CASCARA: Castration Sensitive Carboplatin, Cabazitaxel and Abiraterone

A Phase II Study of Carboplatin, Cabazitaxel and Abiraterone in High Volume Metastatic Castration Sensitive Prostate Cancer

Prostate Cancer Clinical Trials Consortium, LLC (PCCTC)

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APPROVAL OF PROTOCOL

Title: *CASCARA: Castration Sensitive Carboplatin, Cabazitaxel and Abiraterone (A Phase 2 Study of Carboplatin, Cabazitaxel and Abiraterone in High Volume Metastatic Castration Sensitive Prostate Cancer)*

Sponsor/Sponsor-Investigator Signature: _____

Print: _____

Date: _____

PCCTC Signature: _____

Print: _____

Date: _____

PROTOCOL AGREEMENT

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision and providing University of Minnesota with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted Good Clinical Practice (GCP) principles, as adopted by applicable laws and regulations, and to abide by the terms of this protocol.

Principal Investigator Signature: _____

Principal Investigator Print: _____

Date: _____

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1. INTRODUCTION

1.1 Overall Study Rationale

More than 900,000 new cases of prostate cancer are diagnosed worldwide each year, and advanced disease remains a major treatment challenge.[1,2] This is a genomically and clinically heterogeneous cancer, with some patients presenting with metastatic disease and others being cured after local surgery or radiation. With advances in next-generation sequencing, the genomic landscape of prostate cancer is being defined more clearly. In a landmark study in 2015, Robinson et al. conducted whole exome and transcriptome sequencing of 150 biopsy specimens from metastatic castration-resistant prostate cancer (mCRPC) tumors.[3] *One exciting finding of this study was that 23% of these biopsy specimens had defects in the DNA repair pathway (BRCA1/2, ATM, etc). Following this study, another found that 12% of metastatic prostate cancers have germline DNA repair mutation.*

These findings dramatically expand the subset of prostate cancer patients who may benefit from DNA damaging therapy including traditional chemotherapies (carboplatin, adriamycin) and more novel agents, including PARP (Poly ADP Ribose polymerase) inhibitors. PARP inhibitors are oral drugs that inhibit PARP enzymes that are involved in the repair of DNA single-strand breaks through base-excision repair.[4,5]

In conjunction with these recent genomic findings, the results of another landmark trial, TOPARP, have resulted in breakthrough therapy designation of olaparib (a PARP inhibitor) for the treatment of BRCA1/2- or ATM-mutated mCRPC.[6] In this phase II clinical trial, among patients with mCRPC and DNA repair mutations, 88% had a response to olaparib. Surprisingly however, there are no studies evaluating a much cheaper and older chemotherapy drug with efficacy in patients with BRCA or DNA repair mutations: carboplatin.

Platinum salts (carboplatin and cisplatin) have both been used for decades to treat patients with ovarian cancer, where BRCA1 and BRCA2 mutations are common. The Triple-Negative Breast Cancer Trial (TNT trial) was a proof-of-concept phase III trial that showed that patients with advanced, triple-negative breast cancer with BRCA1/2 mutations had a greater response and progression-free survival to carboplatin than with docetaxel.[7]

While abiraterone and docetaxel are now being used for high volume metastatic castration sensitive prostate cancer based on impressive results from the LATITUDE and CHAARTED studies, there remains a significant opportunity to improve outcome in patients with aggressive castration sensitive disease. For instance, 20% of patients on LATITUDE progressed on abiraterone in 1 year.[8] Similarly, in CHAARTED, 20% of patients had clinical progression at 1 year.[9]

The study hypothesizes that the combination of cabazitaxel and carboplatin will increase response rates and the percentage of patients without clinical or radiographic progression at 1 year. Secondary outcomes will include progression-free survival, time to PSA nadir and PSA progression in addition to evaluating the safety and toxicity of this regimen. While this trial will include *all* patients with high volume, metastatic castration sensitive disease, the study will perform somatic genetic sequencing and molecular subtyping with PAM50 in archival tumor biopsies in patients after enrollment to understand if there is a differential response to carboplatin/cabazitaxel in patients with luminal or basal subtypes.

In prostate cancer, prior trials evaluating response in mCRPC have shown that carboplatin and cabazitaxel has efficacy even in cohort that is not specifically enriched for mutations in DNA repair. For instance, in a phase II trial by Corn et al evaluating the addition of carboplatin to cabazitaxel, 149 were randomized to receive cabazitaxel or cabazitaxel plus carboplatin. Progression-free survival (the primary endpoint) was increased with the combination (5.7 versus 4.0 months). Partial responses in those with measurable disease were also more frequent with the combination (17 of 33 [52 percent]) versus 5 of 35 [14 percent]).[10]

Similarly, Pomerantz et al recently published a retrospective analysis of patients treated at Dana Farber showing that patients with germline BRCA2 mutations have an enhanced response to carboplatin and docetaxel.[11] In this study, a subgroup of 141 men received at least 2 doses of carboplatin and docetaxel for castration-resistant disease (94% were also taxane refractory). These patients were categorized according to the absence or presence of pathogenic germline mutations in BRCA2 based on DNA sequencing from whole blood. 133 of these men were taxane resistant by the time they received docetaxel and carboplatin. They observed that the presence of pathogenic germline BRCA2 variants was associated with increased responsiveness to platinum chemotherapy on the basis of the PSA decline at 12 weeks for each patient from baseline to 12 weeks of follow-up. Notably, among the 8 BRCA2 carriers, 6 (75%) had a PSA declines >50% whereas 23 of the 133 men (17%) who lacked a deleterious BRCA2 germline variant had PSA declines >50% (absolute difference, 58%; 95% CI, 27%-88%; P < .001). Finally, Aparicio et al also showed that the addition of carboplatin to cabazitaxel benefits men with mCRPC and aggressive variant prostate cancer (AVPC); median PFS in the overall population was 7.4 months in the cabazitaxel + carboplatin group vs 4.59 months in the cabazitaxel-only group (P = .004).[12]

Given this data evaluating combination treatment with carboplatin and cabazitaxel in mCRPC showing both improved efficacy and tolerable safety when compared to cabazitaxel alone, this study will evaluate dose levels of carboplatin AUC 4 with cabazitaxel 20 mg/m^2 which was reduced slightly from the recommended phase II dose of 25mg/m^2 found on the phase I portion of the trial by Corn et al.

As part of this study, the contribution of circulating tumor cells (CTCs) and cell-free DNA (cfDNA) in understanding PARP inhibitor resistance and reversion mutations will be explored. Recently, Quigley et al. demonstrated that cfDNA can detect BRCA2 reversion mutations in prostate cancer patients that originally responded to and then became resistant to olaparib and talazoparib. These same mutations also confer resistance to platinum chemotherapy and will be explored in this study.[13]

Finally, Feng et al have shown that similar to breast cancer, prostate cancer can be segregated into molecular subtypes[14]. They recently demonstrated that PAM50 segregates prostate cancer into three reproducible subtypes in both retrospective cohorts and on prospective validation: luminal A (33.3%-34.3%), luminal B (28.5%- 32.6%), and basal (34.1%-37.1%). Luminal B prostate cancers exhibited the worst clinical prognoses, followed by basal and luminal A subtypes (10-year biochemical recurrence-free survival: 29/39/41%; distant metastasis-free survival: 53/73/73%; prostate cancer-specific survival: 78/86/89%; overall survival: 69/80/82% respectively) on both univariable and multivariable analyses accounting for standard clinicopathologic prognostic factors. While both luminal-like subtypes were associated with increased AR expression and signaling, only luminal B prostate cancers were significantly associated with post-operative response to androgen deprivation therapy (ADT) in a subset analysis matching patients based on clinicopathologic variables (interaction p=0.006, luminal B 10-year metastasis: 33% (treated) vs.

55% (untreated), non-luminal B: 37% (treated) vs. 21% (untreated)). Thus in this study, primary prostate tissue as well as archival or fresh metastatic biopsies will be classified by molecular subtype to help understand if there are disparate responses between subtype and sensitivity to carboplatin and cabazitaxel.[14] Of the 61 patients, ~40% are predicted to have the basal subtype (24 patients).

As an exploratory endpoint, we will investigate whether there is an increased response to carboplatin/cabazitaxel in patients with basal vs. luminal A/B subtypes.

1.2 Rationale

Although abiraterone and docetaxel are now standard of care options for patients with castration sensitive metastatic prostate cancer there remains a significant opportunity to improve outcome in patients with aggressive castration sensitive disease. For instance, 20% of patients on LATITUDE progressed on abiraterone in 1 year.[8] Similarly, in CHAARTED, 20% of patients had clinical progression at 1 year.[9]

Further, we have come to understand that DNA repair mutations are enriched in metastatic prostate cancer, as compared to primary prostate cancer, and can often portend resistance to docetaxel.[3,7,15] As such, we hypothesize that the combination of cabazitaxel and carboplatin with maintenance with abiraterone and ADT will increase initial response rates in patients with high volume castration sensitive disease. Further, we hypothesize that identification of patients with distinct biological subtypes can serve to identify patients in whom this approach may lead to enhanced positive outcomes. In particular we seek to evaluate the outcome of patients with DNA repair defects and basal/luminal subtyping who are treated with this regimen.

The primary objective of this study will be to measure the percent of subjects with PSA and/or radiographic progression by 1 year after study treatment initiation and compare this to what was seen in LATITUDE where abiraterone and prednisone was studied in men with metastatic castration sensitive prostate cancer.[8] The study hypothesizes that the combination of cabazitaxel and carboplatin (with maintenance abiraterone and ADT) will increase response rates from the 80% of patients remaining on trial without PSA or radiographic progression to 92%. Secondary outcomes will include evaluating the progression-free survival, time to PSA nadir and PSA progression, as well as safety and toxicity of the combination of carboplatin and cabazitaxel with ADT followed by abiraterone. While this trial will include *all* patients with high volume, metastatic castration sensitive disease, somatic genetic sequencing data will be collected and molecular subtyping of both blood and tissue will be done in patients upon enrollment to understand if there is a differential response to carboplatin/cabazitaxel in patients with homologous repair defects (HRD) or luminal or basal subtypes.

Implications: If positive, this combination could proceed to larger studies to evaluate this combination in metastatic castration sensitive prostate cancer. Further, this study will enrich understanding of the percent of patients that have DNA repair mutations in the metastatic castration sensitive space (via genetic testing) and will evaluate if patients with DNA repair mutations or basal subtyping are more sensitive to dual blockade with taxane and platinum.

2. OBJECTIVES

2.1 Primary Objective

To determine the proportion of patients who have PSA or radiographic progression as determined by RECIST 1.1 or PCWG3 criteria by 1-year after initiation of anti-tumor treatment that consists of ADT, cabazitaxel, carboplatin and abiraterone.

2.2 Secondary Objectives

- To determine the progression-free survival in persons with high volume metastatic castration sensitive prostate cancer treated with cabazitaxel and carboplatin in combination with ADT
- To determine the time to PSA nadir in this population
- To determine the time to PSA progression
- To determine the safety and tolerability of combination treatment of cabazitaxel and carboplatin in persons with metastatic prostate cancer
- Incidence of homologous repair defects (HRD) in this population
- To compare PSA complete response rate (PSA <0.2 ng/mL) at 1 year in patients with and without mutations in DNA repair genes as well as various molecular subtypes (luminal/basal)

2.3 Exploratory Objectives

- To obtain CTCs to evaluate for reversion mutations, conformational changes, and validate HRD phenotype with Epic Sciences.
- To analyze and track changes in cfDNA, particularly for the emergence of alterations that would confer resistance.
- To apply the PAM50 classifier to subtype archival primary or metastatic prostate cancer samples into basal or luminal A vs. B subtypes to gauge response to carboplatin and cabazitaxel.

3. STUDY DESIGN

3.1 General Study Design

This is a phase II two-stage clinical trial in patients with metastatic castration sensitive prostate cancer. The objective of the study is to determine the efficacy and further define the safety of the treatment combination. This study will evaluate dose levels of carboplatin AUC 4 with cabazitaxel 20 mg/m^2.

All participants will continue on their prescribed androgen deprivation therapy (ADT) throughout the study period, unless it is no longer of benefit. Refer to Sections 5.4 and 5.6 for duration of therapy.

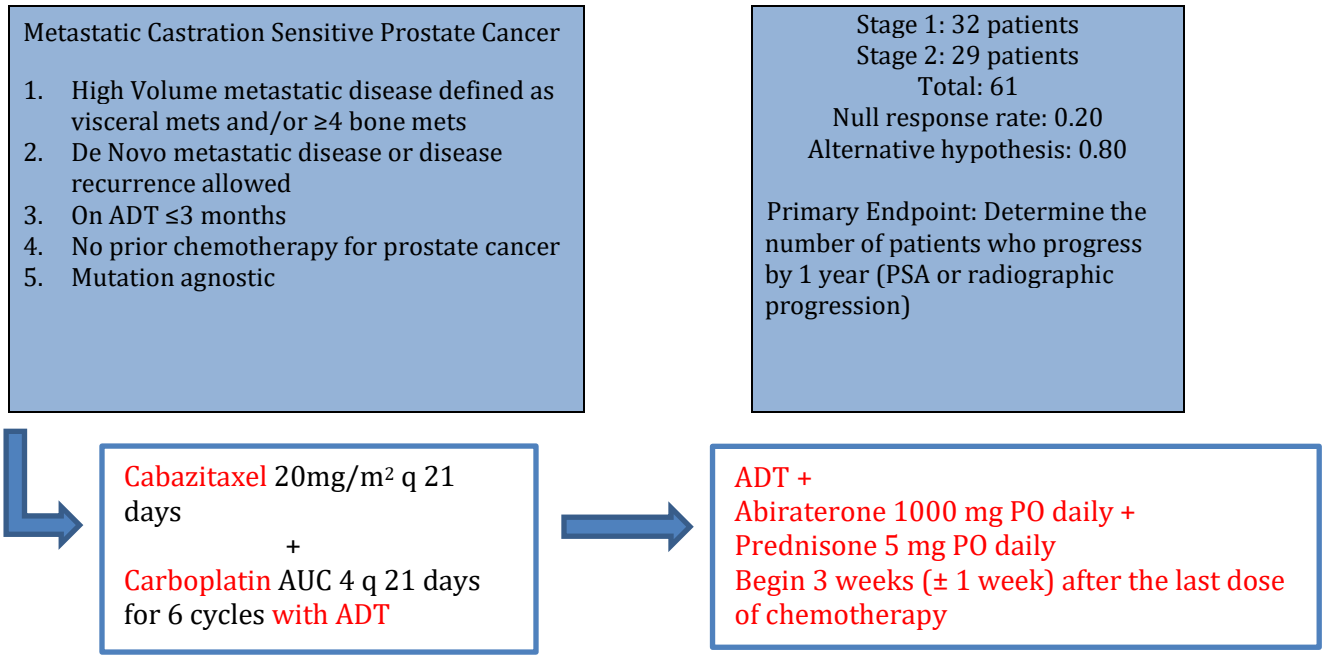
Patients will be treated with carboplatin and cabazitaxel for 6 cycles unless an event described in Section 5.4 occurs earlier. Patients are eligible for abiraterone therapy in the absence of disease progression even if the full 6 cycles of chemotherapy were not given. Prior to the start of standard of care abiraterone, an End of Chemotherapy/Start of Abiraterone visit should be done 3 weeks (± 1 week) after the last dose of chemotherapy. At this visit, a post-chemotherapy/pre-abiraterone PSA level should be documented.

