A phase II study in mCRPC on the pharmacodynamic effects of budesonide on cabazitaxel (Jevtana®): A randomised, open-label multicenter study: CABARESC

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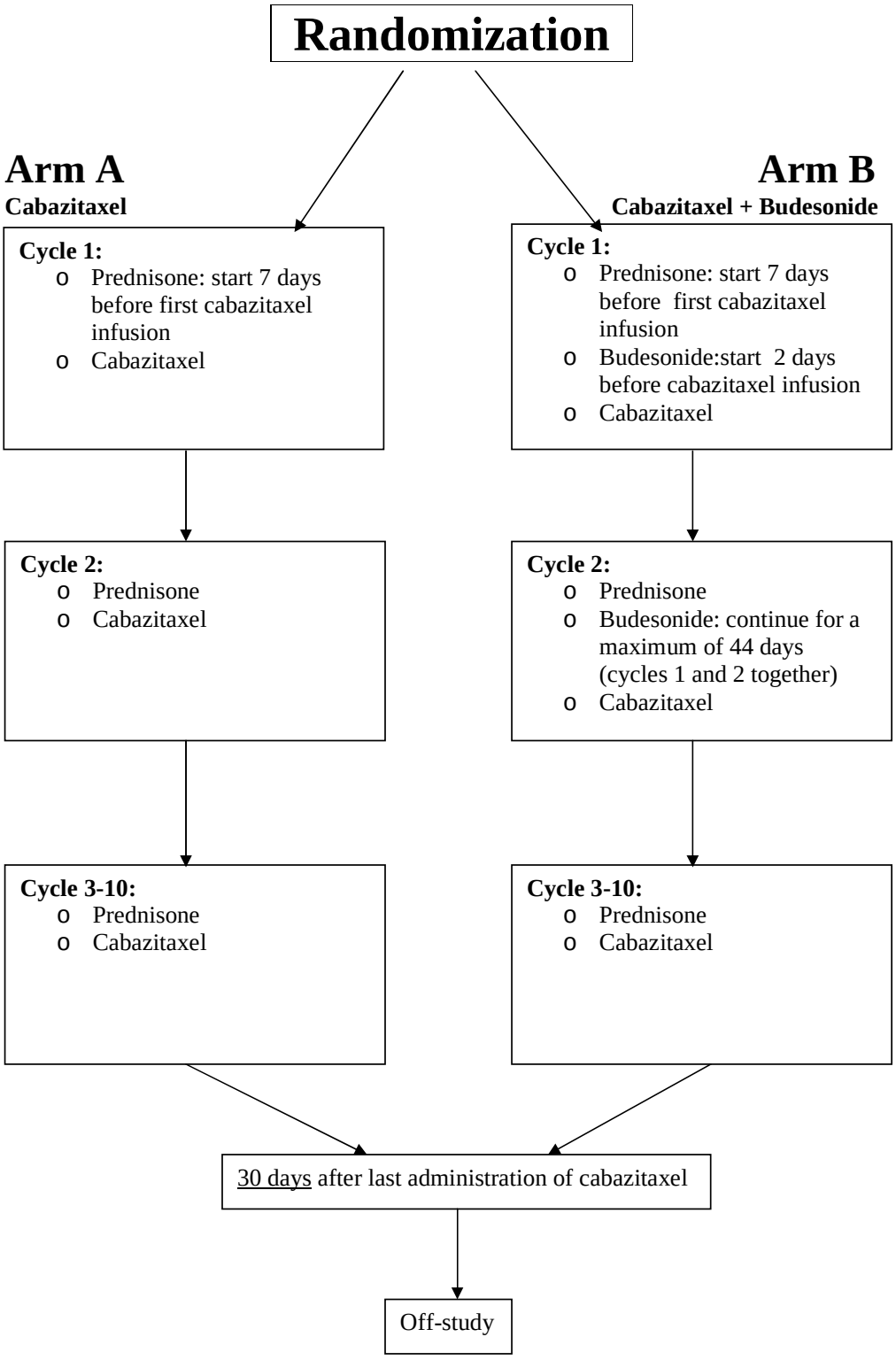
Synopsis

Title	A phase II study in mCRPC on the pharmacodynamic effects of budesonide on cabazitaxel (Jevtana®): A randomised, open-label multicenter study: CABARESC
Study Phase	II
Study Objectives	Primary objectives: To study the effects of budesonide on the grade of cabazitaxel induced diarrhea Secondary objectives: To study the effects of budesonide on other side effects of cabazitaxel (e.g. myelotoxicity) To study the pharmacogenetics of cabazitaxel To study the effects of budesonide on the incidence, duration and severity of cabazitaxel induced diarrhea based on the data collected by patient diaries. To study the effects of cabazitaxel and/or budesonide on PSA levels
Patient population	Adult patients; age ≥18 years, with mCRPC, previously treated with a docetaxel-containing regimen
Study design	Patients will be randomly assigned to the treatment groups through a centralized stratified randomization process using the following stratification factors: center, age (18-64 years versus 65 years and older) and previous radiotherapy on back, abdomen and/or pelvis no versus yes. Patients will be randomized to one of the two treatment arms: Arm A: Cabazitaxel Arm B: Cabazitaxel + Budesonide
Duration of treatment	Maximum of 10 cycles cabazitaxel. In arm B, budesonide should be used from two days before the first cabazitaxel administration during 44 consecutive days
Number of patients	250 (125 patients per arm)
Adverse events	Adverse events should be documented if observed and serious adverse events should be reported immediately.
Planned start of recruitment	October 2011
Planned end of recruitment	January 2015

Scheme of study



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2. Introduction

2.1 Cabazitaxel: background

In June 2010, the tubulin-binding taxane cabazitaxel (Jevtana®; Sanofi-Aventis) in combination with prednisone was registered by the Food & Drug Administration (FDA) for the treatment of patients with hormone-refractory metastatic prostate cancer whose disease progresses after docetaxel treatment [1]. Registration in the European Union was obtained in April 2011 [2]. Both constitutive and acquired resistance to docetaxel treatment can be caused by expression of the drug transporter p-glycoprotein (P-gp, ABCB1) by cancer cells, encoded by the ABCB1 gene, which cause the drug to be pumped out of the cell. Unlike the other approved taxanes, paclitaxel and docetaxel, cabazitaxel was selected for clinical development as a result of its poor affinity for p-glycoprotein [3-5] . Cabazitaxel has better anti-proliferative activity on insensitive cell lines compared to docetaxel. Using cell lines with acquired resistance to doxorubicin, vincristine, vinblastine, paclitaxel and docetaxel, cabazitaxel had a resistance factor ranging from 1.8-10 compared to a resistance factor of ranging from 4.8-59 for docetaxel [6]. Also, cabazitaxel has larger potential to cross the blood-brain barrier compared with paclitaxel and docetaxel [7].

In a large randomized trial by de Bono *et al*., cabazitaxel was compared with mitoxantrone[8]. Mitoxantrone is often administrated in patients who progress after docetaxel treatment because of favorable palliative response, without an improvement in overall survival [9]. The trial included 755 patients with hormone-refractory metastatic prostate cancer who had previously received a docetaxel containing regimen. Patients were randomized to receive 12 mg/m^2 mitoxantrone (n= 377) or 25 mg/m^2 cabazitaxel (n= 378) intravenously over 1 hour every three weeks concomitantly with 10 mg oral prednisone daily. Patients treated with cabazitaxel showed a 30% reduction in the risk of death and a statistically significant improved median survival of 2.4 months compared to the mitotraxone group. Also, the investigator assessed tumor response was 14.4% in the cabazitaxel group compared with 4.4% in the mitotraxone group [8].

Cabazitaxel is given as a 1-hour infusion in a three weekly schedule [8]. The dose limiting toxicity as found in two phase I studies is myelosuppression and the maximum tolerated dose was reached at 30 mg/m^2. The recommended phase II doses were 20 mg/m^2 and 25 mg/m^2, respectively [5,8]. The prednisone is given as 5 mg, twice daily.

