Randomized multicenter, phase III trial evaluating the safety of 2 schedules of cabazitaxel (bi-weekly *versus* tri-weekly) plus prednisone in elderly men (≥ 65 years) with metastatic castration-resistant prostate cancer (mCRPC) previously treated with a docetaxel-containing regimen

Abbreviated Title of Protocol	CABASTY
EudraCT N°	2016-001179-60
Version number	7
Date	17th September 2021

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SPONSOR	**ARTIC** **Georges Pompidou European Hospital** **20 rue Leblanc,** **75908 Paris Cedex 15, France**	Signature of the Clinical Operations Director: Réza ELAIDI Date: September 17,2021

SIGNATURE PAGE

Randomized multicenter, phase III trial evaluating the safety of 2 schedules of cabazitaxel (bi-weekly *versus* tri-weekly) plus prednisone in elderly men (≥65years) with metastatic castration-resistant prostate cancer (mCRPC) previously treated with a docetaxel-containing regimen (CABASTY)

EudraCT N°: 2016-001179-60

Version 7 –17th September 2021

I, investigator, have reviewed this protocol CABASTY:

Entitled: "Randomized multicenter, phase III trial evaluating the safety of 2 schedules of cabazitaxel (bi-weekly versus tri-weekly) plus prednisone in elderly men (≥ 65 years) with metastatic castration-resistant prostate cancer (mCRPC) previously treated with a docetaxel-containing regimen "

And I have fully discussed the objectives of this study and the contents of this protocol with the Sponsor's representative(s).

I agree to conduct the study according to this protocol and to comply with its requirements, subject to ethical considerations.

I agree to keep confidential the content of the protocol, not to disclose it to any third party and to use it only for the purpose of conducting this registry.

I understand that, should the decision be made by the Sponsor to terminate prematurely or suspend the registry at any time for whatever reasons, such decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the registry I will communicate immediately such decision in writing to the Sponsor.

Date Investigator name:

Signature

Sponsor coordinator:

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SYNOPSIS – PROTOCOL

EudraCT number	2016-001179-60	Version 7	Date: 17 September 2021
Title	Randomized multicenter, phase III trial evaluating the safety of 2 schedules of cabazitaxel (bi-weekly versus) plus prednisone in elderly men (≥ 65 years) with metastatic castration resistant prostate cancer (mCRPC) previously treated with a docetaxel-containing regimen (CABASTY).		
Abbreviated title	CABASTY		Phase III
Sponsor	ARTIC		
Countries	Multi-countries		
Indication	Metastatic castration resistant prostate cancer (mCRPC)		
Primary objective	• To evaluate the incidence of grade ≥ 3 neutropenia (measured at Day 7 and Day 14) and/or neutropenic complications (febrile neutropenia, neutropenic infection) with two schedules of cabazitaxel (bi-weekly versus tri-weekly) plus prednisone in elderly men (≥ 65 years) with mCRPC previously treated with a docetaxel-containing regimen.		
Secondary Objectives	The following parameters will be evaluated in each arm: • Dose reductions and dose delays • Radiological progression-free survival (rPFS) • Time to PSA progression • Time to first symptomatic Skeletal-Related Event (SRE) and incidence of SREs • Time to opioid treatment (if relevant) • Prostate-specific antigen (PSA) response rate • Quality of Life (FACT-P) • Objective response rate (ORR) in measurable lesions (RECIST criteria 1.1 –Appendix G) • Overall Survival (OS) • Factors influencing survival (duration of response to first androgen deprivation therapy (ADT), serum testosterone, cumulative dose of cabazitaxel, neutrophils/lymphocytes ratio, Gleason score, geriatric assessment G8, grade ≥3 neutropenia). • Time to onset of grade ≥3 neutropenia • Grade ≥3 neutropenia duration (from date of onset of grade ≥ 3 until grade ≤ 2) • Analysis of grade ≥3 neutropenia and/or neutropenia by cycle • Adverse events		
Sub-study objective (in selected sites only)	<u>Primary</u> To evaluate the relationship between baseline MDSCs / MDSC decline and responsiveness to cabazitaxel (both Q2W and Q3W schedules) Cabazitaxel responsiveness is defined by biochemical response, radiological response, and duration of response. <u>Secondary</u> • To evaluate the relationship between NLR and MDSCs at baseline and during cabazitaxel treatment • To evaluate the relationship between baseline NLR and NLR		

	kinetics (conversions) with cabazitaxel responsiveness • To evaluate the relationship between changes in peripheral blood immune populations (regulatory T-cells, T-effector (exhausted phenotypes) and natural killer [NK] cells) and cabazitaxel responsiveness • To evaluate changes in peripheral blood immune populations at failure on cabazitaxel,with particular focus on CD38-positive MDSC subsets • To associate MDSC functionality including T-effector cell function and proliferative capacity (from frozen PBMCs) with cabazitaxel responsiveness • To determine a relationship between of the immunological peripheral blood phenotype with molecular prostate cancer genotype utilizing cell-free tumor derived DNA sequencing (low pass WGS/targeted NGS)
Methodology	Randomized, open-label, phase 3 trial comparing cabazitaxel 25mg/m2 every 3 weeks versus cabazitaxel 16mg/m2 every 2 weeks in mCRPC patients aged ≥ 65 years. <u>Exploratory substudy</u> Blood samples will be collected in France (4 or 5 sites).Blood processing will take place at Cochin Laboratory Dpt (Paris, France).
Inclusion criteria	1. Patient aged ≥ 65 years with mCRPC previously treated with docetaxel 2. Medical or surgical castration with castrate level of testosterone (< 50 ng/dl) based on the EAU definition of castrate level of testosterone 3. Progressive disease according to PCWG2 (Appendix H) 4. Histologically proven prostate carcinoma 5. Health status allowing use of chemotherapy: G8 > 14; or G8 score ≤ 14 with geriatric assessment concluding to reversible impairment allowing use of chemotherapy 6. ECOG-PS 0, 1 or 2(ECOG-PS 2 should be related to prostate cancer) 7. Adequate hematologic, liver and renal functions: a) Neutrophil count ≥1.5 10^9/L b) Haemoglobin ≥10 g/ dL c) Platelet count ≥100.10^9/L d) Total bilirubin ≤ 1 the upper limit of normal (ULN) e) Transaminases ≤ 1.5 ULN f) Serum creatinine ≤ 2.0 ULN 8. Ongoing LHRH therapy at study entry 9. Signed informed consent
Exclusion criteria	1. History of severe hypersensitivity reaction (≥grade 3) to docetaxel 2. History of severe hypersensitivity reaction (≥grade 3) to polysorbate 80 containing drugs 3. Uncontrolled severe illness or medical condition (including

