THE UNIVERSITY OF TEXAS MD ANDERSON CANCER CENTER

DIVISION OF CANCER MEDICINE

An Open Label Phase I/II Study of Cabazitaxel with or without Carboplatin in Patients with Metastatic Castration-Resistant Prostate Cancer.

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List of abbreviations

AE	Adverse event
ANC	Absolute Neutrophil Count
BID	Twice a Day
CAT (or CT scan)	Computed Axial Tomography
CBC	Complete Blood Count
CR	Complete Response
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EKG	Electrocardiogram
ESR	Expedited Safety Report
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigators' Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IST	Investigator-Sponsored Trial
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NSAE	Non-Serious Adverse Event
PD	Progressive Disease
PFS	Progression Free Survival
PO	By Mouth
PR	Partial Response
QD	Once Daily
QOL	Quality of Life
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SD	Stable Disease
ULN	Upper Limit of Normal
WBC	White Blood Count

1.0 INTRODUCTION AND RATIONALE

1.1 Disease Background and Trial Rationale

Docetaxel-based chemotherapy remains first-line therapy for patients with metastatic castration-resistant prostate cancer (mCRPC). This practice was established in 2004, when data from two randomized phase III trials showed a median improvement in survival of approximately two months when docetaxel-based regimens were compared to mitoxantrone (1,2). While the prolongation in survival in both studies was statistically significant, the relatively short duration of benefit underscored the need for novel agents. Although there has not been a standard second-line therapy after progression on docetaxel, mitoxantrone with corticosteroids has commonly been used based on its ability to provide symptom palliation (3). Other non-taxane microtubule targeting agents such as ixabepilone have produced only modest objective responses (in both PSA and measurable disease) in phase II trials (4). Thus, there is continued interest in identifying chemotherapy agents that are active following progression on docetaxel.

The concept that patients can respond to another taxane after progressing on docetaxel is important. The recent approval of cabazitaxel by the FDA, based upon the results of the phase III TROPIC study demonstrating a survival benefit for cabazitaxel over mitoxantrone, provides further validation of this concept (5). Cabazitaxel is a novel semi-synthetic taxane developed specifically to overcome docetaxel-resistance. In this study, mCRPC patients that had progressed during and after treatment with docetaxel were randomized to cabazitaxel (25mg/m^2 q 3wk) or mitoxantrone (12mg/m^2 q 3wk). Both arms also received daily prednisone. The median overall survival for patients treated with cabazitaxel versus mitoxantrone was 15.1 versus 12.7 months, respectively. Although not all patients in the TROPIC trial were "docetaxel-refractory" (defined by evidence of disease progression during therapy or within 30 days of the last taxane dose) it is clear that patients derived clinical benefit from cabazitaxel (6). Based on the TROPIC results, it is anticipated that cabazitaxel will become the new standard second-line therapy for patients with mCRPC who were previously treated with docetaxel. This promising advance suggests that further study of cabazitaxel is warranted to explore its potential to overcome taxane resistance.

Early studies demonstrated that platinum analogues have demonstrated modest single agent activity in patients with mCRPC. Canobbio et al. administered weekly carboplatin and reported a pooled response rate of 17%, including reductions in prostate-specific antigen (PSA) levels (7). Using a similar weekly regimen, Miglietta et al. reported that 28% of patients experienced ≥ 50% decrease in PSA levels and a mean duration of response > 6 months (8). Jungi et al. administered carboplatin on an

every-28-day schedule and reported a clinical benefit in 48% of patients, which included decreased pain, improved performance status, and stabilization of metastases (9). In all three studies, toxicities were rare.

More recent studies have demonstrated clinical responses to platinum- based therapy in combination with other agents. The addition of a platinum compound to a taxane was first proposed as a rational therapy strategy based on preclinical models of ovarian cancer demonstrating synergy between the two classes of agents (10). In patients with mCRPC, multiple phase II studies have demonstrated significant activity of regimens combining carboplatin with a taxane and estramustine in the front-line setting (11-13). Several studies, however, have cast doubt on the contribution of estramustine to taxane/carboplatin regimens, particularly since estramustine is associated with higher toxicity (14,15). Ross et al., tested the activity of docetaxel/carboplatin in 34 patients that had progressed during or within 45 days after the completion of docetaxel (16). PSA declines of $\geq$50% were noted in 18 % of patients and measurable responses in 14% of patients. The median duration of PSA response was 5.7 months and the therapy was well tolerated. As patients in this study would not be anticipated to respond to "re-challenge" with docetaxel alone, these results support the hypothesis that carboplatin has the potential to overcome docetaxel resistance mechanisms. It has also been proposed that the activity of platinum agents in mCRPC is linked to a subset of advanced cancers with heterogeneous morphology that display a clinical course reminiscent of small-cell prostate carcinomas (SCPCs). We have named these variants "anaplastic" based on shared clinical features with SCPC, including their responsiveness to platinum-based chemotherapy (17,18).

As predicted from their non-overlapping toxicity profiles, the addition of carboplatin to a taxane appears to be safe and well-tolerated. In a recent study of paclitaxel/carboplatin therapy in 25 patients with mCRPC previously treated with docetaxel, Grade 3 or 4 adverse hematologic events occurred in 11/25 (44%) patients but without neutropenic fever or grade 3-4 non-hematological toxicity (19). In a small series of patients with mCRPC who received docetaxel/carboplatin after prior taxane-based therapy, mild to moderate fatigue was the main adverse event reported (20). There were no episodes of febrile neutropenia or peripheral neuropathy reported. In a third study of docetaxel/carboplatin in 34 patients with mCRPC who were refractory to docetaxel, Grade 3 or 4 adverse events occurred in 56% of patients but with only one episode of febrile neutropenia (16). The use of growth-factor support was not described in these three reports.

With this background, there is a compelling biologic and clinical rationale to combine cabazitaxel with carboplatin. The purpose of the present study is to test the hypothesis that the addition of carboplatin to cabazitaxel will be

superior to cabazitaxel alone in the patients with mCRPC. Using a randomized, open-label phase II study design, we hypothesize that progression-free survival will be longer in patients treated with cabazitaxel/carboplatin vs cabazitaxel alone.

The primary endpoint of this study is to demonstrate a 50% improvement in median progression free survival (from 2.8 to 4.2 months) when carboplatin is added to cabazitaxel versus cabazitaxel alone in patients with mCRPC.

Progression Free Survival (PFS) is the primary endpoint. PFS will be a composite endpoint defined as the time from study entry to first occurrence of **any** of the following:

- Progression of measurable disease by RECIST criteria. To be considered measurable, baseline lymph nodes, visceral metastases, and soft tissue metastases must be $\geq$ 1.5 cm in longest dimension. Equivocal RECIST progression must be confirmed by a follow up scan $\geq$ 6 weeks later.
- Two or more new areas by bone scan attributable to prostate cancer (rather than flare) OR new/increasing size of lytic lesions by CT scan or MRI. Equivocal progression on bone scan must be confirmed by other imaging modalities (eg, CT or MRI) and/or performing a confirmatory bone scan $\geq$ 6 weeks later.
- Need for palliative radiation involving more than one site
- Surgery or kyphoplasty to any neoplastic bone lesion
- Cancer-associated clinical deterioration as determined by the treating physician.
- Receipt of any additional prostate cancer specific therapy as prescribed by the treating physician.

PSA progression alone will not be used to define progression.

