A Selective Cabazitaxel Therapeutic Pathway for Castration-Resistant Prostate Cancer with Integrated Biomarkers

Protocol Number(s): UCDCC#261; SA-2014-11231
Indication: Castration-Resistant Prostate Cancer (CRPC)
Phase: II
Funding Source: Sanofi
Therapeutic Area: Urologic Oncology
Compound: Jevtana®/cabazitaxel

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Participating Centers: UC Davis Comprehensive Cancer Center

Protocol History:

Original	June 25, 2015
Revision	September 22, 2015
Revsion	March 15, 2016
Revision	July 7, 2016
Revision	June 1, 2017
Revision	September 15, 2017
Revision	May 23, 2018

IND Exempt #: 129871

IND Sponsor: University of California Davis Comprehensive Cancer Center

PROTOCOL SIGNATURE PAGE

Protocol Number: UCDCC#261

Protocol Title: A Selective Cabazitaxel Therapeutic Pathway for Castration-Resistant Prostate Cancer with Integrated Biomarkers

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated, in accordance with all stipulations of the protocol and in accordance with Good Clinical Practices, local regulatory requirements, and the Declaration of Helsinki.

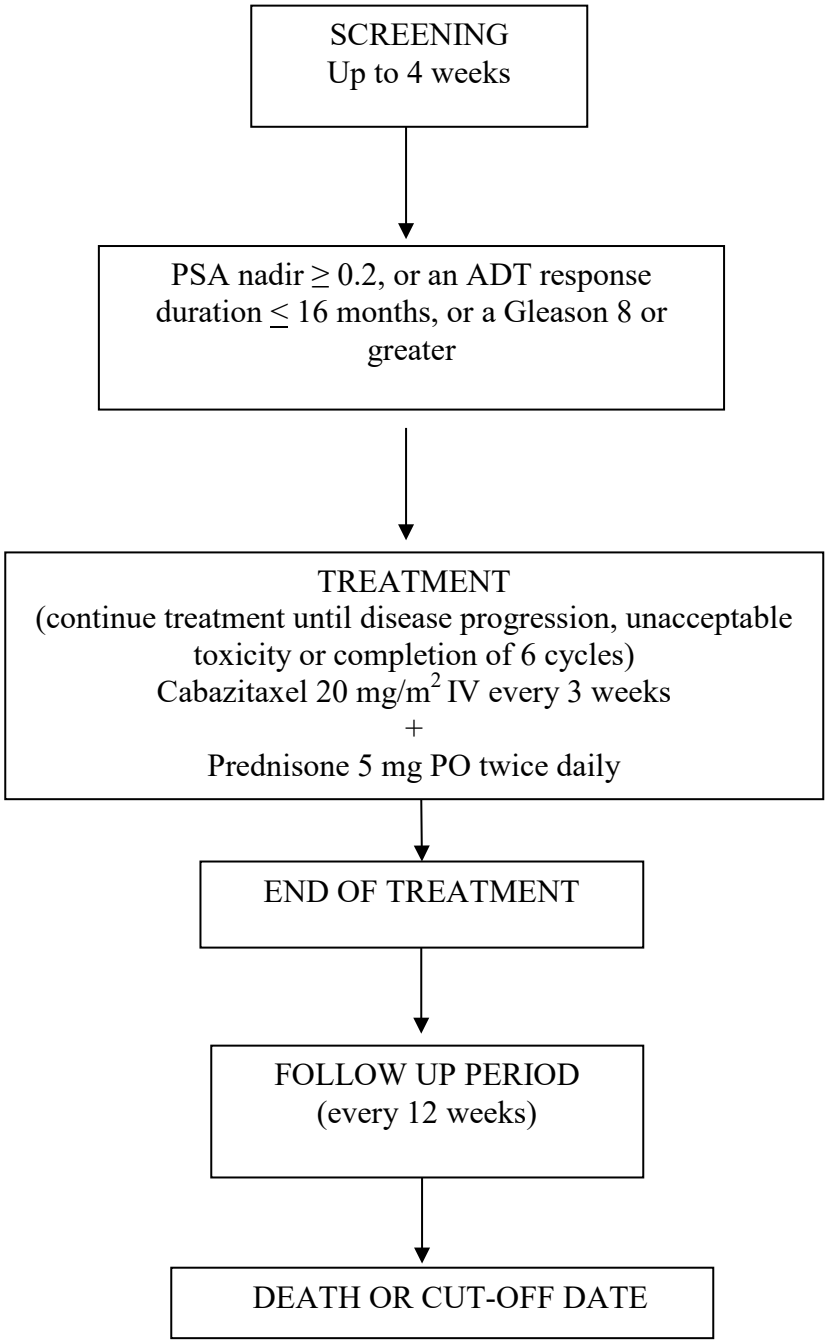
I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study agent(s) and the conduct of the study.

_____
Investigator Name (print)

_____
Investigator Signature

_____
Date

STUDY SCHEMA



LIST OF ABBREVIATIONS

ABCB1	ATP-binding cassette sub-family B member 1
ADT	Androgen Deprivation Therapy
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Amino Transferase
ANC	Absolute Neutrophil Count
AR	Androgen Receptor
AST	Aspartate Amino Transferase
AUC	Area Under Curve
BP	Blood Pressure
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CBZ	Cabazitaxel
CHF	Congestive Heart Failure
CI	Confidence Interval
CNS	Central Nervous System
C_{max}	Maximum plasma concentration
CR	Complete Response
CRF	Case Report Form
CRPC	Castrate Resistant Prostate Cancer
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP3A	Cytochrome P3A
DLT	Dose Limiting Toxicity
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EDTA	Ethylene Diamine Tetraacetic Acid
FDA	Food and Drug Administration
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony Stimulating Factor
h / hr	Hour
Hb	Hemoglobin
HCG	Human Chorionic Gonadotrophin
HDPE	High Density Polyethylene
HIV	Human Immunodeficiency Virus
HPBMC	Human Peripheral Blood Mononuclear Cells
HPFB/TPD	Health Products and Food Branch/Therapeutic Products Directorate
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ID	Identification (number)
IRB/EC	Institutional Review Board/ Ethics Committee
ITT	Intention To Treat
i.v.	Intravenous
K_{el}	Elimination rate constant
Kg	Kilogram

L	Litre
LD	Longest Diameter
LDH	Lactate Dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
min	Minute
ml	Milliliter
MBC	Metastatic Breast Cancer
MRI	Magnetic Resonance Imaging
MRP1	Multidrug resistance-associated protein 1
MTD	Maximum Tolerated Dose
MTX	Mithoxantrone
MUGA	Multi Gated Acquisition Scan
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSAIDS	Non-Steroidal Anti-Inflammatory Drugs
NOEL	No Observed Effect Level
ORR	Overall Response Rate
OS	Overall Survival
PCNA	Proliferating Cell Nuclear Antigen
pCR	Pathological Complete Response
PCGW2	Prostate Cancer Clinical Trials Working Group
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression Free Survival
PI	Principal Investigator
PK	Pharmacokinetics
PO	Per os/ By mouth / Orally
PR	Partial Response
PSA	Prostate Specific Antigen
PT	Prothrombin Time
PS	Performance Status
PTT	Partial Thromboplastin Time
q	Every
RBC	Red Blood Cells
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious Adverse Event
SD	Stable Disease
SGOT	Serum Glutamate Oxaloacetate Transaminase
SGPT	Serum Glutamate Pyruvate Transaminase
SOC	Standard of Care
T_{max}	Time at which C_{max} is reached
t1/2	Elimination half-life
ULN	Upper Limit of Normal
µg	Microgram
VEGF	Vascular Endothelial Growth Factor
Vz	Volume of Distribution
WBC	White Blood Cell
WHO	World Health Organization

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1. INTRODUCTION

1.1 Background and Study Rationale

Castration resistant prostate cancer (CRPC) remains an incurable and heterogeneous disease. Patients have variable responses to initial androgen deprivation therapy[1] and subsequent agents inhibiting the androgen axis once it is castration resistant. Some of the second line androgen axis inhibitors' lack of efficacy can be predicted by the response to primary androgen deprivation therapy. As such, a potential exists to identify these patients and treat them effectively with chemotherapy. Cabazitaxel was approved in 2011 for the treatment of patients with CRPC who were previously treated with a docetaxel-containing regimen. [2] Cabazitaxel will be the study agent in the clinical trial.

Patients with an initial limited response to primary androgen deprivation therapy or whose tumors are of high Gleason score (8-10) tend to have minimal subsequent response to abiraterone and enzalutamide as frontline metastatic CRPC treatments. [3-6] Data suggest that 25-33% of patients will not respond to abiraterone or enzalutamide. Stratification of response to initial androgen deprivation therapy by prostate specific antigen (PSA) level suggests that a PSA nadir of <0.2, 0.2-4.0, and >4.0 results in median overall survival of 75, 44, and 13 months, respectively. [1] In addition, those with a duration of response <16 months or an initial Gleason score tumor >= 8 have a significantly worse (overall survival) OS.[7] Patients with an initial limited response to ADT also have limited responses to abiraterone and enzalutamide. Data suggest that patients receiving docetaxel after abiraterone or enzalutamide have approximately a 40% reduced response. Additionally, in CRPC patients who have received a prior taxane (docetaxel), primary resistance to subsequent abiraterone or enzalutamide is seen in up to 35% of patients (based on observations from the COU-301 and AFFIRM trials). We propose to select patients with a PSA nadir ≥0.2, or an ADT response duration <16 months, or a Gleason 8 or greater for therapy with cabazitaxel. We will collect serial serum to interrogate for development of a gene signature consistent with response and eventual resistance to cabazitaxel. The PSA will be measured at UC Davis and the definitions used for inclusion are specific to UC Davis testing methodology.