	uncontrolled diabetes mellitus) 4. Concurrent or planned treatment with strong inhibitors or strong inducers of cytochrome P450 3A4/5 (a one week wash-out period is necessary for patients who are already on these treatments) (see Appendix E) 5. ECOG-PS >2 not related to prostate cancer disease 6. G8 ≤ 14 with geriatric assessment contra-indicating standard cabazitaxel regimen 7. Concomitant vaccination with yellow fever vaccine 8. Patient who cannot be regularly followed or cannot answer to quality of life questionnaires because of psychological, social, familial or geographic reasons. 9. Participation in another clinical trial with any investigational drug within 30 days prior to study enrolment.
Treatment	• Arm A : cabazitaxel 25 mg/m² on Day 1 of a 3-week cycle plus daily prednisone or • Arm B: cabazitaxel 16 mg/m² on Day 1 and Day 15 of a 4-week cycle plus daily prednisone. • Treatment will be continued for a maximum of 10 cycles unless there is documented disease progression or unacceptable toxicity. • Standard cabazitaxel premedication will be used. • Prophylactic G-CSF (GRANOCYTE) will be injected from Day 3 to Day 7 (5 days) after every administration of cabazitaxel. • All new hormonal treatment, including ODM-201, prior to study entry is allowed. • Patients who received Radium-223 are eligible for this study. • Treatment with LHRH should not be discontinued.
Primary evaluation criteria	• Grade ≥3 neutropenia (measured at D7 and D14 of each cycle) and/or neutropenic complications (febrile neutropenia, neutropenic infection or sepsis) during the overall treatment period
Secondary evaluation criteria (endpoints)	• Dose reductions and dose delays • Radiological progression-free survival (rPFS) • PSA response and time to PSA progression • Time to first symptomatic Skeletal-Related Event (SRE) and incidence of SREs • Time to opioid treatment (if relevant) • Quality of life (FACT-P) • Objective response rate (ORR) in measurable lesions (RECIST) • Overall Survival (OS • Quality of Life (FACT-P) • Factors influencing survival (duration of response to first ADT, serum testosterone, cumulative dose of cabazitaxel, neutrophils/lymphocytes ratio, Gleason score, G8, grade ≥3 neutropenia) • Time to onset of grade ≥3 of neutropenia • Grade ≥3 neutropenia duration (from date of onset of grade ≥ 3 until grade ≤ 2) Analysis of grade ≥3 neutropenia and/or neutropenia by cycle • Adverse events

Outcome(s) sub-study	**Primary:** • Proportion of patients achieving a best objective response of SD, PR or CR according to RECIST 1.1 specifically comparing those achieving >30% and >50% decrease in MDSC post-induction compared to those who did not achieve this reduction. • Proportion of patients achieving a >50% PSA response at 12 weeks and at any time specifically comparing those achieving >30% and >50% decrease in MDSC post-induction compared to those who did not achieve this reduction. • Radiological progression-free survival (rPFS) according to PCWG2 • criteria for all patients, in relation to percentage MDSC change (% maximum change and those achieving >30% and >50% decrease) **Secondary:** • Correlations between extent of MDSC (continuous) and NLR decline (continuous) • Differences in peripheral blood immune populations (MDSCs, regulatory T-cells, T-effector and natural killer [NK] cells) with cabazitaxel responsiveness for Q2W and Q3W dosing schedule at week 6 and week 12 • Association between MDSC decline (>30% or >50%) with neutropenia (presence or absence) • Associations between cabazitaxel dose, presence of neutropenia (C1D8), NLR conversion (wk6 and wk12) and MDSC decline (wk6 and wk12) • To evaluate changes in peripheral blood immune populations at failure on cabazitaxel, with particular focus on CD38-positive MDSC subsets • Associations between baseline MDSC and molecular underpinning (from cfDNA, specifically studying MYCN amplification and PTEN / TP53 aberration)
Sample size determination	Of 131 patients treated with cabazitaxel every 3 weeks at HEGP, 40% developed grade ≥3 neutropenia. In the 2 pilot studies conducted with cabazitaxel 16 mg/m2 bi-weekly, the range of grade ≥3 neutropenia was 15% in the Finnish cohort [Kellolumpu – Lehtinen P et al. ASCO GU 2015] and 16.5% in HEGP cohort [Clement A et al, BJU Int. 2017 Mar 28. doi: 10.1111/bju.13855]. A sample size of 77 to 90 evaluable patients per arm will achieve 80% power to detect a 20% difference in G3 neutropenia incidence between the 2 arms. The incidence in group cabazitaxel 25 mg/m2 q3w is assumed to be 32% and 12% on bi-weekly cabazitaxel arm. The test used is a two-sided Fisher's exact test at 0.05 significance level. Assuming 10% non-evaluable patients, 85 to 100 patients should be included in each arm for a total of 170 to 200. Patients will be stratified according to G8 score (< 14 vs. ≥ 14), and age (< 70 vs. ≥ 70) before randomization.

	Exploratory sub-study The trial is powered on a clinical endpoint, namely to detect a 20% difference in G3 neutropenia incidence between arms (32% in arm A vs 12% arm B; power 80% with two-sided alpha of 5%, correcting for 10% non-evaluable patients (=17 patients). From the 153 to 180 evaluable patients, we have 76 to 90 patients in each arm, of which we expect 40-60 evaluable patients for translational studies (calculations performed on 25 per arm). In arm A, we expect 8 patients (32% of patients) with G3 neutropenia, and 17 patients that do not. In arm B, we expect 3 patients (12% of patients) with G3 neutropenia, and 22 patients that do not. For the MDSC analyses, we therefore will be comparing 11 patients with G3 neutropenia to 39 patients. For all continuous variables, including all immune subpopulations present in blood, mean (sd) will be presented if the distribution seems to be symmetric and in case of a skewed distribution the median and IQR. For categorical data, number and percentage will be presented. For comparison of continuous data linear regression analyses or correlation (Spearman or Pearson) will used. For comparison of continuous data with categorical data logistic regression analysis will be used. For comparison of two sets of categorical data the chi-square test of Fisher's exact test will be utilized. For the radiological PFS analyses the estimates of the hazard ratio and corresponding 95% confidence interval will be tested using a Cox Proportional hazard model. For the overall survival, a stratified log-rank test will be used to compare between groups.	
N patients	Total: 170 to 200 (85 to 100 per arm) Exploratory substudy: 40-60 patients	
Trial duration	Accrual Treatment duration (average) First patient first visit Last patient last visit Analyse of Primary Endpoint	42 months Arm A:30 weeks (up to 10 cycles) Arm B: 40 weeks (up to 10 cycles) May 2017 November 2021 March 2022

LIST OF ABBREVIATIONS

ADT	Androgen deprivation therapy
AE	Adverse Event
ALT	Alanine Aminotransferase
ANC	Absolute neutrophil count
AR	Androgen receptor
ASCO	American Society of Clinical Oncology
ASR	Annual safety report
AST	Aspartate Aminotransferase
BSA	body surface area
BUN	Blood Urea Nitrogen
cCR	Clinical Complete Response
CR	Complete Response
CRF	Case Report Form
CT	Computed Tomography
CTCAE v4.0	Common Terminology Criteria for Adverse Events – Version 4.0
DES	Diethylstilbestrol
DHT	Dihydrotestosterone
DILs	Dear Investigator Letters
DLT	Dose limiting toxicity
ECOG	Eastern Cooperative Oncology Group
ESMO	European Society of Medical Oncology
EU	European Union
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy - Fatigue
FACT-P	Functional Assessment of Cancer Therapy-Prostate
FDA	Food and Drug Administration
G-CSF	Granulocyte Colony-Stimulating Factor
HR	Hazard ratio
IP	Investigational product
ITT	Intent-to-treat
LDH	Lactate Dehydrogenase
LHRH	Luteinizing Hormone Releasing Hormone
mCRPC	Metastatic castration-resistant prostate cancer
MDSC	Myeloid-Derived Suppressor Cells
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
OS	Overall survival
NLR	Neutrophil-to-Lymphocyte Ratio
PCWG2	Prostate Cancer Working Group 2
PD	Progressive disease
PFS	Progression-free survival
PMN	Polymorphonuclear cells
PSA	Prostate-specific antigen
PR	Partial Response
SRE	Skeletal-Related Event
SUSAR	Suspected Unexpected Severe Adverse Reaction
SAE	Serious Adverse Event
TEAE	Treatment-emergent adverse event
T	Testosterone
WBC	White blood cell

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1. INTRODUCTION AND STUDY RATIONALE

There is growing evidence that the older men have more aggressive prostate carcinomas [1]. If elderly patients with localized prostate carcinoma are more likely to receive a curative treatment than their younger counterparts [2], the trend is in inverse proportion for older patients with metastatic disease who receive less frequently chemotherapy probably due to concerns about tolerability [3].