Abiraterone with prednisone continues until disease progression or other event described in Section 5.6. After 1 year post Cycle 1 Day 1 of chemotherapy, abiraterone may continue at the discretion of the treating physician.

Disease assessments (PSA, CT of chest/abdomen/pelvis, and bone scan) should be performed per standard of care every 12 weeks ± 5 weeks in the absence of disease progression. Study visits for all participants will occur at 1 Year and 2 Years from Cycle 1 Day 1 of chemotherapy, unless a participant has progression or a change in therapy prior to these visits.

The primary objective is to determine the percent of subjects that have PSA or radiographic progression by 1 year from Cycle 1 Day 1 of chemotherapy. Secondary objectives will include determining the progression-free survival, time to PSA nadir and time to PSA progression of carboplatin and cabazitaxel in combination with ADT.

Figure 1. CASCARA phase II study schema



3.2 Inclusion Criteria

To be included in this study, patients should complete all screening procedures and meet all of the following criteria:

3.2.1 Willing and able to provide, or have a legally authorized representative provide, written informed consent and HIPAA authorization for the release of personal health information. A signed informed consent must be obtained before screening procedures are performed.

NOTE: HIPAA authorization may be either included in the informed consent or obtained separately.

3.2.2 Histologically confirmed prostate cancer.

3.2.3 High volume metastatic disease defined as visceral metastases and/or ≥4 bone metastases on standard CT or bone scan imaging. Patients with high volume disease on novel imaging scans including Axumin PET or PSMA PET are only eligible if they meet criteria on standard CT and bone scan.

3.2.4 ADT for ≤3 months by Day 1 of study chemotherapy; Prior episodes of ADT are allowed (i.e. ADT used previously in courses of radiation). *Note: Standard of care ADT continues for the duration of this study.*

3.2.5 Testosterone <50 ng/dL for patients who have initiated ADT >1 month prior to study treatment start. Patients must continue primary ADT with an LHRH analogue if they have not undergone orchiectomy. Patients who have not yet started ADT at the time of enrollment may initiate ADT via LHRH agonist or antagonist therapy during the screening period and will not be required to document a castrate level of testosterone prior to initiating chemotherapy.

3.2.6 ECOG Performance Status 0 or 1 (see Appendix A)

3.2.7 Patient has adequate bone marrow and organ function as defined by the following laboratory values:

- Absolute neutrophil count ≥ 1.5×10^9/L.
- Platelets ≥ 100×10^9/L.
- Hemoglobin ≥ 9 g/dl.
- Serum creatinine ≤ 1.5mg/dL or estimated creatinine clearance ≥ 50 ml/min
- In the absence of liver metastases, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) <2.5 x ULN. If the patient has liver metastases, ALT and AST <5 x ULN
- Total bilirubin < ULN; or total bilirubin ≤3.0 x ULN or direct bilirubin ≤1.5 x ULN in patients with well-documented Gilbert's Syndrome.

3.2.8 Sexually active persons must use a condom during intercourse while taking study drugs and for 30 days after stopping treatment and should not father a child in this period. A condom is required to be used also by vasectomized persons in order to prevent delivery of the drug via seminal fluid. Fertile participants must use a condom with spermicide (double barrier method).

3.2.9 Age ≥ 18 years

3.3 Exclusion Criteria

3.3.1 Prior exposure to any chemotherapy, PARPi, or immunotherapy for prostate cancer.

3.3.2 Pure Small Cell Carcinoma

3.3.3 Prior abiraterone, apalutamide, darolutamide, or enzalutamide, unless therapy was for < 4 weeks

3.3.4 Radiation therapy (including palliative radiotherapy to a metastatic lesion) within 14 days or major surgery (e.g., open abdominal, pelvic, thoracic, orthopedic or neurosurgery) within 28 days of the date of the first dose.

3.3.5 Other systemic therapies for prostate cancer within 28 days or 5 half-lives, whichever is shorter, prior to day 1 of chemotherapy (with the exception of anti-androgens like bicalutamide).

3.3.6 PSA <2.0 ng/mL at diagnosis.

3.3.7 If present, peripheral neuropathy must be ≤ Grade 1

3.3.8 Patients with an active second malignancy that could, in the investigator's opinion, potentially interfere with the patient's ability to participate and/or complete this trial.

3.3.9 Patients with central nervous system (CNS) involvement unless they meet ALL of the following criteria:

- At least 4 weeks from prior therapy completion (including radiation and/or surgery) prior to starting the study treatment
- Clinically stable CNS tumor at the time of screening.
- Baseline screening for CNS metastases is not required unless presence of signs and/or symptoms of involvement

3.3.10 Known history of severe hypersensitivity to drugs formulated with polysorbate 80.

3.3.11 Patients with severe psychiatric illness/social situations that would limit compliance with study requirements in the judgment of treating investigator.

3.3.12 Patient has a history of non-compliance to medical regimen or inability to grant consent.

4. ENROLLMENT PLAN

4.1 Enrollment Plan

4.1.1 Anticipated Enrollment

This study is anticipated to enroll 61 patients.

4.1.2 Subject Recruitment

Potential research subjects will be identified by a member of the subject's treatment team, the site investigator, or research team at participating centers from Medical Oncology, Radiation Oncology and Urology offices. Investigators will screen medical records for suitable research study subjects and discuss the study and their potential for enrolling in the research study.

4.2 Eligibility Confirmation

Confirmation of eligibility will be completed centrally by the PCCTC prior to treatment start. A record of patients who fail to meet eligibility criteria (i.e., screen failures) will be maintained. A complete, signed informed consent and HIPAA authorization are required as part of eligibility confirmation. To complete the eligibility confirmation process, the study site must email the signed completed study-specific eligibility checklist, all source documents verifying eligibility, any supporting documents, and the signed informed consent to the PCCTC at pcctc@mskcc.org. Once the enrollment packet is received and reviewed at the PCCTC and if eligibility is confirmed, assignment to treatment can occur and the patient will be enrolled in Medidata Rave®, the Electronic Data Capture (EDC) system for this study. Sponsor Investigator will be knowledgeable of all registrations. Participating sites will register patients locally per their Institutional guidelines in addition to central registration with the PCCTC. All patients must sign an IRB-approved informed consent prior to starting any protocol-specific procedures; however, evaluations performed as part of routine care prior to informed consent can be used for screening and eligibility confirmation.

5. EVALUATIONS AND TREATMENTS

5.1 Study Procedures

Continue treatment until disease progression, unacceptable toxicity, any criteria in Section 5.4 (Duration of Chemotherapy) or Section 5.6 (Duration of Abiraterone), or for a maximum of 1 year from Cycle 1 Day 1 of chemotherapy. After 1 year, abiraterone may continue at the discretion of the treating physician.

All participants continue on their prescribed androgen deprivation therapy (ADT) throughout the study period, unless it is no longer of benefit. Refer to Sections 5.4 and 5.6 for duration of therapy.

Prior to the start of standard of care abiraterone, a post-chemotherapy/pre-abiraterone PSA should be documented along with ensuring that there are no ongoing side effects related to chemotherapy. This visit should occur three weeks (± 1 week) after the last dose of chemotherapy as the End of Chemotherapy/Start of Abiraterone Visit.

Visits every 12 weeks (± 5 weeks) from Cycle 1 Day 1 of chemotherapy should occur as standard of care including PSA measurement and disease status assessment (CT scan of chest/abdomen/pelvis and a bone scan).

If disease progression or change in therapy status occurs prior to the 1 Year or 2 Year visits, the patient is followed for survival only, up until 2 years from Cycle 1 Day 1 of chemotherapy.

The 1 Year Visit occurs at 1 year (± 2 weeks) from Cycle 1 Day 1 of chemotherapy for all participants, unless they have progressed or have had a change in therapy status. Disease status at 1 year fulfills the primary endpoint. Patients may continue to receive standard of care abiraterone independent of this study at the discretion of the treating physician.

The 2 Year/End of Study Visit occurs at 2 years from Cycle 1 Day 1 of chemotherapy for all participants who have not progressed or had a change in therapy. This is the final study visit/data collection time point. If a subject has progressed or had a change in therapy, only disease and survival status to be documented by chart review or other means.

Virtual visits are permitted at all time points (including screening) in lieu of in-clinic visits for relevant activities including physical exam, medical history, assessment of symptoms and side effects.

The following assessments and procedures will occur during the study. A schedule of assessments is provided in Appendix B.

5.1.1 Informed consent and research/HIPAA authorization

Before initiating any protocol-specific screening activities, the scope of the study should be explained to each patient. Patients should be consented in accordance with Section 11.6 Written Informed Consent, including completion of a research/HIPAA authorization.

5.1.2 Inclusion/exclusion criteria

During the screening period, subject eligibility will be determined according to the inclusion and exclusion criteria (Section 3.2 Inclusion Criteria and Section 3.3 Exclusion Criteria).

5.1.3 Demographics and medical history

Demographics and medical history collected will include:

- Date of birth (or age if date of birth is not allowed to be collected by local regulations)
- Significant past and ongoing conditions
- Details and dates of the primary therapy (e.g., pathologic stage, type of therapy)
- Details of prior prostate cancer biopsies and surgeries
- Details and dates of prior hormonal and non-hormonal therapies for prostate cancer
-

5.1.4 Pre-treatment Evaluation

Clinical (within 14 days prior to start of study treatment)

- Complete history and physical examination, including vitals, height, weight, and baseline evaluation of symptoms, pain and medications
- Performance Status (ECOG scale)
- EKG

Laboratory (within 14 days prior to start of study treatment)

- Complete blood count including differential and platelet count
- Chemistry panel: Alkaline phosphatase, albumin, total bilirubin, BUN, calcium, creatinine, glucose, LDH, AST, ALT, sodium, potassium, bicarbonate, chloride, magnesium, phosphorus
- PT/INR + PTT
- PSA
- Testosterone level (may be obtained within 28 days prior to start of study treatment)
- CTCs and cfDNA

Radiographic and diagnostic studies (within 28 days prior to start of study treatment)

- Radionuclide bone scan (Technetium or NaF PET/CT acceptable)
- CT scan of the chest, abdomen and pelvis (with IV contrast if kidney function is adequate. NaF PET/CT or MR abdomen/pelvis is acceptable).
- Subjects who have initiated ADT prior to study enrollment do not require 28-day window bone or CT scan. Available pre-treatment scans within 90-days of starting ADT can be used for screening.

Germline and Somatic Sequencing

Data will be collected for subjects who have reports of germline and/or somatic sequencing results. This sequencing will be obtained as part of standard care using any CLIA-certified next generation sequencing (NGS) assay, either prior to or upon study entry. If there is remaining tissue available from the standard-of-care biopsy, archival tissue will be collected to allow for future analysis on a centralized platform.

5.1.5 Evaluations while receiving chemotherapy

Refer to Section 5.4 for duration of chemotherapy.

- **Every 3 weeks before each cycle of chemotherapy, and as part of standard of care at 3 weeks (± 1 week) after the last dose of chemotherapy/prior to start of abiraterone:** disease specific physical examination, interim history pertaining to any change from baseline, current medications, and treatment-related toxicities. Laboratory studies should include CBC with differential and serum chemistries (sodium, potassium, chloride, bicarbonate, glucose, magnesium, calcium, albumin, BUN, creatinine, LDH, AST, ALT, total alkaline phosphatase, total bilirubin, phosphorus), testosterone, and PSA (labs from up to 3 days prior may be used prior to cycles).
- **At each visit and when reported by the patient**, concomitant treatments and medications must be recorded.
- **Assess patient for toxicity (observed or reported by patient).** During the 1st 3 cycles only, confirm no early stopping rule event (hospitalization for neutropenic sepsis or Grade 3 or 4 diarrhea) as defined in Section 10.5 has occurred.
- **Imaging (CT chest/abdomen/pelvis and bone scan)** is done every 12 weeks from Cycle 1 Day 1 of chemotherapy or as clinically indicated (PSA is done every 3 weeks during chemotherapy).

5.1.6 Evaluations While Receiving Abiraterone

Every 12 weeks (± 5 weeks) from Cycle 1 Day 1 of chemotherapy the following disease assessment should be done per standard of care:

- CT scan of the chest/abdomen/pelvis (with IV contrast if kidney function is adequate. NaF PET/CT or MR abdomen/pelvis is acceptable)
- Radionuclide bone scan (Technetium or NaF PET/CT acceptable)
- PSA level

Patients on abiraterone should be evaluated per standard of care. While there are no protocol-defined requirements during standard of care abiraterone treatment, it is recommended that patients be followed with PSA, routine lab assessments, and a clinical assessment with review of symptoms and side effects every 12 weeks.

Recommended laboratory assessments include CBC with differential and serum chemistries (sodium, potassium, chloride, bicarbonate, glucose, magnesium, calcium, albumin, BUN, creatinine, LDH, AST, ALT, total alkaline phosphatase, total bilirubin, phosphorus), and PSA.

More frequent assessments may be required based on the dose modification plan in Section 5.5.2 if toxicity occurs.

Refer to Section 5.6 for the duration of abiraterone therapy.

5.1.7 Correlative Studies

5.1.7.1 Circulating Tumor Cells

The Epic Sciences CTC Detection and Characterization platform will be used for the analysis of CTCs in this study. The platform has the ability to enumerate CTCs and evaluate protein biomarker expression and subcellular localization within individual CTCs. Research kits will be provided for the collection of 10 mL of whole blood at baseline (Cycle 1 Day 1), Cycle 2 Day 1, and at the Time of Progression/Change in Therapy visit or 2 Year visit (End of Study), whichever occurs first. Specimens will be shipped to Epic Sciences for processing and analysis.

5.1.7.2 Circulating tumor cfDNA

Blood for cfDNA will be collected at baseline (Cycle 1 Day 1), Cycle 2 Day 1, and at the Time of Progression/Change in Therapy visit or 2 Year visit (End of Study), whichever occurs first. The samples will be stored for future analysis using a CLIA-certified NGS assay.

5.1.7.3 Germline and somatic sequencing

Germline and somatic sequencing using a multigene cancer risk panel can be done prior to or upon study entry as part of standard care. Genetic sequencing of either archival or fresh tissue from the primary prostate or metastatic site can be done using any CLIA-certified lab or cancer risk panel including but not limited to FoundationOne, Myriad, Color Genomics, Invitae, Ambry, UCSF500, etc. Data will be collected for subjects who have reports of germline and/or somatic sequencing results from NGS testing.