These data raises the question of how best to manage mCRPC patients with poor prognostic features. Based on the likelihood of attaining more rapid anti-tumor responses, one approach to poor prognosis disease would be to utilize cytotoxic chemotherapy. In a phase III trial, the novel anti-microtubule agent cabazitaxel has been shown to significantly increase overall survival in metastatic CRPC previously treated with docetaxel.[2] Importantly, the superiority of cabazitaxel over the comparator treatment (mitoxantrone) persisted in patients with measurable visceral or soft-tissue metastatic disease and those with multiple poor prognosis factors. In view of these facts, we will test the hypothesis that treatment of this patient population with cabazitaxel will result in a Therapeutic response defined as a PSA response rate ≥ 50% reduction from baseline. This will exceed historical controls for this patient population.

1.2 Cabazitaxel (Jevtana®)

1.2.1 Preclinical Data

Cabazitaxel (also known as XRP6258, RPR116258A) is a semisynthetic taxane promoting tublin assembly and stabilizing microtubules. It is derived from 10-deacetyl Baccatin III, which is extracted from European yew needles. It was selected for development based on a better antiproliferative activity on resistant cell lines than docetaxel. Using cell lines with acquired resistance to doxorubicin, vincristine, vinblastine, paclitaxel and docetaxel, the resistance factors ranged from 1.8 to 10 and 4.8 to 59, for cabazitaxel and for docetaxel, respectively. Cabazitaxel exhibited a broad spectrum of in vivo antitumor activity, not only in docetaxel -sensitive tumor models, but also in tumors models in which docetaxel was either poorly active or not active. The best antitumor efficacy was obtained with the schedules allowing the administration of the highest amount of drug. In addition, this compound was found to penetrate the blood brain barrier and marked antitumor activity was obtained in nude mice bearing intracranial glioblastomas.

In general, nonclinical data suggest that the toxicity effects observed with cabazitaxel are consistent with those reported for other taxane class anticancer drugs.

More information on the preclinical data is available in the clinical Investigator's Brochure.

1.2.2 Summary of Clinical Data

In single agent, 3 Phase I studies were conducted to determine the schedule and the recommended dose, one study investigating the disposition of radiolabeled cabazitaxel, one Phase 2 study in patients with metastatic breast cancer (MBC), and one Phase 3 study in patients with mCRPC. One Phase I/II study has been conducted with cabazitaxel plus prednisone in combination with capecitabine.

The 3 Phase 1 studies in solid tumors (TED6188, TED6189, TED6190) have been completed. There were 2 partial responses in patients with prostate cancer in Phase 1 studies evaluating the every 3 week schedule; 2 PR out of 8 patients with metastatic HRPC in TED6190 at 25 mg/m^2 suggesting potential biological and clinical activity in patients with prostate cancer.

The safety profile was comparable in TED6188 and TED6190, with the intermittent schedule (1hour infusion every 3 weeks). The dose limiting toxicity (DLT) of cabazitaxel was neutropenia and its infectious complications at the highest dose tested, 30 mg/m^2 in TED6188 and 25 mg/m^2 in TED6190.

As a result, the dose levels of 20 mg/m^2 and 25 mg/m^2 every 3 weeks were defined as the recommended doses for further clinical development with the intermittent schedule.

In TED6189 with the weekly schedule, the maximum tolerated dose (MTD) was reached at 12 mg/m^2, at which the DLT was diarrhea. As a result, the dose level of 10 mg/m^2 was defined as the recommended dose for further clinical development with this weekly schedule.

One Phase 2 study in patients with taxane- and/or anthracycline-resistant metastatic breast cancer has been completed (ARD6191). In this study patients were treated with a starting dose of 20 mg/m^2 cabazitaxel every 3 weeks with the option to dose-escalate cabazitaxel based on favorable tolerability at Cycle 1. In 20 of 71 patients, the cabazitaxel dose was escalated from 20 to 25 mg/m^2 after the first cycle. The most frequently occurring toxicities overall were Grade 3 and 4 neutropenia (73.2%), fatigue (50.7%), nausea (43.7%), diarrhea (39.4%), myalgia (25.4%), anorexia (25.4%), weight loss (25.4%), and vomiting (23.9%). The overall response rate was 14.1% with 2 complete responses (CR) and 8 partial responses (PR).

One Phase 3 study was conducted in mCRPC patients previously treated with docetaxel containing regimen. This study compared cabazitaxel (CBZ) plus prednisone to mitoxantrone (MTX) plus prednisone (EFC6193). A total of 755 patients were randomized (378 patients in CBZ arm and 377 patients in MTX arm). A statistically significant increase in OS was observed in patients treated with CBZ plus prednisone compared to patients treated with MTX plus prednisone, with a HR of 0.70 (95%CI: 0.59 – 0.83), a log-rank p-value of 0.0001. The median OS was 15.1 months (95%CI: 14.1 – 16.3) in CBZ arm versus 12.7 months (95%CI: 11.6 – 13.7) in MTX arm.

Refer to the Investigator's Brochure for additional information about cabazitaxel.

1.3 Correlative Studies

We will collect serum and tumor tissue samples for molecular markers or signature predictive of cabazitaxel benefit (to include status of androgen receptor (AR) pathway, AR splice variants, androgen biosynthetic pathway genes, ATP-binding cassette sub-family B member 1 (ABCBI), multidrug resistance-associated protein 1 (MRP1), and other mediators of taxane resistance). The correlative studies will seek to identify both signatures of resistance to AR axis inhibitors and signatures of sensitivity to cabazitaxel.

To validate and establish controls for these correlative studies prior to testing of clinical samples, we will establish an MTA to obtain laboratory grade cabazitaxel for pre-clinical use. A variety of castration-resistant prostate cancer cell lines and xenografts will be treated with Jevtana and samples assayed for correlative biomarkers. This will validate assay standards via pre-clinical samples rather than limited quantities of liquid biopsy material (cfDNA, CTCs) or solid biopsy material. The MTA will request for cabazitaxel formulations for both in vitro and in vivo experiments. No funding is requested for these experiments.

2. STUDY OBJECTIVES AND ENDPOINTS

Primary Objectives:

The primary objective of this study is:

To test whether men with a poor initial response to ADT have a better therapeutic response to cabazitaxel as compared to historical controls of frontline metastatic CRPC therapy with abiraterone or enzalutamide. Therapeutic response is defined as a PSA response rate $\geq$ 50% reduction from baseline.

Secondary Objectives:

The secondary objectives of this study are:

- To determine the RECIST v1.1 response rate, progression free survival (PFS) by PCWG2 criteria, and overall survival (OS).
- To evaluate safety and toxicity profile of cabazitaxel in patients with CRPC.

Biological Objectives:

- To collect serum and tumor tissue samples for molecular markers or signature predictive of cabazitaxel benefit (to include status of AR pathway, androgen biosynthetic pathway genes, ABCBI, MRP1, and other mediators of taxane resistance).

Primary Endpoint:

PSA response rate (defined as $\geq$ 50% reduction from baseline)

Secondary Endpoints:

Safety:

- Adverse events, serious adverse events, and discontinuations (CTCAE 4.03)

Efficacy:

- RECIST response (Radiographic disease progression)
- **Progression-free survival (PFS)** defined as the time interval between the date of enrollment and the date of the first documentation by PCWG2 criteria.
- **Overall survival** defined as the time interval from the date of enrollment to the date of death due to any cause

Biomarkers:

- To interrogate serum and tumor tissue specimens for molecular markers or signature predictive of cabazitaxel benefit (to include status of AR pathway, androgen biosynthetic pathway genes, ABCB1, MRP1, and other mediators of taxane resistance, among others).

3. SUBJECT SELECTION

Patients will be recruited in the medical, urologic, and radiation oncology clinics of the University of California Davis Medical Center and participating centers. The study population will include those patients with newly confirmed castration-resistant prostate cancer or those who have progressed following up to one treatment with abiraterone or enzalutamide. The number of patients enrolled on this phase II study is 45.

3.1 Inclusion Criteria

Patients will be men with new onset CRPC and each patient must meet all of the following inclusion criteria to be enrolled in the study:

1. Histologically confirmed prostate adenocarcinoma.

2. Metastatic disease.

3. Able and willing to provide informed consent and to comply with the study procedures.

4. Castration resistant disease defined as evidence of radiological and/or PSA progression despite castrate levels of testosterone (serum testosterone < 50 ng/dL (1.7 nmol/L)). For PSA progression, there must be at least 2 sequential rises at a minimum of 1-week intervals. The first PSA value must be ≥0.2 (Prostate Cancer Working Group 2 (PCWG2) criteria).

5. Patient may have been treated with up to one androgen receptor pathway inhibitor prior to enrollment into this trial.

6. Age ≥18.

7. Eastern Cooperative Oncology Group (ECOG) performance status 0-2.

8. At least 21 days have passed since completing radiotherapy (exception for radiotherapy: at least 7 days since completing a single fraction of ≤ 800 cGy to a restricted field or limited-field radiotherapy to non-marrow bearing area such as an extremity or orbit) at the time of registration.

9. At least 21 days have passed since receiving any investigational agent at the time of registration.

10. At least 21 days have passed since major surgery.

11. Neuropathy ≤ grade 1 at the time of registration.

12. Has recovered from all therapy-related toxicity to ≤ grade 2 (except alopecia, anemia and any signs or symptoms of androgen deprivation therapy) at the time of registration.

13. Poor prognosis disease as defined by any of the following:
    - PSA nadir ≥ 0.2, **or**
    - Gleason score 8-10, **or**
    - Time from ADT initiation to CRPC of ≤16 months.

14. Adequate hematologic, hepatic, and renal function:
    - Hemoglobin ≥ 90 g/L
    - Neutrophils ≥ 1.5 x 10^9 /L
    - Platelets ≥ 100 x 10^9/L
    - AST < 1.5 x ULN
    - ALT < 1.5 x ULN
    - Bilirubin ≤ 1.0 x ULN (exceptions for Gilbert's syndrome)
    - Creatinine ≤ 1.5 x ULN

3.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study.