At present, physicians are tempted to treat elderly metastatic castration-resistant prostate cancer (mCRPC) patients with new androgen receptor (AR)-targeted agents, such as abiraterone acetate or enzalutamide, since they have proven to prolong overall survival (OS), are orally delivered, and well tolerated [4-7]. However, because prostate cancer is a heterogeneous disease [8], all of the patients will not respond to AR-targeted agents [9]. Indeed, some of them present a primary resistance to these agents, and others will develop an acquired resistance in course of time. Moreover, retrospective studies, involving a small number of patients, suggest that once a patient has progressed with an AR-targeted agent, he will poorly respond to another AR-targeted agent [9]. Finally, the place of first-line androgen deprivation therapy (ADT) for advanced prostate cancer is now strongly challenged. The results of CHAARTED and STAMPEDE trials demonstrate that the addition of 6 cycles of docetaxel to ADT in patients with hormone-sensitive metastatic prostate cancer is associated with a survival benefit of more than one year versus ADT alone [10-11]. A systematic review and meta-analysis of randomized studies in hormone-sensitive prostate cancer also confirms that ADT plus 6 cycles docetaxel significantly prolongs survival in hormone-sensitive metastatic prostate cancer [12] and this regimen is now recommended as standard of care by ESMO guidelines [13].

Older age is not a contra-indication to chemotherapy. Many elderly patients tolerate it as well as younger patients. Since 2004, a docetaxel-based regimen is recommended by all international guidelines for the treatment of mCRPC, since it provide a survival advantage while reducing pain and improving health-related quality of life (HR-QoL) [13-16]. In the TAX-327 trial, the OS benefit of 3-weekly docetaxel plus prednisone compared with mitoxantrone plus prednisone was consistent among groups of age [16]. In men aged of at least 75 years, the 3-weekly schedule resulted in more dose reductions than the weekly schedule (22% versus 8%, p = 0.007), but tolerability was otherwise comparable [16]. In a prospective survey involving 333 mCRPC patients aged of at least 70 years, a taxane-based regimen was associated with a significantly longer OS, progression-free survival (PFS), and clinical benefit (based on pain and analgesic consumption) than a non-taxane regimen, even in frail patients [17].

Cabazitaxel is a new taxane developed to overcome docetaxel resistance [18]. In the TROPIC trial, cabazitaxel plus prednisone significantly prolonged OS versus mitoxantrone plus prednisone in mCRPC patients progressing during or after docetaxel therapy [19]. It has been also shown that cabazitaxel retains its antitumor activity in patients progressing on AA or enzalutamide, with a higher efficacy than docetaxel [20]. However, cabazitaxel is associated with a high incidence of grade ≥ 3 neutropenia; although a large European compassionate-use program has clearly shown that this haematological toxicity is manageable, even in patients aged of at least 75 years [21]. A prophylactic management of adverse events, including an increased use of granulocyte-colony stimulating factor (G-CSF), could significantly reduce the risk of febrile neutropenia and/or neutropenic complications in elderly patients [21].

Recently, it has been shown that, in a phase III trial involving 344 patients, a bi-weekly administration of docetaxel plus prednisone in mCRPC is better tolerated than a three-weekly administration [22]. The efficacy of bi-weekly docetaxel was also better than three-weekly docetaxel with a longer time to progression (TTP), and a significant OS benefit. The slightly higher cumulative dose of docetaxel received in the bi-weekly arm may have contributed to these results. Docetaxel bi-weekly plus prednisone is

recommended by SIOG guidelines as an acceptable treatment option for unfit elderly patients [16]. Two pilot studies conducted in Finland [23] in HEGP in Paris [24] suggest that cabazitaxel 16 mg/m2 biweekly plus prednisone is effective and better tolerated with a much lower risk of grade ≥3 neutropenia and neutropenic complications. We would like to confirm the improved safety profile of cabazitaxel bi-weekly regimen in a randomized trial comparing cabazitaxel 25mg/m2 every 3 weeks versus cabazitaxel 16 mg/m2 every 2 weeks until disease progression or unacceptable toxicity. G-CSF will be given systematically according to European Organization for Research and Treatment of Cancer (EORTC) recommendations [25].

1.1 Preclinical studies previously conducted with cabazitaxel

Cabazitaxel (also known as XRP6258, RPR116258A) is a semisynthetic compound derived from the 10¬deacetyl Baccatin III, which is extracted from European yew needles. This new taxoid which promotes the tubulin assembly in vitro and stabilizes microtubules against cold-induced depolymerization as efficiently as docetaxel 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 poorly or not active. A trend for schedule-dependency was observed with maximum tolerated dosages 4.8-fold higher with an intermittent schedule than with a split dose schedule. 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.

The below referenced studies reflect the reported adverse events at the time of the last cabazitaxel Investigator's Brochure (Edition 13, November 18, 2011). Please refer to the current version of the cabazitaxel Investigator's Brochure as well as the updated safety information contained in the Investigational New Drug safety letters for further updates.

1.2 Summary of clinical data

During clinical development, a total of 565 patients were enrolled and/or randomized to receive cabazitaxel in 3 Phase 1 studies (TED6188, TED6189, and TED6190), 1 study investigating the disposition of radiolabeled cabazitaxel (BEX6702), 1 Phase 2 study with single agent cabazitaxel in patients with breast cancer (ARD6191) and the Phase 3 pivotal study in patients with metastatic prostate cancer (EFC6193). In addition, there were 33 patients enrolled into a Phase 1 study (TCD6945) in combination with capecitabine in metastatic breast cancer. More information on the clinical data is available in the clinical Investigator's brochure.

1.2.1 Phase I

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 partial responses out of 8 patients with mCRPC in TED6190 at 25 mg/m2 suggesting potential biological and clinical activity in patients with prostate cancer.

The safety profile was comparable in TED6188 and TED6190, with the intermittent schedule (1-hour infusion every 3 weeks). The dose limiting toxicity (DLT) of cabazitaxel was neutropenia and its infectious complications at the highest dose tested, 30 mg/m² in

TED6188 and 25 mg/m² in TED6190. The median time to neutrophil nadir was not dose-dependent and was at 11 days in TED6188 and 12 days in TED6190.

As a result, the dose levels of 20 mg/m² and 25 mg/m² 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/m², at which the DLT was diarrhoea. As a result, the dose level of 10 mg/m² was defined as the recommended dose for further clinical development with this weekly schedule.

In TCD6945 study conducted in advanced breast cancer patients, the recommended dose was defined as cabazitaxel 20 mg/m² on D1 and capecitabine 1000 mg/m² twice daily from D1 to D14 every 3 weeks. DLT were all grade 4 neutropenia lasting more than 7 days.

1.2.2 Phase II

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 favourable tolerability at Cycle 1, this was allowed further to a protocol amendment. In 21 of 71 patients, the cabazitaxel dose was escalated from 20 to 25 mg/m2 after the first cycle. The most frequently occurring toxicities overall were grade 3 and 4 neutropenia (73.2%), fatigue (50.7%), nausea (43.7%), diarrhoea (39.4%), myalgia (25.4%), anorexia (25.4%), weight loss (25.4%), and vomiting (23.9%). The overall response rate was 14.6% with 2 complete responses (CR) and 5 partial responses (PR).

1.2.3 Phase III

One Phase 3 study was conducted in mCRPC patients previously treated with docetaxel containing regimen. This study compared cabazitaxel plus prednisone to mitoxantrone plus prednisone (EFC6193). A total of 755 patients were recruited (378 patients in cabazitaxel arm and 377 patients in mitoxantrone arm). A statistically significant increase in OS was observed in patients treated with cabazitaxel plus prednisone compared to patients treated with mitoxantrone plus prednisone, with a hazard ratio (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 cabazitaxel arm versus 12.7 months (95%CI: 11.6 – 13.7) in mitoxantrone arm.