5.1.7.4 Luminal/basal subtyping

If there is remaining tissue available from a prior standard-of-care biopsy, archival tissue will be collected to allow for future analysis using the PAM50 assay. The PAM50 test is the only clinically utilized classifier of luminal versus basal cell-derived disease (developed originally in breast cancer). The test measures the expression of 50 classifier genes and 5 control genes used to identify the intrinsic subtypes of breast cancer (luminal A, luminal B, basal, and Her2). The PAM50 classifier has been applied to 1,567 prostate cancer specimens from high-risk patients treated with prostatectomy (with long-term clinical follow-up). For this study, in collaboration with Dr. Felix Feng's lab, archival tissue from a primary prostate or metastatic tumor biopsy will be sent to Decipher Grid, a high-density microarray platform, for the PAM50 classifier and subtyping to understand if there is a differential response to carboplatin and cabazitaxel in patients with luminal A, luminal B or basal subtypes of prostate cancer.

5.2 Treatment Plan

5.2.1 Chemotherapy dose and schedule

Each cycle is 3 weeks (21 days). A ± 3-day window is allowable for administration of chemotherapy for scheduling purposes for Cycle 2 and beyond. Patients should continue ADT throughout the trial.

Chemotherapy continues for 6 cycles total unless in the absence of unacceptable toxicity, disease progression or reasons listed in Section 5.4.

5.2.2 Dosing schedule

Dosing Regimens

Cabazitaxel 20 mg/m² + carboplatin AUC 4 intravenously on Day 1 of each 3-week cycle, plus prednisone 5 mg PO BID.

Cabazitaxel and carboplatin each will be administered intravenously over 60 minutes.

A new cycle of therapy may not begin until all of the following criteria are met:

- ANC ≥ 1,500/mm^3,
- platelet count ≥ 75,000/mm^3,
- non-hematological toxicities (except alopecia) have recovered to Grade ≤ 1.

Refer to Section 5.3 for toxicity management and dose modifications.

If the patient does not meet the criteria to start a new cycle, they should return weekly until treatment can be given; however, if treatment is delayed for more than 2 weeks, the patient should permanently discontinue chemotherapy (unless a longer delay is discussed with the Study Sponsor). If medically appropriate, such patients should begin abiraterone and prednisone.

Prior to the start of standard of care abiraterone, a visit should occur at 3 weeks (± 1 week) after the last dose of chemotherapy.

Pre-medications

Required IV pre-medications will include an antihistamine (diphenhydramine 25 mg, or other antihistamine), steroid (dexamethasone 20 mg or equivalent steroid), and H2 antagonist (Ranitidine or other H2 antagonist with the exception of cimetidine). These pre-medications will be administered by IV infusion, at least 30 minutes prior to each dose of Cabazitaxel or per institutional standard of care guidelines. Antiemetic prophylaxis with ondansetron, granisetron, or dolasetron or other appropriate antiemetics per institutional practice can be administered whenever it is necessary.

Supportive Care

All patients will receive primary prophylaxis with granulocyte-colony stimulating factor (filgrastim, pegfilgrastim) for white blood count support per standard practice.

Potential Cabazitaxel/Concomitant Drug interactions

Cabazitaxel is a substrate of the cytochrome **P450 (CYP) 3A4** isoenzyme and P-glycoprotein (Pgp). Concomitant use of cabazitaxel with strong CYP3A4 inhibitors is expected to increase cabazitaxel concentrations, and should be avoided if possible. See Appendix C for more information. Consider alternative therapies that do not inhibit or induce the CYP3A4 isoenzyme.

5.3 Toxicity Management and Dose Modification for Chemotherapy

5.3.1 Guidelines for individual patient dose modifications for toxicity

Dose Modification/Toxicity Management for Cycles 2-6

Criteria for Toxicity and Treatment Modification: All toxicities encountered during the study will be evaluated according to the grading system in NCI Common Terminology Criteria for Adverse Events v5.0 (CTCAE v5.0). Every effort will be made to administer the full dose regimen to maximize dose-intensity. If possible, toxicities will be managed symptomatically. If toxicity occurs, the appropriate treatment will be used to ameliorate signs and symptoms including antiemetics for nausea and vomiting, and antidiarrheals for diarrhea.

Cabazitaxel and Carboplatin Dose Reductions

The following sections discuss management of expected toxicity, which may include a dose reduction of one or both drugs based on the table below. A one-time dose reduction is permitted for each drug. Once reduced, a dose cannot be re-escalated.

Table 1. Permissible Dose Reductions

	Initial dose	First Dose Reduction	Second Dose Reduction
Cabazitaxel	20 mg/m^2	15 mg/m^2	None, must discontinue treatment
Carboplatin	AUC 4	AUC 3	None, must discontinue treatment

Dose modifications for hematologic toxicity

No dose reductions or interruptions are required for anemia that can be managed by RBC transfusion. According to the value observed at the date of the planned retreatment, new cycles of therapy may not begin until ANC ≥ 1,500/mm^3 and platelet count ≥ 75,000 /mm^3.

If cabazitaxel and carboplatin treatment must be delayed due to hematologic toxicity, a maximum of 2 weeks delay is allowed. If treatment has to be delayed for more than 2 weeks for toxicity, the patient should come off treatment.

Note: Hospitalization for neutropenic sepsis during the first 3 cycles (approximately 63 days) of chemotherapy meets the criteria for an early stopping rule event per Section 10.5.

In addition to recording of the toxicity as an adverse event (and SAE), a stopping rule event must be reported per Section 7.2.3.

Table 2. Dose modifications for hematologic toxicity, worst grade during previous cycle[1]

Toxicity	Cabazitaxel[2]	Carboplatin[3]
Grade 3-4 neutropenia for < 7 days	None	None
Grade ≥3 neutropenia for>7 days	Dose Reduce one level	None
febrile neutropenia or neutropenic infection	Dose Reduce one level	Dose Reduce one level
Grade 4 Thrombocytopenia	None	Dose Reduce one level

[1]All toxicities encountered during the study will be evaluated according to the grading system in NCI CTCAE v5.0.

[2]May reduce cabazitaxel to a minimum dose of 15 mg/m^2. If further toxicity, the patient must come off treatment.

[3]May reduce carboplatin to a minimum dose of AUC 3. If further toxicity, the patient must come off cabazitaxel and if toxicity persists on single agent carboplatin at an AUC of 3, they must come off both agents.

Dose modifications for hepatic toxicity

In case of increase of bilirubin to >1.5 to ≤3 x ULN (any AST), reduce cabazitaxel dose to 15 mg/m^2. If further toxicity (bilirubin >3 x ULN), the patient must come off treatment.

Dose modifications for renal insufficiency

Carboplatin dose should be held if creatinine clearance drops to ≤ 15 ml/min. The cause of renal insufficiency will be investigated and corrected if possible. If creatinine clearance returns to > 15 ml/min based on the Cockroft-Gault formula within 2 weeks of treatment interruption, treatment can be resumed at the prior carboplatin dose. No cabazitaxel dose adjustment is necessary in patients with renal impairment not requiring hemodialysis. Patients presenting with end-stage renal disease (creatinine clearance ≤15 mL/min/1.73 m2), should be monitored carefully during treatment.

Nausea and vomiting

A prophylactic anti-emetic treatment should be given to the patients in all cycles. The use of a 5HT3 antagonist is recommended, for example ondansetron 8-16 mg IV or equivalent. 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 cabazitaxel dose to 15 mg/m^2. If the patient's cabazitaxel dose was already reduced (regardless of reason) or further toxicity, chemotherapy will be permanently discontinued.

If despite dose reduction, Grade 3 nausea or Grade ≥ 3 vomiting still occur, the chemotherapy will be permanently discontinued.

Diarrhea

No prophylactic treatment for diarrhea is recommended in Cycle 1. However, following the first episode of diarrhea, the patient should receive symptomatic treatment with loperamide 4 mg orally and then 2 mg orally following each new episode until recovery of diarrhea (no more than 16 mg daily). If despite the use of loperamide, Grade ≥3 diarrhea still occurs, reduce the cabazitaxel dose to 15 mg/m^2. If the patient's cabazitaxel dose was already reduced

(regardless of reason) or despite dose reduction, Grade ≥3 diarrhea still occurs, the chemotherapy will be permanently discontinued.

Note: Grade 3 or 4 diarrhea during the first 3 cycles (approximately 63 days) of chemotherapy meets the criteria for an early stopping rule event per Section 10.5. In addition to recording of the toxicity as an adverse event, a stopping rule event must be reported per Section 7.2.3.

Hypersensitivity Reactions

Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of cabazitaxel, thus facilities and equipment for the treatment of hypotension and bronchospasm should be available. Severe hypersensitivity reactions can occur and may include generalized rash/erythema, hypotension and bronchospasm. Premedicate all patients per Section 5.2 prior to each cabazitaxel infusion.

Observe patients closely for hypersensitivity reactions, especially during the first and second infusions. Severe hypersensitivity reactions require immediate discontinuation of the JEVTANA infusion and appropriate therapy. Cabazitaxel is contraindicated in patients with a history of severe hypersensitivity reactions to cabazitaxel or to other drugs formulated with polysorbate 80.

Mucositis Oral

If Grade 3 or worse mucositis oral occurs, study drugs should be withheld for up two weeks until resolution to Grade ≤ 1. Treatment may then be resumed, but the dose of study drug(s) should be reduced as permissible for all subsequent doses. In case of Grade 4 mucositis oral, the chemotherapy will be permanently discontinued.

Peripheral neuropathy

In case of symptoms or signs experienced by the patient, dose modification should be performed.

- Grade ≤1: No change
- Grade 2: Delay treatment until improvement or resolution, then reduce by one dose level of cabazitaxel
- Grade ≥3: Patient will go off protocol therapy

Other Toxicities

Alopecia and nail changes will not require dose modification.

In case of DVT/PE, treatment (all chemotherapy drugs) will be held at least for 1 week and restarted after initial treatment of the thromboembolic event, if the treating physician and the Study Chair concur that this is to the benefit of the patient.

For other Grade 2 non-hematological toxicity that interferes with the patient's quality of life, treatment may be held for up to 2 weeks beyond the planned treatment and patient re-evaluated. If toxicity resolves to Grade 1 or less, therapy can be resumed at the same dose if deemed safe by the treating physician.

For Grade 3 or Grade 4 non-hematological toxicity, treatment must be held and patient re-evaluated. If toxicity resolves to Grade 1 or less within 2 weeks of the planned treatment, therapy may be resumed at the same dose if deemed safe by the treating physician. In cases

of Grade 3-4 non-hematological toxicity that resolves to Grade 2 or less, therapy may be resumed but with a reduced dose of cabazitaxel at 15mg/m^2. If cabazitaxel dose was previously reduced, the patient must permanently discontinue chemotherapy.

Recurrent Grade 3 or Grade 4 non-hematological toxicities not resolved with permissible dose reductions or any delay in scheduled therapy for more than 2 weeks must permanently discontinue chemotherapy.

5.4 Duration of Chemotherapy

Chemotherapy treatment continues for 6 cycles (21 days/cycle) unless there is:

- Disease progression (refer to Section 8)
- Unacceptable toxicity requiring more than 1 dose level reduction for either or both drugs
- A greater than 2-week delay in the start of new treatment cycle due to toxicity, other medical issues, or inability of the patient to maintain the schedule
- Patient withdrawal from study
- Study closure

Three weeks (± 1 week) after the last dose of chemotherapy and prior to the start of standard of care abiraterone, an end of chemotherapy/start of abiraterone visit should occur. The purpose of this visit is to ensure there are no ongoing side effects related to chemotherapy and to document a post-chemotherapy/pre-abiraterone PSA. Refer to Section 5.5 for Abiraterone Administration Guidelines.

If a patient is discontinued from chemotherapy prior to 6 cycles, the reason(s) for discontinuation should be documented; however, they should continue on study as planned if medically appropriate, beginning abiraterone as described in Section 5.5.

Follow-up should continue every 12 weeks (± 5 weeks) until the development of castration resistant disease or two years from Cycle 1 Day 1 of chemotherapy (whichever comes first).

5.5 Abiraterone Administration, Toxicity Management, and Dose Modifications

Abiraterone begins 3 weeks (± 1 week) after the last dose of chemotherapy (i.e., the equivalent of Cycle 7 Day 1 if 6 cycles of chemotherapy are given) and after the post-chemotherapy PSA has been collected.

5.5.1 Planned dose

Abiraterone acetate 1000 mg is taken orally once daily, concomitantly with oral low-dose prednisone 5mg. Tablets should be swallowed whole with water.

Abiraterone acetate must be taken on an empty stomach. No food should be consumed for at least 2 hours before the dose of abiraterone acetate is taken and for at least one hour after the dose of abiraterone acetate is taken.

All patients will remain on a stable regimen of ADT (LHRH agonists or antagonist) or have had surgical castration. Dosing (dose and frequency of administration) will be consistent with product label and should not change during the study.

5.5.2 Dose modification and management of toxicity

In clinical studies in subjects with mCRPC, the most common AEs related to abiraterone acetate monotherapy have included fatigue most likely attributable to the underlying

disease; and hypertension, fluid retention/edema, and hypokalemia due to mineralocorticoid excess caused by compensatory ACTH drive. In this study, low-dose prednisone is expected to mitigate these effects through abrogation of the ACTH drive. A prednisone dose increase from 5 to 10 mg/day is permitted if hypokalemia persists despite optimal potassium supplementation and adequate oral intake, or if any of the other mineralocorticoid effects persist.

Following prolonged therapy with corticosteroids, subjects may develop Cushings syndrome characterized by central adiposity, thin skin, easy bruising, and proximal myopathy. Withdrawal of the corticosteroid may result in symptoms that include fever, myalgia, fatigue, arthralgia, and malaise. This may occur even without evidence of adrenal insufficiency.

Abiraterone dose reduction is permitted for AE management. At each dose reduction, 1 tablet of abiraterone acetate will be removed. Up to two dose reductions are allowed for abiraterone, e.g., 750 mg (4→3 tablets), and 500 mg (3→2 tablets). After resolution of the AE, dose re-escalation may occur to protocol dose level (1000 mg) after discussion with the Study Chair. Permission to re-escalate must be documented.

5.5.3 Guidelines for abnormal liver function test

For patients who develop liver function test abnormalities:

- Grade 3 (ALT and/or AST > 5X ULN but ≤ 20X ULN or total bilirubin > 3X ULN but ≤ 10X ULN): Abiraterone should be interrupted. Treatment may be restarted once liver function tests return to the patient's baseline or to AST and ALT ≤2.5X ULN and total bilirubin ≤1.5X ULN at a reduced dose of abiraterone 750 mg once daily.
- Grade 4 (ALT and/or AST > 20X ULN or total bilirubin > 10X ULN): Abiraterone should be interrupted. The decision to restart treatment at a reduced dose will be made in consultation with the Study Chair on an individual basis.

For patients who resume treatment, serum transaminases and bilirubin should be monitored at a minimum of every 2 weeks for 3 months and monthly thereafter.

If liver function test abnormality recurs at the dose of 750 mg once daily, treatment should be interrupted until liver function tests return to the patient's baseline or to AST and ALT ≤ to 2.5X ULN and total bilirubin ≤ 1.5X ULN. Treatment can restart at a daily dose of abiraterone 500 mg.

If liver function test abnormality recurs at the reduced dose of 500 mg once daily, study drug should be discontinued.