1. Prior therapy with cabazitaxel or to other drugs formulated with polysorbate 80.

2. Prior taxanes for CRPC.

3. (Deleted as of Rev May 23, 2018.)

4. Other condition, illness, psychiatric condition, or laboratory abnormality that may increase the risk associated with administration of cabazitaxel, study participation, or may interfere with the interpretation of study results and in the judgment of the investigator would make the patient inappropriate for entry into this study.

5. Histologic evidence of small cell/neuroendocrine prostate cancer.

6. Patients with reproductive potential who do not agree to use accepted and effective method of contraception during the study treatment period and up to 6 months after the last administered dose. The definition of "effective method of contraception" will be based on the investigator's judgment.

3.3 Inclusion of Minorities

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

4. INVESTIGATIONAL PLAN

4.1 Treatment Schedule

Cabazitaxel 20 mg/m^2 intravenous infusion over 1 hour (Day 1) every 3 weeks, plus prednisone 10mg orally given daily. A cycle is defined as a 3-week (21 days) period.

Study drug will be administered only to eligible patients under the supervision of the investigator or identified subinvestigator(s).

Agent	Dose	Route	Schedule
Cabazitaxel	20 mg/m^2	I.V.	q3w
Prednisone	5 mg	P.O.	Twice Daily

4.2 Premedication for Cabazitaxel Treatment

Premedication is recommended at least 30 minutes prior to each dose of cabazitaxel with the following intravenous medications to reduce the risk and/or severity of hypersensitivity:

- antihistamine (dexchlorpheniramine 5 mg, or diphenhydramine 25 mg or equivalent antihistamine),
- corticosteroid (dexamethasone 8 mg or equivalent steroid),
- H2 antagonist (ranitidine 50 mg or equivalent H2 antagonist).

Antiemetic prophylaxis is recommended and can be given orally or intravenously as needed. Appropriate prophylactic antiemetic therapy will be according to local hospital procedures.

4.3 Antidiarrheal Medications

Severe diarrhea may occur and death related to diarrhea and electrolyte imbalance has been reported with cabazitaxel. Intensive treatment with antidiarrheal medications along with hydration is recommended.

4.4 Toxicities and Dose Adjustments for Cabazitaxel

Every effort will be made to administer the full dose regimen to maximize dose-intensity.

Doses will be reduced for hematologic and other adverse events. Dose adjustments are to be made according to the system showing the greatest degree of toxicity. Adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events Version 4.03 (CTCAE).

The guidelines which follow outline dose adjustments for several of these toxic effects. If a patient experiences several adverse events and there are conflicting recommendations, please use the recommended dose adjustment that reduces the dose to the lowest level. Doses that have been reduced for toxicity must not be re-escalated.

Table 1. Cabazitaxel Reduction Level

Starting dose	**20 mg/m^2**
-1	15 mg/m^2
Upon dose reduction, administer G-CSF (or equivalent) per institutional or standard guidelines in subsequent cycles. Patients requiring a second dose reduction are to be taken off study.	

A treatment delay ≥4 days should be justified and documented in the source notes and case report forms. Treatment may be delayed no more than 2 weeks to allow recovery from acute toxicity. In case of treatment delay greater than 2 weeks, patient should discontinue study treatment, unless there is strong evidence of clinical benefit to justify continuation of dosing with study treatment.

4.4.1 Hematologic and Non-Hematologic Adverse Events

Table 2: Dose Modifications for cabazitaxel for Hematologic Toxicity

Toxicity	**Grade**	**Dose Modification**
Neutropenia	Grade 2	If not recovered on D21, delay[1] next infusion until recovery to grade ≤1 (neutrophil ≥1.5x10^9/L). 1st episode: no dose reduction required. 2nd episode: reduce by 1 dose level.
	Grade 3 & 4	No dose reduction if isolated and duration ≤7 days. If duration more than 7 days or not recovered on D21, delay[1] next infusion until ANC ≥1.5x10^9/L and: 1st episode: Administer prophylactic G-CSF treatment in subsequent cycles or reduce by 1 dose level. 2nd episode: Withdraw from study treatment; or 1st episode despite prophylactic G-CSF: Reduce dose by 1 dose level. 2nd episode despite prophylactic G-CSF: Withdraw from study treatment.
Febrile neutropenia or neutropenic infection	Grade 3 & 4	Delay[1] next infusion until recovery and ANC ≥1.5 x 10^9/L and: 1st episode: reduce the dose and administer prophylactic G-CSF treatment in subsequent cycles if available. 2nd episode: Withdraw from study treatment.
Thrombocytopenia	Grade 2	Delay[1] next infusion until recovery to grade ≤ 1 (platelets ≥75 x 10^9/L). No dose reduction required.
	Grade 3 & 4	Delay[1] infusion until platelets ≥75 x 10^9/L. If grade 3 without delay, no dose reduction required. If grade 4 with or without delay, or grade 3 with delay 1st episode: Reduce dose by 1 dose level. 2nd episode: Withdraw from study treatment in case of recurrence.
Dose reduction levels provided in Table 1. [1] Maximum of 2 weeks delay, otherwise the patient will be withdrawn from study treatment.		

Blood counts will be performed in case of fever or infection. Blood count should be monitored weekly for the first cycle to determine if granulocyte colony-stimulating factor or dosage modification is needed. Study treatment should not be given to patients with neutrophil counts <1.5 x10^9 /L.

Deaths due to sepsis following severe neutropenia have been reported in patients treated with cabazitaxel. Neutropenic complications should be managed promptly with antibiotic support and

use of G-CSF should be considered according to American Society of Clinical Oncology (ASCO) guidelines[1].

No dose modification will be made for anemia; patients will be supported appropriately by the treating physician.

Table 3: Dose Modifications for cabazitaxel for Non-Hematologic Toxicity

Toxicity	**Grade**	**Dose Modification**
Diarrhea	Grade 2	Delay[1] next infusion until recovery (grade ≤1) No dose reduction required.
	Grade 3 & 4	Delay[1] next infusion until recovery (grade ≤1): 1st episode: Reduce dose by 1 dose level. 2nd episode: Withdraw from study treatment.
Stomatitis	Grade 2	Delay[1] next infusion until recovery (grade ≤1) No dose reduction required.
	Grade 3 & 4	Delay[1] next infusion until recovery (grade ≤1): 1st episode: Reduce dose by 1 dose level. 2nd episode: Withdraw from study treatment.
Cutaneous Reactions	Grade 2	Delay[1] next infusion until recovery (grade ≤1). No dose reduction required.
	Grade 3	Delay[1] next infusion until recovery (grade ≤1): 1st episode: Reduce dose by 1 dose level. 2nd episode: Withdraw from study treatment.
	Grade 4	Withdraw from study treatment.
Creatinine increase	Grade 2, 3, & 4	No delay; in case of creatinine >1 x ULN:calculate creatinine clearance using the Cockcroft-Gault equation on D21: if ≥60 ml/min, no dose modification if clearance ≥40 ml/min and < 60ml/min, reduce dose by one dose level if clearance <40 ml/min, Withdraw from study treatment.
Neurological toxicity[2]	Grade 2	No delay. Reduce by 1 dose level

[1] Smith, TJ, Khatcheressian GL, Lyman GH, et al: 2006 Update of Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-Based Clinical Practice Guideline. J Clin Oncol 24: 3187-3205. 2006

	Grade 3 & 4	Withdraw from study treatment.
Bilirubin Elevation	Grade 2	Delay[1] until recovery to bilirubin ≤1.0 x UNL and reduce dose by 1 dose level
	Grade 3 & 4	Withdraw from study treatment.
Transaminases Elevation	Grade 2	Delay[1] until recovery to AST/ALT ≤1.5 x UNL and reduce dose by 1 dose level
	Grade 3 & 4	Withdraw from study treatment.
Hypersensitivity	Grade 3	No dose reduction. See Table 5 for management of hypersensitivity due to study drug. Withdraw from study treatment in case of 2nd grade 3 episode.
	Grade 4	Withdraw from study treatment.
Dose reduction levels provided in Table 1. [1] Maximum of 2 weeks delay, otherwise the patient will be withdrawn from study treatment. [2] Including hearing disorders.		

4.4.2 Diarrhea

No prophylaxis should be given; most of all, loperamide should not be prescribed prophylactically. Patients should stop any laxative treatment and avoid food and beverage, which might accelerate intestinal transit.

Diarrhea can be life threatening and may lead to dehydration, electrolyte imbalance, or sepsis. Diarrhea should be treated promptly with loperamide. Patients with diarrhea should be carefully monitored, especially patients with previous external radiation therapy, and should be given fluid and electrolyte replacement if they become dehydrated. Loperamide should be given to patients when they leave hospital.

Diarrhea ≥ Grade 3 in the absence of neutropenia ≥Grade 3:

In addition to the general precautions and prompt treatment with loperamide, patients should be given antibiotic support if they develop ileus, fever or neutropenic complications. Subsequent chemotherapy treatments should be delayed in patients until return of pretreatment bowel function for at least 24 hours without need for anti-diarrheal medication. Subsequent doses of study drug should be decreased by 1 dose level according to Table 3.

Diarrhea ≥Grade 3 associated with neutropenia ≥Grade 3:

In addition to prompt treatment with loperamide and fluid and electrolyte replacement, aggressive treatment with antibiotic support is recommended. Complete blood count (CBC) should be assessed every 3 days [-1/+0] until ANC resolves to ≥1500/µL. Subsequent chemotherapy treatments should be delayed in such patients for up to 2 weeks until return of pretreatment bowel function for at least 24 hours without need for anti-diarrheal medication and until ANC resolves to ≥1.5 x 10^9/L. Following recovery, the dose of study drug should be reduced by 1 dose level (see Table 1).

