brochure.

5.4.2 Sanofi Group Entity Pharmacovigilance Contact

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

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Fax/email of SAE Reports to Sanofi:
Fax: 908-203-7783
E-mail: CL-CPV-Receipt@sanofi.com

5.4.3 Bayer - Obligations and Responsibilities of the IST/ISS Sponsor

All serious adverse events should be reported to Bayer within 24 hours. In the event of such an event, the investigator should refer to the Pharmacovigilance section of the contract for reporting procedures and report SAE to Bayer.

Requirements for Reporting of Serious Adverse Events:
All SAEs must be reported to Bayer within 24 hours of the Principal Investigator's awareness and must include the following minimum information:

1. The name and contact information of the reporter
2. The name of the study drug(s)
3. A description of the reported SAE
4. A patient identified by one or more of the following:

a. Patient initials
b. Patient number
c. Knowledge that a patient who experienced the adverse event exists
d. Age
e. Sex

An investigator assessment of study drug causality. For studies with combination therapy, a separate causality assessment should be provided for each study drug.
Additional data which would aid the review and causality assessment of the case include but are not limited to:

The date of onset
The severity
The time from administration of study drug(s) to start of the event
The duration and outcome of the event
Any possible etiology for the event
The final diagnosis or syndrome, if known
Action(s) taken, if any

5.4.4 Bayer Global Pharmacovigilance Contact

The Investigator may report serious adverse drug reactions (SADRs) using either:
1. An ADEERS form (Adverse Event Expedited Reporting System) available at http://ctep.cancer.gov/reporting/adeers.html
2. A MedWatch form available at: http://www.fda.gov/medwatch/

All reports shall be sent electronically to:

Electronic Mailbox: DrugSafety.GPV.US@bayer.com

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Facsimile:	(973) 709-2185
Address:	Global Pharmacovigilance - USA
Mail only:	Bayer HealthCare P.O. Box 915 Whippany, NJ 07981-0915
Address:	100 Bayer Blvd., Whippany, NJ 07981
FDX or UPS only	67 Whippany Road, Whippany, NJ 07981 for UPS

Reports for all Bayer products can also be phoned in via the Clinical Communications Dept
Phone: 1-888-842-2937

6. Follow Up, Laboratory Testing, and Diagnostic Imaging

Clinic visits will be scheduled at the beginning of each treatment module, with blood samples taken for serum testing of CBC, comprehensive metabolic panel, LDH, PSA, and testosterone panel during these visits. During the first (abiraterone) treatment module, laboratory tests will be repeated every 2 weeks for the first 4 weeks, then every 4 weeks afterwards. Follow up and treatment visits will be scheduled every 4 weeks. During second (cabazitaxel and carboplatin) treatment module, follow up, laboratory tests, and treatment visits will be scheduled every 3 weeks. During the third (enzalutamide and radium-223) treatment module, laboratory tests will be repeated every 2 weeks for the first 4 weeks, then every 4 weeks afterwards. Follow up and treatment visits will be scheduled every 4 weeks.

Baseline evaluation, including informed consent, medical history, physical examination, vital signs, height, weight, performance status, laboratory testing, and imaging with CT chest/abdomen/pelvis scan and bone scan should be obtained no greater than 8 weeks before initiation of trial treatment regimen.

Repeat CT chest/abdomen/pelvis scan and bone scan should be repeated every 12 weeks to coincide with the completion of each treatment module.

Evaluation for adverse events will take place on all scheduled study visits during all three modules of treatment, as well as every 4 weeks until week 12 of the the post-treatment surveillance period. Monitoring for adverse events will stop after that, as patients will have been off of the rapidly cycling study regimen for 12 weeks, and side effects from treatment drugs would have anticipated to have resolved by this time.

Peripheral blood will be collected in PAXgene Blood RNA tubes on the first day of each new treatment module, the first day of the post-treatment surveillance period, and at week 12 of the post-treatment surveillance period (unless there has been progression).