5.5.4 Guidelines for hypertension, hypokalemia, and fluid retention/edema due to mineralocorticoid excess

The study drug should be used with caution in subjects with a history of cardiovascular disease. The study drug may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition. Caution should be exercised when treating subjects whose underlying medical conditions might be compromised by increases in blood pressure, hypokalemia, or fluid retention. Subjects should be monitored for hypertension, hypokalemia, and fluid retention at least once a month. If hypokalemia persists despite optimal potassium supplementation and

adequate oral intake, or if any of the other mineralocorticoid effects persist, the dose of prednisone may be increased from 5 to 10 mg/day.

5.6 Duration of Abiraterone Treatment

Abiraterone treatment continues for 1 year from Cycle 1 Day 1 of the chemotherapy with the option to continue, unless one of the following criteria applies earlier:

- subject decides to discontinue abiraterone treatment
- disease progression
  - symptomatic disease progression at any time
  - objective clinical disease progression
- intercurrent illness that prevents further administration of treatment
- unacceptable AE(s) that may or may not be directly related to treatment but that, in the judgment of the treating physician, makes it dangerous for the subject to be retreated
- general or specific changes in the patient's condition that render the patient unacceptable for further treatment, in the judgment of the investigator

After the initiation of Abiraterone, PSA assessment and scans should continue every 12 weeks (± 5 weeks) as standard-of-care until the development of castration resistant disease or two years from Cycle 1 Day 1 of chemotherapy (whichever comes first).

Because an excessive rate of withdrawals can render the study uninterpretable, unnecessary withdrawal of subjects should be avoided. When a subject discontinues treatment early, the investigator should make every effort to contact the subject and to perform a final evaluation. The reason(s) for withdrawal should be recorded. Follow-up for adverse events (AEs) should be maintained until the later of at least 30 days after completion of all study treatments, or until resolution of all AEs at least possibly related to study treatment(s).

6. DRUG INFORMATION

6.1 Cabazitaxel

(Adapted from package insert- please see package insert for further details)

6.1.1 Classification and mode of action

Cabazitaxel is a microtubule inhibitor belonging to the taxane class. It is prepared by semi-synthesis with a precursor extracted from yew needles. Cabazitaxel binds to tubulin and promotes its assembly into microtubules while simultaneously inhibiting disassembly. This leads to stabilization of microtubules, which results in the inhibition of mitotic and interphase cellular functions.

It has a molecular formula of $C_{45}H_{57}N0_{14}C_3H_6O$ and a molecular weight of 894.01 (for the acetone solvate) 835.93 (for the solvent free).

Cabazitaxel is a white to off-white powder. It is lipophilic, practically insoluble in water and soluble in alcohol.

6.1.2 How supplied

Cabazitaxel 60 mg/1.5 mL is supplied as a kit consisting of the following: cabazitaxel injection 60 mg/1.5 mL: contains 60 mg cabazitaxel in 1.5 mL polysorbate 80 and diluent for cabazitaxel injection: contains approximately 5.7 mL of 13% (w/w) ethanol in water for injection. The vial of cabazitaxel is a clear glass vial with a grey rubber closure, aluminum cap, and light green plastic flip- off cap. The vial of diluent is a clear glass vial with a grey rubber closure, gold-color aluminum cap, and colorless plastic flip-off cap. Both vials are in a blister pack in one carton.

6.1.3 Preparation

Cabazitaxel should be prepared in accordance with the package insert and institutional protocol.

6.1.4 Administration

Cabazitaxel should be administered in accordance with the package insert and institutional protocol.

6.1.5 Incompatibilities

Do not use polyvinyl (PVC) or polyurethane equipment or devices for preparation and administration of cabazitaxel infusion solution.

6.1.6 Handling and safety precautions

Cabazitaxel is a cytotoxic anticancer drug and caution should be exercised when handling and preparing Cabazitaxel solutions. Appropriate mask, protective clothing, eye protection, gloves and Class II vertical-laminar-airflow safety cabinets are recommended during preparation and handling.

If cabazitaxel (first or second solution) should come into contact with the skin, immediately and thoroughly wash with soap and water. If cabazitaxel (first or second solution) should come into contact with mucosa, immediately and thoroughly wash with water.

6.1.7 Storage and stability

Cabazitaxel should be stored at 25°C (77°F) with excursions permitted between 15-30°C (59-86°F). Do not refrigerate.

Chemical and physical stability of the infusion solution has been demonstrated for 24 hours under refrigerated conditions. As both the first diluted solution and the second (final) infusion solution are supersaturated, the solutions may crystallize over time. If crystals and/or particulates appear, the solutions must not be used and should be discarded.

Any unused product or waste material should be disposed of in accordance with local requirements.

6.1.8 Availability

Cabazitaxel will be supplied by Sanofi (drug sponsor).

6.1.9 Dispensing

Cabazitaxel should be stored in a secure area according to local regulations. It is the responsibility of the Investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

6.1.10 Investigational product records at investigational sites

It is the responsibility of the Investigator to ensure that a current record of investigational product disposition is maintained at each study site where investigational product is inventoried and disposed. Records or logs must comply with applicable regulations and guidelines, and should include:

- Amount received and placed in storage area.
- Amount currently in storage area.
- Label ID number or batch number.
- Dates and initials of person responsible for each investigational product inventory entry/movement.
- Amount dispensed to and returned by each subject, including unique subject identifiers.
- Amount transferred to another area for dispensing or storage.
- Non-study disposition (e.g., lost, wasted, broken).
- Amount returned to sponsor, if applicable.
- Amount destroyed at study site, if applicable.

6.1.11 Return of investigational product

Upon completion or termination of the study, all unused investigational product that cannot be transferred to an open cabazitaxel protocol must be returned to the supplier, if not authorized to be destroyed at the site. Empty vials should be discarded at the investigative site according to appropriate drug disposal procedures.

All drug returns must be accompanied by the appropriate documentation and be clearly identified by protocol number and study site number on the outermost shipping container. Details regarding packing supplies for return, as well as the address to which such supplies should be sent, will be provided to the study sites.

6.1.12 Destruction of investigational product

If cabazitaxel is destroyed at the site, it is the Investigator's responsibility to ensure that:

- Procedures for proper disposal have been established according to applicable regulations, guidelines, and institutional procedures;
- Written authorization for disposal/destruction has been granted;
- Arrangements have been made for the disposal; and
- Appropriate records of the disposal have been documented.

6.1.13 Adverse event information

Incidence of reported AEs in >5% of patients receiving cabazitaxel/prednisone or mitoxantrone/prednisone in randomized phase III study.

Adverse event	Cabazitaxel/prednisone (n=371)		Mitoxantrone/prednisone (n=371)	
	Grade 1-4 n (%)	Grade 3-4 n (%)	Grade 1-4 n (%)	Grade 3-4 n (%)
Blood and lymphatic				
Neutropenia	347 (94%)	303 (82%)	325 (87%)	215 (58%)
Febrile	27 (7%)	27 (7%)	5 (1%)	5 (1%)
Anemia	361 (98%)	39 (11%)	302 (82%)	18 (5%)
Leukopenia	355 (96%)	253 (69%)	343 (93%)	157 (42%)
Thrombocytopeni	176 (48%)	15 (4%)	160 (43%)	6 (2%)
Cardiac				
Arrhythmia	18 (5%)	4 (1%)	6 (2%)	1 (<1%)
Gastrointestinal				
Diarrhea	173 (47%)	23 (6%)	39 (11%)	1 (<1%)
Nausea	127 (34%)	7 (2%)	85 (23%)	1 (<1%)
Vomiting	83 (22%)	6 (2%)	38 (10%)	0
Constipation	76 (20%)	4 (1%)	57 (15%)	2 (<1%)
Abdominal pain	64 (17%)	7 (2%)	23 (6%)	0
Dyspepsia	36 (10%)	0	9 (2%)	0
General				
Fatigue	136 (37%)	18 (5%)	102 (27%)	11 (3%)
Asthenia	76 (20%)	17 (5%)	46 (12%)	9 (2%)
Pyrexia	45 (12%)	4 (1%)	23 (6%)	1 (<1%)
Peripheral edema	34 (9%)	2 (<1%)	34 (9%)	2 (<1%)
Mucosal	22 (6%)	1 (<1%)	10 (3%)	1 (<1%)
Pain	20 (5%)	4 (1%)	18 (5%)	7 (2%)
Infections				
Urinary tract	29 (8%)	6 (2%)	12 (3%)	4 (1%)
Metabolism and nutrition				
Weight loss	32 (9%)	0	28 (8%)	1 (<1%)
Anorexia	59 (16%)	3 (<1%)	39 (11%)	3 (<1%)
Dehydration	18 (5%)	8 (2%)	10 (3%)	3 (<1%)
Musculoskeletal				
Back pain	60 (16%)	14 (4%)	45 (12%)	11 (3%)
Arthralgia	39 (11%)	4 (1%)	31 (8%)	4 (1%)
Muscle spasms	27 (7%)	0	10 (3%)	3 (<1%)
Nervous system disorders				
Peripher al	50 (13%)	3 (<1%)	12 (3.2%)	3 (<1%)
Dysgeusia	41 (11%)	0	15 (4%)	0
Dizziness	30 (8%)	0	21 (6%)	2 (<1%)
Headache	28 (8%)	0	19 (5%)	0
Renal and urinary tract				
Hematuria	62 (17%)	7 (2%)	13 (4%)	1 (<1%)
Dysuria	25 (7%)	0	5 (1%)	0
Respiratory				
Dyspnea	43 (12%)	4 (1%)	16 (4%)	2 (<1%)
Cough	40 (11%)	0	22 (6%)	0

Adverse event	Cabazitaxel/prednisone (n=371)		Mitoxantrone/prednisone (n=371)	
	Grade 1-4 n (%)	Grade 3-4 n (%)	Grade 1-4 n (%)	Grade 3-4 n (%)
Skin				
Alopecia	37 (10%)	0	18 (5%)	0
Vascular				
Hypotension	20 (5)	2 (<1%)	9 (2%)	1 (<1%)

Note: Elderly population: Certain Grade 1-4 adverse reactions were reported at ≥5% higher in patients 65 years of age or greater compared to younger patients. These include fatigue (40% vs. 30%), neutropenia (97% vs. 89%), asthenia (24% vs. 15%), pyrexia (15% vs. 8%), dizziness (10% vs. 5%), urinary tract infection (10% vs. 3%), and dehydration (7% vs.

The incidence of gastrointestinal adverse reactions is greater in the patients who have received prior radiation. In a randomized trial comparing 20 mg/m^2 and 25 mg/mg^2 of cabazitaxel (PROSELICA), diarrhea was reported in 41% (297/732) of patients who had received prior radiation and in 27% (118/443) of patients without prior radiation. Of the patients who had previously received radiation, more patients on the 25 mg/m^2 arm reported diarrhea, compared to patients on the 20 mg/m^2 arm.

Cystitis, radiation cystitis, and hematuria, including that requiring hospitalization, has been reported with cabazitaxel in patients who previously received pelvic radiation. In PROSELICA, cystitis and radiation cystitis were reported in 1.2% and 1.5% of patients who received prior radiation, respectively. Hematuria was reported in 19.4% of patients who received prior radiation and in 14.4% of patients who did not receive prior radiation. Cystitis from radiation recall may occur late in treatment with JEVTANA. Monitor patients who previously received pelvic radiation for signs and symptoms of cystitis while on cabazitaxel. Interrupt or discontinue cabazitaxel in patients experiencing severe hemorrhagic cystitis. Medical and/or surgical supportive treatment may be required to treat severe hemorrhagic cystitis.

6.1.13 Potential drug interactions

Cabazitaxel is primarily metabolized through CYP3A. No formal drug interaction studies have been conducted for cabazitaxel, but concomitant administration of strong CYP3A inhibitors is expected to increase concentrations of cabazitaxel. **Co-administration of strong or moderate CYP3A inhibitors is prohibited while patients are on study treatment.**

The concomitant administration of strong CYP3A inducers is expected to decrease cabazitaxel concentrations and is recommended against while patients are on study treatment.

A complete list can be found at http://medicine.iupui.edu/clinpharm/DDIs/table.asp. This table can be found in Appendix C.

All patients must have medication lists reviewed prior to study entry and while on study prior to each cycle. **If a medication on this list is absolutely required for a patient while on study, please contact the Study Chair to discuss the risks and benefits and alternatives. This list is not exhaustive, and the treating physician should review all patient medications.** Premedication with dexamethasone is allowed per protocol (Section 5.2.2), although chronic daily dosing is prohibited.

6.2 Carboplatin

(Adapted from package insert- please see package insert for further details)

6.2.1 Classification and mode of action

Carboplatin, like cisplatin, produces predominantly interstrand DNA cross-links rather than DNA-protein cross-links. This effect is apparently cell-cycle nonspecific. The aquation of carboplatin, which is thought to produce the active species, occurs at a slower rate than in the case of cisplatin. Despite this difference, it appears that both carboplatin and cisplatin induce equal numbers of drug-DNA cross-links, causing equivalent lesions and biological effects.

Carboplatin is a crystalline powder with the molecular formula of C6H12N204Pt and a molecular weight of 371.25. It is soluble in water at a rate of approximately 14 mg/mL, and the pH of a 1% solution is 5-7. It is virtually insoluble in ethanol, acetone, and dimethylacetamide.

6.2.2 Supply

PARAPLATIN (carboplatin aqueous solution) INJECTION

NDC 0015-3210-30 **50 mg**/5 mL aqueous solution in multidose vials (with white flip- off seals), individually cartoned.

NDC 0015-3211-30 **150 mg**/15 mL aqueous solution in multidose vials (with white flip-off seals), individually cartoned.

NDC 0015-3212-30 **450 mg**/45 mL aqueous solution in multidose vials (with white flip-off seals), individually cartoned.

NDC 0015-3216-30 **600 mg**/60 mL aqueous solution in multidose vials (with white flip-off seals), individually cartoned.

6.2.3 Preparation

PARAPLATIN (carboplatin aqueous solution) INJECTION is a premixed aqueous solution of 10 mg/mL carboplatin.

PARAPLATIN aqueous solution can be further diluted to concentrations as low as 0.5 mg/mL with 5% Dextrose in Water (D5W) or 0.9% Sodium Chloride Injection, USP.

When prepared as directed, PARAPLATIN aqueous solutions are stable for 8 hours at room temperature (25° C). Since no antibacterial preservative is contained in the formulation, it is recommended that PARAPLATIN aqueous solutions be discarded 8 hours after dilution.

6.2.4 Administration

PARAPLATIN is usually administered by an infusion lasting 60 minutes or longer. No pre- or post-treatment hydration or forced diuresis is required.

6.2.5 Handling and safety precautions

Procedures for proper handling and disposal of anti-cancer drugs should be considered. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate. Appropriate mask, protective clothing, eye protection, gloves and Class II vertical-laminar-airflow safety cabinets are recommended during preparation and handling.

If carboplatin should come into contact with the skin, immediately and thoroughly wash with soap and water. If carboplatin should come into contact with mucosa, immediately and thoroughly wash with water and call employee health/pharmacy.

6.2.6 Storage and stability

Unopened vials of PARAPLATIN (carboplatin aqueous solution) INJECTION are stable to the date indicated on the package when stored at 25° C (77° F); excursions permitted from 15°-30° C (59°-86° F) [see USP Controlled Room Temperature]. Protect from light.