The secondary endpoints were supportive of the positive data regarding the primary OS endpoint. Progression-free survival (PFS), defined as the earliest date of radiological tumour progression, PSA progression, pain progression, or symptom deterioration or death due to any cause, was statistically significantly longer in the cabazitaxel group compared with the mitoxantrone group ($p<0.0001$, HR = 0.74 [95% CI, 0.64 - 0.86]), and median PFS was 2.8 months versus 1.4 months. Response rates for PSA and tumour assessments, as well as the time to PSA and tumour progression when defined as radiological progression or death were statistically significant in favour of cabazitaxel. If pain response and time to pain progression were not statistically different between cabazitaxel and mitoxantrone, considering that mitoxantrone was approved based on its activity on pain management in mCRPC, the results show that cabazitaxel achieve at least the same level of activity than mitoxantrone on these pain-related endpoints.

Treatment emergent AE (TEAEs) were experienced by 95.7% of patients in the cabazitaxel group and 88.4% of patients in the mitoxantrone group; 57.4% of patients in

the cabazitaxel group and 39.4% of patients in the mitoxantrone group had at least one grade 3-4 TEAE. In the cabazitaxel group 39.1% of patients had at least 1 serious adverse event (SAE) compared with 20.8% of patients in the mitoxantrone group. Study treatment discontinuation due to a TEAE was reported in 18.3% of patients in the cabazitaxel group and 8.4% of patients in the mitoxantrone group.

The most frequent toxicity in the cabazitaxel group were neutropenia and its clinical consequences of febrile neutropenia and infections. Based on laboratory assessments, 81.7% of patients in the cabazitaxel group and 58.0% of patients in the mitoxantrone group had grade 3-4 neutropenia. Patients treated with cabazitaxel also had higher rates of infections grade 3-4 with or without concomitant severe neutropenia (10.2% cabazitaxel, 5.1% mitoxantrone) and febrile neutropenia (7.5% cabazitaxel, 1.3% mitoxantrone).

Gastrointestinal disorders of all types (Grade 3-4) were more common in the cabazitaxel group (12.4% versus 1.6%). Notably, Grade 3-4 diarrhoea was more common on cabazitaxel (6.2%) compared with mitoxantrone (0.3%). Incidence of Grade 3-4 stomatitis (0% in both groups) and mucositis (0.3% in both groups) was similar in both treatment groups.

Renal and urinary AE grade 3-4 also were more common in the cabazitaxel group (8.6% versus 2.4%). These events consisted of renal failure and impairment (3.2% cabazitaxel, 0.3% mitoxantrone) as well as renal obstructive disorders (0.8% cabazitaxel, 0.5% mitoxantrone). In the cabazitaxel group, 15 patients were reported to have acute renal AEs grade 3-4, the aetiology of which was multifactorial consisting of pre-renal, renal, or obstructive causes. According to laboratory values, the incidence of all grade /grade 3-4 creatinine increase was 15.6%/1.3% in cabazitaxel arm and 11.6%/0.5% with mitoxantrone. In addition, more haematuria was reported in cabazitaxel arm versus mitoxantrone (62 patients/16.7% versus 14 patients/3.8%). In cabazitaxel arm, no clear possible explanation such as local infection/obstruction/progression, or anticoagulation/aspirin therapy, or thrombocytopenia was found for 21 patients. In prior studies conducted in metastatic breast cancer, a total of 6 patients (2 in the ARD6191 and 4 in the TCD6945) experienced cystitis without local infection including 5 haemorrhagic cystitis (3 cystitis were documented with biopsy).

Deaths due to causes other than disease progression within 30 days of last study drug dose were reported in 18 (5%) in the cabazitaxel group and 3 (<1%) in the mitoxantrone group. Of the 18 deaths in the cabazitaxel group, 8 were the result of neutropenia and/or infection, 4 were due to cardiac events (2 cardiac arrest, 1 cardiac failure and 1 ventricular fibrillation), 1 was due to dehydration and hydro-electrolyte imbalance, 3 were pre- or post-renal events leading to renal failure, and 2 were due to other causes, including a death of unknown aetiology and a death from a cerebral haemorrhage following a fall in a patient taking concomitant clopidogrel.

Based on the results of this study, a dossier to register cabazitaxel in hormone refractory metastatic prostate cancer patients previously treated with docetaxel-containing regimen has been submitted in several countries worldwide. It has been approved by the FDA in 2010 and in the EU and other countries.

Moreover, an economic evaluation is now required in France for innovative drugs expecting an ASMR (Amélioration du Service Medical Rendu) ranging from 1 to 4, since the publication of decree in October 2012. As the ASMR of cabazitaxel was 3 for it indication in second-line therapy, it appears relevant to perform an economic evaluation as ancillary study alongside the present trial, and then to collect economical data in the French context.

Exploratory sub-study

Inflammatory cells are known to play an important role in cancer progression. A vast body of evidence now supports that the tumour microenvironment has a key role in altering and expanding (immature) myeloid cells[27, 28], turning them into potent tumour-promoting and/or immunosuppressive cells with relevance to cancer progression and treatment resistance[29,30]. Immunophenotyping studies have identified immature neutrophil and monocytic cells (polymorphonuclear and monocytic myeloid-derived suppressor cells; PMN-MDSCs and M-MDSCs) which comprise a distinct population in functionality compared to their mature counterparts in murine models[30,31]and in a variety of human cancers[32,33]. These MDSC subsets have shown to play an important role supporting tumor growth directly through inhibition of senescence and indirectly through suppression of T-cell function. These MDSCs have secondary to their effects on the immune response also shown to decrease apoptosis of cancer cells in response to genotoxic stressors by secretion of specific cytokines [30], [42]. Interestingly higher MDSC levels were found in patients following 2nd generation hormonal treatment (abiraterone and enzalutamide), but not following one or two lines of taxane treatment, suggesting that taxanes might directly target MDSCs[34].

We have recently identified a strong relationship between MDSCs and neutrophil-to-lymphocyte ratio (NLR)[35]. A high NLR constitutes increased granulocytes and/or decreased lymphocytes, harbouring a poor prognosis across a variety of cancer subtypes[37]. In prostate cancer patients a high neutrophil-to-lymphocyte (NLR) ratio also demonstrates a poor prognosis[36], with a high NLR ratio prior to initiation of treatment with abiraterone[38], enzalutamide[39], docetaxel[40] or cabazitaxel[41] associating with a worse overall survival. Importantly, a conversion from high NLR (≥3) to low (<3) NLR associates with improved survival and higher PSA response rates (66.4% versus 33.6%) to cabazitaxel chemotherapy[42].

Cabazitaxel shows a linear dose-exposure relationship on $AUC_{0\text{-}48h}$. The proportional decrement in the absolute neutrophil counts was studied in the initial phase I pharmacokinetic (PK) trial to investigate this PK/pharmacodynamic (PD) relationship. The value of $AUC_{0–48h}$ to obtain a 50% decline in neutrophils was 206 µg h/l, which corresponded to a dose of approximately 20 mg/m^2 [43]. In the phase III registration trial, grade ≥3 neutropenia following cabazitaxel 25 mg/m^2 chemotherapy was seen in 82% of patients treated with the drug[44]. Post-hoc analyses have identified that the occurrence of grade ≥3 neutropenia during docetaxel and cabazitaxel therapy associated with a prolonged OS and a higher confirmed PSA response. Not surprisingly, the presence of grade ≥3 neutropenia was more common in patients with lower baseline NLR (NLR<2 or <3 for docetaxel or cabazitaxel, respectively), due to lower baseline neutrophils[45,46]. Interestingly, a prognostic risk classification showed worst outcome when patients demonstrated both a high baseline NLR and the absence of a grade ≥3 neutropenia following docetaxel[46], suggesting the immunological and/or inflammatory landscape can alter the dose-exposure-effect relationship.