If the external laboratory that performs the peripheral blood CTC testing is ready to receive and process the specimen, peripheral blood will be collected in Streck Cell-Free DNA blood collection tubes on the first day of each new treatment module, and the first day of the post-treatment surveillance period. If not, this tube will not be drawn, as these samples cannot be frozen and stored for later analysis.

During the post-treatment surveillance period, as long as disease progression has not yet been demonstrated, patients will adhere to every 4 week follow up and lab draws until week 12 of the

surveillance period. After week 12, lab draws will remain every 4 weeks, but interval for office visits will be extended to every 12 weeks. Imaging will be performed every 12 weeks until disease progression.

Once disease progression is demonstrated during the post-treatment surveillance period, the patient will come off study, and the schedule for follow up, labs, imaging, AE monitoring, and treatment will no longer be defined by the timepoints designated by the trial. Long term survival data will be collected via chart review and phone discussions.

Once off study, patients will remain eligible for any of the treatment agents that were already received as part of the study, although how the patient responded and tolerated the drug previously will be taken into consideration. The selection of agent (or combination of agents), as well as the interval for follow up, labs, and imaging, will be at the treating physician's discretion.

	Baseline	**Treatment**			**Post-Treatment Surveillance***
		Module 1	**Module 2**	**Module 3**	
Informed Consent	Once				
Medical History	Once				
Physical Examination	Once	Q4 weeks	Q3 weeks	Q4 weeks	Q4 weeks until week 12, then q12 weeks**
Vital Signs/Weight	Once	Q4 weeks	Q3 weeks	Q4 weeks	Q4 weeks until week 12, then q12 weeks**
Performance Status	Once	Q4 weeks	Q3 weeks	Q4 weeks	Q4 weeks until week 12, then q12 weeks**
CBC with differential	Once	Q4 weeks	Q3 weeks	Q4 weeks	Q4 weeks**
CMP	Once	Q2 weeks for the first 4 weeks, then Q4 weeks	Q3 weeks	Q2 weeks for the first 4 weeks, then Q4 weeks	Q4 weeks**
PSA	Once	Q4 weeks	Q3 weeks	Q4 weeks	Q4 weeks**
Testosterone	Once	Q4 weeks	Q3 weeks	Q4 weeks	Q4 weeks**
LDH	Once	Q4 weeks	Q3 weeks	Q4 weeks	Q4 weeks**
ECG	Once	Q4 weeks			
AE Monitoring	Once	Q4 weeks	Q3 weeks	Q4 weeks	Q4 weeks until week 12
CT C/A/P	Once	Q12 weeks	Q12 weeks	Q12 weeks	Q12 weeks**
Bone Scan	Once	Q12 weeks	Q12 weeks	Q12 weeks	Q12 weeks**
PAXgene Blood RNA tube	None	At start of module	At start of module	At start of module	At start of surveillance, then Q12 weeks, until week 12
Streck Cell-Free DNA	None	At start of	At start of	At start of	At start of

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blood collection tube***		module***	module***	module***	surveillance***

*Once disease progression has been demonstrated, the schedule for follow up, blood work, imaging, and AE monitoring is no longer defined by the timepoints designated by the trial. Instead, intervals will be at the discretion of the treating physician, depending on decisions made on subsequent lines of therapy.
** Until disease progression
***Only if the external laboratory that performs the peripheral blood CTC analysis is ready to receive and process the specimen

6.1 Criteria for Discontinuation of Study Regimen
The study regimen may be discontinued for any of the following reasons:

- Intolerable, recurrent, or sustained adverse effects of the study regimen despite appropriate dose reduction and best supportive management.
- Noncompliance with study regimen or follow up appointments.
- Patient choice to withdraw from trial.
- Investigator or physician discretion.