PARAPLATIN (carboplatin aqueous solution) INJECTION multidose vials maintain microbial, chemical, and physical stability for up to 14 days at 25° C following multiple needle entries.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Solutions for infusion should be discarded 8 hours after preparation.

6.2.7 Dispensing

Carboplatin should be stored in a secure area according to local regulations. It is the responsibility of the Investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

6.2.8 Investigational product records at investigational sites

It is the responsibility of the Investigator to ensure that a current record of investigational product disposition is maintained at each study site where investigational product is inventoried and disposed. Records or logs must comply with applicable regulations and guidelines, and should include:

- Amount received and placed in storage area.
- Amount currently in storage area.
- Label ID number or batch number.
- Dates and initials of person responsible for each investigational product inventory entry/movement.
- Amount dispensed to and returned by each subject, including unique subject identifiers.
- Amount transferred to another area for dispensing or storage.
- Non-study disposition (e.g., lost, wasted, broken).
- Amount returned to sponsor, if applicable.
- Amount destroyed at study site, if applicable.

6.2.9 Return of investigational product

Upon completion or termination of the study, all unused investigational product that cannot be transferred to an open carboplatin protocol must be returned to the supplier, if not authorized to be destroyed at the site. Empty vials should be discarded at the investigative site according to appropriate drug disposal procedures.

All drug returns must be accompanied by the appropriate documentation and be clearly identified by protocol number and study site number on the outermost shipping container. Details regarding packing supplies for return, as well as the address to which such supplies should be sent, will be provided to the study sites.

6.2.10 Destruction of investigational product

If carboplatin is destroyed at the site, it is the Investigator's responsibility to ensure that:

- Procedures for proper disposal have been established according to applicable regulations, guidelines, and institutional procedures;
- Written authorization for disposal/destruction has been granted;
- Arrangements have been made for the disposal; and
- Appropriate records of the disposal have been documented.

6.2.11 Adverse event information

Table 3. Adverse experiences in patients with ovarian cancer[16]

		First Line Combination Therapy* Percent	Second Line Single Agent Therapy** Percent
Bone Marrow			
Thrombocytopenia	< 100,000/mm^3	66	62
	< 50,000 / mm^3	33	35
Neutropenia	<2000 cells/mm^3	96	67
	<1000 cells/mm^3	82	21
Leukopenia	<4000 cells/mm^3	97	85
	<2000 cells/mm^3	71	26
Anemia	< 11 g/dL	90	90
	< 8g/dL	14	21
Infections		16	5
Bleeding		8	5
Transfusions		35	44
Gastrointestinal			
Nausea and vomiting		93	92
Vomiting		83	81
Other GI side effects		46	21
Neurologic			
Peripheral neuropathies		15	6
Ototoxicity		12	1
Other sensory side effects		5	1
Central neurotoxicity		26	5

	First Line Combination Therapy* Percent	Second Line Single Agent Therapy** Percent
Renal		
Serum creatinine elevations	6	10
Blood urea elevations	17	22
Hepatic		
Bilirubin elevations	5	5
SGOT elevations	20	19
Alkaline phosphatase elevations	29	37
Electrolytes loss		
Sodium	10	47
Potassium	16	28
Calcium	16	31
Magnesium	61	43
Other side effects		
Pain	44	23
Asthenia	41	11
Cardiovascular	19	6
Respiratory	10	6
Allergic	11	2
Genitourinary	10	2
Alopecia	49	2
Mucositis	8	1

***Use with Cyclophosphamide for Initial Treatment of Ovarian Cancer:** Data are based on the experience of 393 patients with ovarian cancer (regardless of baseline status) who received initial combination therapy with carboplatin and cyclophosphamide in two randomized controlled studies conducted by SWOG and NCIC (see **CLINICAL STUDIES**).

Combination with cyclophosphamide as well as duration of treatment may be responsible for the differences that can be noted in the adverse experience table.

****Single Agent Use for the Secondary Treatment of Ovarian Cancer:** Data are based on the experience of 553 patients with previously treated ovarian carcinoma (regardless of baseline status) who received single-agent carboplatin.

In the narrative section that follows, the incidences of AEs are based on data from 1893 patients with various types of tumors who received carboplatin as single- agent therapy.

Hematologic Toxicity

Bone marrow suppression is the dose-limiting toxicity of PARAPLATIN. Thrombocytopenia with platelet counts below 50,000/mm^3 occurs in 25% of the patients (35% of pretreated ovarian cancer patients); neutropenia with granulocyte counts below 1000/mm^3 occurs in 16% of the patients (21% of pretreated ovarian cancer patients); leukopenia with WBC counts below 2000/mm^3 occurs in 15% of the patients (26% of pretreated ovarian cancer patients). The nadir usually occurs about day 21 in patients receiving single-agent therapy. By day 28, 90% of patients have platelet counts above 100,000/mm^3; 74% have neutrophil counts above 2000/mm^3; 67% have leukocyte counts above 4000/mm^3.

Marrow suppression is usually more severe in patients with impaired kidney function. Patients with poor performance status have also experienced a higher incidence of severe leukopenia and thrombocytopenia.

The hematologic effects, although usually reversible, have resulted in infectious or hemorrhagic complications in 5% of the patients treated with carboplatin, with drug related death occurring in less than 1% of the patients. Fever has also been reported in patients with neutropenia.

Anemia with hemoglobin less than 11 g/dL has been observed in 71% of the patients who started therapy with a baseline above that value. The incidence of anemia increases with increasing exposure to PARAPLATIN. Transfusions have been administered to 26% of the patients treated with carboplatin (44% of previously treated ovarian cancer patients).

Bone marrow depression may be more severe when PARAPLATIN is combined with other bone marrow suppressing drugs or with radiotherapy.

Gastrointestinal Toxicity
Vomiting occurs in 65% of the patients (81% of previously treated ovarian cancer patients) and in about one-third of these patients it is severe. Carboplatin, as a single agent or in combination, is significantly less emetogenic than cisplatin; however, patients previously treated with emetogenic agents, especially cisplatin, appear to be more prone to vomiting. Nausea alone occurs in an additional 10 to 15% of patients. Both nausea and vomiting usually cease within 24 hours of treatment and are often responsive to antiemetic measures. Although no conclusive efficacy data exist with the following schedules, prolonged administration of carboplatin, either by continuous 24-hour infusion or by daily pulse doses given for 5 consecutive days, was associated with less severe vomiting than the single-dose intermittent schedule. Emesis was increased when carboplatin was used in combination with other emetogenic compounds. Other gastrointestinal effects observed frequently were pain, in 17% of the patients; diarrhea, in 6%; and constipation, also in 6%.

Neurologic Toxicity
Peripheral neuropathies have been observed in 4% of the patients receiving carboplatin (6% of pretreated ovarian cancer patients) with mild paresthesias occurring most frequently. Carboplatin therapy produces significantly fewer and less severe neurologic side effects than does therapy with cisplatin. However, patients older than 65 years and/or previously treated with cisplatin appear to have an increased risk (10%) for peripheral neuropathies. In 70% of the patients with pre-existing cisplatin-induced peripheral neurotoxicity, there was no worsening of symptoms during therapy with carboplatin. Clinical ototoxicity and other sensory abnormalities such as visual disturbances and change in taste have been reported in only 1% of the patients. Central nervous system symptoms have been reported in 5% of the patients and appear to be most often related to the use of antiemetics.

Although the overall incidence of peripheral neurologic side effects induced by carboplatin is low, prolonged treatment, particularly in cisplatin pretreated patients, may result in cumulative neurotoxicity.

Nephrotoxicity
Development of abnormal renal function test results is uncommon, despite the fact that carboplatin, unlike cisplatin, has usually been administered without high-volume fluid

hydration and/or forced diuresis. The incidences of abnormal renal function tests reported are 6% for serum creatinine and 14% for blood urea nitrogen (10% and 22%, respectively, in pretreated ovarian cancer patients). Most of these reported abnormalities have been mild and about one-half of them werereversible.

Creatinine clearance has proven to be the most sensitive measure of kidney function in patients receiving carboplatin, and it appears to be the most useful test for correlating drug clearance and bone marrow suppression. Twenty-seven percent of the patients who had a baseline value of 60 mL/min or more demonstrated a reduction below this value during carboplatin therapy.

Hepatic Toxicity
The incidences of abnormal liver function tests in patients with normal baseline values were reported as follows: total bilirubin, 5%; SGOT, 15%; and alkaline phosphatase, 24%; (5%, 19%, and 37%, respectively, in pretreated ovarian cancer patients). These abnormalities have generally been mild and reversible in about one-half of the cases, although the role of metastatic tumor in the liver may complicate the assessment in many patients. In a limited series of patients receiving very high dosages of carboplatin and autologous bone marrow transplantation, severe abnormalities of liver function tests were reported.

Electrolyte Changes
The incidences of abnormally decreased serum electrolyte values reported were as follows: sodium, 29%; potassium, 20%; calcium, 22%; and magnesium, 29%; (47%, 28%, 31%, and 43%, respectively, in pretreated ovarian cancer patients). Electrolyte supplementation was not routinely administered concomitantly with carboplatin, and these electrolyte abnormalities were rarely associated with symptoms.

Allergic Reactions
Hypersensitivity to carboplatin has been reported in 2% of the patients. These allergic reactions have been similar in nature and severity to those reported with other platinum-containing compounds, i.e., rash, urticaria, erythema, pruritus, and rarely bronchospasm and hypotension. Anaphylactic reactions have been reported as part of postmarketing. These reactions have been successfully managed with standard epinephrine, corticosteroid, and antihistamine therapy.

Injection Site Reactions
Injection site reactions, including redness, swelling, and pain, have been reported during postmarketing surveillance. Necrosis associated with extravasation has also been reported.

Other Events
Pain and asthenia were the most frequently reported miscellaneous adverse effects; their relationship to the tumor and to anemia was likely. Alopecia was reported (3%). Cardiovascular, respiratory, genitourinary, and mucosal side effects have occurred in 6% or less of the patients. Cardiovascular events (cardiac failure, embolism, cerebrovascular accidents) were fatal in less than 1% of the patients and did not appear to be related to chemotherapy. Cancer-associated hemolytic uremic syndrome has been reported rarely.

Malaise, anorexia and hypertension have been reported as part of postmarketing surveillance.

6.2.12 Overdosage

There is no known antidote for PARAPLATIN (carboplatin aqueous solution) INJECTION overdosage. The anticipated complications of overdosage would be secondary to bone marrow suppression and/or hepatic toxicity.

6.2.13 Potential drug interactions

The renal effects of nephrotoxic compounds may be potentiated by PARAPLATIN.

6.3 Abiraterone

(Adapted from package insert for Zytiga - please see package insert from appropriate drug manufacturer for further details)

6.3.1 Pharmacology

Abiraterone acetate is a prodrug of abiraterone, an irreversible inhibitor of 17α hydroxylase/C17, 20-lyase (cytochrome P450c17 [CYP17]), a key enzyme required for testosterone synthesis. This enzyme is found in the testes, adrenals, and prostate tumors.

6.3.2 Formulation

Refer to package insert.

6.3.3 Storage and stability

Storage and Handling Store at 20°C to 25°C (68°F to 77°F); excursions permitted in the range from 15°C to 30°C (59°F to 86°F)

6.3.4 Contraindications

Abiraterone acetate is contraindicated in persons who are or may become pregnant.

6.3.5 Warnings and precautions

Mineralocorticoid excess: Use abiraterone acetate with caution in patients with a history of cardiovascular disease. The safety of abiraterone acetate in patients with LVEF < 50% or NYHA Class II to IV heart failure was not established. Control hypertension and correct hypokalemia before treatment. Monitor blood pressure, serum potassium and symptoms of fluid retention at least monthly.

Adrenocortical insufficiency: Monitor for symptoms and signs of adrenocortical insufficiency. Increased dosage of corticosteroids may be indicated before, during and after stressful situations.

Hepatotoxicity: Can be severe and fatal. Monitor liver function and modify, interrupt, or discontinue abiraterone acetate dosing as recommended.

6.3.6 Adverse reactions

The most common adverse reactions (≥10%) are fatigue, joint swelling or discomfort, edema, hot flush, diarrhea, vomiting, cough, hypertension, dyspnea, urinary tract infection and contusion. The most common laboratory abnormalities (>20%) are anemia, elevated alkaline phosphatase, hypertriglyceridemia, lymphopenia, hypercholesterolemia, hyperglycemia, elevated AST, hypophosphatemia, elevated ALT and hypokalemia.

6.3.7 Drug interactions

CYP3A4 Inducers: Avoid concomitant strong CYP3A4 inducers during abiraterone acetate treatment. If a strong CYP3A4 inducer must be co-administered, increase the abiraterone acetate dosing frequency.

CYP2D6 Substrates: Avoid co-administration of abiraterone acetate with CYP2D6 substrates that have a narrow therapeutic index. If an alternative treatment cannot be used, exercise caution and consider a dose reduction of the concomitant CYP2D6 substrate.

6.3.8 Patient counseling information

See FDA-approved patient labeling (Patient Information)

- Patients should be informed that abiraterone acetate and prednisone are used together and that they should not interrupt or stop either of these medications without consulting their physician.
- Patients receiving GnRH agonists should be informed that they need to maintain this treatment during the course of treatment with abiraterone acetate and prednisone.
- Patients should be informed that abiraterone acetate should not be taken with food and that no food should be consumed for at least two hours before the dose of abiraterone acetate is taken and for at least one hour after the dose of abiraterone acetate is taken. They should be informed that the tablets should be swallowed whole with water without crushing or chewing. Patients should be informed that taking abiraterone acetate with food causes increased exposure and this may result in adverse reactions.
- Patients should be informed that abiraterone acetate is taken once daily and prednisone is taken once daily according to their physician's instructions.
- Patients should be informed that in the event of a missed daily dose of abiraterone acetate or prednisone, they should take their normal dose the following day. If more than one daily dose is skipped, patients should be told to inform their physician.
- Patients should be apprised of the common side effects associated with abiraterone acetate, including peripheral edema, hypokalemia, hypertension, elevated liver function tests, and urinary tract infection. Direct the patient to a complete list of adverse reactions in PATIENT INFORMATION.
- Patients should be advised that their liver function will be monitored using blood tests.
- Patients should be informed that abiraterone acetate may harm a developing fetus; thus, persons who are pregnant or who may be pregnant should not handle abiraterone acetate uncoated tablets without protection, e.g., gloves.
- Patients should also be informed that it is not known whether abiraterone or its metabolites are present in semen and they should use a condom if having sex with a pregnant person. The patient should use a condom and another effective method of birth control if they are having sex with people of childbearing potential. These measures are required during and for one week after treatment with abiraterone acetate.

Further information about abiraterone can be found in the manufacturer's package insert.

6.4 Prednisone

(Adapted from package insert- please see package insert for further details)

6.4.1 Pharmacology

Glucocorticoids are quickly and completely absorbed from the GI tract.

6.4.2 Formulation

Refer to package insert.