2.2 Metabolism of cabazitaxel

After intravenous administration, cabazitaxel is mainly metabolized by cytochrome P450 iso-enzymes CYP3A4 and CYP3A5. CYP2C8 also plays a minor role in its metabolism [10]. Cabazitaxel has linear pharmacokinetics and is consistent with a three-compartment pharmacokinetic model with half lives in the initial, intermediate and terminal phase of 4.4 min, 1.6 hours, and 1.6 hours respectively. The plasma clearance is relatively fast (population pharmacokinetic estimate of 48.5 L/h). *In vivo*, cabazitaxel is highly (93%) bound to the proteins albumin and lipoprotein. The drug has a low binding to α1-acid glycoprotein [10].
Cabazitaxel and its metabolites are mainly excreted in the feces (76% of the dose) and to a lesser extent (3.7% of the dose) excreted in the urine.

As mentioned earlier, myelosuppression is a common side effect of cabazitaxel treatment in the randomized trial by de Bono *et al* [8]. Neutropenia occurs in almost all patients (94%) and 82% of patients experience ≥ grade 3 neutropenia when treated with 25 mg/m^2 cabazitaxel. Febrile neutropenia occurs in 8% of the patients treated with cabazitaxel. Another

hematological side effect observed was anemia (97%). Grade 3 anemia was seen in 11% of the patients.

Of the non-hematological toxicities, diarrhea is the side effect most commonly observed in the trial by the Bono *et al*. Diarrhea occurs in 47% of all patients treated with 25 mg/m^2 cabazitaxel, combined with prednisone. Of these patients, 21.7%, 19.1% and 6.2% experience grade 1, 2 and 3 diarrhea respectively. Other common observed non-hematological side-effects were fatigue (37%) and nausea (34%), of which 5% and 2% respectively was ≥ grade 3.

2.3 Budesonide: Background

In the intestine, budesonide is a locally active corticosteroid at the level of the terminal ileum and the ascending colon. It is registered in the Netherlands for the treatment of M. Crohn induced diarrhea with a recommended dose of 9 mg/day, taken in the morning. After absorption, budesonide has a 90% first pass effect in the liver, resulting in a very low systemic availability. Because of its low systemic availability, budesonide has a very favourable safety profile[11]. The addition of budesonide to a prednisone containing regimen is necessary because of its local anti-inflammatory effects in the terminal ileum and ascending colon. Prednisone is given in a low dose because of its presumed anti-tumor effects in prostate cancer; however, these levels are too low to prevent the occurrence of diarrhea during cabazitaxel treatment [8].

In an earlier small study, budesonide reduced the incidence of diarrhea with at least 2 grades in 86% of the irinotecan treated and 57% of the 5-FU treated patients [12]. In another, more recent, prospective randomized, double blind, placebo controlled study budesonide was tested for prevention of irinotecan induced diarrhea in patients with advanced colon cancer [11]. Although not statistically significant, potentially due to the relatively small sample size, in the budesonide treated group, diarrhea (defined as >4 extra stools a day) could be prevented in 58.3% of the patients compared to a 38.5% of the patients in the placebo arm. Also, patients in the budesonide group had less and shorter episodes of diarrhea compared to placebo [11]. Weber *et al*. examined the potential of budesonide to prevent diarrhea in ipilimumab treatment in patients with melanoma, however this study failed to show a preventive effect of budesonide [13].

2.4 Circulating tumor cells

Over the past few years, circulating tumor cells (CTC) measured in the peripheral blood have drawn major attention and FDA-approval has been obtained for the use of CTC as a prognostic tool in patients with metastatic breast, colorectal and prostate cancer [16] using the CellSearch method (Veridex LCC, Raritan, New Jersey).

Several relatively large studies have shown that baseline CTC counts are a strong independent prognostic factor for survival in patients with metastatic castrate-resistant prostate carcinoma (mCRPC) [16-18]. In 231 patients with metastatic CRPC, patients with a favorable baseline count (< 5 CTC) had a longer overall survival (OS) of 21.7 months compared to 11.5 months in patients with > 5 CTC [16]. Moreover, when patients converted in CTC count during treatment, their prognosis changed accordingly; patients who changed from a favorable to an unfavorable CTC count had a similar median OS to patients with an unfavorable count throughout treatment and vice versa. Importantly, CTC changes during treatment are stronger and at an earlier timepoint associated with OS than PSA at all time points during therapy and predict outcome much earlier than conventional response evaluation by radiology [17-18].
In addition to CTC enumeration, isolation and subsequent characterization of CTC enables their use as a predictive marker. As a consequence of elapsed time and treatment given, metastases differ substantially from primary tumors, and it is expected that treating patients based on metastatic characteristics would result in better patient selection [19]. As obtaining biopsies from metastases is often painful and complicated, CTC are an attractive alternative, serving as a "liquid biopsy".

2.5 Biopsies

As stated before, cabazitaxel has significant side effects. Moreover, as not every patient with mCRPC responds to cabazitaxel, it would be worthwhile to be able to predict which patient will benefit from continued taxane treatment and which patient will not. Therefore, biomarkers that predict response to taxane-based chemotherapy for mCRPC are more than welcome. Studying longitudinal changes in gene expression in tumor tissue of cabazitaxel-treated patients will enable us to unravel the mechanisms of sensitivity and resistance to taxanes, cabazitaxel in specific.
Currently, research to define biomarkers that predict sensitivity for cabazitaxel in preclinical human prostate cancer (PC) xenograft mouse models is being performed in the Erasmus MC protocol EMC 2479 (102-11-05). A gene expression profile that corresponds with cabazitaxel response will be obtained from cabazitaxel-treated PC xenograft to obtain a cabazitaxel-related biomarker profile for mCRPC patients. Such a profile would be extremely helpful to select patients that will benefit from cabazitaxel in the future and would allow for tailored decision making and personalized medicine.

2.6 Study Rationale

Cabazitaxel is a new drug to be used for the treatment of metastatic castrate resistant prostate cancer (mCRPC) after progression on docetaxel therapy. Unfortunately, a relatively high incidence of diarrhea (median onset after 7 days of therapy) is limiting its dose/use.
The aim of this study is to assess the prophylactic effect of budesonide on cabazitaxel induced diarrhea. The hypothesis is that the local anti-inflammatory effects of budesonide will have a favorable effect on the incidence of diarrhea in cabazitaxel treatment. As the previous pharmacokinetic safety study MEC 11-091 shows no clear interaction between cabazitaxel and budesonide, the Cabaresc study will be enrolled [20].

3. Study objectives

3.1 Primary objectives:

- To study the effects of budesonide on the grade of cabazitaxel induced diarrhea

3.2 Secondary objectives:

- To study the effects of budesonide on other side effects of cabazitaxel (e.g. myelotoxicity)
- To study the pharmacogenetics of cabazitaxel
- To study the effects of budesonide on the incidence, duration and severity of cabazitaxel induced diarrhea based on the data collected by patient diaries.
- To study the effects of cabazitaxel and/or budesonide on PSA levels.

3.3 Tertiary objectives

- To generate a gene-expression profile composed of RNAs and micro RNAs (miRNA's) specific for CTC among a background of leucocytes and investigate whether this profile will enable prediction of cabazitaxel response.
- To gain insight into the mechanisms of sensitivity and resistance to cabazitaxel by means of comparing CTC characteristics before the first and third cycle of cabazitaxel.
- To enumerate CTC at baseline and this way establish whether both treatment arms are well-balanced in terms of prognosis.
- To assess treatment effect of cabazitaxel at a more robustly way and at an earlier time-point than with prostate specific antigen (PSA) levels and changes thereof.