With regard to secondary endpoints, we will explore the potential for biochemical markers of bone turnover to predict response to therapy. Skeletal complications are a major cause of morbidity and mortality in men with CRPC. Previous studies have demonstrated that bone specific alkaline phosphatase (BAP) and urine N-telopeptides (uNtx) correlate with the presence and extent of bone metastases, prognosis, and response to treatment (21-23). In this study, we will further explore the potential for BAP and uNtx as predictive and prognostic biomarkers in patients with mCRPC receiving cabazitaxel-based therapy.

1.2 Drugs

Cabazitaxel (also known as XRP6258 and RPR116258A) is a new taxoid, which promotes tubulin assembly *in vitro* and stabilizes microtubules against cold-induced depolymerization as efficiently as docetaxel. Cabazitaxel was selected for development based on its pharmacological profile, including a

reduced recognition by the P-glycoprotein (coded by mdr-1 gene), efficacy in a broad spectrum of tumor models sensitive as well as resistant or refractory to docetaxel and activity against intra-cranial tumors.

Three single-agent dose and schedule finding studies in solid tumors (V101-103) to determine the Maximum Tolerated Dose (MTD) and dose-limiting toxicities (DLT) of cabazitaxel in patients with advanced solid tumors have been completed (24-26). These studies have demonstrated a promising safety profile and early clinical activity especially in patients with breast cancer, sarcoma, and prostate cancer. A total of 77 patients were treated with approximately 241 cycles of the treatment. Doses of 10-30 mg/m^2 were administered as a one-hour infusion every three weeks in studies V-101 and 103. The MTD in study V-101 was 30 mg/m^2, while it was 25 mg/m^2 in study V-103. The DLTs were grade 4 neutropenia >5 days and febrile neutropenia in V-101 while grade 3 diarrhea at 15 mg/m^2 and febrile neutropenia and grade 4 neutropenia > 5 days at 25 mg/m^2 were DLTs in study V-103. 1.5-12 mg/m^2 doses were administered as a one-hour infusion weekly for 4 weeks followed by one-week rest in study V-102. The MTD in study 102 was 12 mg/m^2 while the DLT was grade 3 diarrhea. Major treatment emergent adverse events reported regardless of relationship in these phase 1 studies were: Fatigue (62-88%), Diarrhea (52-76%), Pain Due to Tumor (43-77%), Nausea (32-72%), Sensory Neuropathy (24-60%), Vomiting (24-44%) Infection/Febrile Neutropenia (19-39%), Fever (19-33%), Cough (13-29%), Dyspnea (13-36%), and Bone Pain (7-28%).

Serious adverse events (SAEs) occurred with similar frequency in study V-101 and V-102 (42.9 and 45.2%, respectively), while they occurred in 24% of patients in study V-103. The most common SAE was febrile neutropenia and most of the SAEs occurred in 1or 2 patients. In study V-101, two patients withdrew from the study due to neutropenic infection and peripheral ischemia, and 17 deaths were reported, all due to disease progression. In study V-102, eight patients withdrew due to adverse events (2 asthenia, 1 sensory neuropathy, 1 diarrhea, 1 peripheral edema, 1 dysuria/hematuria, 1 bile duct obstruction, and 1 elevated transaminases), and 15 deaths were reported, all due to disease progression, except one death due to pneumonia. In study V-103, no patient withdrew from the study due to adverse events, and 22 deaths were reported, all due to disease progression.

Because of differing MTD reached in studies, the dose of 20 mg/m² administered every 3 weeks as a one-hour intravenous (IV) infusion was initially selected for further development. A Phase II study (Study ARD6191/2001) was performed in metastatic breast cancer (MBC) patients who were resistant to prior taxane therapy given either as adjuvant therapy (Stratum 1) or as first-line or second-line therapy (Stratum 2) (27). Safety and anti-tumoral activity were assessed at the dose of 20 mg/m² every 3 weeks at

the first cycle, with possible intra-patient escalation to 25 mg/m^2 at Cycle 2 was allowed in the absence of any toxicity grade >2 at Cycle 1. A total of 71 patients were treated with a total of 345 cycles of treatment in Arm A. Two (2) CR and 8 PR were observed in as treated patients with an overall response rate (ORR) of14.1%. The response rates were 14.6% and 9.5% in stratum 1 and stratum 2, respectively. The median progression free survival time (PFS) was 2.7 months and the median overall survival (OS) was 12.3 months. Grade 3 or 4 neutropenia was reported in 73% in the overall population. Major treatment emergent adverse events reported regardless of relationship in this phase II study were Fatigue (51%), Nausea (44%), Diarrhea (40%), Myalgia (25%), Anorexia (25%), Weight loss (25%), Vomiting (24%) Infection/Febrile Neutropenia (18%), Headache (18%), Sensory Neuropathy (17%), Constipation (16%), and Bone Pain (16%).

In this study, 29.6% of patients reported serious adverse events; most common SAEs were hypersensitivity reaction (4.2%), and infection without neutropenia (4.2%). Four patients withdrew from the study due to non-fatal adverse events (2 elevated transaminases, 1 hepatitis, 1 hypersensitivity reaction), while 52 deaths were reported during the study, 50 of them were due to disease progression, 1 patient died due to unknown cause, while the other died due to shock with respiratory failure. One phase I/II study combining Cabazitaxel with capecitabine in Metastatic Breast Cancer patients whose disease progressed after anthracycline and taxane is ongoing. The MTD in this study was reached with Cabazitaxel at 20mg/m^2 on Day 1 and capecitabine at 1,000 mg/m^2 bid day1 –14, Q3W. Patients in the part 2 component of the study are being treated with this dose. Cabazitaxel at 25 mg/m^2 in combination with Prednisone every 3 weeks was recently investigated in a phase III randomized study in hormone refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen. Preliminary safety data from both the above studies have shown an acceptable safety profile of cabazitaxel either in combination with capecitabine or with prednisone.

In the recently completed TROPIC trial, the most common toxic effects of cabazitaxel were hematological (5). The most frequent hematological grade 3 or higher adverse events were neutropenia (82%), leukopenia (68%), and anemia (11%). The incidence of febrile neutropenia was 8% but these events occurred prior to the routine incorporation of growth factor support. The most common nonhematological grade 3 or higher adverse event was diarrhea, which was managed expectantly. Grade 3 peripheral neuropathy was uncommon (reported in three [1%] patients). Overall, peripheral neuropathy (all grades) was reported during the study in 52 (14%) patients in the cabazitaxel group. Peripheral edema (all grades) occurred in 34 (9%) patients.

Taxanes (paclitaxel or docetaxel) are now commonly used in combination with platinum agents (Cisplatin or Carboplatin). The duplets have become the mainstay of treatment for NSCLC, ovarian cancer, and several other common tumor types (28-31) . A phase I study of weekly Docetaxel and Carboplatin (continuous weekly therapy for up to 12 weeks) showed DLT (grade 3/4 myelotoxicity) at doses of Docetaxel 35 mg/m^2 and Carboplatin AUC: 2.5. The MTD on this continuous weekly regimen was Docetaxel: 35 mg/m^2 and Carboplatin AUC: 2 weekly (32). A phase II study of docetaxel (75 mg/m^2) and carboplatin (AUC=6) as second-line treatment in NSCLC showed the median survival was 31 weeks and 1-year survival was 32% (33). For a full list of adverse events related to treatment with carboplatin, please reference the prescribing information at the following link:

http://www.health.gov.il/units/pharmacy/trufot/alonim/242.pdf

2.0 OBJECTIVES

2.1 Primary Objectives

- To determine the maximum tolerated dosage (MTD) of cabazitaxel-carboplatin in the phase I portion of the study.

- To evaluate progression free survival achieved with cabazitaxel-carboplatin versus cabazitaxel alone in men with metastatic castration resistant prostate cancer (mCRPC) in the phase II portion of the study.