6.4.3 Storage and stability

Prednisone should be stored at room temperature

6.4.5 Administration

Prednisone is administered orally.

6.4.6 Availability

Prednisone is commercially available, and commercial sources will be used.

6.4.7 Contraindications

Corticosteroids should be used cautiously in patients with hypothyroidism, cirrhosis, ocular herpes simplex, existing emotional instability or psychotic tendencies, nonspecific ulcerative colitis, diverticulosis, fresh intestinal anastamoses, peptic ulcer, renal insufficiency, hypertension, osteoporosis, and myasthenia gravis. Immunization procedures (especially smallpox) should not be undertaken in patients on corticosteroids.

6.4.8 Human toxicology

AEs associated with prednisone use are: fluid and electrolyte disturbances, congestive heart failure in susceptible persons, hypertension, euphoria, personality changes, insomnia, mood swings, depression, worsening of infection (i.e., tuberculosis), exacerbation or symptoms of diabetes, psychosis, muscle weakness, osteoporosis, vertebral compression fractures, pancreatitis, esophagitis, peptic ulcer, dermatologic disturbances, convulsions, vertigo, headache, endocrine abnormalities, ophthalmic changes, and metabolic changes. Some patients have experienced itching and other allergic, anaphylactic or hypersensitivity reactions. Withdrawal from prolonged therapy may result in symptoms including fever, myalgia, and arthralgia. Phenytoin, phenobarbital, and ephedrine increase metabolic clearance of corticosteroids.

Further information about prednisone can be found in the manufacturer's package insert.

6.5 Filgrastim

(Adapted from package insert- please see package insert for further details)

6.5.1 Formulation

Filgrastim is a 175 amino acid protein manufactured by recombinant DNA technology. It has a molecular weight of 18,800 daltons. It is a sterile, clear, colorless, preservative-free liquid available for parenteral administration. The product is available in single use vials and prefilled syringes containing either 300 mcg or 480 mcg.

6.5.2 Pharmacokinetics

The half-life of filgrastim is approximately 3.5 hours. It is systemically degraded.

6.5.3 Adverse events

Filgrastim is contraindicated in patients with known hypersensitivity to *E coli*-derived proteins, pegfilgrastim, filgrastim, or any other component of the product. Rare cases of splenic rupture have been reported following the administration of filgrastim. Patients who report left upper abdominal pain and/or shoulder tip pain should be evaluated for an enlarged spleen or splenic rupture.

Allergic reactions to filgrastim, including anaphylaxis, skin rash, and urticaria, have been reported in postmarketing experience. The majority of reported events occurred upon initial exposure. In some cases, symptoms recurred with re-challenge, suggesting a causal relationship. In rare cases, allergic reactions including anaphylaxis, recurred within days after initial anti-allergic treatment was discontinued. If a serious allergic reaction occurs, appropriate therapy should be administered, with close patient follow-up over several days. Filgrastim should be permanently discontinued in patients with serious allergic reactions.

In the placebo-controlled trials, more common AEs included pyrexia, bone pain, rash, cough, and dyspnea.

Cytopenias resulting from an antibody response to exogenous growth factors have been reported on rare occasions in patients treated with other recombinant growth factors. There is a theoretical possibility that an antibody directed against filgrastim may cross-react with endogenous G-CSF, resulting in immune-mediated neutropenia, but this has not been observed in clinical studies.

6.5.4 Dosage and administration

The recommended dosage of filgrastim are daily subcutaneous injections of 300 or 480 mcg depending upon body weight.

6.5.5 Storage and stability

Filgrastim should be stored at 2 to 8 degrees Celsius in the carton to protect from light.

7. SAFETY EVALUATION

U.S. regulations require that a sponsor reports Serious Adverse Events (SAEs) occurring with use of its product in a clinical trial if it is unexpected and felt to be related to use of the drug. The PCCTC will facilitate this evaluation with the site investigator and Sponsor-Investigator. An AE should be identified, SAE and Expectedness determined, and causality assessed by the investigator using the definitions that follow.

7.1 Definitions

7.1.1 Adverse Event

An Adverse Event (AE) is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated

with the use of an investigational product, whether or not related to the investigational medicinal product. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, drug interaction, or the significant worsening of the indication under investigation that is not recorded elsewhere on the eCRF under specific efficacy assessments. Anticipated fluctuations of pre-existing conditions, including the disease under study, that do not represent a clinically significant exacerbation or worsening are not considered AEs.

7.1.2 Related Adverse Event, i.e., Adverse Drug Reaction (ADR)

There is a reasonable possibility according to the sponsor that the product may have caused the event.

7.1.3 Serious Adverse Events

Any untoward medical occurrence that at any dose:

a. Results in death,

b. 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),

c. Requires inpatient hospitalization or results in prolongation of existing hospitalization,

d. Results in persistent or significant disability/incapacity,

e. Is a congenital anomaly/birth defect, or

f. 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.

7.1.4 Progression of malignancy

Progression of a patient's malignancy should not be considered an AE, unless in the investigator's opinion, study treatment resulted in an exacerbation of the patient's condition. If disease progression results in death or hospitalization while on study or within 30 days of the last dose, progressive disease will be considered an SAE.

7.1.5 Hospitalization or prolongation of hospitalization

Hospitalization encompasses any inpatient admission (greater than 24 hours) resulting from a precipitating, treatment-emergent AE. For chronic or long-term patients, inpatient admission also includes transfer within the hospital to an acute or intensive care inpatient unit. Hospitalizations for administrative reasons or a non-worsening preexisting condition should not be considered AEs (e.g., admission for workup of a persistent pretreatment laboratory abnormality, yearly physical exam, protocol-specified admission, elective surgery). Preplanned treatments or surgical procedures should be noted in the baseline documentation. Hospitalization because of an unplanned event will be deemed an SAE.

Prolongation of hospitalization is any extension of an inpatient hospitalization beyond the stay anticipated or required for the original reason for admission.

7.1.6 Significant disability

Disability is a substantial disruption of the patient's ability to conduct normal life functions.

7.1.7 Congenital anomaly

If the partner of a patient becomes pregnant during the course of the study, the treating physician must be notified immediately. All confirmed pregnancies must be immediately reported to the Study Chair. All pregnancies should be followed until resolution (i.e., voluntary or spontaneous termination or birth) and assessed for congenital anomalies and birth defects, to the extent feasible from an ethical and practical perspective.

7.1.8 Medically significant event

An event that is not fatal or life-threatening and that does not necessitate hospitalization may be considered serious if, in the opinion of the investigator, it jeopardizes the patient's status and might lead to medical or surgical intervention to prevent any of the above outcomes. Such medically significant events could include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias that do not result in inpatient hospitalization, vasculitis, "generalized edema", or the development of drug dependency or abuse.

7.1.9 Unexpected Adverse Events

An unexpected AE is any event which by nature or severity is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

An expected ADR with a fatal outcome should be considered unexpected unless the local/regional product labeling specifically states that the ADR might be associated with a fatal outcome.

7.1.10 Causality

Causality is a determination of whether there is a reasonable possibility that the drug may have caused or contributed to an AE. It includes assessing temporal relationships de-challenge/re-challenge information, association (or lack of association) with underlying diseases, and the presence (or absence) or a lack of one or more likely causes.

The Investigator must determine if an AE is in some way related to the use of the study drug. This relationship should be described as follows:

<u>Unlikely</u>

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

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

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

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

Unknown
Based on the evidence available, causality cannot be ascribed

7.2 Recording and Grading of Adverse Events

7.2.1 Recording

All observed or volunteered AEs, regardless of treatment group, severity, suspected causal relationship, expectedness, or seriousness will be recorded. AEs will be collected during the chemotherapy and at the End of Study Treatment/Start of Abiraterone Visit 3 weeks (± 1 week) after the last dose of chemotherapy.

After the End of Study Treatment/Start of Abiraterone Visit, only AEs documented in the medical record are required.

A clinically significant change in a physical examination finding or an abnormal test result should be recorded as an AE, if it:

- is associated with accompanying symptoms
- requires additional diagnostic testing or medical or surgical intervention
- leads to a change in study dosing or discontinuation from the study
- requires additional concomitant drug treatment or other therapy, or
- is considered clinically significant by the investigator

An abnormal test result that is subsequently determined to be in error does not require recording as an AE, even if it originally met one or more of the above criteria.

All SAEs that occur any time a patient is on study (i.e., as soon as the informed consent has been signed) or within 30 days of the last dose of study drug(s) must be recorded, regardless of the suspected relationship to the drugs. Any SAE occurring more than 30

days after the last dose of the study drugs must be recorded if a causal relationship to them is suspected. Study drug in reference to SAE collection will include cabazitaxel, carboplatin, abiraterone and prednisone.

7.2.2 Grading severity

All AEs will be graded based on the NCI CTCAE version 5.0.

7.2.3 Events meeting the definition of an Early Stopping Rule Event

Early stopping rules are in place for excessive toxicity during the first 3 cycles (approximately 63 days) of chemotherapy. Events that count toward an early stopping rule event are:

- hospitalization for neutropenic sepsis
- grade 3 or 4 diarrhea based on CTCAE v5.0

In addition to recording such events as an adverse event, the event must be reported as an early stopping rule event. Refer to Section 10.5 for additional information. In the event that a stopping boundary is triggered, study enrollment will be suspended and the Sponsor-Investigator, IRB and DSMC will be notified.

7.3 Reporting Serious Adverse Events

7.3.1 Reporting serious adverse events

- All SAEs, events determined to be medically significant by the treating Investigator, and unknown reactions or unexpected events should be reported to the PCCTC **within one business day** of knowledge of the event using the contact information below. The initial report should include the following information at a minimum:
  - protocol # and title
  - subject identification number, sex, age at event
  - date the event occurred
  - description of the SAE
  - causal relationship to the study treatment(s)

SAE reporting will be facilitated by the PCCTC in accordance with the UMN IRB Regulations and FDA guidelines.

FDA website for guidance in reporting SAEs:

http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm

For clinical trials conducted under an IND, SAE reporting will be performed in accordance with Code of Federal Regulations Title 21 volume 5 Part 312 subpart B (21CFR312.32):

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.32

SAEs will be reported on a MedWatch form and should be submitted to the PCCTC Project Coordinator within one business day of awareness of the event. The PCCTC will facilitate all SAE report form submissions to lead site/sponsor and Sanofi within one business day of PCCTC awareness. PCCTC is responsible for informing all participating sites about all unexpected SAEs that are either possibly, probably, or definitely related to the study intervention. PCCTC is responsible for informing all participating sites within one business day about a

life-threatening event or death that is unforeseen and indicates participants or others are at increased risk of harm.

If the SAE is death and determined to be possibly, probably or definitely related to the investigational drug or any research related procedure, the event must be reported to the PCCTC via e-mail (pcctc@mskcc.org) immediately and the PCCTC will report to the Sponsor-Investigator within one business day of becoming aware of the event.

Grade, relationship, action taken, concomitant medications, outcome, etc. should be reported to the PCCTC as soon as possible.

Follow-up of AEs should continue until the event and any sequela resolve or stabilize at a level acceptable to the investigator.

SAE contact information for the PCCTC is listed below.

PCCTC:
Prostate Cancer Clinical Trials Consortium
Email: pcctc@mskcc.org

7.3.2 Reporting of SAEs to Sanofi

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

- All Serious Adverse Events (SAEs) and Adverse Events of Special Interest (AESI), if any. These events must be transmitted within one business day of the PCCTC's awareness or identification of the event.
- Results of any relevant complementary exams performed to obtain the final diagnosis of any SAE (e.g., hospital discharge summary, autopsy, consultation) will be made available to Sanofi group entity upon request.
- Other events or periodic reports (e.g. Development Safety Update Report (DSUR)), submitted to Regulatory Authority must be provided to Sanofi.
- Other significant safety issues or findings in a study pertaining to safety of product must be transmitted within 1 working day to the Sanofi GPE. (e.g., Data Safety Monitoring Board recommendations).
- The study report of any IST/ISS must contain a section describing safety review and conclusion.
- The reference safety information to be used by the IST/ISS sponsor for evaluation of expectedness of adverse events shall be the Investigator Brochure.

The PCCTC will report to **Sanofi Group Entity Pharmacovigilance Contact** via fax or email, attention Sanofi Pharmacovigilance (PV)

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

7.4 Safety Reports

- The PCCTC will distribute outside safety reports to the participating sites.
- Participating sites must submit safety reports to their institution's IRB/PBs per participating site guidelines.

8. CRITERIA FOR OUTCOME ASSESSMENT/THERAPEUTIC RESPONSE

8.1 Measurement of Response in Patients with Measurable Soft Tissue or Nodal Disease

For patients with measurable disease, response and progression will be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria.[17] Changes in only the longest diameter (unidimensional measurement- LD) of the tumor lesions are used in the RECIST criteria.

> **Note:** lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy. 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 28 days before the beginning of the treatment. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

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

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

Conventional CT and MRI. 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.

8.1.1 Measurable disease / target lesions

All measurable lesions (lesions that can be accurately measured in at least one dimension [longest diameter to be recorded] as ≥10mm with spiral CT) up to a maximum of 2 lesions per organ and 5 lesions 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 the suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as a reference by which to characterize the objective tumor response.

Lymph node metastases must measure 1.5 cm or greater in short axis diameter to be considered target lesions, while other target lesions must measure 1 cm or greater (with spiral CT scans).[18]

Complete Response (CR):	Disappearance of all target lesions
Partial Response (PR):	At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD
Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started (including baseline LD), or the appearance of one or more new lesions
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started (including baseline LD)

8.1.2 Evaluation of non-target lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level
Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s), and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD):	Appearance of one or more new lesions, and/or unequivocal progression of existing non-target lesions

Although a clear progression of non-target lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the study chair.

8.1.3 Evaluation of best overall response

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

8.1.4 Confirmation

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat studies no less than 4 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum of 12 weeks after study entry.

8.1.5 Duration of overall response

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

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

8.2 Evaluation of Bone Disease

PCWG3 criteria will be used to document evidence of disease progression in bone lesions as described by Scher, et al. 2016.

8.2.1. Imaging of baseline bone disease

The use of bone scan as the standard for bone imaging is retained in PCWG3, with the presence or absence of metastasis recorded first. A quantitative measure of disease burden, such as lesion number, the bone scan index, or lesion area, is also suggested, recognizing that these measures require further analytical and prospective clinical validation. Changes in lesions considered metastatic on bone scintigraphy should be followed and assessed serially using a bone scan assessment form. Areas/lesions on bone scintigraphy that are suggestive can be assessed further with CT or MRI and followed separately, but such supplemental imaging should not be used to establish indicator lesions for the purposes of a trial.

Different modalities for imaging bone metastases can provide different information for the same patient. However, because of the lack of standards for reporting disease presence or changes after treatment, positron emission tomography imaging with sodium fluoride, fluorodeoxyglucose, choline, or prostate-specific membrane antigen, bone marrow MRI (body MRI), and other modalities that are in use to image bone, should be approached as new biomarkers subject to independent validation.