- To study the correlation between gene expression profiles and clinical parameters in order to develop a biomarker profile for the prediction of cabazitaxel response in mCRPC patients
- To study mechanisms of resistance during cabazitaxel treatment
- To study possible serum biomarkers in human blood samples
- To validate gene expression profiles, related to cabazitaxel response and found in tumor tissue, in CTCs

4. Patient selection criteria

4.1 Inclusion criteria:

- Metastatic castrate resistant prostate cancer (mCRPC) patients with documented disease progression, defined as:
  documented rising PSA levels (at least 2 consecutive rises in PSA over a reference value taken at least 1 week apart, or a PSA rise of $\geq$ 2.0 µg/l), appearance of new lesions or documented disease progression based on CT scan or bone scan.
- Previous treatment with a docetaxel-containing regimen
- Age $\geq$ 18 years;
- WHO performance status $\leq$ 1 (see appendix B);
- Adequate renal function (within 21 days before randomization) defined as serum creatinin $\leq$ 1.5 x ULN and/or calculated creatinin clearance $\geq$ 50ml/min, according to MDRD formula (appendix F).
- Adequate hepatic functions (within 21 days before randomization) defined as: total bilirubin $\leq$ 1.0 x ULN; alanine aminotransferase (ALAT) and aspartate aminotransferase (ASAT) $\leq$2.5x ULN, in case of liver metastasis < 5 ULN; alkaline phosphatase (AF) < 5x ULN) In case of bone metastasis, AF < 10x ULN is accepted;
- Adequate hematological blood counts (within 21 days before randomization) defined as (absolute neutrophil count (ANC) $\geq$1.5 x 10^9/L and platelets $\geq$ 100 x 10^9/L);
- Castration, either surgically or by continued LHRH agonist therapy

- Written informed consent according to ICH-GCP

4.2 Inclusion criteria for the side-study concerning biopsie(s) (in selected centers):

- Eligible to participate according to the Cabaresc protocol
- Metastatic/Primary lesion(s) of which a histological biopsy can be obtained are:
  a. Safely accessible
  b. In patients not having bleeding disorders (such as haemophilia) or bleeding complications from biopsies, dental procedures or surgery.
  c. In patients having an adequate coagulation status as measured by PTT < 1.5 x ULN and platelet count > 100 x 10^9/L
  d. neutrophiles should be ≥1.5x 10^9/L
- In case patients are using anti-coagulant medication, treating physicians will assess whether patients should temporary stop any anti-coagulant medication at some time before biopsy.

4.3 Exclusion criteria:

- Impossibility or unwillingness to take oral drugs;
- Serious illness or medical unstable condition requiring treatment, symptomatic CNS-metastases or history of psychiatric disorder that would prohibit the understanding and giving of informed consent;
- Use of medications or dietary supplements known to induce or inhibit CYP3A (see section 5.8)
- Known hypersensitivity to corticosteroids
- Any active systemic or local bacterial, viral, fungal - or yeast infection.
- Ulcerative colitis, Crohn's disease or celiac disease (active or in medical history)
- Ostomy
- Planned/active simultaneous yellow fever vaccine
- Geographical, psychological or other non-medical conditions interfering with follow-up

5. Study outline

5.1 Study period

The current plan is to start enrolment in the last quarter of 2011. Enrolment should be completed within 3 years. After the last patient has completed the last cycle of cabazitaxel and the data have been validated, the final analysis will be performed.

5.2 Inclusion, randomization and start of study treatment

113 evaluable patients are needed in both arms. Under the assumption that 10% of patients will be enrolled erroneously (e.g. not eligible) or will not be evaluable, a total of 250 patients with mCRPC will be recruited. After a patient meets all inclusion and exclusion criteriahe may be randomized by using the web-based application TOP, managed by the CTC, into one of the two treatment arms:

Arm A: Cabazitaxel
Arm B: Cabazitaxel + Budesonide

All participating centres will be given access to this application and will thus be able to randomize patients. Patients should start study treatment within 2 weeks after randomization. If, for any reason, cabazitaxel treatment is not initiated within 2 weeks after randomization,

eligibility criteria for study enrolment should be re-assessed and documented in the medical chart and the CRF.

An interim safety analysis has been performed after the first 57 evaluable patients included in each arm have completed 2 cycles of cabazitaxel. When patients stop treatment due to severe toxicity in the 1st cycle and no 2nd cycle of cabazitaxel is administered, patients were also considered evaluable and included for analysis. In case the percentage of patients with grade 3-4 diarrhea in the budesonide arm was more than 15% higher compared to the control group, the study would be stopped. The interim analysis did not meet the stopping rule and therefore the study will continue accrual.
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5.3 Evaluation
Of all diarrhea due to cabazitaxel treatment, 50% occurs in the 1st treatment cycle according to de Bono et al. [8]; 90% of all diarrhea occurs in the 1st and 2nd cycle. Therefore, the aim is to determine patients evaluable after completing two cycles of cabazitaxel. When patients stop treatment due to severe toxicity in the 1st cycle and no 2nd cycle of cabazitaxel is administered, patients will also be considered evaluable and included for analysis.

5.4 Study treatment
In arm A and arm B, cabazitaxel will be administrated intravenously at a dose of 25 mg/m² during a one-hour infusion every 3 weeks. Chemotherapy will be continued until progression (at the discretion of the treating physician), unacceptable toxicity or until 10 cycles have been administered (whichever comes first).

In arm B, budesonide will be administered once daily in the morning, one hour before breakfast as oral medication consisting three capsules (3x3 mg), during 44 consecutive days, beginning two days before the first cycle of cabazitaxel. In case of delay of cabazitaxel, budesonide should be continued unless this is contraindicated. . Patient compliance will be assessed through a (short) patient diary

5.5 Premedication and concomitant medication
In this study, the recommended premedication/concomitant medication will not be considered study treatment. All patients will receive the mandatory concomitant treatment with prednisone 10 mg daily. Prednisone should be used at least for 1 week prior to the start of cabazitaxel. All patients will continue 10 mg of prednisone daily during cabazitaxel treatment until 20 days after the last cabazitaxel administration. The 10 mg prednisone will preferably be administered 2 times a day; as 5 mg in the afternoon and 5 mg in the evening

The recommended premedication scheme for cabazitaxel should be implemented at least 30 minutes before every administration of cabazitaxel. Infusion should happen intravenously to reduce the risk and severity of possible anaphylaxis.
Premedication consists of:

- Granisetron 1 mg intravenous infusion
- Dexamethason 8 mg intravenous infusion
- Ranitidin 50 mg added to the dexamethason, intravenous infusion
- Clemastine 2 mg intravenous infusion.

5.6 Duration of study treatment
Chemotherapy treatment will continue for a maximum of 10 cycles, unless the patient presents with signs of disease progression, unacceptable toxicity or any other reason why continuation of the treatment is no longer in the patient's best interest.

5.7 Dose adaptation of cabazitaxel and management of toxicity
All patients should start with the maximum dose level (i.e. 25 mg/m2). A lower dose is not allowed at start. Dose delay or reduction should be applied, for cabazitaxel only, in case of hematological or nonhematological toxicities as defined below and by using CTCAE version 4. Dose reduction will occur relative to the dose used in the previous treatment cycle. Once a dose has been reduced, escalation of the dose in subsequent cycles is not recommended. If toxicity continues or reoccurs despite a dose reduction, cabazitaxel treatment should be stopped. However, treatment may be discontinued earlier if this is in the best patient's interest (at the discretion of the treating physician).

Dose reduction

Dose Level	*Cabazitaxel Q3 weeks*
0	25 mg/m^2
-1	20 mg/m^2

The dose will be calculated according to BSA and no dose capping will be applied.

Delay of cabazitaxel cycles
A delay of treatment is defined as ≥ 4 days delay. Cabazitaxel cycles may be delayed as long as necessary to recover from toxicity.