As defined by PCWG2 guidelines, the earliest time point that PSA progression can be determined is at 12 weeks. This is in line with the understanding that a favorable PSA response may be delayed for 12 weeks or more, even with cytotoxic chemotherapy. Similarly, the earliest time point for determination of radiographic progression is also at the end of each module (12 weeks) given trial design.

The design of the treatment schedule is such that the treatment modality will be changed regardless of response observed. For patients whose disease are found to be progressing at the end of a treatment module (12 weeks), their treatment is already planned to be transitioned to another agent, which is in line with standard of care for disease progression, and would not constitute a need to discontinue the study regimen and withdraw from trial.

Patients who do not complete all three treatment modules will be considered dropped out, and not included in the primary and secondary endpoint analyses. However, whenever possible, attempts will be made to collect overall survival data of patients that have discontinued the study regimen.

7. Statistical Plan
In this trial, all patients will be treated using the rapid-cycling non-cross reactive treatment model as detailed above. Given that cycling therapies is a novel concept in prostate cancer management, there are no similar trials or statistics available that can be used for direct historical comparison. The 3 month time to disease progression quoted as part of the statistical design of this clinical trial is obtained primarily from the AFFIRM and PREVAIL trials, where mCRPC patients were randomized to receive either enzalutamide or placebo.

The placebo arm of the AFFIRM study is most closely comparable to our patient cohort, in that they will have received multiple different prostate cancer therapies, and will be actively surveyed on primary ADT alone following completion of the rapidly cycling regimen. The AFFIRM placebo arm had a median time to PSA progression of 3.0 months, and radiographic PFS of 2.9 months [4]. However, though our patients will be treatment-experienced following the 9 months of treatment, they will not be considered treatment-refractory as were those enrolled on AFFIRM. We gain additional insight from the PREVAIL trial into the natural history and rate of progression of CRPC that has not yet developed multi-drug

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resistance. In the cohort of treatment-naïve mCRPC men receiving placebo, median time to PSA progression was 2.8 months, and radiographic PFS 3.9 months [7].

As our composite primary endpoint utilizes the earliest evidence of PSA or radiographic progression to define disease progression, we believe that 3 months is a reasonable control.

Another trial considered as a historical control is the ASCENT trial, which treated chemotherapy-naïve mCRPC patients with intermittent docetaxel [45]. Of the patients that met study criteria to receive a break from chemotherapy, the median duration of the first chemotherapy holiday was 18 weeks (4.5 months). This figure is higher than 3 months, but did not factor in patients who did not meet requirements to go on drug holiday. This cohort also had no prior exposure or resistance to abiraterone or enzalutamide, which likely factors into the longer interval to progression. This study still serves as a good internal check, to demonstrate that our 3-month time to disease progression is reasonably chosen.

The median time to PSA progression in our cohort of patients will be estimated using a Cumulative Incidence Competing Risk (CICR) analysis with mortality from any cause considered a competing risk. To test whether the estimated median time to progression is significantly greater than historical time to progression of 3 months, a likelihood ratio test will be used. The maximum likelihood estimates of parameters, using either the exponential or Weibull distribution, obtained from the observed data will be compared to a median time to disease progression of 3 months [46]. For a study with 36 months accrual and a follow-up period of 24 months from the last patient's entry, a sample size of 33 patients that complete all three treatment modules of the study regimen will provide 90% power for a one-sided test at the 5% level to detect an increase in median time to disease progression from 3 months to 5 months [47]. We will plan to screen 60 patients (treat a total of 40 patients) on study in order to account for any potential patient dropout, defined as anyone who does not complete all three treatment modules.

In addition to the above, we will also perform an intention-to-treat analysis of all enrolled patients in order to account for any early progressions or deaths.

Overall survival will be estimated using the method of Kaplan-Meier. Comparison will be made with historical OS data from the PREVAIL and COU-AA-302 trials (32.4 and 34.7 months, respectively) [3, 7] where treatment-naïve mCRPC patients received long term follow up during which they received multiple different active therapies.