4.4.3 Other Toxicities

For grade ≥3 toxicities except fatigue, local reaction, fluid retention, anemia and other toxicities that merely are uncomfortable but do not cause serious morbidity to patients, cabazitaxel should be held for a maximum of 2 weeks from the planned date of reinfusion until resolution to grade ≤1, then reinstituted, if medically appropriate. A dose reduction of subsequent doses will be left to the investigator's judgment. These patients will be withdrawn from study treatment if >1 dose reduction is needed. Any measures such as frozen gloves or socks or scalp cooling cap to prevent nail toxicity or alopecia are left to the investigator judgment.

Table 4: Intervention for hypersensitivity

Symptom and Severity	**Intervention Recommendation**
Mild symptoms: localized cutaneous reaction such as mild pruritus, flushing, rash.	• Consider decreasing the rate of infusion until recovery of symptoms, stay at bedside • Then, complete study drug infusion at the initial planned rate
Moderate symptoms: any symptom such as generalized pruritus, flushing, rash, dyspnea, back pain during infusion, hypotension with systolic blood pressure (BP) >80 mm Hg not listed above (mild symptoms) or below (severe symptoms).	• Stop study drug infusion, • Give diphenhydramine 50 mg i.v. and/or i.v. dexamethasone 10 mg, • Resume study drug infusion within 3 hours following recovery of hypersensitivity reaction. Administer study drug over 2 hours for all subsequent treatments.
Severe symptoms, such as: bronchospasm, generalized urticaria, systolic BP ≤80 mm Hg, angioedema.	• Stop study drug infusion; • Give IV diphenhydramine 50 mg and/or i.v. dexamethasone 10 mg and/or epinephrine as needed. • Severe hypersensitivity reactions require immediate discontinuation of the cabazitaxel infusion and administration of appropriate therapy.
Anaphylaxis (Grade 4 reaction)	Withdraw from study treatment.

Management of subsequent cycles

The recommended pretreatment for subsequent infusions is 50 mg diphenhydramine i.v. or other i.v. H1 antihistaminic agent and 10 mg dexamethasone i.v. 30 minutes prior to study drug infusion. For patients who experience moderate or severe hypersensitivity reactions, the study drug should be administered over 2 hours for subsequent treatment courses in addition to premedication as noted above. These patients must be informed of the potential risk of recurrent allergic reactions and must be carefully monitored.

If the initial reaction is grade 4 for allergy (anaphylaxis), the patient will receive no further treatment and will go off protocol therapy.

If a second severe reaction (grade 3) recurs despite additional premedications as outlined above, the patient will go off protocol therapy.

In case of late occurring hypersensitivity symptoms, e.g., appearance within 1 week after treatment of a localized or generalized pruritus, symptomatic treatment may be given (e.g., oral antihistamine), additional oral or i.v. premedication with antihistamine may also be given for the next cycle of treatment depending on the intensity of the reaction observed. No dose reductions will be made in any case.

4.5 Dose Modifications for Prednisone

Prednisone can be discontinued for the onset or exacerbation of diabetes mellitus, hypertension, gastrointestinal ulceration or bleeding, severe neurological side effects, or other serious adverse events which the Investigator considers to be a contraindication to continuing steroids. Prednisone may be reinstituted with the resolution of the adverse events at the discretion of the Investigator. The reason for altering the dose or discontinuing prednisone should be documented in the medical record.

4.6 Concomitant Medications

Concomitant drugs that are strong CYP3A inducers or strong CYP3A inhibitors should be avoided. Concomitant administration of strong CYP3A inhibitors is expected to increase concentrations of cabazitaxel. The concomitant administration of strong CYP3A inducers is expected to decrease cabazitaxel concentrations. If patients require co-administration of a strong CYP3A inhibitor, consider a 25% JEVTANA dose reduction.

4.6.1 Permitted concomitant medications

Prednisone will be prescribed to all patients receiving Cabazitaxel as per the local standard of care. The recommended dose is 5 mg given twice daily by mouth (or 10 mg once daily). Sites can adjust the dose per standard of care.

All supportive care medications are permitted. It is encouraged that changes in bisphosphonate or denosumab usage to not occur during the study treatment on this protocol unless the deletion or change is for toxicity associated with the baseline bisphosphonate or denosumab usage. If the

patient is not on a bisphosphonate or denosumab at study entry, bisphosphonates or denosumab should not be initiated during the study treatment so as not to confound adverse events or skeletal related events during the study treatment. If there is any change or initiation of bisphosphonate or denosumab usage during study treatment, the reason should be documented.

In the event a patient requires therapeutic administration of G-CSF, the patient should receive this prophylactically in subsequent cycles.

4.6.2 Prohibited concomitant medications

Treatment with any other anticancer therapy except steroids is not allowed and is considered a protocol violation unless the patient has documented disease progression or has terminated further study treatment.

Patients will be removed from study treatment for any cancer-related radiation therapy while on study treatment. Lesions which are symptomatic or cause unstable bone should be irradiated before the start of study treatment. Initiation of any radiotherapy after study treatment has begun will constitute disease progression.

4.7 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue for 6 cycles or until:

- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from study
- Requirement for treatment with a prohibited medication
- Any seizure
- Disease progression defined as:
  - Symptomatic progression: worsening of cancer-related symptoms mandating a change in anti-cancer therapy (radiation or chemotherapy) or ≥ 2 level decrease in ECOG PS

  AND/OR

  - Radiological progression: RECIST Criteria v1.1 for measurable disease or appearance of ≥ 2 new bone lesions on whole body bone scan confirmed on a subsequent scan

  AND/OR

  - PSA progression: After a minimum of 12 weeks of treatment, PSA increase ≥ 25% (minimum ≥ 2 ng/mL) above baseline in patients without a PSA decline OR PSA increase that is ≥ 25% (minimum ≥ 2ng/ml) above nadir in patients with a PSA decline, confirmed by a second value ≥ 3 weeks later.

4.8 Removal of Subjects from Study

Patients can be taken off the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

- Patient voluntarily withdraws from treatment (follow-up permitted);
- Patient withdraws consent (termination of treatment and follow-up);
- Patient is unable to comply with protocol requirements;
- Patient demonstrates disease progression (unless continued treatment with study drug is deemed appropriate at the discretion of the investigator);
- Patient experiences toxicity that makes continuation in the protocol unsafe;
- Treating physician judges continuation on the study would not be in the patient's best interest;
- Lost to follow-up.

Within six weeks of withdrawal, all study procedures outlined for the Progression/Off Treatment visit should be completed. The primary reason for a patient's withdrawal from the study is to be recorded in the source documents.

If a patient does not return for a scheduled visit every effort should be made to contact the patient. In any circumstance, every effort should be made to document patient outcome and reason for withdrawal if possible. The investigator should request the patient return all unused product, request the subject return for a final visit if applicable, and follow with the subject regarding any unresolved adverse events.

If the subject withdraws from the trial and also withdraws consent for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

If any patient should die during the study or within 28 days of stopping study treatment, the Investigator will inform the IRB and Sanofi. The cause of death should be recorded in detail, within 24 hours, on a serious adverse event (SAE) form and reported to institutional, federal and any other appropriate committees.

4.9 Duration of Follow Up

Participants will be followed for 2 years after they are taken off protocol treatment or until death, whichever occurs first. Participants taken off protocol treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event(s).

5. DRUG INFORMATION

5.1 Cabazitaxel (Jevtana®)

5.1.1 Formulation

Cabazitaxel is supplied as a sterile, non-pyrogenic, non- aqueous yellowish to brownish yellow solution contained in a 15 mL clear glass vial, stoppered with a chlorobutyl rubber closure coated with a transparent ETFE coating. The rubberclosure is crimped to the vial with an aluminum cap covered with a light green plastic flip-off cap. Single-dose vial, containing a total of 60 mg of cabazitaxel expressed as anhydrous and solvent-free basis, per 1.5 mL of solution. The fill volume has been established to include an overfill, [i.e., 1.5 mL (nominal volume) + 0.33 mL]. This overfill was determined to ensure that a 10 mg/mL concentration is obtained in the premix and that 60 mg dose can be extracted.

The diluent used for the preparation of the premix is a sterile, non-pyrogenic solution containing a 13% w/w ethanol solution in water for injection. This solution is contained in a 15 mL clear glass vial, stoppered with a chlorobutyl rubber closure coated with a transparent ETFE coating. The rubber closure is crimped to the vial with either an aluminum cap covered with a light grey plastic flip-off cap or a gold-color aluminum cap covered with a clear plastic flip-off cap.

Each vial of diluent is overfilled to ensure that a 10 mg/mL concentration is obtained in the Premix and that 60 mg dose can be extracted. [ie, 4.5 mL (nominal volume) + 1.17 mL]. The solution is a clear colorless liquid.

5.1.2 Supplier

Cabazitaxel will be supplied by Sanofi at no cost to study patients.

5.1.3 **Storage Conditions**

Store between +15°C and +30°C. Do not refrigerate. The solvent was also shown to be stable under these conditions. All vials must be kept in their box until use.

5.1.4 Preparation and administration of cabazitaxel

The preparation of the cabazitaxel infusion solution for administration requires the preparation of a premix solution at 60 mg/6 mL (nominal concentration). This must be done with a 13% m/m ethanol solution in water for injection (the "diluent") supplied with the cabazitaxel concentrate for solution for infusion ("preparation of the premix solution"). Then the premix solution must be diluted in an infusion vehicle ("preparation of the infusion solution") prior to administration.

5.1.4.1 Preparation of the premix solution under aseptic conditions (First Dilution)

Set aside the required number of solvent vials (one solvent vial for each vial of cabazitaxel). For each cabazitaxel vial:

- Using a syringe fitted with a needle, withdraw the ENTIRE CONTENTS of the diluent vial and inject it into the corresponding vial of cabazitaxel. Direct the needle onto the inside wall of the cabazitaxel vial and inject slowly to limit foaming.