5.7.1 Myelosuppression
Neutropenia:
In case of grade 3 neutropenia for ≥ 7 days, clinical neutropenia or neutropenia accompanied with fever ≥ 38.0°C the next cycle should be given with one level of dose reduction.
At the day of cabazitaxel infusion ANC should be ≥ 1.5 x 10^9/L. If this is not the case, treatment should be delayed until ANC ≥ 1.5 x 10^9/L.
Thrombocytopenia:
In case of a ≥ 3 grade thrombocytopenia, the next cycle should be delayed until platelets are ≥100 x 10^9/L, and treatment should be continued at one level of dose reduction in the next cycle.

5.7.2 Nausea/Vomiting
Prophylactic anti-emetic treatment may be considered during cabazitaxel treatment. If despite the anti-emetic treatment, the nausea/vomiting is considered ≥ grade 3, dose reduction of one level should be made.

5.7.3 Diarrhea
If diarrhea CTCAE grade ≥ 2 occurs (defined as increase of ≥4 stools per day over baseline) , patients should receive symptomatic treatment with loperamide, consisting of 4 mg following the first episode of diarrhea. After this first dose, 2 mg for each following episode until the diarrhea is resolved, with a maximum of 16 mg daily. If despite the loperamide use, the ≥ grade 2 diarrhea continues or re-occurs, the next cycle should be postponed and a dose reduction of one level should be made.

5.7.4 Stomatitis
Grade 2-3: cabazitaxel treatment should not continue until resolution of stomatits to grade ≤ 1. In case of grade 3 stomatitis the dose of subsequent treatment cycles should be reduced by one level. In case of grade 4 stomatitis the patient will go off study

5.7.5 Peripheral neuropathy
Grade 2: Postpone further treatment until improvement to gade ≤ 1. The dose of the next treatment cycle should be reduced by one dose level.

5.7.6 Skin toxicity
Grade 3: delay until resolved to ≤ grade 1 with a maximum of two weeks and reduce the dose of the next treatment cycle of cabazitaxel by one dose level.

5.7.7 Liver Toxicity
In case of increase of ASAT and/or ALAT to > 2.5 x ULN or bilirubin to >ULN, delay cabazitaxel treatment for up to 2 weeks until ASAT and/or ALAT returned to ≤ 2.5 x ULN or bilirubin <ULN. The dose in the next treatment cycles should be reduced by one level only if the liver toxicity that occurred in the previous cycle was clinically significant (i.e. up to the discretion of the treating physician).

5.7.8 Other toxic effects
In case of grade 2, manage symptomatically, adjust dose in next treatment cycle of cabazitaxel with one dose level. In case of grade 3, cabazitaxel treatment should be delayed until resolution to grade 1; dose reduction is on physician's discretion.

5.8 Concomitant medication
Both cabazitaxel and budesonide are primarily metabolized through CYP3A. Therefore no concomitant administration of strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) or inducers (phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, Phenobarbital, St. John's Wort) are allowed during the study (see Appendix C).
No over the counter anti-diarrheal medication are allowed during the study period.

5.9 Expected toxicity cabazitaxel
Most common side effects of cabazitaxel (as written in the drug label) include:
Often (>10%): neutropenia, anemia, leukopenia, thrombocytopenia, diarrhea, fatigue, nausea, vomiting, constipation, asthenia, abdominal pain, hematuria, back pain, anorexia, peripheral neuropathy, pyrexia, dyspnea, dysgeusia, cough, arthralgia and alopecia.
See table 1 for extensive adverse event information as included in the drug label.

5.10 Expected toxicity budesonide
The side-effects of budesonide are expected to be mild because of the short treatment interval. Continuous use of budesonide has the following side-effects (as written in the drug label):
Often (1-10%): cushing syndrome, growth disorders, dyspepsia, muscle cramps, palpitations, visual disorders, nervousness.
Rare (0.1-1%): tremor, rash, pruritus, hypokalaemia.

6. Study Assessments

6.1 Flowchart

Procedure	Prior to randomization (within 21 days)	1st and 2nd cycle	3rd -10th cycle	End of study (30 days after last cabazitaxel administration)
Informed consent	**X**			
Physical exam	**X**	Day of cabazitaxel infusion, pre-infusion	Day of cabazitaxel infusion, pre-infusion	**X**
Hematology [1])	**X**	Day of cabazitaxel infusion (pre-infusion) or max 1 week prior to infusion and every 6-8 days after infusion	Day of cabazitaxel infusion (pre-infusion) or max 1 week prior to infusion and every 6-8 days after infusion	**X**
Biochemistry [2])	**X**	Max 1 week prior to infusion		**X**
Diarrhea [3])		Weekly	Day of cabazitaxel infusion, pre-infusion	**X**
PSA	**X**	Day of cabazitaxel infusion, pre-infusion	Day of cabazitaxel infusion, pre-infusion	**X**
Full blood for DNA analysis [4])		Day of the first cabazitaxel cycle, pre-infusion (only first cycle, after given ICF)		
Full blood for CTC [6])		Prior to 1st cycle	Prior to 3rd cycle	
Biopsy [7])		Within 21 days before 1st cycle cabazitaxel		**X**
Full blood for serum markers [8])		Prior to 1st cycle		After last cycle cabazitaxel
Adverse events		Day of cabazitaxel infusion (pre-infusion)[&]	Day of cabazitaxel infusion (pre-infusion)[&]	**X**
Diarrhea diaries [5])		7 days before 1st cycle until start 3rd cycle	Dairy should be returned to the local study staff at the start of the 3rd cycle.	

[1])	WBC, ANC, Platelets, Hemoglobin
[2])	Alkaline phosphatase, LDH, Bilirubin, ASAT, ALAT, Gamma glutamyl transpeptidase (γGT), Serum creatinin, Na+, K+, Calcium, Phosphate, Albumin, other clinically indicated tests
[3])	Should be assessed by investigator, according to CTCAE criteria v4 (See Appendix D)
[4])	When patients signed additional informed consent (See section 6.3)
[5])	Defecation pattern and consistency, to be entered daily by patient in patients diary.
[&])	In cycles 1-10 adverse events will be assessed before every new infusion at the outpatient clinic.
[6])	When patient signed additional informed consent
[7])	After additional consent has been signed; separately for both biopsies
[8])	When patient signed additional informed consent

Monitoring toxicity:
In cycles 1-10 adverse events will be assessed before every new infusion at the outpatient clinic.
based on the CTCAE criteria v4 (See Appendix D) .

6.2 Baseline screening

- Patient history and physical examination, within two weeks prior to the study (regular work-up).
- Smoking status should be assessed. A non-smoker will be defined as someone who does not smoke or has stopped smoking for over (the last) four weeks. When the patient is a smoker, the amount of cigarettes/cigars smoked daily, should be assessed.
- A complete blood count, and serum biochemistry which involves sodium, potassium, calcium, phosphorus, serum creatinin, calculation of creatinin clearance (Cockcroft-Gault formula), ASAT, ALAT, gamma glutamyl transpeptidase (γGT), lactate dehydrogenase (LDH), alkaline phosphatase (AF), total bilirubin, albumin and PSA within 21 days prior to randomization.
- Blood for DNA-analysis according to the cabaresc study (see section 6.3) and in the Erasmus MC according to protocol MEC 02.1002. (if written informed consent for this study)

6.3 DNA analysis

Two blood collection tubes (7 ml each) will be drawn from those patients who have consented separately. This blood will be used to be able to link DNA characteristics to for example toxicity using pharmacogenetics. In the Erasmus MC, blood is drawn from every patient who gives consent for this database according to protocol MEC 02.1002. In other hospitals, blood will be drawn according to the Cabaresc protocol. Two full blood collection tubes (K3 EDTA) should be stored in a ≤ -20°C freezer at the local centre until the end of the study. Blood collection tubes will be collected on behalf of the principal investigator at the local centre after the blood collection of the last patient in that centre has been performed. Pharmacogenetic analysis will be done at the Erasmus MC. The blood collection tubes will be stored for 15 years.