PSA response rates to the overall regimen and each individual treatment module will be evaluated independently and compared to historical controls and presented as descriptive statistics. From large phase III pre-chemotherapy studies, abiraterone and enzalutamide have PSA response rates of 62% [3] and 78% [7], respectively. Past experience with regimens that include a taxane and a platinum agent, PSA response rates have ranged 69-88% [32, 33]. There is limited data available for cabazitaxel and carboplatin, but recently reported phase II trial of this combination demonstrated a 52% partial response rate as evaluated by RECIST radiographic criteria [35].

Since baseline PSA levels for treatment modules 2 and 3 will be affected by the agents introduced in prior treatment modules, we expect PSA response rates of the individual modules to be lower than expected from historical comparison. However, if a patient is considered to be a responder based on PSA in a previous treatment module, and the PSA remains stable or continues to decline on a

subsequent treatment module, argument can be made that the patient is a responder to that module as well even if PSA declines of 50% are not attained.

Changes to alkaline phosphatase levels will be tracked for each treatment module, the overall treatment regimen, and at time of disease progression. While alkaline phosphatase (ALP) is not a well-studied endpoint in prostate cancer trials, its serum levels often correlate with bone metastases status [48], and normalization of ALP levels has been suggested to predict better survival [49]. ALP levels will be compared to the upper limits of normal (ULN) for all laboratory testing performed in the study period and calculated as a ratio. ALP will be considered to be persistently abnormal if the levels are continuously greater than a ratio of 1 and considered to normalize if there is at least one value with a ratio of 1 or less. Fine and Gray's Competing Risk Regression (CRR) will be used to estimate a hazard ratio comparing the risk of progression betweein patient groups with abnormal and normalized ALP levels while accounting for the presence of competing risks. This analysis will be performed to determine whether normalized ALP levels, correlates with time to disease progression.

Safety will be assessed through summaries of adverse events, vital signs, physical examinations, ECGs, and clinical laboratory test data. The number and percentage of patients with adverse events will be presented as descriptive statistics.

The six-gene scores following each individual treatment module will be compared to baseline pre-treatment scores using a paired T-test. Changes to the six gene score over sequential time points will also be evaluated using linear mixed model. Additionally, we will perform statistical analysis to determine whether the baseline six-gene scores can predict treatment response or whether the post-treatment six-gene score is associated with clinical treatment outcomes, including PSA and radiographic response.

The number and percentage of men with AR-V7 positivity will be evaluated at baseline, with the completion of each treatment module, and at follow up. The prevalence of AR-V7 in treatment-naïve mCRPC patients remain the subject of further investigation, but we can assume it to be approximately one third [39]. We will track AR-V7 expression changes over the course of treatment. We hypothesize that men who are either AR-V7 positive at baseline or develop it over the course of treatment, will have similar outcomes to AR-V7 negative men with the rapidly-cycling treatment regimen. Fine and Gray's Competing Risk Regression will be used to estimate a hazard ratio comparing time to disease progression between the two groups.

8. Data Handling and Record Keeping

8.1 Electronic Data Capture (EDC) System

All eCRFs will be entered directly into a web-based electronic research application portal known as REDCap. REDCap's role-based access control security and audit capability ensures that the research data is protected from unauthorized access, modification, and exposure. Key features of this web-based database system include allowing access and data entry from multiple sites, with each site having a separate pool of data as necessary. All data stored in the REDCap system is backed up daily. Detailed audit services include any data field level changes, who made the changes, when the changes were made, the old value and the new value. Data from REDCap can easily be extracted to excel or flat text file formats for easy import into SAS or other statistical software packages.

8.2 Verification of EDC System

Once the database has been set up the PI will test the system. The testing will include confirmation of the proper functioning of valid value checks, subject ID generation, derived variable computations, data extracts and system reports.

8.3 Entering data

Since electronic CRFs will be used, data entry will be conducted onsite by clinicians who have been granted appropriate access to do so.