- The addition of the ENTIRE CONTENTS of 1 diluent vial ensures a minimal extractable volume of the premix solution of 6 mL, containing 10 mg/mL of cabazitaxel.

- Remove the syringe and needle and gently mix the reconstituted solution by repeated inversions for at least 45 seconds. Do not shake.

- Allow the premix solution to stand for 5 minutes at room temperature to allow foam to dissipate. The solution is homogeneous and contains no visible particulate matter. It is normal for foam to persist after this time period.

The premix solution contains 10 mg/mL of cabazitaxel. Then the premix solution must be diluted in an infusion vehicle so as to obtain the required dose for administration. The second dilution should be done immediately (within 30 minutes) to obtain the final infusion as detailed in 5.1.4.2.

5.1.4.2 Preparation of the infusion solution under aseptic conditions (Second (Final) Dilution)

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

- Aseptically, with a syringe and needle, withdraw the volume of the premix solution containing 10 mg/mL of cabazitaxel that corresponds to the required dose (mg) for administration of cabazitaxel

- Inject the required premix volume into a r 250 mL infusion container (containing either 5% dextrose solution or 0.9% sodium chloride solution). If the cabazitaxel dose is greater than 65 mg, a larger IV carrier volume is permitted so as not to

exceed the maximum concentration of 0.26 mg/mL.

- Remove the syringe and thoroughly mix the final infusion solution by gently inverting the bag. The final infusion may crystallize over time—do not use and discard preparation if crystallization occurs.

The concentration of the infusion should be between 0.10 mg/mL and 0.26 mg/mL (based on Maximum Tolerated Dose of 30 mg/m² and a Body Surface Area [BSA] of 2.1 m²).

Mix the contents of the infusion container manually by gently inverting the bag or bottle.

5.1.4.3 **Storage period of premix and infusion solution**

The premix solution of cabazitaxel should be used immediately after preparation and within 1 hour at ambient temperature.

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

5.1.4.4 **Risks and Precautions**

Neutropenic deaths have been reported with cabazitaxel. Frequent blood counts should be obtained to determine if initiation of G-CSF and/or dose modifications should be considered. Weekly blood counts are essential during Cycle 1 and before each treatment cycle. Cabazitaxel should not be administered to patients with a neutrophil count ≤1500 cells/mm^3. Use caution in patients with hemoglobin < 10 g/dL. Primary prophylaxis with G-CSF should be considered in patients with high-risk clinical features (age > 65 years, poor performance status, previous episodes of febrile neutropenia, extensive prior radiation ports, poor nutritional status, or other serious comorbidities) that predispose them to increased complications from prolonged neutropenia. Therapeutic use of G-CSF and secondary prophylaxis should be considered in all patients considered to be at increased risk for neutropenia complications.

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 can occur, especially during the first two infusions, and may include rash, erythema, hypotension, and bronchospasm. For a severe hypersensitivity reaction, cabazitaxel should be discontinued immediately and appropriate therapy administered. Cabazitaxel is contraindicated in patients with a past history of severe hypersensitivity to cabazitaxel or drugs formulated with polysorbate 80 (e.g., docetaxel).

Death related to diarrhea and subsequent electrolyte imbalance has been reported. Dosage should be modified with grade 3 or 4 diarrhea. Nausea and vomiting are also common. Patients should be rehydrated and treated with antiemetics and antidiarrheals as needed.

There have been cases reported of death due to renal failure. Renal function should be monitored

closely.

Patients with impaired hepatic function are excluded as it is likely to increase cabazitaxel concentrations.

Patients $\geq$ 65 years old should be monitored closely as they are more likely to experience fatal outcomes, especially secondary to neutropenia.

Other toxicities include (all grades):

- Blood and lymphatics: neutropenia (94%); febrile neutropenia (7%); anemia (98%); leukopenia (96%), and thrombocytopenia (48%)

- Cardiac: arrhythmias (including atrial fibrillation/flutter, tachycardia, complete arteriovenous [AV] block, bradycardia, and supraventricular tachycardia [SVT]) (5%)

- Gastrointestinal: diarrhea (47%); nausea (34%); vomiting (22%); constipation (20%); abdominal pain (17%); dyspepsia/reflux (10%)

- General disorders: fatigue (37%); asthenia (20%); pyrexia (12%); peripheral edema (9%); mucositis (6%); pain (5%)

- Infections: urinary tract infection (8%)

- Nutrition: anorexia (16%); dehydration (5%); decreased weight (9%)

- Musculoskeletal: back pain (16%); arthralgia (11%); muscle spasms (7%)

- Nervous system: peripheral neuropathy (sensory and motor) (13%); dysgeusia (11%); dizziness (8%); headache (8%)

- Urinary tract: hematuria (17%); dysuria (7%)

- Respiratory: dyspnea (12%); cough (11%)

- Dermatologic: alopecia (10%)

- Vascular: Hypotension (5%)

5.2 Prednisone

Prednisone is a corticosteroid used for the treatment of many cancers and is usually given along with other anticancer drugs. In this protocol it will be administered orally at a dose of 10 mg per day.

5.2.1 Formulation

For prednisone, refer to the package insert or summary of product characteristics of details on description, administration, and precautions for use.

5.2.2 Supplier

Prednisone is commercially available in 2.5 mg, 5 mg, 10 mg, 20 mg, and 50 mg tablets.

5.2.3 Storage condition

Store away from heat, light, and moisture at room temperature.

5.2.4 Risks and Precautions

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

Other toxicities include:

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

Withdrawal of prednisone after prolonged therapy may result in symptoms such as fever, myalgias, and arthralgia, which could be symptoms of adrenal insufficiency.

6. ASSESSMENT OF EFFECTS

6.1 Safety assessment

The adverse effects of the drug will be assessed from adverse events, vital signs and by clinically significant changes in the laboratory evaluations and ECGs. Adverse events (AE) will use the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE). This study will utilize the CTCAE Version 4.03 for adverse event reporting.

6.2 Efficacy assessments

All efficacy assessments will be assessed from the time of registration.

6.2.1 Radiological Response

Subjects that have measurable disease at screening will be evaluated for response on the basis of RECIST criteria v1.1. Tumor measurements using physical examination, spiral CT scan and/or MRI or other appropriate techniques deemed suitable by the investigator will be performed at screening within 28 days of subject registration and repeated at the end of Cycle 2 (6 weeks), end of Cycle 4 (12 weeks), then every 12 weeks. In case of partial or complete response, tumor measurements will be repeated after at least 6 weeks for confirmation.

6.2.2 PSA response

The PSA response criteria will be defined as per modified PSA Working Group Criteria[2].

Response: Definition of response: ≥50% decline in PSA from baseline maintained for at least 3 weeks and measured by the same laboratory, and without evidence of other disease progression documented at time of confirmatory values. PSA response duration will commence on the date of the first 50% decline in PSA.

Non Response: Failure to achieve PSA response or progression criteria.

Progression:
Patients without a PSA decline: PSA increase ≥ 25% (minimum ≥ 2 ng/mL) above baseline after minimum of 12 weeks on treatment, confirmed by a second value ≥ 3 weeks later.

- Patients with a PSA decline: PSA increase ≥ 25% (minimum ≥ 2ng/mL) above nadir in patients, confirmed by a second value ≥ 3 weeks later.

[2] Bubley, GJ, et al., Eligibility and response guidelines for phase II clinical trials in androgen-independent prostate cancer: recommendations from the Prostate-Specific Antigen Working Group. J Clin Oncol, 1999. 17(11): p. 3461-7.

Clinical Benefit
Patients are considered to have had a clinical benefit if they experience a PSA or measurable radiological response of any duration or stable disease for ≥ 12 weeks (no symptomatic progression, PSA progression, or objective disease progression).

Disease Progression
Disease Progression is defined as the development of symptomatic or radiological progression at any time or PSA progression after 12 weeks [i.e. PSA progression alone prior to 12 weeks does not constitute progressive disease]. Progression will be classified as any of the following:

a. Symptomatic progression: worsening of cancer-related symptoms mandating a change in anti-cancer therapy (radiation or chemotherapy) or ≥ 2 level decrease in ECOG PS.
b. Radiological progression: RECIST criteria v1.1 for measurable disease or appearance of ≥ 2 new bone lesions on whole body bone scan confirmed on a subsequent scan.
c. PSA progression: After a minimum of 12 weeks of treatment, PSA increase ≥ 25% (minimum ≥ 2 ng/mL) above baseline after minimum of 12 weeks on treatment in patients without a PSA decline **OR** PSA increase that is ≥ 25% (minimum ≥ 2ng/ml) above nadir in patients with a PSA decline, confirmed by a second value ≥ 3 weeks later.

7. STUDY CALENDAR

Pre-study evaluations are to be conducted within 14 days prior to registration. Scans must be done ≤28 days prior to registration. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours of the next cycle of therapy.

All assessments must be performed prior to administration of any study medication. All study assessments and medications should be administered within the 28 day screening period as indicated in section 4.0.

Evaluation	**Pre-Treatment**	**Pre-Treatment**	**Day 1 of each Cycle[8]**	**End of Cycle 2, 4, then every 12 weeks**	**End of Treatment[10]**	**Safety Visit** (28 days after taken off protocol treatment)	**Follow Up** (Every 3 months from time of Off Treatment)[12]
Window	-28 to -1 day	-14 to -1 day	± 3 days	± 4 days	± 4 days	± 4 days	± 7 days
Medical History	X						
*Physical Exam including: height[6], weight, BSA[7], performance status[11], clinical tumor measurements (if applicable)		X	X			X	X[9]
Vital signs[5]		X	X			X	X[9]
Hematology: CBC, differential		X	X[14]			X	
Biochemistry: creatinine (serum), sodium, potassium, total bilirubin, alkaline phosphatase, AST, ALT, LDH, GGT, albumin		X	X			X	
Testosterone (total)	X[1]			X	X		
PSA		X	X		X		
Urine test		X					
ECG		X			X		
Chest/abdomen/pelvis CT scan (MRI if appropriate)	X[1]			X[2]	X		X[2]
Whole body Bone scan	X[1]			X[2]	X		X[2]
Correlative Samples: Plasma, Serum, Whole Blood		X		X[3]	X		
Archival Tumor Tissue		X					
Oral corticosteroids prior to cabazitaxel infusion			X				
Cabazitaxel infusion			X				
Prednisone			→				
Adverse events and Concomitant Medications	X[4]		Continuously				

Evaluation	Pre-Treatment	Pre-Treatment	Day 1 of each Cycle[8]	End of Cycle 2, 4, then every 12 weeks	End of Treatment[10]	Safety Visit (28 days after taken off protocol treatment)	Follow Up (Every 3 months from time of Off Treatment)[12]

[*]Complete physical examination at screening only; subsequent physical examinations are limited to signs and symptoms of disease or toxicity.