From patients who have consented to participate in the pharmacogenetic substudy, a separate informed consent will be asked for the use of blood that may remain after completion of the pharmacogenetic analyses. This blood will be used for future research in the context of prostate cancer and its treatment. The maximum storage period will remain unchanged. These patients will also be asked permission for the use of their study data in connection with the results of the pharmacogenetic and future research.

6.4 Evaluation during the study

- Before start of every cabazitaxel cycle (max 1 week before infusion), hematology (Hb, WBC, ANC and platelets) and PSA assessment will be performed. 6-8 days *after* the cabazitaxel infusion hematology (Hb, WBC, ANC and platelets) should be assessed.
- Max one week before start of the first two cycles of cabazitaxel, and at the end of the treatment (i.e. 30 days after last cabazitaxel administration), serum biochemistry which involves sodium, potassium, calcium, phosphorus, creatinin, calculation of creatinin clearance (Cockcroft-Gault formula), ASAT, ALAT, gamma glutamyl transpeptidase (γGT), lactate dehydrogenase (LDH), alkaline phosphatase (AF), total bilirubin and albumin will be performed.
- In cycles 1-10 adverse events will be assessed before every new infusion at the outpatient clinic.
- Patients will be instructed to use loperamide in case of diarrhea (defined as increase of ≥ 4 stools per day over baseline) according to normal protocol (start 4 mg, every two hours 2 mg as long as diarrhea continues until a maximum of 16 mg). Before start of study, patients will receive a loperamide prescription and are asked to record the use of loperamide in a patient diary. When loperamide shows no effect, patients should be admitted.
- During the first two cycles, until 20 days after second Cabazitaxel administration, patients will keep a study diary in which they provide the following information:
  - Daily side effects
  - Concomitant medication (including possible use of loperamide)
  - Daily defecation habits (frequency, consistency).

6.5 CTC analysis

Peripheral venous blood will be drawn from patients who have consented separately, at two time-points, just before start of the first and before the third cycle of cabazitaxel. At both time-points two extra vacutainers of 10 mL will be drawn, one CellSave and one EDTA tube, both combined with a regular blood draw so no extra draw is necessary. Batches containing both vacutainers will be supplied to all centers. The day of collection, blood samples need to be sent by regular mail to:

Erasmus MC Cancer Institute
Laboratorium MTI
Be-410
Postbus 2040
3000CA Rotterdam, the Netherlands
Tel: 010 704 14 18

Upon arrival at the laboratory, both samples will be processed within maximally 96 hours after collection using the CellSearch method. In brief, this method relies on immunomagnetic isolation of epithelial cells using ferrofluid-coupled anti-epithelial cell adhesion molecule (EpCAM)-antibodies and staining of these cells with DAPI and fluorescence labeled antibodies directed against cytokeratin 8/18/19 and CD45. Cells positive for DAPI and cytokeratin, but negative for the leukocyte marker CD45 are considered to be CTC. In a similar way, cells can be isolated and processed for further characterization by the CellSearch profile. Here, only an immunomagnetic enrichment of EpCAM-positive cells is done, without futher staining.
From the CellSave tube, a tube with a special cell preservative, CTC will be counted from 7.5 mL of blood. From the EDTA tube, also 7.5 mL of blood will be used, but in this case to isolate CTC. After isolation, tumor cells will be lysed and stored at -80ºC until further

processing. From the isolated CTC RNA, miRNA will be extracted to compose a gene expression profile, by real-time quantitative polymerase chain reaction, containing genes specific for tumor cells that can be measured in the background of leukocytes remaining after isolation of EpCAM-positive cells. Importantly, the list of genes that will be assessed in CTC remains to be determined and will be composed using data from ongoing work in the laboratory exploring genes associated with sensitivity to cabazitaxel in preclinical models and from the literature.

The gene-expression CTC profiles enables to investigate:
- Whether baseline CTC gene expression profiles are associated with outcome to cabazitaxel in terms of CTC response (change in CTC levels baseline versus before the 3rd cycle) and overall survival.
- mechanisms involved in sensitivity and resistance to cabazitaxel by comparing molecular CTC signatures before and after cabazitaxel.

Additionally, plasma will be evacuated and stored at -80°C for maximally 15 years for research purposes yet to be determined.

6.6 Biopsies and profiling

All patients who are eligible and have given additional consent in the selected centers, while having their prostate still in situ or are suffering from metastatic lesions with or without their prostate in situ; will be asked to participate in this side-study. After giving consent, the patients will undergo biopsy of the prostate or biopsy of a metastatic lesion (preferably biopsies of the prostate). If feasible, patients will be asked to undergo a second biopsy, after cabazitaxel treatment. The first (baseline) biopsy will take place within 21 days before start of cabazitaxel treatment. The second biopsy will be performed after the discontinuation of cabazitaxel because of disease progression, toxicity or any other reason why cabazitaxel infusion is no longer in the best interest of the patient. The second biopsy should be done within 30 days after the last infusion with cabazitaxel and neutrophiles should be $\geq 1 \times 10^9$/L.
To determine if a prostate biopsy will have a good chance of providing sufficient cancerous tissue, the treating physician will perform a digital rectal examination before the biopsies are taken. If feasible, biopsies of metastatic lesions will be performed.
In case of a procedure such as a palliative transurethral resection of the prostate (TURP), rest material will be used.
Needle biopsies will be taken according to the institution's protocol, which includes the prophylactic use of antibiotics. The maximum possible amount of material to be obtained of the prostate or metastases is at the discretion of the treating physician. Researchers will be informed when patients will undergo their biopsy so they can be present to directly process the collected tissue material.
Immediately after tumor collection, the samples will be frozen by one of the sub investigators from the Erasmus MC at the hospital were the biopsy will take place. Next, frozen-section analysis will be carried out by an uro-pathologist to check for the presence of cancerous tissue. Translational analysis such as RNA analysis will be done. RNA will only be isolated using the Qiagen allprep kit®, from tissue that consists of at least 70% of tumor. Using microarray analysis, gene expression will be profiled. Biomarkers that were previously found in prostate cancer xenografts will be validated using QPCR.

Besides the biopsies, also two blood collection tubes (7mL EDTA) will be drawn to be able to determine possible serum biomarkers. The first tube will be drawn within one week before the

first administration of cabazitaxel, and the second tube will be drawn within 30 days after the final cabazitaxel administration.

7. Statistical considerations

7.1 Sample size considerations

The primary aim of this trial is to evaluate whether the addition of budesonide to cabazitaxel results in a lower proportion of patients with grade 2-4 diarrhea during the 1st two cycles. It is assumed that the incidence of grade 2-4 diarrhea during the first two cycles in the control group will be 25%. In order to detect a clinically relevant reduction of absolute 15% (equivalent to an incidence of 10% grade 2-4 diarrhea in the budesonide arm), using a 2-sided significance level $\alpha = 0.05$ and a power $1 - \beta = 0.80$, 113 evaluable patients per arm are necessary. Assuming a 10% drop-out rate, e.g. due to ineligibility, a total of 250 patients will be recruited.

7.2 Diarrhea incidence analysis

The main endpoint of this study is the difference in incidence of grade 2-4 diarrhea in the budesonide co-treated arm compared to the arm without budesonide. The proportion of patients with diarrhea (grade 2, 3 and 4) during the first two cycles cabazitaxel will be compared between arm A (cabazitaxel) and arm B (cabazitaxel and budesonide) with a Chi^2-test. Also, the proportion of patients with grade 1-4 diarrhea after 2 cycles, grade 2-4 diarrhea after 4 cycles, and grade 1-4 diarrhea after 4 cycles will be compared between arm A and arm B a Chi^2-test. All analyses will be performed according to the intention-to-treat principle, i.e. patients will be analysed according to the treatment arm they were randomized to. However patients who were not eligible and therefore erroneously included in the trial will be excluded from all analyses.