  The objective of this study is to demonstrate a 50% improvement in median progression free survival (from 2.8 to 4.2 months) when carboplatin is added to cabazitaxel versus cabazitaxel alone in patients with mCRPC.

Progression Free Survival (PFS) is the primary endpoint. PFS will be a composite endpoint defined as the time from study entry to first occurrence of **any** of the following:

- Progression of measurable disease by RECIST criteria. To be considered measurable, baseline lymph nodes, visceral metastases, and soft tissue metastases must be ≥1.5 cm in longest dimension. Equivocal RECIST progression must be confirmed by a follow up scan > 6 weeks later.
- Two or more new areas by bone scan attributable to prostate cancer (rather than flare) OR new/increasing size of lytic lesions by CT scan or MRI. Equivocal progression on bone scan must be confirmed by other imaging modalities (eg, CT or MRI) and/or performing a confirmatory bone scan ≥6 weeks later.
- Need for palliative radiation involving more than one site
- Surgery or kyphoplasty to any neoplastic bone lesion
- Cancer-associated clinical deterioration as determined by the treating physician.

- Receipt of any additional prostate cancer specific therapy as prescribed by the treating physician.

PSA progression alone will not be used to define progression.

2.2 Secondary Objectives

- To assess PSA response rate (percentage of patients with ≥50 % decline)
- To correlate changes in bone specific alkaline phosphatase and urine n-telopeptides with response
- To evaluate overall survival. Overall survival is defined as the time interval between the time of study entry and date of death.
- To evaluate safety and toxicity
- To evaluate influence of the anaplastic phenotype on response to therapy
- To collect and archive serum, plasma, and urine samples in study patients for later hypothesis generating associations.

3.0 STUDY PLAN

3.1 Description of the Protocol

This is a multi-center, open label, randomized phase I/II study. Prior to initiating randomization, a dose-escalation phase I study will be conducted (at MDACC only) to identify the starting doses of cabazitaxel and carboplatin to be used in combination for cycle #1 in arm B (see section 5.0). Once those doses are established, eligible patients will subsequently be randomized 1:1 during the phase II portion of the trial to treatment with either:

(A) Cabazitaxel alone 25 mg/m^2, plus prednisone

or

(B) Cabazitaxel (25 mg/m^2) + carboplatin (AUC 4), plus prednisone

All patients receiving treatment in both arms will receive primary prophylaxis with colony stimulating factor, either filgrastim or pegfilgrastim.

Randomization between the two treatment arms will occur during the phase II portion of the trial. Randomization will be stratified based on:

- ECOG PS 0 versus ECOG 1/2
- Chemotherapy naïve vs received prior docetaxel-based chemotherapy (responder) vs. received prior docetaxel-based chemotherapy (non-responder) vs. received prior chemotherapy other than docetaxel

- Anaplastic phenotype (as defined in Inclusion criteria #2) vs adenocarcinoma

3.2 Duration of Study Participation

Each patient will be treated until disease progression, death, unacceptable toxicity, patient withdrawal, or for a maximum of ten cycles.

4.0 SELECTION OF PATIENTS

This study will enroll castrate-resistant prostate cancer patients with metastatic disease.

4.1 Inclusion Criteria

Inclusion Criteria for All Patients

1. Histologic evidence of prostate adenocarcinoma.

2. In addition to patients with adenocarcinoma, patients with "anaplastic" features are also eligible as defined by **at least one** of the following:
   a) Histologic evidence of small cell prostate cancer (patients with small cell carcinoma on histology are not required to demonstrate castration-resistant progression)

   b) Any of the following metastatic presentations:
      (i) exclusive visceral metastases
      (ii) radiographically predominant lytic bone metastases identified by plain X-ray or CT scan
      (iii) bulky (≥5 cm in longest dimension) lymphadenopathy
      (iv) Bulky (≥5cm) tumor mass in the prostate/pelvis
      (v) Low PSA (≤ 10 ng/ml) at initial presentation (prior to androgen ablation or at symptomatic progression in the castrate-setting) plus high volume (≥20) bone metastases
      (vi) Elevated serum LDH (≥ 2 x ULN) or elevated serum CEA (≥ 2 x ULN) in the absence of other etiologies
      (vii) Short interval (≤ 180 days) to castrate-resistant progression following initiation of hormonal therapy

3. Castration-resistant prostate cancer. Patients must have surgical or ongoing chemical castration (with LHRH agonists or LHRH antagonists), with a baseline testosterone level < 50ng/dL.

4. Metastatic disease. Patients must have evidence for metastatic prostate cancer by bone scan and/or CT/MRI (i.e., soft tissue, visceral, lymph node). If lymph node, visceral and/or soft-tissue metastases are the only evidence of metastasis, at least one lesion must be ≥1.5 cm in diameter.

5. Patients may have received prior treatment with androgen ablative therapies (such as bicalutamide, ketoconazole, DES, abiraterone, Xtandi, ARN-509) and/or "targeted" therapies (such as tyrosine kinase inhibitors). Androgen ablative therapies must be discontinued ≥3 days prior to initiation of study treatment with the exception of abiraterone and/or enzalutamide, which may be continued during study treatment per the practice preference of the treating physician. Patients who are predicted to benefit from an antiandrogen withdrawal response should be tested for this possibility before being considered for eligibility to this study. Targeted therapies must be discontinued ≥ 2 weeks before initiation of study treatment.

6. Both chemotherapy-naïve and patients previously treated with chemotherapy are eligible. Chemotherapy pretreated patients may have received a maximum of two prior systemic cytotoxic chemotherapies completed at least 3 weeks prior to initiation of study treatment.

7. Patients must have documented evidence of progressive disease as defined by any of the following:
   a) PSA progression: minimum of 2 rising values (3 measurements) obtained a minimum of 7 days apart with the last result being at least ≥ 2.0 ng/mL
   b) New or increasing non-bone disease (RECIST)
   c) Positive bone scan with 2 or more new lesions (PCWG2).

8. For purposes of stratification, patients will be categorized as "responders" or "non-responders" based on their response to prior docetaxel-based therapy.
   - Responders will have demonstrated objective responses to first-line docetaxel as determined by **any** of the following:
     1. Decrease in PSA level ≥50% from baseline, maintained for ≥6 weeks
     2. Partial or complete response in lymph nodes and soft tissue metastases by RECIST

     Responders must have received ≥ 225mg/m^2 (~ 3 cycles) of docetaxel.

   - Patients not meeting response criteria above will be considered as non-responders. We anticipate 2 general categories of non-responders based on the following disease phenotypes:
     1. Progressive disease on therapy without any objective evidence of response ("primary-resistant disease")
     2. Progressive disease on therapy with prior objective evidence of response, but response duration is ≤ 6 weeks ("docetaxel refractory disease").

     Non-responders are eligible even if they have received <225mg/m^2 of docetaxel

9. If present, peripheral neuropathy must be ≤ grade 2

10. The following pretreatment laboratory data within 14 days before registration:
    a) Absolute neutrophil count (ANC) ≥ 1,500/ml(unless due to bone marrow infiltration by tumor in which case ANC ≥500/ml are allowed)
    b) Platelets ≥ 100,000/ml (unless due to bone marrow infiltration by tumor in which case ≥50,000/ml are allowed)
    c) Total bilirubin ≤ Upper Limit of Normal with the exception of isolated hyperbilirubinemia due to Gilbert's syndrome or if the patient has liver metastases and/or acute tumor-associated illness ≤ 4x ULN.
    d) SGPT, (ALT) AND/OR SGOT (AST) ≤ 1.5 × the ULN or if patient has liver metastases and/or acute tumor-associated illness, ≤ 4x ULN.
    e) Patient has creatinine clearance ≥30 ml/min. using the Cockroft-Gault equation.