1. Within 28 days of registration.
2. Radiology to be repeated at the end of Cycle 2 (6 weeks), Cycle 4 (12 weeks), then every 12 weeks. Patients that go off treatment without radiological progression will have scans repeated every 3 months until documented disease progression.
3. At Baseline, end of Cycle 4, and End of Treatment
4. Baseline symptoms will be documented prior to starting study treatment. Adverse Events collection will begin from the time of first dosing. Adverse events will be coded as per CTCAE v4.03.
5. Vitals: temperature, systolic and diastolic blood pressure, respiratory rate, and pulse.
6. Height is required at Baseline only.
7. BSA should be calculated prior to each dose of chemotherapy.
8. One cycle consists of 3 weeks.
9. Survival status only.
10. End of treatment is at the time the decision is made to take the patient off study treatment.
11. ECOG only.
12. All patients will be followed to death or for a maximum of 2 years.
13. Weekly CBC and differential is required during Cycle 1

8. CORRELATIVE/SPECIAL STUDIES

Correlative samples will be collected at Baseline, at the end of Cycle 4 and at the end of treatment. The correlative samples are mandatory.

The correlative samples consist of: Tumor tissue from the time of diagnosis or the most recent biopsy (prior to the initiation of study treatment), serum, and plasma/buffy specimens for molecular markers or signature predictive of cabazitaxel benefit (to include status of AR pathway, androgen biosynthetic pathway genes, ABCB1, MRP1, and other mediators of taxane resistance, among others.

Tumor Sample Guidelines: Tumor specimens from the diagnostic biopsy or the most recent biopsy (prior to the initiation of study treatment) should be submitted for banking along with a completed specimen submission form and a copy of the corresponding pathology report.

Please submit 1 H&E stained slide (with the location of the tumor circled by pathology) along with 10-15 unstained slides. Slides should be cut at ~5 microns and mounted on positively charged (+) slides. Ship specimens to UC Davis according to the instructions provided in the appendix.

Blood Sample Collection Guidelines
With the patient's consent, serial serum and plasma/buffy specimens will be collected within 28 days prior to study treatment, at the conclusion of cycle 4 (+/- 10 days) and at the conclusion of treatment (+/-10 days). Blood samples will be collected using standard venipuncture techniques. A total of 20 mL of whole blood will be drawn at each time point.

Serum Collection: Whole blood will be collected in 10 mL red top vacutainer tubes (BD Vacutainer #367820) and allowed to clot for 45-60 minutes. Serum will be separated from cells within 60-90 minutes of venipuncture. Serum is separated from clotted blood by centrifugation at 1800 x g for ten minutes. Using a pipette, serum will then equally aliquoted into .5 mL aliquots (up to eight cryovials). All cryovials should then be frozen as rapidly as possible and stored in a -70°C or colder freezer until shipping to UC Davis according to the instructions provided in the appendix.

Plasma/Buffy Collection: Whole blood will be collected in 10 mL purple top EDTA tubes (BD Vacutainer #366643). Tube should be centrifuged as soon as possible at approximately 800 x g for 10 minutes. Plasma should be transferred to a 15 mL conical tube and centrifuged a second time at 1000 – 1500 x g for 10 minutes. After the second centrifugations, aliquot plasma equally into 0.5 mL aliquots (up to eight cryovials). The buffy coat, a whitish layer of cells between the plasma and the red blood cell layers, should be collected from the original purple top tube and split into two labeled cryovials. All cryovials should then be frozen as rapidly as possible and stored in a -70°C or colder freezer until shipping to UC Davis.

Samples will be collected at the following time points (+/- window):

- Within 28 days prior to study treatment.
- At the conclusion of cycle 4 (+/-10 days).
- At the conclusion of treatment (+/- 10 days).

Specimen Banking

Patient samples collected for this study will be retained at UC Davis. Specimens will be stored indefinitely or until they are used up. If future use is denied or withdrawn by the patient, best efforts will be made to stop any additional studies and to destroy the specimens.

The Sponsor-Investigator, Christopher Evans, MD, will be responsible for reviewing and approving requests for clinical specimen from potential research collaborators outside of UC Davis. Collaborators will be required to complete an agreement (a Material Transfer Agreement or recharge agreement) that states specimens will only be released for use in disclosed research. Any data obtained from the use of clinical specimen will be the property of UC Davis for publication and any licensing agreement will be strictly adhered to.

The specimens, DNA, and their derivatives may have significant therapeutic or commercial value. The Informed Consent form contains this information and informs the subject that there is the potential for financial gain by UC Davis, the investigator or a collaborating researcher or entity.

The following information obtained from the subject's medical record may be provided to research collaborators when specimens are made available:

- Diagnosis
- Collection time in relation to study treatment
- Clinical outcome – if available
- Demographic data

9. SAFETY AND REPORTING REQUIREMENTS

9.1 Adverse Event Definition

Adverse event (AE) means any untoward medical occurrence in a patient or subject administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this 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 a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug.

For this protocol an abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.

Any other AE not listed as an expected event in the Investigator’s Brochure or in this protocol will be considered unexpected.

9.2 Adverse Event Documentation

Any patient enrolled in the trial who signed the consent form and received at least one dose of cabazitaxel will be eligible for adverse event reporting. Adverse events will use the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE). This study will utilize the CTCAE Version 4.03 for adverse event reporting.

All AEs must be recorded on case report forms (CRFs). Documentation must be supported by an entry in the subject's file. Each event should be described in detail along with start and stop dates, severity, relationship to investigational product as judged by the Investigator, action taken and outcome.

9.3 Severity of Adverse Events

The severity of an AE is graded as follows:

Mild (grade 1): the event causes discomfort without disruption of normal daily activities.

Moderate (grade 2): the event causes discomfort that affects normal daily activities.

Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.

Life-threatening (grade 4): the patient was at risk of death at the time of the event.

Fatal (grade 5): the event caused death.

9.4 Serious Adverse Event Definition

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

- Results in death.
- Is life-threatening (Note: the term "life-threatening" refers to an event/reaction in which the patient was at risk of death at the time of the event/reaction. It does not refer to an event/reaction which hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalization or prolongation of an existing hospitalization
- Results in persistent or significant disability or incapacity. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a congenital anomaly/birth defect.
- 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.

Clarification should be made between the terms *serious* and *severe* because they ARE NOT the same. The term *severe* is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as a severe headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above and is usually associated with events that pose a threat to a patient's life or functioning. A severe AE does not necessarily need to be considered serious. For example, persistent nausea of several hours duration may be considered severe nausea but may not be considered an SAE. On the other hand, a stroke resulting in only a minor degree of disability may be considered mild but would be defined as an SAE based on the above noted criteria. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

9.5 Procedures for Reporting Serious Adverse Events (SAEs)

9.5.1 Safety Reporting Requirements for IND Exempt Studies

For Investigator Sponsored IND Exempt Studies there are some reporting requirements for the FDA in accordance with the guidance set forth in 21 CFR 314.80.

Post-marketing 15-Day 'Alert Report'

The Sponsor-Investigator is required to notify the FDA of each adverse drug experience that is both serious and unexpected and is assessed by the investigator to be possibly related to study treatment as soon as possible but in no case later than 15 calendar days of initial receipt of the information. An unexpected adverse event is one that is not already described in the Investigator Brochure. Such reports (2 copies) are to be submitted to the FDA at the following address: Central Document Room, 5901-B Ammendale Rd., Beltsville, MD 20705-1266.
All 15-Day Alert Reports submitted to the FDA by the Sponsor-Investigator must also be faxed to Sanofi.

9.5.2 Responsibility for Reporting Serious Adverse Events to Sanofi

Report SAEs (initial and follow up), including pregnancy and overdose to Sanofi Pharmacovigilance using the MedWatch 3500A form. The SAE from must be faxed to Sanofi within 1 working day of awareness of the SAE. The foregoing is applicable to all SAEs, irrespective of causality.

Sanofi Group Entity Pharmacovigilance Contact:

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

Fax: 908-203-7783

E-mail: USPVmailbox@sanofi-aventis.com

9.5.3 Reporting to the Institutional Review Board

Both serious and non-serious adverse events will be reported in accordance with UCD IRB Administration and UCD Cancer Center Office of Clinical Research (OCR) policies. The UC Davis IRB can be reached at (916) 703-9151.

Participating site(s) will report adverse events per institution's IRB guidelines.

9.5.4 Follow up of Adverse Events and Serious Adverse Events

For the SAEs that have been deemed by the investigator as unrelated to protocol treatment, the SAE reporting period begins after the first dosing and ends on the date of scheduled Safety Visit (4 weeks follow-up visit) or 28 days after discontinuation of the study drug, whichever is later. For the SAEs that have been deemed by the investigator as at least possibly related to protocol treatment, the SAE must be reported even if this occurs after the date of scheduled Safety Visit (4 weeks follow-up visit) or 28 days after discontinuation of the study drug.