7.3 Interim analysis

An interim safety analysis has been be performed after the first 57 evaluable patients included in each arm have completed 2 cycles of cabazitaxel. When patients stopped treatment due to severe toxicity in the 1st cycle and no 2nd cycle of cabazitaxel is administered, patients were also be considered evaluable and included for analysis. In case the percentage of patients with grade 3-4 diarrhea was the budesonide arm is more than 15% higher compared to the control group, the study would be stopped. The interim analysis did not meet the stopping rule and therefore the study will continue accrual.

7.4 Safety analysis

Clinical and laboratory toxicity/symptomatology will be graded according to NCI common criteria, CTCAE v 4. The adverse events which are not reported in NCI common criteria will be graded as: mild, moderate, severe, life-threatening. The analysis of treatment toxicity will be done primarily by tabulation of the incidence of adverse events with CTCAE v4 grade 2 or more, by treatment arm and cycle.

7.5 Statistical analysis plan.

A detailed statistical analysis plan (SAP) will be made for the final analysis. It will be discussed with the study coordinators and can only affect the exploratory analyses, but not the primary (confirmatory) analysis on which the sample size is based.

7.6 Statistics side study concerning biopsie(s)

Due to lack of information on the possible biomarkers, proper sample size calculation is not feasible. To be able to perform a proper analysis at the end of the study, and due to the broad spectrum of biomarkers we will be looking at, as many patients as possible will be asked to sign additional informed consent.

8. Registration procedure

Prior to enrolment in the study and prior to any study related procedure, the patient and investigator or his/ her delegate must personally sign and date the informed consent form. Original informed consent forms must be stored in the Investigator Site File (provided by the Clinical Trial Center) at the local participating site, together with the entire patient information sheet. After patient meets all inclusion and exclusion criteria, he can be randomized using the web-based application TOP, managed by the Erasmus MC Clinical Trial Center Daniel den Hoed. All participating centres will be given access to this application and will thus be able to randomize patients. Patients should start study treatment within 2 weeks after randomization.

If, for any reason, cabazitaxel treatment is not initiated within 2 weeks after randomization, eligibility criteria for study enrolment should be re-assessed and documented in the medical chart and the CRF.

During randomization, patients will be stratified by center, age (18-64 years versus 65 years and older), previous radiotherapy on back, abdomen and/or pelvis (no versus yes), using the minimization procedure, ensuring balance within each stratum and overall balance

Each patient will be given a unique patient study number. Patient subject number and result of randomization will be given immediately by TOP via email notification.

9. Datamanagement

Data will be collected on a paper CRF (case report form) designed for this study. New patients will be randomized by using the web-based application TOP. However, the paper randomization form (form 1) should also be completed and submitted to the Clinical Trial Center afterwards. Because of source data verification of the first included patient in each site during a routine monitoring visit, the copies of the CRF of the first included patient should be submitted to the Clinical Trial Center upon completion, and the original CRF pages should be kept at the site. The original forms will be taken by the monitor after the monitoring visit. For all other patients, the original CRFs should be submitted to the Clinical Trial Center upon completion., unless otherwise indicated by the Clinical Trial Center . All CRF pages related to cycle 1 and 2 (including baseline forms) should be completed and submitted to the Datacenter within 6 weeks after completion of cycle 2 (or cycle 1 if cycle 2 was not given).

All CRF pages, including Query Forms and Data Correction Forms should be signed and dated by the local investigator or his/her delegate.

All patient diaries should be collected at the participating sites, a copy should be sent to the Clinical Trial Center after completion of 2 cycles of cabazitaxel (or after 1 cycle if cycle 2 as not given). The local site is responsible for entering the correct study specific subject ID number on the patient diary before submitting it to the Datacenter.

10. Safety reporting

10.1 Section 10 WMO event
In accordance to section 10, subsection 1, of the WMO, the Princible Investigator will inform the subjects and the accredited METC of any occurrence that might have a negative impact on the initial risk/benefit assessment of the study. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardise the subjects' health. It is the study coordinator's responsibility to keep all subjects informed.

10.2 Definitions of AE and SAE

Definition of an AE
Any untoward medical occurrence in a subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
An AE can therefore be the appearance of (or worsening of any pre- existing)unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) that is temporally associated with the use of a medicinal product, regardless the causal relationship with the medicinal product or study procedure.
Examples of an AE include:

- An exacerbation of a chronic or intermittent pre-existing condition including an increase in frequency and/or intensity of the condition;
- A newly detected or diagnosed condition following administration of study treatment even though it may have been present prior to the start of the study;
- Signs, symptoms, or clinical sequelae of a suspected interaction;
- Signs, symptoms, or clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE or SAE);
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE; however, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfill the definition of an AE or SAE.
- Examples of an AE do not include:
  - A medical or surgical procedure (the condition that led to the procedure is an AE);
  - Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen;
  - The disease/disorder being studied or expected progression, signs or symptoms of the disease/disorder being studied, unless they are more severe than expected for the subject's condition. However in case of doubt about whether or not a sign or symptom is related to the disease being studied, it should be reported as an AE.

Definition of an SAE
A serious adverse event is defined as any AE or untoward medical occurrence that meets one or more of the following criteria:

a. Results in death
b. Is life-threatening (*)
c. Requires hospitalization or prolongation of existing hospitalization (**)
d. Results in disability/incapacity (***)

e. Is a congenital anomaly/birth defect
f. Results in any other medically important condition (i.e. important adverse reactions that are not immediately life threatening or do result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes

listed above), e.g. secondary malignancy, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of drug dependency or drug abuse.

(*)The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

(**) In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting.
Complications that occur during hospitalization are AEs, if a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen fromm baseline does not meet the SAE criteria. Situations in which an untoward medical occurrence did not occur (e.g. social and/or convenience admission to a hospital) do not meet the SAE criteria and should therefore not be reported as SAEs. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

(***)The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs
Progression of the disease under study, or any clinical sign of disease progression meeting any of the SAE criteria, will not be reported as a SAE. This exception for SAE reporting can only be applied if the adverse event is definitely causally related to disease progression to the local investigator.. However, if the progression of the underlying disease is greater than that which would normally be expected for the subject, or if the investigator considers that there was a causal relationship between treatment with study medication or protocol design/procedures and the disease progression, then this must be reported as an SAE. Any new primary cancer must be reported as an SAE.

Clinical Laboratory Abnormalities and Other Abnormal Assessments as AEs and SAEs
Abnormal laboratory findings (e.g., clinical chemistry, hematology, and urinalysis) or other abnormal assessments (e.g., ECGs, MUGA scans and vital signs) that are judged by the investigator as clinically significant, induce clinical signs or symptoms, or require therapy, will be recorded as AEs or SAEs if they meet the definition of an AE or SAE. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs.
However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the subject's condition, or that are present or detected at the start of the study and do not worsen, will not be reported as AEs or SAEs.
The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

10.3 Adverse and serious adverse events reporting

The investigator is responsible for the detection and documentation of adverse events meeting the criteria and definition of an AE or SAE, as mentioned in section 10.2. During the study, the investigator or site staff will be responsible for detecting, documenting and reporting AEs and SAEs. All adverse events reported spontaneously by the subject or observed by the local investigator or his/her staff will be recorded on the CRF at each contact.

Adverse events and/or adverse drug reactions will be recorded according to the Common Terminology Criteria (CTCAE) scale version 4.0 (see appendix D). If no appropriate AE term is available, a standard severity score should be used for grading such toxicities (1=mild; 2=moderate; 3=severe; 4=life-threatening; 5=fatal).