Many strategies have been suggested to target MDSCs, and one of these is through anti-CD38 targeting antibodies. CD38 is a member of the ribosyl cyclase family that is widely expressed on the surface of nonhematopoietic cells and diverse immune cells, including MDSC subsets[47,49]. The receptor/ ligand activity of CD38 has also been documented on exhausted anti-prostate specific CD8-T-cells and on tumour cells itself[50,51.] Importantly, CD38 regulation has been suggested as important regulatory checkpoint associating with acquired resistance to anti-PD-1/PD-L1 immunotherapy[51]. Dual blockade of checkpoint and CD38 improves anti-tumour immune responses, and this could partly be explained through decreased levels of MDSCs. Therefore CD38

expression on MDSCs (and tumour cells) requires further study, and whether deregulation following cabazitaxel resistance could play a role in taxane resistance.

These retrospective studies warrant further prospective evaluation of MDSC levels as the key predictor of cabazitaxel responsivenss, in comparison to NLR and neutropenia. Therefore we wish to initiate a strong biomarker-driven program in the CABASTY clinical trial.

Hypothesis

- High baseline NLR is prognostic for outcome (OS and inferior response)
- NLR is reflective of MDSC counts and low lymphocytes/lymphocyte dysfunctionality
    - High MDSC associates with primary resistance to enzalutamide/abiraterone
    - Low lymphocytes/lymphocyte dysfunction associates with short duration of response
- MDSC are targeted by cabazitaxel. Decrease in MDSC count associates with improved OS and PSA response, and duration of response
- Increased cabazitaxel cumulative dose will lead to incremental decrease in MDSC counts (PD)
- MDSC are increased following cabazitaxel failure which may lead to potential combinations of taxanes with other agents targeting MDSCs.

Baseline MDSC levels are prognostic for outcome to cabazitaxel chemotherapy. Early MDSC decline during treatment associates with enhanced responsiveness, duration of response and overall survival. MDSC levels associate with decline in NLR and neutropenia, and MDSC decline may be dependent of cabazitaxel exposure and of metronomical dosing schedule (Q2W).

2. STUDY OBJECTIVES

2.1 Primary objective

- To evaluate the incidence of grade ≥ 3 neutropenia (measured at Day 7 and Day 14) and/or neutropenic complications (febrile neutropenia, neutropenic infection) with two schedules of cabazitaxel (bi-weekly versus tri-weekly) plus prednisone in elderly men (≥ 65 years) with mCRPC previously treated with a docetaxel-containing regimen.

2.2 Secondary objectives

The following parameters will be evaluated in each arm:

- Dose reductions and dose delays
- Radiological progression-free survival (rPFS)
- Time to PSA progression
- Time to first symptomatic Skeletal-Related Event (SRE) and incidence of SREs
- Time to opioid treatment (if relevant)
- Prostate-specific antigen (PSA) response rate
- Analysis of grade ≥3 neutropenia and/or neutropenia by cycle

- Quality of Life (FACT-P) (appendix D)
- Objective response rate (ORR) in measurable lesions (RECIST criteria 1.1; Appendix G)
- Overall Survival (OS)
- Factors influencing survival (duration of response to first ADT, serum testosterone, cumulative dose of cabazitaxel, neutrophils/lymphocytes ratio, Gleason score, geriatric assessment G8, grade ≥3 neutropenia)
- Time to onset of grade ≥3 of neutropenia
- Grade ≥3 neutropenia duration (from date of onset of grade ≥ 3 until grade ≤ 2) Adverse events

2.3 Exploratory sub-study objective

Primary

- To evaluate the relationship between baseline MDSCs / MDSC decline and responsiveness to cabazitaxel (both Q2W and Q3W schedules)
- Cabazitaxel responsiveness is defined by biochemical response, radiological response, and duration of response,

Secondary

- To evaluate the relationship between NLR and MDSCs at baseline and during cabazitaxel treatment
- To evaluate the relationship between baseline NLR and NLR kinetics (conversions) with cabazitaxel responsiveness
- To evaluate the relationship between changes in peripheral blood immune populations (regulatory T-cells, T-effector (exhausted phenotypes) and natural killer [NK] cells) and cabazitaxel responsiveness
- To evaluate changes in peripheral blood immune populations at failure on cabazitaxel, particular focusing on CD38-positive MDSC subsets
- To associate MDSC functionality including T-effector cell function and proliferative capacity (from frozen PBMCs) with cabazitaxel responsiveness
- To determine a relationship between of the immunological peripheral blood phenotype with molecular prostate cancer genotype utilizing cell-free tumor derived DNA sequencing (low pass WGS/targeted NGS)

3. METHODOLOGY

Randomized, open-label, phase 3 trial comparing cabazitaxel 25 mg/m^2 on Day 1 of a 3-week cycle plus daily prednisone versus cabazitaxel 16 mg/m^2 on Day 1 and Day 15 of a 4-week cycle in mCRPC patients aged ≥ 65 years.

Exploratory sub-study

Blood samples will be collected in France (4 or 5 sites).Blood processing will take place at Cochin laboratory Dpt (Paris, France)

Study procedures are presented in table 1 and table 2 below:

Table 1- Study procedures	Screening	Randomization visit	Each subsequent visit (±2 days)	End of treatment 30 days after last cycle Or upon progression
Week	D-30 to D-1	C1D1[d]	Every 3 weeks (arm A) or 2 weeks (arm B)	
Data collection				
Informed consent	X			
Inclusion/exclusion criteria	X	X		
Medical/oncologic history	X			
Concomitant medications	X	X	X	X
Physical examination	X	X		X
Vital signs	X	X	X	X
ECOG/PS	X	X	X	X
G8	X			
ADL, IADL, CISRG	X			
FACT-P		X	X	X
Skeletal-Related Events		X	X	X
Pain status (VAS)	X	X	X	X
Hematology	X	X[a]	Every week	X
Biochemistry	X	X[a]	X	X
Dipstick test	X	X	X	X
Serum PSA	X	X	X	X
Serum Testosterone	X			X
CT-Scan (abdominal/pelvic/chest) or MRI Whole body [b]	X		Every 3 months (±7 days)	X
Bone scan[b]	X		Every 3 months (±7 days)	X
Cabazitaxel		X	X	
Toxicity				
Adverse events	X			
Treatment				
Cabazitaxel		X	X	
G-CSF[c]		X	X	
Follow-up[e]				
Survival status (by phone or medical visit)+ Subsequent therapies				

[a] Blood tests (hematology and biochemistry): within 3 days prior to enrolment
[b]Tumour assessment (CT-Scan (abdominal/pelvic/chest) or whole body MRI and Bone scan):
- within 30 days prior to the date of randomization
- every 3 months (±7 days)
- within 7 days prior to End of Treatment or upon progression

[c]G-CSF (GRANOCYTE) will be injected from Day 3 to Day 7(5 days) after every administration of cabazitaxel.
[d] First dose to be administered within 3 days following randomization.
[e] from EOT until end of study
1 cycle tri-weekly (Arm A)= D1-D21
1 cycle bi-weekly (Arm B) = D1-D14 (equal to two administration of cabazitaxel)

Table 2 Exploratory sub-study

Trial period	**Screening phase**	**Treatment cycles**				**End of Treatment**
Treatment cycle/ Title:	Baseline	C1D8	Wk6	Wk9	Wk12	Discontinuation
Laboratory Assessments Performed by Local Laboratory						
CBC with differential						
ARM A (25mg/m^2)	X	X	X	X	X	X
ARM B (16mg/m2)	X	X	X		X	X
Blood sample collection for biomarker analysis						
Blood for MDSC, neutrophils and plasma biomarkers (30ml)						
ARM A (25mg/m^2)	X	X[b]	X		X	X
ARM B (16mg/m^2)	X	X[b]	X		X	X
Blood RNA seq (2.5ml)[a]						
ARM A (25mg/m^2)	X					
ARM B (16mg/m^2)	X					

a. An additional Paxgene blood tube for RNA sequencing.

b. If patients have CBC collected in central facitility that can ficoll samples for biomarker studies

Biomarker schedule

Arm A (25mg/m^2): Baseline – Week 6 – Week 12 - at progression

Arm B (16mg/m^2): Baseline – Week 6 – Week 12 - at progression

Optional sample points are at C1D8.