8.4 Data Validation Process

As part of the data validation process, edit check programs will be embedded in the database thru valid-value, valid-range and missing value alerts specified for each field as necessary. Valid-value edit checks include:

- Requiring the user to enter a coded value taken from a list that is presented on the CRF. If a value not on the list is entered the user will be prompted to check the value and enter a value on the list.
- Requiring the user to enter a value within a particular range of possible values for a continuous measure. If a value outside the range is entered the user will be prompted to check the value and re-enter.

In addition to the univariate field alerts specified above, there will be multivariate alerts built into the database design:

- Confirming that only valid options are selected in a 'choose all that apply' multiple choice field, where the range of options deemed valid depends on some other parameter.
- Confirming that diastolic blood pressure reading is less than the associated systolic blood pressure reading.
- Confirming that "other, specify" is completed when "other" is selected.
- Confirming that eligibility criteria are met.

As well as cross-module alerts such as:

- Comparing the dates and times of all assessment time points to confirm that they occur in an appropriate sequence.

8.5 Data Cleaning and Discrepancy Management

Any discrepancies identified through this process will be highlighted and corrected in the system.

8.6 Data Security

The EDC database is approved by Mount Sinai IT Security and HIPAA and operates using high-end servers located in the Secured Mount Sinai Data Center. All data stored in the REDCap system is backed up daily. Access to the database is controlled by policies requiring the PI to authorize user and user roles. Quick view audit service allows authorized user to see who accessed records for view or edit and detailed audit services include seeing any data field level changes, who made the changes, when the changes were made, as well as the value before and after the change.

8.7 Quality Control Procedures

Comprehensive edit checks will be used to clean data. Patient data will be entered continuously. All changes to the data and the database structure will be recorded in an automatic audit trail. Random checks will be done by the PI to ensure data accuracy and completeness. A final database will be declared when all data has been entered, the data entry verified, the data validated and the database defined as clean. After declaration of a final database the data will be exported from REDCap to excel for import to SAS and both the database and the SAS datasets will be locked and protected from changes. All statistical analyses for the final analysis will be performed on the locked SAS datasets.

8.8 Medical and Adverse Event Coding

Coding of Adverse Events occurring during the study will be performed by the Clinical Research Manager according to the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 while coding of concomitant medications, prior anti-cancer therapy and further therapy will be performed according to the World Health Organization-Drug Dictionary Enhanced (WHO-DDE). These dictionaries contain the respective classifications of adverse events and drugs in proper classes. When dictionary entries and verbatim terms (either for adverse events for medications) do not directly match, the PI will review the entry as well as other related information such as comment fields to identify the most appropriate match. In the event there are compound verbatim events (either AEs or medications) listed in the CRF, such events must be split into more than one record for purposes of medical coding. The PI will be responsible for splitting the compound events into separate **entries.**

8.9 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

8.10 Records Retention

The Investigator must retain drug disposition records (if applicable), source documents, and case histories designed to record all observations and other data pertinent to the investigation (e.g. case report form) for the maximum period required by applicable regulations and guidelines, or Institution procedures.

If a change in the PI occurs, the records shall be transferred to a mutually agreed upon designee (e.g., another Investigator, IRB).

8.11 Subject Privacy

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

It is the responsibility of the research staff to ensure that protocol subjects received, understands, and signs the informed consent document before enrolling the patient onto this trial. Personnel must provide a HIPAA form and obtain acknowledgment before the subject participates in this study.

All subject data will be identified by a subject identification number and subject initials only, to protect the subject's privacy. The data will be blinded accordingly in all data analysis. However, in compliance with federal guidelines, the investigator will permit a representative from Mount Sinai Health System audit committee to review that portion of the subject's medical record that is directly related to the study. This will include all relevant study documentation including medical histories to verify eligibility, laboratory test results to verify transcription accuracy, X-ray reports, admission/discharge summaries for hospital/outpatient admissions while the subject is on-study and autopsy reports for deaths occurring during the study. As part of the required content of informed consent, the subject will be informed that his medical record may be reviewed. Should access to the medical record require a separate waiver or authorization, it is the PI's responsibility to obtain such permission from the patient in writing before the subject is entered into the study.

9. Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of EC/IRB members and their affiliate to the sponsor.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. See Attachment D for a copy of the Subject Informed Consent Form. This consent form will be submitted with the protocol for review and approval by the EC/IRB for the study. The formal consent of a subject,

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using the EC/IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

10. Financial Considerations

See attached clinical trial and correlative study budget spreadsheets.

11. Publication Plan

Our abstract with preliminary results will be submitted to the American Society of Clinical Oncology (ASCO) Annual Meeting and the ASCO Genitourinary Cancers Symposium in early 2019. The final manuscript will be completed by early 2020, and be targeted for the Journal of Clinical Oncology or Clinical Cancer Research though the ultimate impact of the publication and target journal will depend on the results.

12. References

1. de Bono, J.S., et al., *Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial.* Lancet, 2010. **376**(9747): p. 1147-54.
2. de Bono, J.S., et al., *Abiraterone and increased survival in metastatic prostate cancer.* N Engl J Med, 2011. **364**(21): p. 1995-2005.
3. Ryan, C.J., et al., *Abiraterone in metastatic prostate cancer without previous chemotherapy.* N Engl J Med, 2013. **368**(2): p. 138-48.
4. Scher, H.I., et al., *Increased survival with enzalutamide in prostate cancer after chemotherapy.* N Engl J Med, 2012. **367**(13): p. 1187-97.
5. Kantoff, P.W., et al., *Sipuleucel-T immunotherapy for castration-resistant prostate cancer.* N Engl J Med, 2010. **363**(5): p. 411-22.
6. Parker, C., et al., *Alpha emitter radium-223 and survival in metastatic prostate cancer.* N Engl J Med, 2013. **369**(3): p. 213-23.
7. Beer, T.M., et al., *Enzalutamide in Metastatic Prostate Cancer before Chemotherapy.* N Engl J Med, 2014.
8. Cheng, L., et al., *Allelic imbalance in the clonal evolution of prostate carcinoma.* Cancer, 1999. **85**(9): p. 2017-22.
9. Mitsiades, N., et al., *Distinct patterns of dysregulated expression of enzymes involved in androgen synthesis and metabolism in metastatic prostate cancer tumors.* Cancer Res, 2012. **72**(23): p. 6142-52.
10. Kantarjian, H.M., et al., *Results of treatment with hyper-CVAD, a dose-intensive regimen, in adult acute lymphocytic leukemia.* J Clin Oncol, 2000. **18**(3): p. 547-61.
11. Thomas, D.A., et al., *Outcome with the hyper-CVAD regimens in lymphoblastic lymphoma.* Blood, 2004. **104**(6): p. 1624-30.
12. Horning, S.J., et al., *Assessment of the stanford V regimen and consolidative radiotherapy for bulky and advanced Hodgkin's disease: Eastern Cooperative Oncology Group pilot study E1492.* J Clin Oncol, 2000. **18**(5): p. 972-80.
13. Cheng, L., et al., *Evidence of independent origin of multiple tumors from patients with prostate cancer.* J Natl Cancer Inst, 1998. **90**(3): p. 233-7.
14. Macintosh, C.A., et al., *Precise microdissection of human prostate cancers reveals genotypic heterogeneity.* Cancer Res, 1998. **58**(1): p. 23-8.
15. Liu, W., et al., *Copy number analysis indicates monoclonal origin of lethal metastatic prostate cancer.* Nat Med, 2009. **15**(5): p. 559-65.