10.4 SUSAR assessment

Upon receipt of a SAE from any of the participating investigators, the Sponsor will:

- Evaluate completeness and causality assessment
- Collect additional data if needed
- Evaluate whether the SAE qualifies as a SUSAR (Suspected Unexpected Serious Adverse Reaction). The last SmPC of the involved products will serve as a reference document

10.5 Expedited Reporting of SAEs and SUSARs

The local investigator or his/her site staff should report all Serious Adverse Events, occurring during cabazitaxel treatment (i.e. until 30 days after last cabazitaxel administration), irrespective of relationship to study treatment within 24 hours by fax to the Clinical Trial Center , fax +31 10 7041028)

The Serious Adverse Event form (SAE form) and fax cover sheet provided by the Clinical Trial Center should be used.

The Sponsor will notify the accredited Ethical Committee of any SAE or SUSAR. All SUSARs and all SAEs that are life-threatening or fatal will be submitted to the accredited Ethical committee within 7 days after first knowledge of the SAE/SUSAR via ToetsingOnline. All other SAEs that occur during the first two cycles of cabazitaxel will be reported within 15 days after first knowledge of the SAE via ToetsingOnline.

All other SAEs that occur in subsequent cycles of cabazitaxel (i.e. >20 days after start of second cabazitaxel cycle) will be reported to the Ethical Committee through line listings each half year. The reason for this approach is to reduce workload for both Sponsor and Ethical Committee, as cabazitaxel is standard treatment in this patient group and it is expected that neutropenic fever and other haematological toxicity that meets the SAE criteria will occur frequently in this patient group, without affecting the further conduct of the study. All SAE reports should be filed in the Investigator Study File.

The Sponsor will report all SAEs/SUSARs to the marketing authorization holder (Sanofi-Aventis).

The Sponsor will report all SUSARs to the other participating investigators through line listings. If there is new information from any trial with the same IMP that may have serious

impact on the safety of the patients treated with that IMP, the Sponsor will inform the investigators in the participating sites immediately

11. Quality assurance & Monitoring

Based on the guideline by the NFU (Dutch Federation of University Medical Centers) about quality insurance in human research ("Kwaliteitsborging van mensgebonden onderzoek") we qualify the risk of this study as 'low' (small chance of serious damage). Monitoring will be performed by Clinical Trial Center Erasmus MC and consists of source document verification, eligibility check, check informed consent procedures and protocol compliance, check complete and timely reporting of SAEs and verification of completeness of the Investigator Site File, conform the study specific Monitoring Plan. Minor and major findings of the monitor will be discussed with the local investigator, and documented in a standard monitoring report that will be provided to the Sponsor. The Sponsor may decide to increase the monitoring frequency or intensity if the results of monitoring require this to ensure patient safety and/or data quality.

The Clinical Trial Center will perform central monitoring on collected data of all patients, i.e. checks on completeness of the data, data inconsistencies, timely reporting of SAEs etcetera, on a regular base. Local investigators will remain responsible for obtaining essential documents that needs to be filed in the Investigator Site File, and for drug accountability. If major violations are found during the random source data verification, such as failure to report SAE's, the Sponsor may decide that additional monitoring is indicated.

12. Ethical considerations

12.1 Ethics

Patients will be asked to participate in this study by their treating physician when they have a treatment indication for cabazitaxel. If the patient is interested in participation, he will be informed about the study and will be given pertinent information as to the intended purpose of the study by one of the study coordinators or research nurses. The procedures and possible hazards, to which the patient will be exposed, will be explained. The patient will also receive information in writing (patient information folder and informed consent form). Prior to the screening evaluation, the informed consent statement must be signed by the patient, and the person who has conducted the informed consent procedure. The patient will be provided with a copy of the patient information folderand a second original of the signed informed consent statement. The patient may withdraw from the study at any time without having to give any reasons and without prejudicing future medical treatment.

Separate informed consent is required for taking a blood sample for DNA analysis. Participation to this sub-study is optional. Therefore, an additional informed consent form must be signed by patients who have decided to participate in this sub-study.

12.2 Ethical committee

The protocol and the informed consent form, as well as any future amendment and termination of the study must be submitted to the Medical Ethical Committee Erasmus MC Rotterdam.

12.3 Declaration of Helsinki
This study will be performed in agreement with the latest versions of the Declaration of Helsinki (http://www.wma.net/en/30publications/10policies/b3/).

12.4 Insurance
For all patients participating in this study, a patient insurance must be arranged, in accordance with the requirements of the Dutch law (W.M.O.). Participating centers must arrange coverage for their own patients and must arrange liability insurance as required by the W.M.O. as well.

13. Publication policy
Concerning the clinical publication is determined that the study coordinators will be first and last author. Sub investigators will be offered an authorship when 12 or more evaluable patients have been included. In case including 12 patients will not be feasible for most centers, the five centers that have included the most evaluable patients will be offered an authorship. The order of authors will be determined by the amount of evaluable patients that was included in each center. All the other sub investigators that have included one or more patients will gain an acknowledgement.

Table I

Incidence of reported adverse reactions and hematologic abnormalities in ≥ 5% of patients receiving Jevtana® in combination with prednisone or mitoxantrone in combination with prednisone.

	JEVTANA 25 mg/m^2 every 3 weeks with prednisone 10 mg daily n=371		Mitoxantrone 12 mg/m^2 every 3 weeks with prednisone 10 mg daily n=371	
	Grade 1-4 n (%)	Grade 3-4 n (%)	Grade 1-4 n (%)	Grade 3-4 n (%)
Any Adverse Reaction				
Blood and Lymphatic System Disorders				
Neutropenia[2]	347 (94%)	303 (82%)	325 (87%)	215 (58%)
Febrile Neutropenia	27 (7%)	27 (7%)	5 (1%)	5 (1%)
Anemia[2]	361 (98%)	39 (11%)	302 (82%)	18 (5%)
Leukopenia[2]	355 (96%)	253 (69%)	343 (93%)	157 (42%)
Thrombocytopenia[2]	176 (48%)	15 (4%)	160 (43%)	6 (2%)
Cardiac Disorders				
Arrhythmia[3]	18 (5%)	4 (1%)	6 (2%)	1 (< 1%)
Gastrointestinal Disorders				
Diarrhea	173 (47%)	23 (6%)	39 (11%)	1 (< 1%)
Nausea	127 (34%)	7 (2%)	85 (23%)	1 (< 1%)
Vomiting	83 (22%)	6 (2%)	38 (10%)	0
Constipation	76 (20%)	4 (1%)	57 (15%)	2 (< 1%)
Abdominal Pain[4]	64 (17%)	7 (2%)	23 (6%)	0
Dyspepsia[5]	36 (10%)	0	9 (2%)	0
General Disorders and Administration Site Conditions				
Fatigue	136 (37%)	18 (5%)	102 (27%)	11 (3%)
Asthenia	76 (20%)	17 (5%)	46 (12%)	9 (2%)
Pyrexia	45 (12%)	4 (1%)	23 (6%)	1 (< 1%)
Peripheral Edema	34 (9%)	2 (< 1%)	34 (9%)	2 (< 1%)
Mucosal Inflammation	22 (6%)	1 (< 1%)	10 (3%)	1 (< 1%)
Pain	20 (5%)	4 (1%)	18 (5%)	7 (2%)
Infections and Infestations				
Urinary Tract Infection[6]	29 (8%)	6 (2%)	12 (3%)	4 (1%)
Investigations				
Weight Decreased	32 (9%)	0	28 (8%)	1 (< 1%)
Metabolism and Nutrition Disorders				
Anorexia	59 (16%)	3 (< 1%)	39 (11%)	3 (< 1%)
Dehydration	18 (5%)	8 (2%)	10 (3%)	3 (< 1%)
Musculoskeletal and Connective Tissue Disorders				
Back Pain	60 (16%)	14 (4%)	45 (12%)	11 (3%)
Arthralgia	39 (11%)	4 (1%)	31 (8%)	4 (1%)
Muscle Spasms	27 (7%)	0	10 (3%)	0
Nervous System Disorders				
Peripheral Neuropathy[7]	50 (13%)	3 (< 1%)	12 (3.2%)	3 (< 1%)
Dysgeusia	41 (11%)	0	15 (4%)	0
Dizziness	30 (8%)	0	21 (6%)	2 (< 1%)
Headache	28 (8%)	0	19 (5%)	0
Renal and Urinary Tract Disorders				
Hematuria	62 (17%)	7 (2%)	13 (4%)	1 (< 1%)