4. SELECTION OF PATIENTS

4.1 Inclusion criteria

All the following conditions must be met by the subject to be eligible in this study:

1. Patient aged ≥ 65 years with mCRPC previously treated with docetaxel
2. Medical or surgical castration with castrate level of testosterone (< 50 ng/dl) based on the EAU definition of castrate level of testosterone
3. Progressive disease according to PCWG2 (Appendix H)

4. Histologically proven prostate carcinoma
5. Health status allowing use of chemotherapy: G8 > 14; or G8 score ≤ 14 with geriatric assessment concluding to reversible impairment allowing use of chemotherapy
6. ECOG-PS 0, 1 or 2 (ECOG-PS 2 should be related to prostate cancer disease)
7. Adequate hematologic, liver and renal functions:
    a. Neutrophil count ≥1.5 10^9/L
    b. Haemoglobin ≥10 g/dL
    c. Platelet count ≥100.10^9/L
    d. Total bilirubin ≤ 1 the upper limit of normal (ULN)
    e. Transaminases ≤ 1.5 ULN
    f. Serum creatinine ≤ 2.0 ULN
8. Ongoing LHRH therapy at study entry
9. Signed informed consent

4.2 Exclusion criteria

None of the following conditions must be met by the subject to be eligible in this study:

1. History of severe hypersensitivity reaction (≥grade 3) to docetaxel
2. History of severe hypersensitivity reaction (≥grade 3) to polysorbate 80 containing drugs
3. Uncontrolled severe illness or medical condition (including uncontrolled diabetes mellitus)
4. Concurrent or planned treatment with strong inhibitors or strong inducers of cytochrome P450 3A4/5 (a one week wash-out period is necessary for patients who are already on these treatments) (see Appendix E)
5. ECOG-PS >2 not related to prostate cancer disease
6. G8 ≤ 14 with geriatric assessment contra-indicating standard cabazitaxel regimen
7. Concomitant vaccination with yellow fever vaccine
8. Patient who cannot be regularly followed or cannot answer to quality of life questionnaires because of psychological, social, familial or geographic reasons
9. Participation in another clinical trial with any investigational drug within 30 days prior to study enrolment.

5. RANDOMIZATION OF PATIENTS

The randomization will occur after control of the whole inclusion and exclusion criteria.

The following information will be required:

- Name of the center and principal investigator,
- Date of screening
- Patient's initial, age and file number,
- G8 score,

The randomization will be stratified by G8 score (< 14 vs. ≥ 14) and age (< 70 vs. ≥ 70) . An adaptive randomization will be used in order to insure timely balance of stratification factors within strata.

The site will be informed of the allocated treatment arm for the patient to be included:

- Arm A: cabazitaxel 25 mg/m² on Day 1 of a 3-week cycle plus daily prednisone
  or
- Arm B: cabazitaxel 16 mg/m² on Day 1 and Day 15 of a 4-week cycle plus daily prednisone.

First dose to be administered within 3 days following randomization.

6. STUDY TREATMENTS

6.1 Investigational product description

6.1.1 Cabazitaxel

- Cabazitaxel is supplied for parenteral administration as a sterile, non-pyrogenic non-aqueous solution contained in a 15 mL clear glass vial closed with a rubber closure. The closure is crimped to the vial with an aluminum cap covered with a light green plastic flip-off cap.
- The solution is clear and yellowish to brownish-yellow.
- Each vial contains 60 mg of cabazitaxel, expressed on 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 (corresponding to 60 mg/mL) concentration is obtained in the premix and that 60 mg dose can be extracted. This must be done with the entire contents [i.e., 4.5 mL (nominal volume) + 1.17 mL) of the solvent for dilution for cabazitaxel.

6.1.2 Solvent vial

- The solvent used for the preparation of the premix is a sterile, non-pyrogenic solution containing a 13 % w/w ratio of ethanol 95 % in water for injection. This solution is contained in a 15 mL clear type I glass vial closed with a rubber closure. The closure is crimped to the vial with either an aluminium cap covered with a light grey plastic flip-off cap or a gold-color aluminium cap covered with a colorless plastic flip off cap.
- The solution is a clear color less liquid.
- Each vial is overfilled to ensure that a 10 mg/mL concentration is obtained in the Premix and that 60 mg dose can be extracted. [i.e., 4.5 mL (nominal volume) + 1.17 mL].

6.1.3 Excipients

- Polysorbate 80 from vegetable origin, for the drug product vial.
- Water for injection and ethanol for the solvent vial.

6.1.4 Storage conditions

- Vials should be stored according to their labelling and kept in their kit until use.

6.1.5 Preparation

- Cabazitaxel drug products should be administered only by intravenous route.

- It is supplied as a kit containing one single-use vial of cabazitaxel concentrate for solution for infusion and one single vial of solvent for dilution. The administration of the product requires two dilutions prior to administration.
- This pharmaceutical dosage form is a concentrate for solution for infusion and must be diluted before administration. First the dosage form is diluted with the solvent supplied (preparation of the "cabazitaxel premix solution"). Then this premix solution must be diluted in an infusion vehicle (preparation of the "cabazitaxel infusion solution"). Each cabazitaxel vial and each corresponding solvent vial are overfilled to ensure that a 60 mg dose can be withdrawn after the preparation of the premix.

Preparation of cabazitaxel premix solution under aseptic conditions

- Use one solvent vial per each vial of cabazitaxel concentrate.
- Withdraw, under aseptic conditions, the entire contents of the solvent vial and inject it into the corresponding vial of cabazitaxel concentrate. Gently mix the reconstituted solution by repeated inversions for at least 45 seconds until obtaining clear and homogenous solution. Do not shake. Let the premix solution stand for a few 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.
- In order to compensate for liquid loss during preparation and to ensure that the JEVTANA initial diluted solution (premix) can be prepared at the concentration of 10 mg/mL and that a nominal volume of at least 6 mL can be withdrawn from the premix vial, the JEVTANA 60 mg/1.5 mL concentrate vials are filled with a 22% overfill (total fill volume 1.83 mL) and the diluent vials with a 26% overfill (total fill volume 5.67 mL).
- The concentration of 10 mg/mL in the premix [60mg/1.5 mL (concentrate) + 4.5 mL (diluent)] can be calculated as follows taking into account the overfilling: 73.2mg/ 1.83 ml (22 % overfill concentrate) + 5.49 mL (overfill diluent *) = 10 mg/mL
- Thus, the preparation obtained ensures a minimal extractable volume of the premix solution of 6 mL corresponding to a concentration of 10 mg/mL of cabazitaxel corresponding to 60mg/6 mL.