11. Men whose partner is a woman of childbearing potential must be willing to consent to using effective contraception while on treatment and for at least 3 months thereafter.

12. Patient or his legally authorized representative must provide written informed consent.

13. Age ≥ 18

14. ECOG performance status ≤ 2

4.2 Exclusion Criteria

1. 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.

2. Samarium-153 within 28 days of registration, or Strontium-89 within 12 weeks (84 days) of registration. Patients who have received 2 or more doses of bone-seeking radioisotopes are not eligible.

3. Current treatment on another therapeutic clinical trial.

4. Prior treatment with cabazitaxel and/or carboplatin

5. Impending complication from bone metastases (fracture and/or cord compression). Properly treated or stabilized fractures and/or cord compression is allowed.

6. Presence of ongoing urinary obstruction (e.g., urinary retention, hydronephrosis) requiring medical intervention. Properly treated urinary obstruction is allowed.

7. Patient has an uncontrolled intercurrent illness (e.g., uncontrolled diabetes, uncontrolled hypertension).

8. Patient has another serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the patient's ability to provide informed consent or with the completion of treatment according to this protocol.

9. Patients with a history of severe hypersensitivity reaction to JEVTANA® (cabazitaxel) or other drugs formulated with polysorbate 80.

10. 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.

5.0 STUDY DRUG ADMINISTRATION

5.1 Dosing Regimens for phase I

Prior to initiating the randomized phase II portion of the study, a dose escalation phase I schema will be utilized to acquire safety data and select the optimal starting doses of cabazitaxel and carboplatin for cycle # 1 for subsequent patients enrolled on Arm B.

As shown below, cohorts of 3 to 6 patients will be treated with cabazitaxel and carboplatin every 3 weeks. The starting dose for cabazitaxel will be 20 mg/m^2 and the starting dose for carboplatin will be an AUC of 3 (dose level 0).

Table 1. Dose Escalation Schedule

	Cabazitaxel	Carboplatin
0	20	AUC 3
1	20	AUC 4
2	25	AUC 4

The dose escalation criteria as described in Table 1 must be met at each dose level during cycle 1 in order to enroll and treat patients at the next dose level.

Applying the 3+3 design, the first cohort of 3 patients will be treated at dose level 0. The algorithm is as follows: (1) If 0 out of 3 patients experiences DLT, the next cohort of 3 patients will be treated at the next higher dose level. (2) If 1 out of 3 patients develop a DLT, additional 3 patients will be treated at the same dose level. If no more DLT develops at the dose, i.e. 1 out of a total of 6 patients develops DLT, the dose escalation continues for the next cohort of 3 patients.
(3) At any given dose, if greater than 1 out 3 patients or 1 out of 6 patients experience DLT, the dose level exceeds the MTD and 3 more patients will be treated at the next lower dose if there are less than 6 patients already treated at that dose. The MTD is the highest dose studied in which one or fewer of 6 patients have a DLT.

Dose-Limiting Toxicities (DLT) and Maximum Tolerated Dose (MTD):
To qualify for DLT, the clinical adverse event (AE) or laboratory abnormality should be drug related as assessed by the treating physician, principal investigator, or sponsor. The DLTs will be defined (according to NCI-CTCAE v 4 grading scale) during the first treatment cycle as follows:

Non-hematological toxicity (grade 3 or 4 only) except:
- Grade 3 fever without documented infection
- Grade 3 nausea, vomiting, or diarrhea in the absence of effective maximal therapy
- Grade 3 mucositis/stomatitis in the absence of effective symptomatic treatment
- Grade 3 fatigue
- Grade 3 anorexia
- Grade 3 Liver function test abnormalities elevation that returns to baseline prior to next treatment cycle
- Peripheral neuropathy grade 3 that returns to grade 1 or less at the initiation of next treatment cycle

Hematological toxicity:
- Febrile neutropenia: fever with clinically or microbiologically documented infection $\geq 38.5°C$ with neutropenia grade 3 or 4
- Neutropenia grade 4 lasting >7 days

- Thrombocytopenia grade 4 >7 days

In case of the occurrence of one DLT at the first cycle, 3 additional patients will be included at the same dose level in order to reach the total number of 6 evaluable patients. A patient will be considered to be evaluable for the toxicity if s/he has received at least one administration of Cabazitaxel and has adequate follow-up in the 1st cycle. Patients who are not treated or are withdrawn during the first 3 weeks of treatment for reasons other than DLT and before the MTD is determined will be replaced.

Analysis of safety data from these patients will be utilized by the Principal Investigator and Supporter to select the optimal starting doses of cabazitaxel to be used in combination with carboplatin for subsequent patients enrolled on the Randomized Phase II portion of the study. Although we do not expect severe toxicity with the proposed combinations, we will assure patient safety through clinical vigilance during the combination phase. The assigned research nurse and the Principal Investigator will review all study patients at weekly intervals during the combination treatment portion of the trial. Any unusual clinical observations will be discussed immediately with the Principal Investigator or a sub-investigator if the PI is absent or not available.

Results from these analyses will be reported to an independent Data Monitoring Committee (DMC) convened at MDACC. The DMC will assess results along with supportive data including other efficacy outcomes and safety data. It will use this data to possibly recommend early stopping or other study modifications.

5.2 Dosing Regimens for phase II

Arm A: Cabazitaxel 25 mg/m² intravenously on Day 1 of each 3 week cycle, plus prednisone 5 mg PO BID.

Arm B: Cabazitaxel 25 mg/m² + carboplatin AUC 4 intravenously on Day 1 of each 3 weeks cycle, plus prednisone 5 mg PO BID

All patients in Arms A and B will receive primary prophylaxis with colony stimulating factor, either filgrastim or pegfilgrastim.

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

5.3 Pre-medications:
Cabazitaxel will be given before carboplatin to limit myelosuppression. Required IV premedications 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 premedications will be administered by IV infusion, at least 30 minutes prior to each dose of cabazitaxel. Antiemetic

prophylaxis with ondansetron, granisetron, or dolasetron can be administered whenever it is necessary.

All patients will receive primary prophylaxis with growth factor support per standard practice.

5.4 Description of Cycles/Treatment Delay
Each cycle will be 3 weeks in duration. For cycles 2 through 10, new cycles of therapy may not begin until ANC $\geq$ 1,500/mm^3, platelet count $\geq$ 75,000/mm^3, and non-hematological toxicities (except alopecia) have recovered to grade $\leq$ 1. Patients will be monitored closely for toxicity. In addition to optimizing supportive care, chemotherapy doses may be adjusted after the first cycle of therapy and/or recovery to grade $\leq$ 1. Each patient will be treated until disease progression, death, unacceptable toxicity or for a maximum of up to ten cycles. At completion of study treatment, prednisone may be discontinued per the practice preference of the treating physician.

5.5 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. Concomitant use with strong CYP3A4 inducers is expected to reduce cabazitaxel concentrations, and should be avoided if possible. Consider alternative therapies that do not inhibit or induce the CYP3A4 isoenzyme.

6.0 PATIENT EVALUATION

6.1 Pretreatment Evaluation:

6.1.1 History and physical examination within 28 days of trial registration, to include: prior local therapies, prior and/or current hormonal treatment, prior systemic therapies (chemotherapy, strontium-89, etc), current symptoms and performance status, current medications and cardiovascular assessment, residual toxicities from prior therapies should be recorded using CTCAE v.4.0, vital signs, height and weight.