Dysuria	25 (7%)	0	5 (1%)	0
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnea	43 (12%)	4 (1%)	16 (4%)	2 (< 1%)
Cough	40 (11%)	0	22 (6%)	0
Skin and Subcutaneous Tissue Disorders				
Alopecia	37 (10%)	0	18 (5%)	0
Vascular Disorders				
Hypotension	20 (5%)	2 (<1 %)	9 (2%)	1 (< 1%)
Median Duration of Treatment	6 cycles		4 cycles	

[1]Graded using NCI CTCAE version 3
[2]Based on laboratory values, cabazitaxel: n =369, mitoxantrone: n = 370.
[3]Includes atrial fibrillation, atrial flutter, atrial tachycardia, atrioventricular block complete, bradycardia, palpitations, supraventricular tachycardia, tachyarrhythmia, and tachycardia.
[4]Includes abdominal discomfort, abdominal pain lower, abdominal pain upper, abdominal tenderness, and GI pain.
[5]Includes gastroesophageal reflux disease and reflux gastritis.
[6]Includes urinary tract infection enterococcal and urinary tract infection fungal.
[7]Includes peripheral motor neuropathy and peripheral sensory neuropathy.

Appendix A: References

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Appendix B: WHO performance status scale

Grade	Performance scale
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.

Appendix C: Possible inhibitors/inducers

Although not many pharmacokinetic interaction studies were performed for cabazitaxel it is expected that strong inhibitors of especially CYP3A will increase the concentrations of cabazitaxel. The use of strong inhibitors of CYP3A simultaneously with cabazitaxel treatment should thus be avoided. Caution is needed when prescribing moderate inhibitors of CYP3A.[14]

Strong inhibitors of CYP3A
A strong inhibitor is an inhibitor that causes a > 5-fold increase in the plasma AUC values or more than 80% decrease in clearance [15].

- indinavir
- nelfinavir
- ritonavir
- atazanavir
- clarithromycin
- itraconazole
- ketoconazole
- nefazodone
- saquinavir
- telithromycin
- voriconazole

Moderate inhibitors of CYP3A
A moderate inhibitor is an inhibitor that causes a > 2-fold increase in the plasma AUC values or 50-80% decrease in clearance.

- aprepitant
- erythromycin
- fluconazole
- grapefruit juice
- verapamil
- diltiazem

Inducers of CYP3A
It is expected that simultaneous use of cabazitaxel with inducers of CYP3A will lower cabazitaxel concentrations. Simultaneous use should thus be avoided. Some of the inducers are:

- fenytoïne
- carbamazepine,
- rifampine
- rifabutine
- rifapentine
- fenobarbital

Appendix D: Common Terminology Criteria for Adverse Events

In the present study, adverse events and/or adverse drug reactions will be recorded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.
At the time this protocol was issued, the full CTCAE document was available on the NCI web site, at the following address: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

Gastrointestinal disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by frequent and watery bowel movements.					

Appendix E: Most important warnings and precautions when using cabazitaxel

Hypersensitivity reactions
All patients should be pre-medicated prior to the initiation of the infusion of cabazitaxel. Patients should be observed closely for hypersensitivity reactions especially during the first and second infusions. 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 reactions can occur and may include generalised rash/erythema, hypotension and bronchospasm. Severe hypersensitivity reactions require immediate discontinuation of cabazitaxel and appropriate therapy. Patients with a hypersensitivity reaction must stop treatment with cabazitaxel.

Risk of neutropenia
Patients treated with cabazitaxel may receive prophylactic G-CSF, as per American Society of Clinical Oncology (ASCO) guidelines and/or current institutional guidelines, to reduce the risk or manage neutropenia complications (febrile neutropenia, prolonged neutropenia or neutropenic infection). 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. The use of G-CSF has been shown to limit the incidence and severity of neutropenia. Neutropenia is the most common adverse reaction of cabazitaxel. Monitoring of complete blood counts is essential on a weekly basis during cycle 1 and before each treatment cycle thereafter so that the dose can be adjusted, if needed. The dose should be reduced in case of febrile neutropenia, or prolonged neutropenia despite appropriate treatment. Patients should be re-treated only when neutrophils recover to a level $\geq$1,500/mm^3.

Risk of nausea, vomiting, diarrhoea and dehydration
If patients experience diarrhoea following administration of cabazitaxel they may be treated with commonly used anti-diarrhoeal medicinal products. Appropriate measures should be taken to re-hydrate patients. Diarrhoea can occur more frequently in patients that have received prior abdomino-pelvic radiation. Dehydration is more common in patients aged 65 or older. Appropriate measures should be taken to rehydrate patients and to monitor and correct serum electrolyte levels, particularly potassium. Treatment delay or dose reduction may be necessary for grade $\geq$3 diarrhoea. If patients experience nausea or vomiting, they may be treated with commonly used anti-emetics.

Peripheral neuropathy
Cases of peripheral neuropathy, peripheral sensory neuropathy (e.g., paraesthesias, dysaesthesias) and peripheral motor neuropathy have been observed in patients receiving cabazitaxel. Patients under treatment with cabazitaxel should be advised to inform their doctor prior to continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness, or weakness develop. Physicians should assess for the presence or worsening of neuropathy before each treatment. Treatment should be delayed until improvement of symptoms. The dose of cabazitaxel should be reduced from 25 mg/m^2 to 20 mg/m^2 for persistent grade >2 peripheral neuropathy.

Risk of renal failure
Renal disorders, have been reported in association with sepsis, severe dehydration due to diarrhoea, vomiting and obstructive uropathy. Renal failure including cases with fatal outcome has been observed. Appropriate measures should be taken to identify the cause and intensively treat the patients if this occurs. Adequate hydration should be ensured throughout treatment with cabazitaxel. The patient should be advised to report any significant change in daily urinary volume immediately. Serum creatinine should be measured at baseline, with each blood count and whenever the patient reports a change in urinary output. Cabazitaxel treatment should be discontinued in case of renal failure ≥CTCAE Grade 3.

Risk of cardiac arrhythmias
Cardiac arrhythmias have been reported, most commonly tachycardia and atrial fibrillation.

Elderly
Elderly patients (≥65 years of age) may be more likely to experience certain adverse reactions including neutropenia and febrile neutropenia.

Patients with liver impairment
Treatment with JEVTANA is contraindicated.

Patients with anaemia
Caution is recommended in patients with haemoglobin <10 g/dl and appropriate measures should be taken as clinically indicated.

Interactions
Co-administration with strong CYP3A4 inhibitors should be avoided since they may increase the plasma concentrations of cabazitaxel).Co-administration with strong CYP3A4 inducers should be avoided since they may lead to decreased plasma concentrations of cabazitaxel.

Excipients
The solvent contains 573.3 mg ethanol 96% (15% v/v), equivalent to 14 ml of beer or 6 ml of wine. Harmful for those suffering from alcoholism. To be taken into account in high-risk groups such as patients with liver disease, or epilepsy.

Appendix F: Glomerular Filtration Rate with MDRD formula

Use the formula below to estimate the Glomerular Filtration Rate (GFR). You may also use a calculator available on the internet via the following URL: http://mdrd.com/

GFR (ml/min/1,73 m2) = (186 x serum creatinin (umol/l) / 88,4) – (1,154 x age (years)) – 0,203

(x 0,742 if female) and (x 1,21 if negroid)