Preparation of cabazitaxel infusion solution under aseptic conditions

- **WARNING: Since foam is normally present, the required dose must be accurately adjusted using a graduated syringe.**
- Withdraw, under aseptic conditions, the volume of the premix solution containing 10 mg/mL of cabazitaxel that corresponds to the required dose (mg) and inject the required premix volume into a 125 to 500 mL infusion container (either 5 % glucose solution for injection or 0.9 % sodium chloride solution for injection). Mix the content of the infusion container manually by gently inverting the bag or bottle. 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 of 2.1 m²).

Infusion conditions

- The recommended infusion duration is one hour. The infusion solution should be used within 8 hours at ambient temperature (including the one hour infusion time) or within a total of 48 hours if refrigerated (including the one hour infusion time).
- The infusion solution should be administered at room temperature under normal lighting conditions.
- Do not use PVC infusion containers for cabazitaxel preparation and administration.
- Do not use polyurethane infusion sets for cabazitaxel preparation and administration
- Glass bottles could also be used.
- Use an in-line filter of 0.22 µm nominal pore size (also referred to as 0.2 µm) during cabazitaxel administration.

Shelf life

- Cabazitaxel premix solution: premix solution should be used immediately after preparation and within 1 hour at ambient temperature.
- Cabazitaxel infusion solution: the infusion solution is stable for 8 hours at ambient conditions (including the 1 hour infusion time) or a total of 48 hours if refrigerated, from preparation to end of infusion.

Recommendations for safe handling

- Cabazitaxel is an antineoplasic agent and, like other potentially toxic compounds, caution should be exercised in handling and preparing cabazitaxel solutions. The use of gloves is recommended.
- If cabazitaxel concentrate, premix solution or infusion solution should come into contact with skin, wash immediately and thoroughly with soap and water. If cabazitaxel concentrate, premix solution, or infusion solution should come into contact with mucous membranes, wash immediately and thoroughly with water.

6.2 Dosage and schedule

6.2.1 Cabazitaxel

- Arm A: Cabazitaxel 25 mg/m² intravenously over 1 hour on Day 1of a 3-week cycle, plus prednisone (or prednisolone) 10 mg orally given daily for a maximum of 10 cycles (ie 30 weeks of treatment)
- Arm B: cabazitaxel 16 mg/m2 on Day 1 and Day 15 of a 4-week cycle plus prednisone (or prednisolone) 10 mg per day, up to 10 cycles (ie 40 weeks of treatment)
- Treatment should be continued for a maximum of 10 cycles in each arm unless there is confirmed disease progression or unacceptable treatment toxicity.
- At least 30 minutes prior to each administration of cabazitaxel, patients will be administered IV premedication including:

- An antihistamine (dexchlorpheniramine 5 mg, diphenhydramine 25 mg, or equivalent). In case of IV antihistamine other than promethazine is not being available, local practice should be followed.
- Corticosteroid (dexamethasone 8 mg or equivalent)
- H2 antagonist (ranitidine or equivalent).
- Antiemetic prophylaxis is recommended and can be given orally or intravenously if necessary.

6.2.2 Prednisone

- All patients will receive continuous treatment with prednisone, either 5 mg orally twice daily, or 10 mg once daily.
- Upon completion of the last cabazitaxel administration, decision to continue or not prednisone will depend of the policy of the treating institute.

6.2.3 LHRH treatment

- All patients will receive continuous treatment with LHRH.
- Upon completion of the last cabazitaxel administration, decision to continue or not LHRH will depend of the policy of the treating institute.

6.2.4 Primary prophylaxis with G-CSF

Primary prophylaxis with Granulocyte Colony-Stimulating Factor (G-CSF) will be injected from Day 3 to Day 7 (5 days) after every administration of cabazitaxel. Until post-nadir ANC recovery to normal or near-normal levels by laboratory standards (NCCN guidelines Myeloid Growth Factors Version 1. 2016.

G-CSF (GRANOCYTE) will be provided by Sponsor for both arms.

IMPORTANT:

- BSA will be calculated prior to each treatment cycle from body weight in kg, recorded prior to each treatment cycle, and height in cm, recorded at baseline. The preferred Dubois and Dubois equation is: BSA in units of m2 = wgt. in kg 0.425 x hgt. in cm 0.725 x 0.007184.
- New cycles of therapy may not begin until Absolute Neutrophil Count (ANC) ≥1500/mm^3, platelet count ≥75 000/mm^3, and non-hematological toxicities (except alopecia) have recovered to baseline or ≤ grade 1. A maximum of 2 weeks delay is allowed between 2 treatment cycles. Patients should come off treatment if treatment delay is more than 2 weeks.

6.3 Adaptation of doses

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

6.3.1 Dose reduction

- Dose can be reduced for cabazitaxel when necessary as described in following sections.

- The dose, which has been reduced for toxicity, must not be re-escalated.
- Only one dose reductions will be allowed per patient. If a second dose reduction is required per the modifications below, the patient should discontinue study treatment.

6.3.2 Dose delay

- Treatment with cabazitaxel may be delayed no more than 2 weeks to allow recovery from acute toxicity.
- In case of treatment delay greater than 2 weeks, patient should discontinue cabazitaxel.

Hematological toxicity

- Dose will be modified in case of hematological toxicity.

***Table 1 - Dose modifications* for hematological toxicity**

Adverse event	Toxicity	
	Grade 2	**Grade 3 or Grade 4**
Neutropenia	delay** next infusion until recovery to grade ≤1 (neutrophil ≥1.5 x 10^9/L). - 1st episode: No dose reduction required. - 2nd episode; reduce cabazitaxel by 1 dose level	No dose reduction if isolated and duration ≤7 days. If duration more than 7 days or not recovered on D21 Delay** next infusion until ANC ≥1.5 x 10^9/L and: - 1st episode despite prophylactic G-CSF: Reduce dose by 1 dose level. Arm A: from 25 to 20 mg/m2 Arm B: from 16 to 13 mg/m2 - 2nd episode despite prophylactic G-CSF: Withdraw from study treatment
Febrile neutropenia or neutropenic infection	Not applicable	Delay** next infusion until recovery and ANC ≥1.5 x 10^9/L and: - 1st episode despite G-CSF: reduce the cabazitaxel dose by 1 dose level - 2nd episode despite G-CSF: Withdraw from study treatment
Thrombocytopenia	Delay** next infusion until recovery to grade ≤ 1 (platelets ≥75 x 10^9/L). No dose reduction required.	Delay** 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 cabazitaxel dose by 1 dose level - 2nd episode: Withdraw from study treatment in case of recurrence

** maximum of 2 weeks delay, otherwise the patient will discontinue cabazitaxel

- Blood counts will be performed in case of fever or infection. Blood count should be monitored at D7 and D14 to determine if G-CSF or dosage modification is needed. Study treatment should not be given to patients with neutrophil counts <1,500 cells/mm^3.
- Deaths due to sepsis following severe neutropenia have been reported in patients treated with cabazitaxel. Neutropenic complications should be managed promptly with antibiotic support and use of G-CSF should be considered according to ASCO guidelines. Infections concomitant with grade 3-4 neutropenia should be reported with the term “neutropenic infection” in the e-CRF.
- No dose modification will be made for anaemia; patients will be supported appropriately by the treating physician (the investigator can refer to ASCO guidelines).

Allergy (anaphylactic and hypersensitivity reactions)

- Hypersensitivity reactions that occur despite premedication are very likely to occur within a few minutes of start of the first or of the second infusion of cabazitaxel. Therefore, during the 1st and the 2nd infusions, careful evaluation of

general sense of well being and of blood pressure and heart rate will be performed for at least the first 10 minutes, so that immediate intervention would occur in response to symptoms of an untoward reaction.