8.2.2 Criteria for progression in bone at study entry

- Two new lesions observed on 99mTc-methylene diphosphonate radionuclide bone scintigraphy
- Confirm ambiguous results by other imaging modalities (e.g., CT or MRI) however only positivity on the bone scan defines metastatic disease to bone

8.2.3 Documentation of baseline bone disease

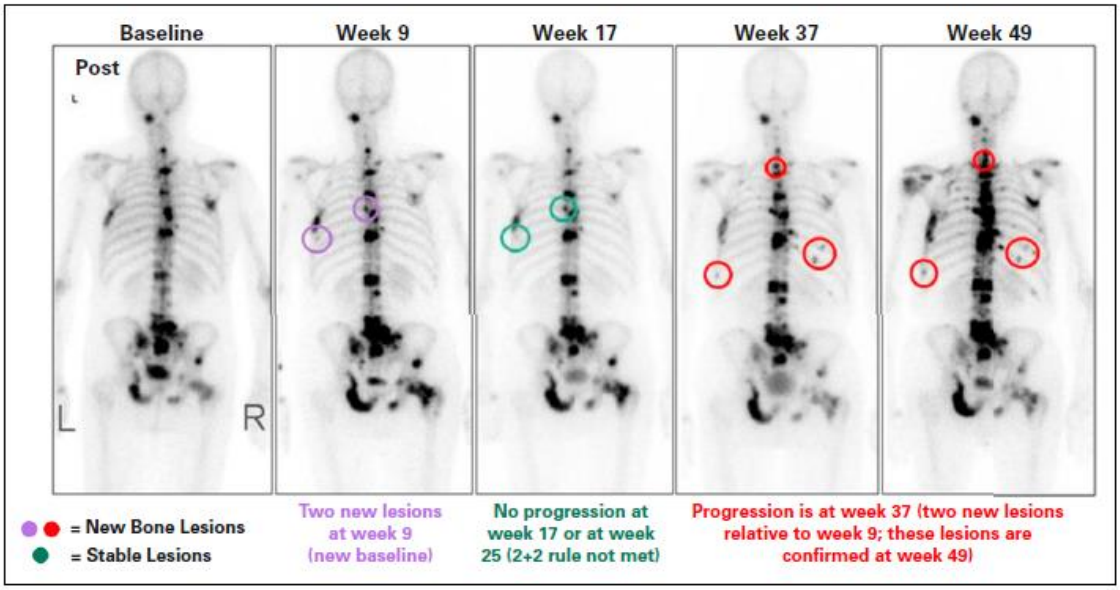
- Presence or absence of metastasis recorded first
- A quantitative measure of disease burden, such as lesional number, the bone scan index, or lesion area, is required
- Changes in lesions considered metastatic on bone scintigraphy should be followed and assessed serially using a bone scan assessment form. Areas/lesions on bone scintigraphy that are suggestive can be assessed further with CT or MRI and followed

separately, but such supplemental imaging should not be used to establish indicator lesions for the purposes of a trial

8.2.4 Following for bone progression during the study

- Exclude pseudo progression in the absence of symptoms or other signs of progression
- At least two new lesions on first post-treatment scan, with at least two additional lesions on the next scan (2+2 rule)
- If at least two additional new lesions are seen on the next (confirmatory) scan, the date of progression is the date of the first post-treatment scan, when the first two new lesions were documented
- For scans after the first post-treatment scan, at least two new lesions relative to the first post-treatment scan confirmed on a subsequent scan
- Date of progression is the date of the scan that first documents the second lesion
- Changes in intensity of uptake alone do not constitute either progression or regression

Figure 2. Controlling for Flare by Applying the 2+2 Rule using the First Post-treatment Scan as Baseline



8.3 PSA Changes

All patients will be evaluated for PSA decline.

a. 30% and 50% PSA Decline: PSA decline of at least 30% and 50%, respectively, from baseline confirmed by a second measurement at least 3 weeks later. The reference for these declines should be a PSA measured within 2 weeks prior to starting therapy.

b. PSA Progression: Serologic progression will be defined as an increase in the PSA level of more than 50% above the nadir reached after the initiation of ADT, with two consecutive increases at least 2 weeks apart

c. PSA Response Duration: The PSA response duration commences on the date of the first 50% decline in PSA. The response duration ends when the PSA value increases by 50% above the nadir, provided that the increase in the absolute-value PSA level is at least 5 ng/mL or back to baseline, whichever is lower.

d. Time to PSA Progression: The start of the time to PSA progression is the day treatment is initiated. The end date is the date of the first PSA rise over the determined PSA PD value.

e. Complete serologic response: A complete serologic response was defined as a PSA level of less than 0.2 ng per milliliter on two consecutive measurements at least 4 weeks apart.

f. Time to PSA nadir: This will be defined as the time from when treatment is initiated until a PSA of <0.2 ng/ml.

8.4 Progressive Disease (PD)

Progressive disease will be defined by <u>any one</u> of the following:

1. Demonstration of castration resistant disease: defined as the time until documented unequivocal clinical, radiographic or serologic progression (defined by PSA progression in Section 8.3) with a testosterone level of ≤50 ng per deciliter (or source documentation of medical castration or surgical castration).
2. Radiographic progression of existing visceral metastatic disease per RECIST criteria including the development of new metastatic lesions.
3. Unequivocal clinical progression caused by disease requiring surgical intervention or palliative radiation to a symptomatic bone metastasis or a decline in clinical status deemed by the investigator to be related to progression of disease rather than comorbidity or adverse events.

9. DATA REPORTING AND REGULATORY REQUIREMENTS

9.1 Data Collection and Management

Data collected during this study will be entered into a secure database.

This study is a multi-institution, investigator-sponsored trial (IST) coordinated by UMN and the PCCTC. The PI at UMN holds the role of Study Chair.

The institutional PI and/or the PCCTC is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects, as well as written records of the disposition of the drug when the study ends.

The institutional PI is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Participating sites will prepare and maintain adequate and accurate case histories as per their standard institutional guidelines. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

Study documentation includes all CRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Study drugs will be shipped from the drug manufacturer to a third-party vendor and then directly to the site for distribution of the drugs to the study patients. Each site will be responsible for drug accountability at their site.

9.1.1 Electronic Case Report Forms (eCRFs)

Standardized eCRFs and CRF Completion Guidelines will be created by the PCCTC for the collection of study data. Access and training for PCCTC Medidata Rave EDC will be made available to participating sites upon local regulatory approval. The participating site investigator is responsible for ensuring eCRFs are completed accurately and in a timely manner.

9.1.2 Source documents

Source documentation refers to original records of observations, clinical findings and evaluations that are subsequently recorded as data. Source documentation will be made available to support the subject's research record.

9.1.3 Record retention

The investigator will maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. After study closure, the investigator will maintain all source documents and study-related documents. Records are to be retained and securely stored until the later of: (a) two (2) years following the date a New Drug Application is approved for the Study Drug that is the subject of the Clinical Trial; or (b) two (2) years after the Investigational New Drug Application for such Study Drug is terminated or withdrawn, or such longer period of time as may be required by Participant policies, applicable laws, rules or regulations.

9.2 Data and Safety Monitoring Plan

The UMN Data Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and patient safety for all UMN institutional clinical studies. The PCCTC will facilitate this responsibility. A summary of DSMC and PCCTC activities for this study may include but is not limited to:

DSMC:

- Monitoring (depending on study accrual)
- Review of suspected adverse reactions considered "serious"
- Auditing

PCCTC:

- DSMC Reports: The PCCTC will generate the report (in a format agreed upon at the onset of the protocol) and provide to Study Chair to submit to DSMC.
- Conference Calls with Participating Sites: The PCCTC will coordinate, schedule, provide reports for this meeting in a format agreed upon at the onset of the protocol as well as participate and take minutes.

- The PCCTC will perform monitoring per the Monitoring Plan (MP) and Data Management Plan (DMP).
- The PCCTC will maintain an electronic regulatory binder for each of the participating sites and supply documentation to UMN as needed.

9.3 Monitoring and Reporting Guidelines

The PI at the UMN Coordinating Center will hold the role of Study Chair. The Study Chair is responsible for the overall conduct of the study and for monitoring its safety and progress at all participating sites. The Study Chair will conduct continuous review of data and subject safety. The PCCTC will generate any necessary reports and participate in meetings as necessary. The discussions are documented in meeting minutes. The discussion will include the number of patients, significant toxicities in accordance with the protocol, doses adjustments, and observed responses.

9.4 Review and Oversight Requirements

9.4.1 Adverse event monitoring

All clinically significant AEs, whether or not unexpected, and whether or not considered to be associated with the use of study drug, will be entered into Medidata Rave®.

All clinically significant AEs entered into Medidata Rave® will be reviewed by the Study Chair. The Study Chair will review and discuss the selected toxicity, the toxicity grade, and the attribution of relationship of the AE to the administration of the study drug(s). In addition, all suspected adverse reactions considered "serious" are entered into Medidata Rave® and will be reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis. The report for this meeting will be prepared by the PCCTC and submitted to the DSMC by the Study Chair.

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and is determined to be related either to the investigational drug or any research related procedure, the Study Chair at the UMN Coordinating Center or the assigned designee and the PCCTC via e-mail (pcctc@mskcc.org) must be notified within 24 hours of knowledge of the event from the participating site(s).

9.4.2 Review of AE rates

<u>Increase in Adverse Event Rates</u>

If an increase in the frequency of Grade 3 or Grade 4 AEs (above the rate reported in the Investigator Brochure or package insert), the Study Chair at the UMN Coordinating Center is responsible for notifying the DSMC at the time the increased rate is identified. The report will be generated by the PCCTC and indicate if the incidence of AEs observed in the study is above the range stated in the Investigator Brochure or package insert.

If at any time the Study Chair stops enrollment or stops the study due to safety issues, the DSMC Chair and DSMC Manager must be notified within **1 business day** via e-mail. The DSMC must receive a formal letter within **10 business days** and the IRB must be notified.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints

10.1.1 Primary endpoint

To determine the proportion of patients with PSA or radiographic progression as determined by RECIST 1.1 or PCWG3 criteria by 1 year post chemotherapy initiation with 6 cycles of carboplatin and cabazitaxel followed by continued abiraterone.

10.1.2 Analysis of the primary endpoint

The point estimate and its 95% confidence interval will be obtained for the percent of patients with PSA or radiographic progression while treated with ADT, carboplatin and cabazitaxel with maintenance abiraterone. A Kaplan-Meier curve will be used to estimate progression given that no competing risks are expected. These data will be compared to patients on LATITUDE using a log-rank test.

10.1.3 Secondary endpoints

- Progression-free survival
- Time to PSA nadir
- Time to PSA progression
- Safety and tolerability of combination treatment of cabazitaxel and carboplatin combination treatment in metastatic prostate cancer
- Incidence of HRD in this population
- PSA complete response rate (PSA <0.2 ng/ml) at 1 year in patients with and without mutations in DNA repair genes as well as various molecular subtypes (luminal/basal).

10.1.4 Analysis of secondary endpoints

For patients with measurable disease at baseline, the objective complete response rate will be descriptively reported. Among patients with objective response, the median duration of response will be estimated using the criteria outlined in Section 8.

The proportion of patients with greater than 50% decline from baseline in serum PSA and patients with PSA nadir at 12 months will be reported in descriptive fashion. Progression-free survival, time to PSA progression and time to PSA nadir will be estimated using the Kaplan-Meier product limit method. Durations will be measured from day 1 of study treatment to first date of PSA progression and PSA nadir, as defined in Section 8.

The incidence and severity of AEs related to treatment regimen will be descriptively reported using Common Toxicity Criteria version 5.

Incidence of HRD will be described as a point estimate and its 95% confidence interval.

To compare the distribution or time to radiographic or PSA progression by 1 year in patients with and without mutations in DNA repair genes as well as luminal vs. basal molecular subtypes, a log-rank test will be used.

10.1.5 Exploratory endpoints

- To obtain CTCs to evaluate for reversion mutations, conformational changes and validate HRD phenotype with Epic Sciences.
- To analyze and track changes in cfDNA, particularly for the emergence of alterations that would confer resistance.
- To apply the PAM50 classifier to subtype archival primary or metastatic prostate cancer samples into basal or luminal A vs. B subtypes.

10.1.6 Analysis of exploratory endpoints

Genomic and molecular predictors of response

Concurrent analysis of CTCs and circulating tumor cfDNA will be done at baseline (Cycle 1 Day 1), Cycle 2 Day 1, and at the 2 Year visit or time of progression/change in therapy status (whichever comes first). CTCs will be analyzed using the Epic Sciences platform and cfDNA will be collected and stored for future analysis, as described in the lab manual. The association between these variables and clinical outcomes will be performed using Fisher's exact test for categorical variables and Mann-Whitney test for continuous variables.

Incidence of luminal A/luminal B and basal subtypes will be described as a point estimate and its 95% confidence interval. Of the 61 patients, ~40% are predicted to have the basal subtype (24 patients). This analysis will be done in Felix Feng's lab as described in the lab manual.

No adjustment for multiple comparisons will be made in this analysis.

10.2 Sample Size Determination

This phase II two-stage trial is designed so that there will be no pause between stage I and enrollment to stage II. An adaptation of Simon's two-stage design[19] will be used. The null hypothesis is that the PSA and radiographic progression rate by 1 year is 0.20 and this will be tested against a one-sided alternative that the progression rate is 8% by 1 year. We will potentially enroll 61 patients with one-interim analysis for futility after 32 patients are enrolled. Since the goal is to estimate the progression rate at a long-term time-point (1 year), we ran a simulated exponential model 10,000 times based on complete follow-up and a one-sided log-rank test through 1 year with interim analysis for 32 patients with incomplete follow-up.

Based on interim analysis of the first 32 patients, we will discontinue the trial if the estimate from the Kaplan-Meier (1-Kaplan-Meier) curve has an estimated 1 year progression of >18%. Assuming the null hypothesis of 20% progression is true, we have a 27% chance of stopping the trial early due to futility. If the rate is higher, the probability of stopping increases. Assuming the alternative hypothesis of 8% progression is true, the overall power will be approximately 81%.

10.3 Analysis Populations

Subject disposition and all efficacy endpoints will be assessed using data from the intent-to-treat population. Safety analysis will include all patients who receive at least one dose of protocol therapy.

10.4 Demographics and Baseline Characteristics

Demographic variables will include age, race, ethnicity, and baseline height and weight. Additional disease specific features will be captured on electronic case report form, including:

- Gleason score at the time of diagnosis
- Year of prostate cancer diagnosis
- Extent of disease at the time of study entry (nodal, bone, visceral metastases (lung, liver, or both).

10.5 Stopping Rules

Early stopping rules will be in place for hospitalization for neutropenic sepsis and grade 3-4 diarrhea. The stopping rules are generated using an adaptation of Pocock stopping boundaries.[19] In the event that a stopping boundary is triggered, study enrollment will be suspended and the PI, IRB and DSMC will be notified.

10.5.1 Hospitalization for neutropenic sepsis within the first three cycles (approximately 63 days)

We expect that the rate will be about 7%. The goal is to construct a boundary based on toxicity such that the probability of early stopping is at most 5% if the rate is equal to 7% and our sample size is 61. With these stipulations, the trial will be stopped and reviewed if 2/2, 3/7, 4/14, 5/21, 6/29, 7/37, 8/46, 9/55 or 10 events occur. The probability of hitting the stopping boundary if the rate is 20% is 87%.