16. Madan, R.A., et al., *Overcoming chemotherapy resistance in prostate cancer.* Clin Cancer Res, 2011. **17**(12): p. 3892-902.
17. Brown, E.M. and D. Nathwani, *Antibiotic cycling or rotation: a systematic review of the evidence of efficacy.* J Antimicrob Chemother, 2005. **55**(1): p. 6-9.
18. Schellhammer, P.F., et al., *Lower baseline prostate-specific antigen is associated with a greater overall survival benefit from sipuleucel-T in the Immunotherapy for Prostate Adenocarcinoma Treatment (IMPACT) trial.* Urology, 2013. **81**(6): p. 1297-302.
19. Beer, T.M., et al., *Enzalutamide in men with chemotherapy-naive metastatic prostate cancer (mCRPC): Results of phase III PREVAIL study.* J Clin Oncol, 2014. **32**(suppl 4; abstr LBA1^).
20. Loriot, Y., et al., *Antitumour activity of abiraterone acetate against metastatic castration-resistant prostate cancer progressing after docetaxel and enzalutamide (MDV3100).* Ann Oncol, 2013. **24**(7): p. 1807-12.
21. Noonan, K.L., et al., *Clinical activity of abiraterone acetate in patients with metastatic castration-resistant prostate cancer progressing after enzalutamide.* Ann Oncol, 2013. **24**(7): p. 1802-7.
22. Schrader, A.J., et al., *Enzalutamide in castration-resistant prostate cancer patients progressing after docetaxel and abiraterone.* Eur Urol, 2014. **65**(1): p. 30-6.
23. Cheng, H.H., et al., *Activity of enzalutamide in men with metastatic castration-resistant prostate cancer is affected by prior treatment with abiraterone and/or docetaxel.* Prostate Cancer Prostatic Dis, 2015. **18**(2): p. 122-7.
24. Schmid, S.C., et al., *Enzalutamide after docetaxel and abiraterone therapy in metastatic castration-resistant prostate cancer.* Adv Ther, 2014. **31**(2): p. 234-41.
25. Arora, V.K., et al., *Glucocorticoid receptor confers resistance to antiandrogens by bypassing androgen receptor blockade.* Cell, 2013. **155**(6): p. 1309-22.
26. van Soest, R.J., et al., *Cross-resistance between taxanes and new hormonal agents abiraterone and enzalutamide may affect drug sequence choices in metastatic castration-resistant prostate cancer.* Eur J Cancer, 2013. **49**(18): p. 3821-30.
27. Mezynski, J., et al., *Antitumour activity of docetaxel following treatment with the CYP17A1 inhibitor abiraterone: clinical evidence for cross-resistance?* Ann Oncol, 2012. **23**(11): p. 2943-7.
28. Schweizer, M.T., et al., *The Influence of Prior Abiraterone Treatment on the Clinical Activity of Docetaxel in Men with Metastatic Castration-resistant Prostate Cancer.* Eur Urol, 2014.
29. van Soest, R.J., et al., *Targeting the Androgen Receptor Confers In Vivo Cross-resistance Between Enzalutamide and Docetaxel, But Not Cabazitaxel, in Castration-resistant Prostate Cancer.* Eur Urol, 2014.
30. Azarenko, O., et al., *Antiproliferative mechanism of action of the novel taxane cabazitaxel as compared with the parent compound docetaxel in MCF7 breast cancer cells.* Mol Cancer Ther, 2014. **13**(8): p. 2092-103.
31. Oh, W.K., M.H. Tay, and J. Huang, *Is there a role for platinum chemotherapy in the treatment of patients with hormone-refractory prostate cancer?* Cancer, 2007. **109**(3): p. 477-86.
32. Nakabayashi, M., et al., *Response to docetaxel/carboplatin-based chemotherapy as first- and second-line therapy in patients with metastatic hormone-refractory prostate cancer.* BJU Int, 2008. **101**(3): p. 308-12.
33. Ross, R.W., et al., *A phase 2 study of carboplatin plus docetaxel in men with metastatic hormone-refractory prostate cancer who are refractory to docetaxel.* Cancer, 2008. **112**(3): p. 521-6.
34. Regan, M.M., et al., *Efficacy of carboplatin-taxane combinations in the management of castration-resistant prostate cancer: a pooled analysis of seven prospective clinical trials.* Ann Oncol, 2010. **21**(2): p. 312-8.