6.1.2 Laboratory studies to be obtained within 28 days of trial registration: serum chemistries (sodium, potassium, chloride, carbon dioxide, magnesium, glucose, calcium, phosphorus, BUN, albumin, total protein, bone specific and total alkaline phosphatase, total bilirubin, LDH), testosterone, PSA, CEA, PAP, chromogranin A, calcitonin, somatostatin, Circulating Tumor Cells (CTCs) and urine for N-telopeptides.

6.1.3 Laboratory studies within 14 days of trial registration: CBC with differential and platelets, creatinine, ALT and/or AST, total bilirubin

6.1.4 Between 42 days prior and 28 days after trial registration, patients with small cell cancer must have an MRI scan of the brain or CT scan of the brain with IV contrast. Patients with anaplastic cancer (i.e. those meeting by criteria OTHER than small cell) should be strongly considered for brain imaging according to the same guidelines at the final discretion of the treating physician.

6.1.5 Within 28 days prior to trial registration, ECG, bone scan, chest x-ray, and CT or MRI scan of the abdomen /pelvis. Patients with abnormal findings on chest x-ray should have chest CT scan per the judgment of the treating physician.

6.1.6 MDACC Only:

With consent of the patient, blood, bone marrow biopsy and aspirate will be collected within 28 days of treatment start for all patients enrolled on the phase II portion of the study (see Appendix D). Previously collected specimens (if obtained and available within 12 weeks of protocol entry) may be requested to substitute for the pre-treatment procedure (to obviate the need for a second biopsy prior to initiating therapy on study). For patients enrolled on the phase I portion of the study, this procedure is optional. Patients on the phase II portion of the study will also be asked for optional collections at time of best response and/or progressive disease.

6.2 On-study Evaluation:

6.2.1 **Before every cycle of chemotherapy (+2 days),** disease specific physical examination (by physician and/or advanced practice nurse), interim history pertaining to any change from baseline, current medications, assessment of ECOG performance status, and treatment-related toxicities will be taken. Laboratory studies should include CBC with differential and platelets and serum chemistries (sodium, potassium, chloride, carbon dioxide, glucose, magnesium, calcium, phosphorus, albumin, total protein, BUN, creatinine, LDH, AST and/or ALT, total alkaline phosphatase, total bilirubin), bone specific alkaline phosphatase, PSA and urine for N-telopeptides. Lab studies should be performed within 7 days prior to each cycle of chemotherapy.

At each visit and when reported by the patient, concomitant treatments and medications must be recorded.

6.2.2 **After each cycle of chemotherapy**: Laboratory studies including CBC with differential and platelets, electrolytes (sodium, potassium, chloride, carbon dioxide), BUN, creatinine, magnesium, total bilirubin and ALT and/or AST are to checked 7-10 days after the administration of cycle #1 of chemotherapy. For subsequent cycles, these labs are strongly recommended but not mandated.

6.2.3 **After every 2 cycles of chemotherapy,** tumor response will be assessed. This should include bone scan and CT or MRI scan of abdomen/pelvis. Patients with abnormal findings on baseline CT scan of the chest should have repeat chest CT scan per the judgment of the treating physician.

Tumor response will be assessed after every 2 cycles of therapy. In practice, this will correspond to evaluations performed prior to initiating cycles 3, 5, 7, 9 and 10 of therapy. Two cycles will typically take 6 weeks. However, since up to a 2 week delay in treatment for any reason is permitted, 2 cycles may last up to (and including) 8 weeks. Restaging studies should be performed within 7 days of initiating the next cycle of chemotherapy.

Testosterone will be repeated at restaging timepoints. CEA, PAP and CTCs will be repeated at restaging timepoints **IF** elevated at baseline.

6.2.4 **Optional blood/tissue collection at maximal response and at disease progression (MDACC only).** At the time of maximal response and/or at End of Treatment, blood, bone marrow biopsy and aspirate will be collected **as described in** Appendix D. Maximal response will be determined by the treating physician when PSA levels have reached a nadir and/or radiographic studies demonstrate best overall response.

6.2.5 **End of Treatment evaluation.** +/-14 days of the time when the patient is taken off treatment, the following will be obtained:

- Physical examination, interim history pertaining to any change from baseline, current medications and treatment-related toxicities will be taken and recorded.
- CBC with differential and platelets and serum chemistries (sodium, potassium, chloride, carbon dioxide, glucose, magnesium, calcium, phosphorus, albumin, total protein, BUN, creatinine, LDH, AST and/or ALT, total alkaline phosphatase, total bilirubin), bone specific alkaline phosphatase, PSA, testosterone and urine for N-telopeptides. CEA, PAP and CTCs will only be performed IF elevated at baseline.
- Imaging studies used for the assessment of response (bone scan, CT or MRI of abdomen and pelvis will be obtained if not done within 28 days of the off-treatment date. Patients with abnormal findings on baseline CT scan of the chest should have repeat chest CT scan per the judgment of the treating physician.

6.2.6 Survival update: Survival updates will take place at 6 month intervals from the off treatment date. This will consist of a phone call or medical record review

6.3 Study Calendar

	Screening	Cycle	Day 7 -10 (cycle 1 only)	After Every 2 cycles	End of Treatment[i]	Follow-Up[f]
Chemotherapy		x				
Medical History	x[a]	x			x	
Physical examination	x[a]	x			x	
Height and Weight	x[a]					
ECOG performance status	x[a]	x			x	x
Adverse Event Monitoring		x				
CBC, differential, platelet count	x[c]	x	x[e]		x	
Serum Chemistry[d]	x[a,c]	x	x[e]		x	
Testosterone	x			x		
PSA, Bone Specific Alkaline Phosphatase, uNTX,	x[a]	x			x	
CEA, PAP, Circulating Tumor Cells (CTCs)	x[a]			x[g]	x[g]	
chromogranin A, calcitonin, somatostatin	x[a]					
CT/MRI Abd and Pelvis	x[a]			x	x	
Chest X-ray	x[a]					
CT/MRI of the chest	x[j]			x[j]	x[j]	
Bone scan	x[a]			x	x	
Brain CT or MRI scan	x[b]					
ECG	x[a]					
Survival Follow-up						x
Blood for Correlative Studies	x[h]	x[h]			x[h]	
BMA/BX for Correlative Studies	x[h]				x[h]	

a Within 28 days of registration

b Between 42 days prior and 28 days after trial registration, patients with small cell cancer must have an MRI scan of the brain or CT scan of the brain with IV contrast. Patients with anaplastic cancer (i.e. those meeting by criteria OTHER than small cell) should be strongly considered for brain imaging according to the same guidelines at the final discretion of the treating physician.

c Within 14 days of registration

d Serum chemistries consist of sodium, potassium, chloride, carbon dioxide, glucose, magnesium, calcium, phosphorus, albumin, total protein, BUN, creatinine, LDH, AST and/or ALT, total alkaline phosphatase, total bilirubin,. At screening, creatinine, ALT and/or AST, and total bilirubin must be done within 14 days of registration. The remaining chemistry tests must be done within 28 days of registration.

e Laboratory studies to be done Day 7 to 10 of Cycle 1 include CBC with differential and platelets, electrolytes (sodium, potassium, chloride, carbon dioxide), BUN, creatinine, magnesium, total bilirubin and ALT and/or AST are to be checked 7-10 days after the administration of Cycle 1 of chemotherapy. For subsequent cycles, these labs are strongly recommended but not mandated.

f Every 6 months from off treatment date.

g Only repeat IF elevated at baseline.

h For patients on phase II: blood, bone marrow biopsy and aspirate will be collected for correlative studies at screening (mandatory) and again at the time of maximal response and/or at disease progression (optional). Blood will also be collected after every 3 weeks before each cycle.

i Within 14 days of stopping treatment on the study. Imaging scans will only be repeated at this visit if not done within the past 28 days.
j At the judgment of the treating physician

7.0 CORRELATIVE STUDIES (MD ANDERSON ONLY)

In an attempt to develop biomarkers that predict response to taxane-based therapy, blood, bone marrow aspirate, and tissue will be collected, analyzed and archived to serve as a resource for future IRB approved studies. Refer to Appendix D for collection and storage procedures. Refer to Appendix H for description of biomarker analysis.