10.5.2 Grade 3-4 Diarrhea within the first three cycles (approximately 63 days)

We expect that the rate of diarrhea will be about 5%. The goal is to construct a boundary based on toxicity such that the probability of early stopping is at most 5% if the rate is equal to 7% and our sample size is 61. With these stipulations, the trial will be stopped and reviewed if 2/4, 3/11, 4/19, 5/29, 6/41, 7/52 or 8 events occur. The probability of hitting the stopping boundary if the rate is 20% is 96%.

11. REGULATORY AND PROTECTION OF HUMAN SUBJECTS

11.1 Ethical Considerations

This study will be conducted in compliance with the protocol, GCP guidelines established by the International Conference on Harmonisation, as adopted by applicable laws and regulations, and the ethical standards set forth in the Declaration of Helsinki.

11.2 Protocol Review Committee

This study will be reviewed by the UMN Protocol Review Committee (PRC) for scientific merit. After initial review and approval, the study will be reviewed at least once a year for scientific progress. Any changes to the protocol are to be reviewed and approved by the PRC.

Participating sites will review this study as per their standard scientific review and approval process.

11.3 Institutional Review Board (IRB) / Independent Ethics Committee (IEC)

The study will be reviewed by the IRB. After initial review and approval, the study will be reviewed at least once a year as per FDA regulations (21 CFR 56.109). Any changes to the protocol and consent form are to be reviewed and approved by the IRB. Participating sites will review this study as per their standard IRB/IEC review and approval process.

It is the responsibility of the PI to keep the IRB informed of the progress of the study, including changes to the protocol or consent form, exceptions or deviations from the protocol, and any new developments which may affect subject safety or willingness to participate.

All protocol amendments must be approved by the participating site's IRB within 90 days of receipt. Failure to do so may result in the suspension of study activities at that site.

Upon approval of the protocol or amendment by a participating site's IRB, a copy of the approval documentation must be submitted (electronic or hardcopy) to the PCCTC. The PCCTC will inform the Study Chair.

11.4 Investigational New Drug Application (IND)

IND application was filed and waived by the FDA.

11.5 Conduct of the Trial

The investigators will obtain informed consent and will conduct the trial in accordance with Federal regulations, institutional requirements, and the Declaration of Helsinki.

Role and Responsibilities

Sponsor Investigator)

The Sponsor Investigator is responsible for performing the following tasks:

- Responsibility for the overall conduct of the study at all participating sites and for monitoring the progress of the study
- Reviewing and ensuring reporting of SAEs
- Reviewing data from all participating sites

The PCCTC

The PCCTC is responsible for performing the following tasks:

- Ensuring that IRB approval has been obtained at each participating site prior to the first patient registration at that site, and maintaining copies of IRB approvals and required regulatory documents from each site.
- Managing subject registration
- Developing and maintaining Clinical Data Management documents and procedures
- CRF development, setup of study database, and subsequent design changes
- Participating in review of content of the CRF against the protocol requirements
- Electronic Data Capture (EDC) system administration (user/site accounts setup, maintenance and revocation)
- Data review, cleaning, query management and resolution
- Establishing procedures for documentation, reporting and submitting of AEs and SAEs to the PCCTC and UMN as outlined in Sections 7 and 9.
- Reviewing SAEs and facilitating regulatory reporting in coordination with Sponsor-Investigator.
- Training participating sites on EDC
- Collecting and compiling data from each participating site
- Facilitating monitoring by securing selected source documents and research records from participating sites for audit, or by auditing at participating sites.

Participating Sites

Participating sites are responsible for performing the following tasks:

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

11.6 Written Informed Consent

Before obtaining consent, members of the study team will review the rationale for the treatment program with the patient. The discussion will review the alternatives available (including hormonal therapy, chemotherapy, or supportive care as appropriate), the potential benefits of this program, the risks and the probability of their occurrence, and the procedures to minimize these risks. Should an AE occur, the provisions available to ensure medical intervention will also be reviewed. Why the risks are reasonable in relation to the anticipated benefits, incentives, or costs that will or may be incurred as a result of participating in the study, as well as the efforts to maintain confidentiality, will also be discussed with the patient.

Patients will be required to sign and date an informed consent form that meets the requirements of the Code of Federal Regulations (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the IRB. The medical record will include a statement that written informed consent was obtained (and document the date that it was obtained) before the patient is enrolled in the study.

The consent form will include the following:

- the nature and objectives, potential toxicities, and benefits of the intended study
- the length of therapy and likely follow-up required
- alternatives to the proposed therapy (including available standard and investigational therapies)
- the name of the investigator(s) responsible for the protocol
- the right of the patient to accept or refuse treatment and to withdraw from participation in this study
- Text regarding the consortium and the coordinating center should be added to all institutional informed consent documents and sections in the research authorization/HIPAA forms (e.g., “Prostate Cancer Clinical Trial Consortium”)

11.7 Protection of Privacy

Patients will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. After this discussion, they will be asked to sign a Notice of Privacy Practice research authorization/HIPAA form. The original signed documents will become part of the patient’s medical records, and each patient will receive a copy of the signed documents. The use and disclosure of protected health information will be limited

to the individuals described in the research authorization form. The research authorization form must be completed by the investigator and approved by the IRB.

11.8 Terminating or Modifying the Study

AE and laboratory data from this trial will be assessed by the Study Chair and DSMC on an ongoing basis. SAEs will be reviewed as they are reported to the lead site/sponsor and PCCTC, and the DSMC will make an assessment regarding the safety of continuing or modifying the study. This assessment will be shared with the investigators either in writing or as part of a teleconference. Should the assessment of either the lead site/sponsor or the PI be that the study should be terminated, the study will be closed to further accrual. Patients who are receiving study treatment(s) will be assessed individually by the investigator to see if it is in the patients' best interest to continue, which might be the case for a patient that is responding to the intervention. Follow-up safety assessments will be performed for all patients who are terminated from the study prematurely.

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APPENDIX A: PERFORMANCE STATUS CRITERIA

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

APPENDIX B: STUDY CALENDAR

Cycle 1 Day 1 (C1D1) of chemotherapy serves as the anchor date for this study. Virtual visits are permitted at all time points (including screening) in lieu of in-clinic visits for relevant activities including physical exam, medical history, assessment of symptoms and side effects.

Study Assessments	**Screening[a]**	**Cycle 1 (± 3 days)** D 1	**Cycle 2 - 6 (± 3 days)** D 1	**End of Chemotherapy/ Start of Abiraterone: 3 weeks (± 1 week)[k] after the last dose of chemo**	**Every 12 weeks (± 5 weeks)[k] from C1D1 until Progression or End of Study Visit**	**At the time of Progression or Change in Therapy Visit[l]** (at any point before the 2 Year/End of Study Visit)	**1 Year Visit from C1D1[m] (±2 weeks)**	**2 Year/End of Study Visit from C1D1[n] (± 28 days)**
Informed Consent	X							
Medical History	X							
Physical Examination	X	X	X	X		X	X	X
Concurrent Medications	X	X	X	X		X	X	X
Documentation of ongoing abiraterone dosing or end date					X	X	X	X
ECOG Performance Status	X	X	X	X		X	X	X
Adverse Event Assessment		X	X	X		X	X	X
Vital Signs	X	X	X	X		X	X	X
Weight and Height[a]	X	X	X	X		X	X	X
CBC + Differential[b]	X	X	X	X		X	X	X
Chemistry panel	X	X	X	X		X	X	X
Serum PSA	X	X	X	X	X	X	X	X
PT/INR + PTT	X							
Serum testosterone	X	X	X	X		X	X	X
12-lead ECG	X							
CTC and cfDNA collection[c]		X	X[c]			X[o]		X[o]
Archival tissue for Germline/Somatic Sequencing[d], PAM50[e]	X							
CT scan of chest/abd/pelvis, bone scan[f]	X				X			
Disease and Survival Status[g]				X	X	X	X	X
Cabazitaxel/Carboplatin Administration[h]		Day 1 of Each Cycle						
GCSF injection[i]		X (D2)						
Abiraterone with prednisone[j]				Start and continue until progression or no longer of benefit				
Androgen Deprivation Therapy (ADT)		Continue per standard of care for the duration of study						

a. Screening procedures must be completed within 14 days of start of study treatment, with the exception of tumor assessments/radiographic studies, which may be performed within 28 day of start of study treatment. Germline and/or somatic sequencing results and archival tissue, if available, may also be obtained outside the screening window. Height can be recorded at baseline (during screening or C1D1 pre-dose) and does not need to be repeated.
b. Screening labs may be used on C1D1 if drawn within 3 days prior to start of treatment, for subsequent cycles, labs may be collected up to 2 days before Day 1 treatment.
c. Blood for CTCs and cfDNA will be collected at 3 time points total: C1D1, C2D1 and at either the Time of Progression/Change in Therapy visit or the 2 Year/End of Study visit, whichever occurs first. See Section 5.1.6 and Lab Manual regarding collection instructions. Blood for CTCs is sent to Epic Sciences for analysis. Blood for cfDNA analysis is collected, processed on-site and banked for future analysis. During chemotherapy, collect prior to day's dose.
d. Germline and/or somatic sequencing of archival tissue from a prior primary prostate or metastatic biopsy is performed as part of standard care using a CLIA-certified NGS platform. Data will be collected for subjects who have NGS sequencing results. The results do not need to be available prior to initiation of protocol therapy, provided there is prior pathologic confirmation of prostate cancer.
e. If any remaining archival tissue is available from a prior standard-of-care biopsy, tissue will be submitted for future analysis using the PAM50 classifier.
f. Tumor assessment to include CT chest/abdomen/pelvis (with IV contrast if no allergy and adequate renal function) and radionuclide bone scan. NaF PET CT or MRI abdomen/pelvis is an acceptable alternative. Subjects who have initiated ADT prior to study enrollment do not require 28-day window tumor assessments for screening; available pre-treatment scans within 90-days of starting ADT can be used for screening.
g. Disease and survival status will be assessed by documenting survival date, cause of death (if applicable), and any new therapies given at time of disease and survival status.
h. Treatment will be administered for 6 cycles unless one of the conditions in Section 5.4 is met.
i. During chemotherapy, GCSF injection or Neulasta is given on Day 2 or provided via the Onpro on-body injector applied on Day 1 of each cycle.
j. Abiraterone and prednisone daily is started at 3 weeks (± 1 week) after the last cycle of chemotherapy, continuing until one of the conditions in Section 5.6 is met.
k. As abiraterone is given per standard of care, all assessments during these timepoints should be conducted as standard of care.
l. The Time of Progression or Change in Therapy visit will only occur if applicable. The visit can occur prior to or after the 1 Year visit (whichever comes first).
m. The 1 Year visit is defined as 12 months after C1D1 of chemo for subjects who have not yet progressed. If a patient progresses prior to 1 year, only disease and survival status to be documented at this visit (i.e. all other assessments are not required).
n. The 2 Year/End of Study visit is defined as 24 months after C1D1 of chemo for subjects who have not yet progressed. If a patient progresses prior to 2 years, only disease and survival status to be documented at this visit (i.e. all other assessments are not required).
o. If a subject progresses prior to 2 years, CTC and cfDNA samples should be collected only at the Progression/Change in Therapy visit and are not required at the 2 year/End of Study visit.

APPENDIX C: MEDICATIONS WITH THE POTENTIAL FOR DRUG-DRUG INTERACTIONS

Drugs Metabolized by Cytochrome P450 (CYP3A)

Generic Name	Brand Names ®	Generic Name	Brand Names ®
Amiodarone	Cordarone	Quinidine	
Amprenavir	Agenerase	Ritonavir	Norvir
Aprepitant	Emend	Saquinavir	Invirase
Atazanavir	Reyataz	Sertraline	Zoloft
Cimetidine	Tagamet	Telithromycin	Ketek
Clarithrymycin	Biaxin	Tetracycline	
Cyclosporine	Gengraf, Neoral, Sandimmune	Verapamil	Calan, Verelan
Delavirdine	Rescriptor	Voriconazole	Vfend
Desipramine	Norpramin		
Diltiazem	Carta, Tiazac		
Doxycycline	Vibramycin		
Efavirenz	Sustiva		
Erythromycin	Ery-tab		
Fluconazole	Diflucan	**AVOID IF POSSIBLE:**	
Fosamprenavir	Lexiva	Aminoglutethimide	Cytadren
Gingko Biloba		Bosentan	Tracleer
Ginseng		Carbamazepine	Carbatrol, Tegretol
Haloperidol	Haldol	Fosphenytoin	Cerebyx
Indinavir	Crixivan	Nafcillin	
Isoniazid		Nevirapine	Viramune
Itraconazole	Sporanox	Oxcarbazepine	Trileptal
Ketoconazole	(oral forms)	Pentobarbital	Nembutal
Lopinavir	(+ ritonavir = Kaletra)	Phenobarbital	Luminal
Metronidazole	Flagyl	Phenytoin	Dilantin
Nefazodone	Serzone	Primidone	Mysoline
Nelfinavir	Viracept	Rifabutin	Mycobutin
Nicardipine	Cardene	Rifampin	Rifadin
Norfloxacin	Noroxin	Rifapentine	Priftin
Posaconazole	Noxafil	St John's Wort	

In addition to the medications listed above, patients should also avoid eating Seville (sour) oranges, grapefruit, starfruit and their juices.

APPENDIX D: GLOSSARY OF ABBREVIATIONS AND ACRONYMS

ADR	adverse drug reaction
ADT	androgen-deprivation therapy
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AR	androgen receptor
ASAEL	Agent Specific Adverse Event List
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
CNS	central nervous system
CR	complete response
CRF	case report form
CRPC	castration resistant prostate cancer
CT	computerized tomography
CTC	circulating tumor cell
CTCAE	Common Terminology Criteria for Adverse Events
DLT	dose-limiting toxicity
DSMC	data and safety monitoring committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
FDA	Food and Drug Administration
GCP	good clinical practice
GnRH	gonadotropin-releasing hormone
HIPAA	Health Insurance Portability and Accountability Act
IEC	Independent Ethics Committee
IND	investigational new drug
IRB	Institutional Review Board
IV	intravenous
LD	longest diameter
LDH	lactate dehydrogenase
LOI	letter of intent
MRI	magnetic resonance imaging
MSKCC	Memorial Sloan Kettering Cancer Center
N	number of subjects or observations
NCI	National Cancer Institute
NIH	National Institutes of Health

PCCTC	Prostate Cancer Clinical Trials Consortium
PCRP	Department of Defense Prostate Cancer Research Program
PCWG2, PCWG3	Prostate Cancer Working Group
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PI	principal investigator
PK	pharmacokinetics
PO	per os (by mouth)
PR	partial response
PSA	prostate-specific antigen
QC	quality control
qd	quaque die (every day)
QOL	quality of life
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RP	radical prostatectomy
SAE	serious adverse event
SD	standard deviation
SD	stable disease
SGOT	serum glutamic oxaloacetic transaminase
SOP	Standard Operating Procedures
ULN	upper limit of normal
WBC	white blood cell