35. Corn, P.G., et al., *A randomized phase I/II study to examine the contribution of carboplatin to cabazitaxel for the treatment of men with metastatic castration-resistant prostate cancer (mCRPC) with and without anaplastic features.* J Clin Oncol, 2014. **32**(suppl 4; abstr 148).
36. Corn, P.G., et al., *A multi-institutional randomized phase II study (NCT01505868) of cabazitaxel (CAB) plus or minus carboplatin (CARB) in men with metastatic castration-resistant prostate cancer (mCRPC).* J Clin Oncol, 2015. **33**(suppl; abstr 5010).
37. Ross, R.W., et al., *A whole-blood RNA transcript-based prognostic model in men with castration-resistant prostate cancer: a prospective study.* Lancet Oncol, 2012. **13**(11): p. 1105-13.
38. Hu, R., et al., *Ligand-independent androgen receptor variants derived from splicing of cryptic exons signify hormone-refractory prostate cancer.* Cancer Res, 2009. **69**(1): p. 16-22.
39. Antonarakis, E.S., et al., *AR-V7 and resistance to enzalutamide and abiraterone in prostate cancer.* N Engl J Med, 2014. **371**(11): p. 1028-38.
40. Scher, H.I., et al., *Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group.* J Clin Oncol, 2008. **26**(7): p. 1148-59.
41. Eisenberger, M., et al., *Phase III Study Comparing a Reduced Dose of Cabazitaxel (20 mg/m2) and the Currently Approved Dose (25 mg/m2) in Postdocetaxel Patients With Metastatic Castration-Resistant Prostate Cancer-PROSELICA.* J Clin Oncol, 2017. **35**(28): p. 3198-3206.
42. Rowinsky, E.K., et al., *Sequences of taxol and cisplatin: a phase I and pharmacologic study.* J Clin Oncol, 1991. **9**(9): p. 1692-703.
43. Cessna, J.T. and B.E. Zimmerman, *Standardization of radium-223 by liquid scintillation counting.* Appl Radiat Isot, 2010. **68**(7-8): p. 1523-8.
44. Zimmerman, B., et al., *Revision of the NIST Standard for 223Ra: New Measurements and Review of 2008 Data.* J Res Natl Inst Stand Technol, 2015. **120**: p. 37-57.
45. Beer, T.M., et al., *Intermittent chemotherapy in patients with metastatic androgen-independent prostate cancer: results from ASCENT, a double-blinded, randomized comparison of high-dose calcitriol plus docetaxel with placebo plus docetaxel.* Cancer, 2008. **112**(2): p. 326-30.
46. Cantor, A., *SAS survival analysis techniques for medical research*. 2nd edition. ed. 2003, Cary, North Carolina,: SAS Institute, Inc. viii, 230p.
47. Lawless, J.F., *Statistical models and methods for lifetime data*. 2nd ed. Wiley series in probability and statistics. 2003, Hoboken, N.J.: Wiley-Interscience. xx, 630 p.
48. Wolff, J.M., et al., *Efficacy of skeletal alkaline phosphatase and prostate-specific antigen in the diagnosis of bone metastasis in cancer of the prostate.* Urol Int, 1998. **61**(1): p. 12-6.
49. Sonpavde, G., et al., *Serum alkaline phosphatase changes predict survival independent of PSA changes in men with castration-resistant prostate cancer and bone metastasis receiving chemotherapy.* Urol Oncol, 2012. **30**(5): p. 607-13.

The radium-223 values in this protocol have been revised as per the United States (US) National Institute of Standards and Technology (NIST) standardization update (agreed on 17 MAR 2015).