All samples will be encoded with a unique identifier at the time of collection. This unique identification number will be cross-referenced to the GU Research Laboratory database that stores the medical records of the patients who have consented to this protocol. Access to the database is limited to the research personnel of the GU Medical Oncology research office. All requests for use of this material must be in the context of IRB approved protocols.

8.0 DOSE MODIFICATIONS/TOXICITY MANAGEMENT FOR CYCLES 2 THROUGH 10

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 v4.0 (CTCAE v4.0). 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.

If cabazitaxel and carboplatin treatment must be delayed due to 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.

8.1 Dose reductions

The cabazitaxel dose can be reduced one time from 25 to 20 mg/m^2 when necessary as described below. The carboplatin dose can be reduced two times from AUC 4 to AUC 3, and from AUC 3 to AUC 2 when necessary as described below. Once reduced, doses cannot be re-escalated.

Table 3. Permissible Dose Reductions

	Initial dose	First Dose Reduction	Second Dose Reduction	Third Dose Reduction
cabazitaxel	25 mg/m^2	20mg/m^2	None, must come off treatment	Not applicable
carboplatin	AUC 4	AUC 3	AUC 2	None, must come off treatment

8.2 Dose modifications for hematologic toxicity

No dose reductions or interruptions are required for anemia as it 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, 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.

Table 4: Dose modifications for hematologic toxicity, worst grade during previous cycle[1].

	Arm A	Arm B	
Toxicity	Cabazitaxel[2]	Cabazitaxel[2]	Carboplatin[3]
Grade 3-4 neutropenia for < 7days	None	None	None
Grade 4 neutropenia for >7 days	Dose Reduce	Dose Reduce	None
Grade 3-4 febrile neutropenia	Dose Reduce	Dose Reduce	Dose Reduce
Grade 4 Thrombocytopenia	Dose Reduce	None	Dose Reduce

[1]All toxicities encountered during the study will be evaluated according to the grading system in NCI Common Terminology Criteria for Adverse Events v4.0 (CTCAE v4.0).
[2]May reduce cabazitaxel to a minimum dose of 20 mg/m^2. If further toxicity, the patient must come off treatment.
[3]May reduce carboplatin to a minimum dose of AUC 2. If further toxicity, the patient must come off treatment.

8.3 Dose modifications for hepatic toxicity
In case of increase of ALT and/or AST to > 1.5 x ULN or bilirubin to > ULN, delay study drug treatment for up to 2 weeks until ALT and/or AST returned to ≤ 1.5 x ULN and bilirubin to ≤ ULN. In patients with liver metastases who had elevated values at baseline up to ≤ 4x ULN, delay study treatment for up to 2 weeks until ALT and/or AST and/or bilirubin

have returned to ≤baseline values. Then retreat patient at reduced dose of cabazitaxel for the next cycle. The cabazitaxel dose may be reduced to a minimum of 20 mg/m2.

8.4 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 ≥ 16 ml/min based on the Cockroft-Gault formula within 2 weeks of treatment interruption, treatment can be resumed at the prior carboplatin dose.

8.5 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. If further toxicity, the patient must come off treatment.
If despite dose reduction, nausea/vomiting still occur at grade ≥ 3, the patient will go off treatment.

8.6 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. If despite dose reduction, diarrhea still occurs at grade ≥3, the patient will go off study.

8.7 Hypersensitivity Reactions

Hypersensitivity reactions that occur despite premedication are very likely to occur within a few minutes of start of the first or of the second infusion of cabazitaxel. Therefore, during the 1st and the 2nd infusions, careful evaluation of general sense of wellbeing and of blood pressure and heart rate will be performed for at least the first 15 minutes, so that immediate intervention would occur in response to symptoms of an untoward reaction. Facilities and equipment for resuscitation along with the medications (i.e., antihistamine, corticosteroids, and epinephrine) must be immediately available. If a reaction occurs, the specific treatment that can be medically indicated for a given symptom (e.g., epinephrine in case of anaphylactic shock, etc.) will be instituted as per Institutional Guidelines and/or physician preference. For management suggestions of acute hypersensitivity, please see Appendix E.

8.8 Stomatitis

If grade 3 or worse stomatitis occurs, study drug(s) should be withheld 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 stomatitis, the patient will go off treatment.

8.9 Peripheral neuropathy

In case of symptoms or signs experienced by the patient, dose modification should be performed
Grade ≤1: No change
Grade 2: Re-treat with reduced dose of cabazitaxel
Grade 3: Patient will go off protocol therapy

8.10 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 attending physician and the PI concur that this is to the benefit of the patient.

For other Grade 2 non-hematological toxicity that is troublesome and intolerable, treatment should be held 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 4 non-hematological toxicity, treatment must be held and patient re-evaluated. If toxicity resolves to Grade 1 or less, 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 will be resumed with a reduced dose of cabazitaxel.

Recurrent Grade 3 or 4 non-hematological toxicities not resolved with permissible dose reductions or any delay in scheduled therapy for more than 2 weeks secondary to any form of toxicity must result in study withdrawal.

9.0 ASSESSMENT OF RESPONSE

Anti-tumor activity will be assessed using computerized tomography (CT) or magnetic resonance imaging (MRI) and bone scan. Complete imaging of the chest, abdomen, pelvis (by CT or MRI) and skeleton (by bone scan). After treatment initiation, these assessments will be repeated after every 2 cycles of therapy,

whenever disease progression is suspected, and at the end of treatment/withdrawal visit.

Progression Free Survival (PFS) is the primary endpoint. PFS will be a composite endpoint defined as the time from study entry to first occurrence of **any** of the following:

- Progression of measurable disease by RECIST criteria. To be considered measurable, baseline lymph nodes, visceral metastases, and soft tissue metastases must be ≥1.5 cm in longest dimension. Equivocal RECIST progression must be confirmed by a follow up scan > 6 weeks later.
- Two or more new areas by bone scan attributable to prostate cancer (rather than flare) OR new/increasing size of lytic lesions by CT scan or MRI. Equivocal progression on bone scan must be confirmed by other imaging modalities (eg, CT or MRI) and/or performing a confirmatory bone scan ≥ 6 weeks later.
- Need for palliative radiation involving more than one site
- Surgery or kyphoplasty to any neoplastic bone lesion
- Cancer-associated clinical deterioration as determined by the treating physician.
- Receipt of any additional prostate cancer specific therapy as prescribed by the treating physician.

PSA progression alone will not be used to define progression.

10.0 CRITERIA FOR RESPONSE AND PROGRESSION

10.1 Measurable Disease Evaluation

Evaluation of measurable disease response will follow the Response Evaluation Criteria in Solid Tumors (RECIST) Guidelines. All tumor measurements must be recorded in centimeters.