The investigator shall provide follow-up information as and when available in a new follow-up SAE form. All SAEs must be followed until resolved, become chronic, or stable unless the subject is lost to follow up. Resolution status of such an event should be documented on the CRF.

The CRF should capture all AEs occurring from cycle 1 day 1 till the date of scheduled Safety Visit (4 weeks follow-up visit) or 28 days after discontinuation of the study drug, whichever is later.

In addition, any known untoward event of any severity that occurs subsequent to the AE reporting period that the Investigator assesses as at least possibly related to the study therapy (i.e., the relationship cannot be ruled out) should also be reported as an AE.

Suggested Reporting Form:

- SAE Report Form
- US FDA MedWatch 3500A: http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm
- Any other form deemed appropriate by the sponsor-investigator

Medwatch 3500A Reporting Guidelines:

In addition to completing appropriate demographic and suspect medication information, the report should include the following information within the Event Description of the MedWatch Form 3500A:

- Treatment regimen (dosing, frequency, combination therapy)
- Protocol description (include number if assigned)
- Description of event, severity, treatment, and outcome, if known
- Supportive diagnostic and laboratory results

- Investigator's assessment of the relationship of the SAE to each investigational product and suspect medication

Follow-up information
Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch Form 3500A and submitting it as follow-up
- Adding supplementary summary information and submitting it as follow-up with the original MedWatch Form 3500A
- Summarizing new information and faxing it with a cover letter including subject identifiers (ie, DOB, initials, subject number), protocol description and number, suspect drug, brief adverse event description, and notation that additional or follow-up information is being submitted

9.5.5 Reporting to the Institutional Review Board

Both serious and non-serious adverse events will be reported in accordance with UCD IRB Administration and UCD Cancer Center Office of Clinical Research (OCR) policies. The UC Davis IRB can be reached at (916) 703-9151.

Participating site(s) will report adverse events per institution's IRB guidelines.

10. STATISTICAL CONSIDERATIONS

10.1 Study Design and Overview of Primary and Secondary Endpoints

This is a phase II, single-arm, open-label study.

The proposed primary endpoint for this single arm trial is PSA response (defined as >= 50% reduction from baseline).

Secondary endpoints include safety, radiologic response as assessed by RECIST, progression free survival, overall survival, and biomarkers for prostate cancer.

10.2 Sample Size Estimation /Accrual Rate

Forty-five patients will be enrolled, of whom we estimate 37 will be evaluable for efficacy. We anticipate accruing 4 patients per month.

In a retrospective analysis of response to various hormonal therapies (including abiraterone or enzalutamide) in patients who had a suboptimal response to prior ADT, defined as duration of ADT benefit <= 16 months (Loriot, ASCO GU 2012), PSA response (>= 50% reduction from baseline) was seen in only 18% of patients. In contrast, patients with ADT benefit lasting > 16 months had a PSA response of 58% with these same hormonal therapies.

The proposed primary endpoint for this single arm trial is PSA response rate (defined as >= 50% reduction from baseline). Assuming that historical response rate is approximately 20%, we anticipate that cabazitaxel will increase this rate to at least 45% or higher. The response rate will be compared to a historical response rate of 20% using the exact binomial test for a single proportion. With 37 subjects, the exact binomial test will have approximately 90% power to detect a difference from the historical response rate if the probability of response with cabazitaxel is 0.45.

10.3 Evaluation of Efficacy

The efficacy analysis population will consist of patients who receive any amount of study drug. PSA response rate will be compared to a historical response rate of 20% using the exact binomial test for a single proportion. For all binary outcomes (PSA response rate and RECIST response rate), confidence intervals for the response rate will be calculated using Wilson's method (1927).

Patients with insufficient follow up to be evaluated for PSA and RECIST response will be excluded from primary analysis of these endpoints; however, a sensitivity analysis will be conducted in which these patients are assumed to have progressive disease.

Medians of time-to-event outcomes will be estimated using the method of Kaplan and Meier, with confidence intervals estimated using Greenwood's method. For analysis of time-to-event outcomes, patients missing all PSA and RECIST assessments will be censored at the date of registration plus one day.

Continuous or ordered biomarkers will be compared between PSA responders and non-responders using the Wilcoxon rank sum test, and categorical biomarkers will be compared between PSA responders and non-responders using Fisher's Exact Test.

10.4 Evaluation of Safety

The safety analysis population will consist of patients who received any amount of study drug. Clinical and laboratory adverse events will be summarized by coded term and severity. Laboratory values will be plotted over time.

11. ADMINISTRATIVE REQUIREMENTS

11.1 Good Clinical Practice

The study will be conducted in accordance with the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) and the appropriate regulatory requirement(s). The investigator will be thoroughly familiar with the appropriate use of the drug as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to

demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

11.2 Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The IRB will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The study will only be conducted at sites where IRB approval has been obtained. The protocol, Investigator's Brochure, informed consent, advertisements (if applicable), written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the investigator. Sanofi requests that informed consent documents be reviewed by Sanofi or designee prior to IRB submission.

11.3 Required Documentation

Before the study can be initiated at any site, the following documentation must be provided to the OCR.

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list
- CVs and medical licensure for the principal investigator and any associate investigators who will be involved in the study
- Form FDA 1572 appropriately filled out and signed with appropriate documentation
- A copy of the IRB-approved consent form
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Executed clinical research contract

11.4 Study Registration

Once signed, informed consent has been obtained and all pretreatment evaluations have been performed, patients will be entered on study according to UCD Office of Clinical Research (OCR) policy. To register a patient, the data manager or designee must complete the Eligibility Checklist and the Patient Registration Form. A patient accession number will then be assigned. Administration of study drug may not be initiated until the patient is registered. See 14.6 for Multicenter Guidelines.

11.5 Patient Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from either the patient or his guardian or legal representative prior to study participation. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all applicable regulatory requirement(s). In accordance with UCD OCR

policy an original signed and dated participant Informed Consent document will reside in a secured location within the UCD OCR. Copies of the signed and dated Informed Consent document will be provided to the study participant and UCD Health System Information Management for inclusion in the participant's UCD Health System Medical Record or per participating site's policies.

11.6 Protocol Deviations

All protocol deviations will be reported in accordance with UCD IRB Administration and UCD Cancer Center OCR policies or the participating site's IRB policies.

11.7 Patient Confidentiality

In order to maintain patient privacy, all study reports and communications will identify the patient by initials and the assigned patient number. Data capture records and drug accountability records will be stored in secure cabinets in the UCD OCR or at the participating institutions. Medical records of patients will be maintained in strict confidence according to legal requirements. The investigator will grant monitor(s) and auditor(s) from Sanofi or its designees and regulatory authority(ies) access to the patient's original medical records for verification of data gathered on the data capture records and to audit the data collection process. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

11.8 Protocol Compliance

The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB and the appropriate regulatory authority(ies). Changes to the protocol will require approval from Sanofi and written IRB approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB may provide, if applicable regulatory authority(ies) permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval /favorable opinion of the IRB. The investigator will submit all protocol modifications to Sanofi and the regulatory authority(ies) in accordance with the governing regulations.

Any departures from the protocol must be fully documented in the source documents.

11.9 On-site Audits

Regulatory authorities, the IRB and/or Sanofi's clinical quality assurance group may request access to all source documents, data capture records, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

11.10 Drug Accountability and Disposal

Accountability for the drug at all study sites is the responsibility of the principal investigator. The investigator will ensure that the drug is used only in accordance with this protocol. Drug accountability records indicating the drug's delivery date to the site (if applicable), inventory at the site (if applicable), use by each patient, and return to Sanofi's or disposal of the drug according to institutional standard procedures (if applicable and if approved by Sanofi) will be maintained by the clinical site. Accountability records will include dates, quantities, lot numbers, expiration dates (if applicable), and patient numbers.

11.11 Premature Closure of the Study

This study may be prematurely terminated, if in the opinion of the investigator or Sanofi, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the investigator or Sanofi by the terminating party.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient complete and/or evaluable data
- Plans to modify, suspend or discontinue the development of the drug

11.12 Record Retention

The investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s).

11.13 Quality Assurance and Control

Quality assurance audits of select patients and source documents may be conducted by the UC Davis Comprehensive Cancer Center Quality Assurance Committee as outlined in the UC Davis Cancer Center Data and Safety Monitoring plan.

Quality control will be maintained by the Quality Assurance team according to OCR policy.

11.14 Data and Safety Monitoring

In addition to the requirements for adverse event reporting as outlined in Section 6, this protocol is also subject to the UC Davis Cancer Center's (UCDCC) Data and Safety Monitoring Plan. The

UCDCC is committed to pursuing high-quality patient-oriented clinical research and has established mechanisms to ensure both scientific rigor and patient safety in the conduct of clinical research studies. The UCDCC relies on a multi-tiered committee system that reviews and monitors all cancer clinical trials and ensures the safety of its participants, in compliance with institutional and federal requirements on adverse event (AE) reporting, verification of data accuracy, and adherence to protocol eligibility requirements, treatment guidelines, and related matters. The Scientific Review Committee (SRC) assumes overall oversight of cancer studies, with assistance and input from two independent, but interacting, committees: the Quality Assurance Committee and the Data Safety Monitoring Committee. A multi-level review system strengthens the ability of the UCDCC to fulfill its mission in conducting high quality clinical cancer research.

As per University of California Davis Cancer Center (UCDCC) Office of Clinical Research (OCR) SOP AM 506: Protocol Specific Meetings, the principal investigator (PI) and clinical research coordinator (CRC) meet at least monthly for ongoing study information, to discuss patient data and adverse events and to determine if dose escalation is warranted, when applicable

According to the UCDCC Data and Safety Monitoring Plan (DSMP), any new serious adverse events related to the drugs being used on this trial are reviewed monthly by the UCDCC Data and Safety Monitoring Committee (DSMC) and any applicable changes to the study are recommended to the PI, if necessary.