10.1.1 RECIST CRITERIA

Target Lesions**:** All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be ≥ 1.5 cm in longest dimension and have suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest dimension for all target lesions will be calculated and reported as the baseline sum of longest diameter. The baseline sum of longest dimensions will be used as the reference by which the objective tumor response is characterized. For equivocal RECIST progression, assessment must be confirmed by a second scan 6 or more weeks later at the discretion of the treating physician.

Non-target Lesions: All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

10.2 Criteria for Response

10.2.1 Evaluation of Target Lesions:

Complete Response**:** The disappearance of all target lesions.

Partial Response**:** At least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter.

Progressive Disease**:** At least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since the treatment started or the appearance of one or more new lesions.

Stable Disease**:** Insufficient shrinkage to qualify for partial response, or insufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter since the treatment started.

10.2.2 Non-Measurable Disease Evaluation

Criteria for Evaluation of Bone Disease

Progression of Bone disease is defined as two or more new areas by bone scan attributable to prostate cancer (rather than flare) OR new/increasing size of lytic lesions by CT scan or MRI. Equivocal progression on bone scan must be confirmed by other imaging modalities (e.g., CT or MRI) and/or performing a confirmatory bone scan $\geq$ 6 weeks later.

11.0 CRITERIA FOR REMOVAL OF PATIENTS FROM STUDY

Patients will be removed from study if they meet any of the following criteria:

- Receipt of 10 cycles of therapy
- Disease progression
- Unacceptable toxicity

- Patient decision to withdraw
- Palliative radiation involving more than one site if in the judgment of the investigator, further treatment would not be in the best interest of the patient.

12.0 PHARMACY

12.1 Drug Formulations

JEVTANA (cabazitaxel) Injection 60 mg/1.5 mL (NDC 0024-5824-11) is supplied as a kit consisting of the following:

- *JEVTANA Injection 60 mg/1.5 mL: contains 60 mg cabazitaxel in 1.5 mL polysorbate 80,*
- *Diluent for JEVTANA Injection 60 mg/1.5 mL: contains approximately 5.7 mL of 13% (w/w) ethanol in water for injection*

Please refer to the Package Insert (Appendix G) for preparation instructions and other additional information about the study drug.

Commercially available carboplatin will be used for this study and will be billed to the patient's medical insurance. 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. Carboplatin Injection is supplied as a sterile, pyrogen-free solution available in 10 mg/mL multiple-dose vials containing 50 mg, 150 mg, or 450 mg of carboplatin for administration by intravenous infusion. Each mL contains: carboplatin 10 mg and water for injection to volume.

Commercially available prednisone will be used for this study. As a standard treatment, it should be billed to the patient's medical insurance.

12.2 Packaging and labeling

This is an open-label study. The investigational product (cabazitaxel) will be packaged in sealed, sterile, single-use vials. The vials containing the investigational product and the kits they are packaged in will be labeled as follows:

a. Supporter's name and address
b. Study number
c. Dosage form

d. Storage conditions
e. Packaging reference number

Batch number and number of vials dispensed to each subject must be recorded in the eCRF/drug accountability form. Each clinical site will be responsible for obtaining commercially available carboplatin.

12.3 Storage Conditions

The investigator or pharmacist will inventory and acknowledge receipt of all shipments of the investigational product. The investigational product must be kept in a locked area with restricted access. The investigational product must be stored and handled in accordance with local regulations, labeling specifications, policies, and procedure.

The investigator or pharmacist will also keep accurate records of the quantities of the investigational products dispensed and used for each subject. The study monitor will periodically check the supplies of investigational product held by the investigator or pharmacist to verify accountability of all investigational product used.

12.4 Concomitant Medications and Therapy

Concomitant therapy with other investigational drugs or immunotherapy is not permitted.

Concomitant radiotherapy is not permitted, except when radiotherapy is used to palliate bone lesions involving ≤ 25% of the bone marrow.

Supportive care, including but not limited to antiemetic medications, may be administered at the discretion of the Investigator. Concurrent treatment with bisphosphonates or RANK Ligand inhibitors is allowed for those patients who received stable doses prior to study entry. However, patients are not allowed to initiate these agents during the study.

13.0 STATISTICAL CONSIDERATIONS

This is a randomized, phase II trial to compare cabazitaxel alone (control) versus cabazitaxel/carboplatin (experimental). The primary endpoint is progression free survival. We hypothesize that progression-free survival will be longer in patients treated with cabazitaxel/carboplatin vs cabazitaxel alone. Recent phase III data comparing cabazitaxel to mitoxantrone monotherapy showed that cabazitaxel

improved overall survival (from 12.7 to 15.1 months) and progression-free survival (from 1.4 to 2.8 months) over mitoxantrone.

13.1 Group sequential design:

The primary outcome for treatment evaluation will be progression free survival (PFS) time. The goal will be to test the hypothesis that cabazitaxel/carboplatin provides a 50% improvement in m = median PFS, from 2.8 to 4.2 months. An accrual rate of 3 patients per month will be assumed. A two-sided group sequential procedure will be used with overall type I error 0.1 and power 0.80 to detect the alternative m = 4.2 months, with interim tests including both outer bounds for superiority and inner bounds for futility (34). The alpha-spending function corresponds to the O'Brien-Fleming boundaries. The final data analysis will be performed after the last patient has been followed at least 6 months or at least 150 events are observed. We will conclude the experimental arm is better than the control arm if the z-score in the final analysis is greater than 1.662. All tests will be based on a standardized log rank statistic, and will be performed using the following cut-offs (35). The number of patients accrued (sample size) required to achieve the necessary numbers of events required by the group sequential tests will be 160 in total (80 per arm).

Table 5: The outer bounds for superiority and inner bounds for futility in the interim analysis based on a group sequential design using statistical software East version 5.2.

No. Events	Z-score cut-off to reject the null hypothesis (Superiority)	Z-score cut-off to accept the null hypothesis (Futility)
78	+/- 2.538	+/- 0.246

13.2 Secondary outcomes:

Additional outcomes that will be recorded and analyzed will include overall survival (OS) time, grade 3 or 4 toxicity. In each treatment arm, the probability of a life-threatening drug-related toxicity will be monitored based on a beta-binomial model, assuming a priori that p = Prob(toxicity) ~ beta(0.5, 1.5). The trial will be terminated if

$$\text{Prob}(p > 0.25 \mid \text{data}) > 0.85.$$

This rule will stop a treatment arm if [# patients with toxicity]/[# patients evaluated] >= 2/3, 3/6, 4/9, 5/12, 6/15, 7/18, 8/22, 9/25, 10/29, 11/32, 12/35, 13/39, 14/42,15/46, 16/49, 17/53, 18/56, 19/60, 20/64, 21/67, 22/71, 23/74, 24/78 or 25/80. The operating characteristics for toxicity are summarized in Table 6.

Table 6. Operating characteristics based on 1000 simulation study

true Prob(tox)	Pr(stop)	Mean # Pts (25%, 75%)
0.05	0.01	80 (80, 80)
0.15	0.11	72 (80, 80)
0.25	0.47	50 (9, 80)
0.35	0.93	21 (2, 28)
0.45	0.99	9 (2, 11)
0.55	1.00	5 (2, 7)

13.3 Data analyses:

Descriptive statistical analysis will be calculated, including histograms or box-plots, proportions, range, means and standard deviations. All adverse events will be analyzed and described, cross-tabulated with treatment arm, and the rates compared using a Fisher exact test. Unadjusted PFS and OS times will be estimated using the Kaplan-Meier method (36). Covariate adjusted comparisons will be done using a Cox model or other appropriate time-to-event regression model to be determined by preliminary goodness-of-fit analyses (37;38).