The UCDCC Scientific Review Committee (SRC) determines if a UCDCC Data and Safety Monitoring Board (DSMB) is required. If required, the DSMC will appoint a DSMB. The DSMB is responsible for reviewing study accrual logs, adverse event information and dose escalation meeting minutes (where applicable) to ensure subject safety and compliance with protocol defined guidelines.

12. USE OF INFORMATION

All information regarding Cabazitaxel supplied by Sanofi to the investigator is privileged and confidential information. The investigator may use this information to accomplish the study, but may not use it for other purposes without consent from Sanofi. In accordance with the agreement between Sanofi and the investigator sponsor, complete study data must be provided to Sanofi. This data and other information obtained from the clinical study may be used by Sanofi for the development of cabazitaxel and may be disclosed by Sanofi to regulatory authority(ies), other investigators, corporate partners, or consultants as deemed necessary by Sanofi.

Upon completion of the clinical study and evaluation of results by Sanofi, the hospital or institution and/or investigator may publish or disclose the clinical trial results pursuant to the terms contained in the applicable Clinical Trial Agreement.

13. REFERENCES

1. Hussain M1, Tangen CM, Higano C, et al. Absolute prostate-specific antigen value after androgen deprivation is a strong independent predictor of survival in new metastatic prostate cancer: data from Southwest Oncology Group Trial 9346 (INT-0162). J Clin Oncol. 2006 Aug 20;24(24):3984-90.

2. de Bono JS, Oudard S, Ozguroglu M, et al: Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet 376:1147-54, 2010

3. de Bono JS, Logothetis CJ, Molina A, et al: Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 364:1995-2005, 2011

4. Ryan CJ, Smith MR, de Bono JS, et al: Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med 368:138-48, 2013

5. Scher HI, Fizazi K, Saad F, et al: Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 367:1187-97, 2012.

6. Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med. 2014 Jul 31;371(5):424-33.

7. Loriot Y, ASCO GU 2012 (abstract 213)

14. APPENDICES

14.1 Performance Status Criteria

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

14.2 List of strong CYP3A inhibitors

List of strong CYP 3A inhibitors

INHIBITORS	Maximum AUC fold increase (AUC ratio)	Substrate for the observed Maximum AUC fold increase	Inhibitor Classification
Telaprevir	77,98 / 9,0	tacrolimus / midazolam	Strong
Indinavir/RIT	36,50	alfentanil	Strong
Tipranavir/RIT	26,91	midazolam	Strong
Ritonavir	26,41	midazolam	Strong
Cobicistat (GS-9350)	19,03	midazolam	Strong
Indinavir	16,25	vardenafil	Strong
Ketoconazole	15,90	midazolam	Strong
Troleandomycin	14,80	midazolam	Strong
Danoprevir/RIT	13.42	midazolam	Strong
Saquinavir/RIT	12,48	midazolam	Strong
Itraconazole	10,80	midazolam	Strong
Voriconazole	9,40	midazolam	strong
Mibefradil	8,86	midazolam	strong
Clarithromycin	8,39	midazolam	Strong
Lopinavir/RIT	7,71	aplaviroc	Strong
Elvitegravir/RIT	6,80	midazolam iv	Strong
Posaconazole	6,23	midazolam	Strong
Telithromycin	6,0	midazolam	Strong
Grapfruit Juice	5,95	midazolam	Strong
Conivaptan	5,76	midazolam	Strong
Nefazodone	5,44	midazolam	Strong
Nelfinavir	5.29	simvastatin	Strong
Saquinavir	5.18	midazolam	Strong
Boceprevir	5.05	midazolam	Strong

14.3 List of strong CYP 3A inducers

Inducers	% AUC decrease	Substrate for the observed % AUC decrease	Inducer Classification
Rifampin	99.7	budesonide	Strong
Mitotane	94.5	midazolam	Strong
Avasimibe	93.5	midazolam	Strong
Phenytoin	89.5	nisoldipine	Strong
Carbamazepine	86.5	quetiapine	Strong
Enzalutamide	85.9	midazolam	Strong
St John's wort*	80	midazolam	Strong
Rifabutin	Not provided	delavirdine	Strong
Phenobarbital	76.6	verapamil	Strong

*An herb (Hypericum perforatum) used for depression, anxiety and/or sleep disorders

14.4 Response Evaluation Criteria in Solid Tumors (RECIST) v. 1.1

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

14.4.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with cabazitaxel.

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

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

14.4.2 Disease Parameters

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

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. *If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol*.

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

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites,

pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

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

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

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

14.4.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

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

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as

assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

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

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

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

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

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

Endoscopy, Laparoscopy. The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers. Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

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

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

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

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

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

14.4.4 Response Criteria

14.4.4.1 Evaluation of Target Lesions

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

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

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

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

14.4.4.2 Evaluation of Non-Target Lesions

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

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

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

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

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances,

and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

14.4.4.3 Evaluation of Best Overall Response

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

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

14.4.5 Duration of Response

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

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

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

14.5 Correlate Sample Submission Form

UC Davis Sample Submission Form: UCDCC#261 – Cabazitaxel in CRPC

Patient Information:

Patient Study ID# _____ **Pt Initials (FML):** _____

Research Blood Timepoint: □ Screening □ End of Cycle 4 □ Off Treatment
(leave blank if shipping tumor submission only)

Collection Date: _____ **Time of Collection:** _____

Shipper Contact Information:

Packaged by: _____ Phone #: _____ Email Address: _____

Specimen Shipping Instructions:

Draw: **1 x 10 ml Purple EDTA Tube** (BD# 366643)
1 x 10 mL Red top Serum Tube (BD# 367820)

EDTA and Serum tubes: Process blood according to instructions in protocol Section 8.0. Ship frozen aliquots on dry ice.
Packaging shipment: Frozen samples should be shipped on sufficient dry ice and in accordance with all applicable state and federal laws. Please include completed requisition forms for all samples submitted and contact the lab manager when shipping. Packages can be shipped Monday-Wednesday ONLY.

Slide Submission: Prepare slides as described in Section 8.0
Packaging shipment: Archival tissue slides may be sent at ambient temperatures with a room-temperature gel pack to protect specimen from temperature fluctuations. In summer months when outdoor temperatures can exceed 90°F, please pack specimens with a refrigerated gel pack. Please include a completed requisition form and a copy of the path report for each sample submitted and contact the lab manager when shipping. Packages can be shipped Monday-Wednesday ONLY.

Packaged Specimens should be shipped using **FedEx Priority Overnight to:** [redacted]

When shipping, please send email notification including FedEx tracking number to: [redacted]

Molecular Pharmacology Shared Resource Use Only

Lab Specimen #_____
Condition of Specimen:
□ **Usable as received**
□ **Usable, not optimal:** _____
□ **Not usable, insufficient or incorrect**
□ **Not usable, other:**_____

Date Received: ☐☐/☐☐/☐☐

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14.6 Multicenter Guidelines

A. Before registration, the site study coordinator should check to make sure that the corresponding Investigational Drug Service or equivalent has study drug in stock.

B. Registrations for this Phase II protocol must be made through the OCR of the University of California, Davis Comprehensive Cancer Center between the hours of 9am and 3pm (Pacific Time), Monday through Friday (except holidays). Documentation of current IRB approval of this protocol by non-UC Davis institutions must be on file prior to registration of patients at these institutions.

C. Pre-study laboratory tests, scans, and x-rays (where applicable), must be completed prior to registration, within the time frame specified in the protocol. The eligibility checklist must be completed. Patients must sign an informed consent prior to registration.

D. Patients may be registered up to 72 hours prior to treatment initiation. All pages of the signed consent, completed checklist and reports from all pre-study laboratory tests, scans and x-rays (where applicable) must be faxed and/or emailed to UC Davis OCR [redacted] in order to register the patient. The UC Davis Protocol Coordinator will review these documents and fax and/or email a registration confirmation (which includes a subject ID number).

   Reminder: Confirm eligibility for ancillary studies and willingness to participate at the same time as eligibility for the treatment study.

E. If the patient is to be registered the same day as the proposed treatment start date, the UC Davis Study Coordinator must be notified by fax and/or 24 hour prior to proposed treatment start date that the site has a patient to register.

F. A patient failing to meet all protocol requirements may not be registered. If you have any questions regarding eligibility, contact the coordinating site PI or Study Coordinator.

NOTE: Administration of study medication may not be initiated until the registration confirmation has been received.

14.7 Data Submission Schedule

All data will be collected using UC Davis data collection forms. Any and all source documentation should be maintained.

- SUBMIT WITHIN 24 HOURS OF REGISTRATION:
  Patient Registration Form

- SUBMIT WITHIN 14 DAYS OF REGISTRATION:
  In-House Pre-Study Evaluation Form (IH-102)

- SUBMIT WITHIN 7 DAYS OF SCREENING FAILURE:
  Patient Screen Failure Form

- SUBMIT WITH 14 DAYS OF CYCLE COMPLETION:
  Adverse Event/Drug Relationship Form

- SUBMIT WITHIN 14 DAYS OF END OF EACH TREATMENT CYCLE:
  In-House Treatment Cycle Form - Oral

- SUBMIT WITHIN 14 DAYS OF EACH RESPONSE ASSESSMENT:
  Tumor Measurement Log

- SUBMIT WITHIN 14 DAYS OF OFF TREATMENT:
  Off Treatment/In Follow-up/Off Study/Expiration Form (IH-301)

- SUBMIT WITHIN 14 DAYS OF KNOWLEDGE OF DEATH IF PATIENT IS STILL ON STUDY OR 30–DAYS IF OFF STUDY:
  Off Treatment/In Follow-up/Off Study/Expiration Form (IH-301)

- SUBMIT WITHIN 2 DAYS OF KNOWLEDGE OF PROTOCOL DEVIATION:
  Notice of Protocol Deviation

- ALL SERIOUS ADVERSE EVENTS MUST BE REPORTED AS OUTLINED IN THE PROTOCOL.