14.0 LEAD SITE REPORTING OBLIGATION TO SUPPORTING AGENCY

IND-exempt studies: All serious adverse events (regardless of relationship or expectedness) will be reported and documented on MD Anderson SAE form and forwarded directly to Sanofi-aventis Pharmaceuticals US Pharmacovigilance within 24 hours of learning of the event using the Serious Adverse Event Reporting Fax Cover Page provided by Sanofi-aventis.

These reports may be sent by **FAX** or **E-MAIL to:**

Reports by **FAX** should be sent to Sanofi-aventis Pharmaceuticals US Pharmacovigilance (908-2037783), within 24 hours of receipt by investigator / sponsor.

FAX transmission should include the following on the provided IST SAE REPORT, fax cover form (below):

Investigator-Sponsored (IST #) study number: _____
Study Title: _____
Name of Principal Investigator: _____

Reports by **E-MAIL** should be sent to: **USPVmailbox@sanofi-aventis.com**, within 24 hours of receipt by investigator/sponsor. E-Mail transmission should include the following:

Investigator-Sponsored (IST #) study number:_____
Study Title:_____
Name of Principal Investigator:_____

For Comparator Drugs / Secondary Suspects (Concomitant Medications), all serious adverse experiences will be forwarded to the product manufacturer.

15.0 PATIENT REGISTRATION PROCEDURES

15.1 For registration procedures for this protocol, please refer to the Multicenter Management Plan in Appendix F.

16.0 DATA AND PROTOCOL MANAGEMENT

Protocol Compliance: The attending physician or advanced practice nurse must see each patient at each treatment visit. All required interim and pretreatment data should be available, and the physician must assess tumor response and must provide a detailed description of toxicity, when appropriate. If dose modifications or treatment interruptions are necessary, the details must be carefully documented. Performance status must be documented at each toxicity assessment.
Data Capture: Data will be entered in the MD Anderson Genitourinary departmental oracle system. Registration data entry and randomization will occur prior to initiation of therapy. All eligibility criteria must be satisfied.

Accuracy of Data Collection: The MD Anderson Principal Investigator will be the final arbiter of response and toxicity, should a difference of opinion exist.

Results from these analyses will be reported to an independent Data Monitoring Committee (DMC) convened at MDACC. The DMC will assess results along with supportive data including other efficacy outcomes and safety data. It will use this data to possibly recommend early stopping or other study modifications.

16.1 Schedule of Data Submission

MD Anderson protocol specific Case Report Forms and/or electronic Case Report Forms will be used for collection of all study data. The schedule for submission of case report forms and pertinent source documents to MD Anderson is as follows:

Case Report Forms/Source Documents	Schedule for Submission
Informed Consent/Patient Authorization for the Release of Personal Health Information	Prior to study registration
Eligibility Checklist	Prior to study registration
On-Study Form Supporting Source Documents (e.g. Pathology reports, Medical Administration Records, Radiology/Laboratory Reports, History and Physical, Progress Notes)	14 days after treatment initiation
Chemotherapy/Treatment by Cycle Form (Chemotherapy, Laboratory Results, Concomitant Medications) Supporting Source Documents	14 days after cycle completion
Adverse Event Form Supporting Source Documents	14 days after cycle completion
Response Assessment Forms (Disease Measurements) Supporting Source Documents	14 days after protocol defined imaging assessment
Off Treatment Supporting Source Documents	14 days after last treatment date
Survival Update Form Supporting Source Documents	14 days after protocol defined survival review
Off Study Form Supporting Source Documents	14 days after patient removed from study

17.0 MULTICENTER PROCEDURES

Participating multicenter institutions will follow the guidelines as addressed below, in the MD Anderson Multicenter Management Plan (Appendix F), and throughout this protocol.

17.1 Principal Investigators

The principal investigator(s) will be responsible for the conduct of the study and monitoring its progress. The responsibility for all reports and data required by MD Anderson will be that of the principal investigator(s).

17.2 Centralized Patient Registration and Randomization

Patients who are candidates for the study will first be evaluated for eligibility by the local investigator. All patients will be registered by designated research staff in the GU department.

All multicenter patients must be registered both locally and centrally with MD Anderson.

At the time of registration, participating institutions will be required to submit a completed and signed eligibility checklist and informed consent document with supporting source documentation.

17.2.1 Eligibility Exceptions

All exceptions to eligibility must first be approved by the Protocol Chair with appropriate rationale following MD Anderson guidelines. If eligibility clarifications are required from participating institutions, all eligibility questions should be routed to the MD Anderson GU Department in order to document the question and Protocol Chair response.

17.3 Guidelines for Reporting Participating Site Serious Adverse Events to MD Anderson:

Any Serious Adverse Event (SAE) will be reported to the MD Anderson GU Department within 24 hours of knowledge of the event. The participating institution will submit the SAE to its own IRB according to institutional policy and must forward a copy of the report to MD Anderson within 5 calendar days. The MD Anderson GU Department will submit participating site SAE reports to the MDACC IRB and Sanofi-aventis.

SAE notifications and reports will be submitted to:

Fax or email a completed SAE Form to:

MD Anderson GU Department (notifications and reports)
Attn: 2011-0727
Fax: 713-563-0857
Email: GU2011-0727@mdanderson.org

AND

GU2011-0727@mdanderson.org (notifications only)

MD Anderson will maintain documentation of all Serious Adverse Events from each institution. MD Anderson will notify all investigators of any serious and unexpected adverse experiences that are possibly related to the study therapy. The investigators are to file a copy in the protocol file and send a copy to their IRB according to their local IRB's policies and procedures.

17.4 Guidelines & Procedures for reporting Violations, Deviations and Unanticipated Problems.

The Protocol Chair: is responsible for ensuring that clear documentation is available in the medical record to describe all protocol deviations, violations, and unanticipated problems. The Protocol Chair will also be responsible for ensuring that all protocol deviations, violations, and unanticipated problems are reported to the MD Anderson IRB per MD Anderson institutional guidelines.

Participating Institutions: Protocol deviations, violations, and unanticipated problems occurring at a participating institution will be submitted to that institution's own IRB. A copy of the participating institution's IRB deviations, violations, and unanticipated problems report will be forwarded to MD Anderson by facsimile or via email within 7 calendar days after the original submission.

17.4.1 Definitions

The definitions for protocol violation and deviation as described by the MD Anderson IRB will be applied for reporting purposes for all institutions participating in the trial.

Protocol Deviation: Noncompliance with the protocol that does not have a significant effect on the subject's rights, safety, welfare, and/or the integrity of the data. Deviations may be caused by the action of the subject, the investigator, the research staff, or natural events.

Protocol Violation: Changes to protocol procedures without prior approval of the IRB/Sponsor. Violations may significantly alter the clinical effectiveness of the treatment or the evaluation of its toxicity and adversely affect patient's safety and rights.

Unanticipated Problems: An incident, experience or outcome, that is unexpected, related or possibly related to participation in the research and suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) that was previously known or recognized. These incidents do not meet the definition of an adverse event. Unanticipated problems are not limited to study participants, and may also include others such as family members and research staff.

MD Anderson GU Department: Upon receipt of the violation/deviation/unanticipated problem report from the participating institution, the Protocol Chair will review and submit the report to the MD Anderson IRB for review.

17.5 Research Team Teleconferences

The MD Anderson and participating institution's PIs and study teams will participate in teleconferences as needed to discuss the following information:

- Status of patients enrolled at sites including
  - Eligibility for trial
  - Status of treatment
  - Adverse Events
  - Response evaluation
  - Any questions or concerns

18.0 REFERENCES

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