- Facilities and equipment for resuscitation along with the medications (i.e., antihistamine, corticosteroids, aminophylline, and epinephrine) must be immediately available. If a reaction occurs, the specific treatment that can be medically indicated for a given symptom (e.g., epinephrine in case of anaphylactic shock, aminophylline in case of bronchospasm, etc) will be instituted. In addition, it is recommended to take the measures listed in **Table 3**

Table 3- Dose modifications for allergy

Adverse events	**Action**
Mild: localized cutaneous reaction, such as: pruritus, flushing, rash.	o Consider decreasing the rate of infusion until recovery of symptoms, stay at bedside o Complete cabazitaxel infusion at the initial planned rate.
Moderate: Generalized pruritus, flushing, rash, dyspnea, back pain during infusion, hypotension with systolic B.P. >80 mmHg	o Stop cabazitaxel infusion o Give IV diphenhydramine 50 mg and/or IV dexamethasone 10 mg o Once all signs and/or symptoms of hypersensitivity reaction disappear, cabazitaxel may be reinfused within 24 hours from the interruption, if medically appropriate, and whenever possible. o Re-administer premedication regimen as described in Section 8.6 when cabazitaxel is reinfused more than 3 hours after the interruption o Administer cabazitaxel over 2 hours for all subsequent infusions
Severe: bronchospasm, generalized urticaria, hypotension with systolic B.P. ≤80 mmHg, angioedema.	o Stop cabazitaxel infusion o Give IV diphenhydramine 50 mg and/or IV dexamethasone 10 mg o Add epinephrine** or bronchodilators and/or IV plasma expanders if indicated o Once all signs and/or symptoms of hypersensitivity reaction disappear, cabazitaxel may be reinfused within 24 hours from the interruption, if medically appropriate, and whenever possible o Re-administer premedication regimen as described in Section 8.6 when cabazitaxel is reinfused more than 3 hours after the interruption o Administer cabazitaxel over 2 hours for all subsequent infusions o If a severe reaction recurs, patient will go off protocol therapy
Anaphylaxis (grade 4 reaction)	Withdraw treatment

Table 4: Suggested Management of Acute Hypersensitivity

Severity of Symptoms	**Treatment Guidelines**
Mild: localized cutaneous reactions such	Consider decreasing the rate of infusion

as mild pruritus, flushing, rash	until recovery from symptoms, stay at bedside and monitor subject, then complete cabazitaxel infusion at the initial planned rate
Moderate: any symptom that is not listed above (mild symptoms) or below (severe symptoms) such as generalized pruritus, flushing, rash, dyspnea,back pain during infusion, and hypotension with systolic BP >80 mmHg	• Interrupt cabazitaxelinfusion • Give diphenhydramine 50 mg IV with or without dexamethasone 10 mg IV; monitor subject until resolution of symptoms • Resume study drug infusion within 3 hours following recovery of hypersensitivity reaction. Administer study drug over 2 hours for all subsequent treatments.
Severe: any reaction such as bronchospasm, generalized urticaria, systolic BP ≤ 80 mmHg, angioedema	• Immediately discontinue cabazitaxel infusion • Give diphenhydramine 50 mg IV with or without dexamethasone 10 mg IV and/or epinephrine as needed; monitor subject until resolution of symptoms • In case of severe hypersensitivity reaction, rechallenge must be performed more than 3 hours after recovery and premedication should be readministered. • If severe reaction recurs despite additional premedication, the patient will go off protocol therapy. •
Anaphylaxis (NCI CTCAE Grade 4 reaction)	• no further study drug administration

- Any hypersensitivity reaction should be recorded as an adverse event.

<u>Management of subsequent cycles</u>

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 (eg, 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.

Nausea/vomiting

- A prophylactic anti-emetic treatment should be given to the patients in all cycles.
- The use of metoclopramide is recommended.
- More aggressive anti-emetic prophylaxis (i.e., ondansetron, etc.) should be given to the patient who has experienced grade ≥3 nausea/vomiting in a preceding cycle.
- If despite the appropriate medication, grade ≥3 nausea/vomiting still occur, reduce the dose of cabazitaxel.
- If despite dose reduction and prophylaxis, nausea/vomiting still occur at grade ≥3, the patient should be withdrawn from treatment with cabazitaxel.

Stomatitis

- If grade 3stomatitis occurs, cabazitaxel should be withheld until resolution to grade ≤1. Treatment may then be resumed, but the dose of cabazitaxel should be reduced from 25 to 20mg/m2 or from 16 mg/m2 to 13 mg/m2 for all subsequent doses.
- In case of grade 4 stomatitis, the patient will be withdrawn from treatment with cabazitaxel.

Diarrhoea

- No prophylactic treatment for diarrhoea is recommended in Cycle 1.
- However, following the first episode of diarrhoea, the patient should be treated with rehydration or antidiarrheal medications as needed.
- In case of grade ≥ 3 diarrhoea or persisting diarrhoea despite appropriate medication, fluid and electrolytes replacement, delay treatment until improvement or resolution, then reduce the dose of cabazitaxel (from 25 to 20mg/m2 or from 16mg/m2 to 13 mg/m2).
- If despite dose reduction, diarrhoea still occurs at grade ≥3, the patient will be withdrawn from treatment with cabazitaxel.

Peripheral neuropathy

- Dose modification should be performed as follows:
  - Grade ≤1: No change
  - Grade 2: Retreat with reduced dose of cabazitaxel (from 25 mg/m2 to 20mg/m2 or from 16 mg/m2 to 13 mg/m2)
  - Grade 3: Patient will be withdrawn from treatment with cabazitaxel

Hematuria

- An imbalance in the incidence of hematuria was observed in the Phase III study in second line mCRPC (EFC6193). More hematuria was reported in cabazitaxel arm versus mitoxantrone arm (62 patients/16.7% versus 14 patients/3.8%). In cabazitaxel arm, no clear possible explanation such as local infection/obstruction/progression, or anticoagulation/aspirin therapy, or thrombocytopenia was found for 21 patients. In addition, in prior studies conducted in metastatic breast cancer, a total of 6 patients (2 in the ARD6191 and 4 in the TCD6945) experienced cystitis without local infection including 5

hemorrhagic cystitis (3 cystitis were documented with biopsy). In PROSELICA phase III trial, haematuria all grades frequency was 20.8% at 25 mg/m2.

- Therefore, in case of hematuria with no clear possible explanation every efforts should be undertaken to document the cause (eg, urine cultures, urinary tract ultrasound, and if no cause identified cystoscopy with or without biopsy).

Liver toxicity

- In case of total bilirubin > 1 to ≤ 1.5 x Upper Limit of Normal (ULN) or AST >1.5 x ULN) reduce cabazitaxel by one dose.
- In case of total bilirubin > 1.5 to ≤ 3 x ULN and AST = any) reduce cabazitaxel dose to 15 mg/m2 (3-weekly arm) or 10 mg/m2 (bi-weeklyarm)
- In case of severe hepatic impairment (total bilirubin > 3 X ULN total bilirubin > 1.5 to ≤ 3 x ULN and AST = any) cabazitaxel should be discontinued.

Other toxic effects

- For grade ≥3 toxicities except fatigue, local reactions, fluid retention, anaemia and other toxicities that merely are uncomfortable but do not cause serious morbidity to patients, chemotherapy should be delayed 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 for subsequent doses will be left to the investigator's judgment.
- 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's judgment.

6.4 Removal of patients from therapy

- Only one dose reduction will be allowed per patient. If a second dose reduction is required per the modifications above written, the patient should discontinue study treatment.

6.5 Concomitant treatments

- Facilities and equipment for the treatment of serious hypersensitivity reactions like hypotension and bronchospasm must be available.
- Antiemetic prophylaxis is recommended and can be given orally or intravenously as needed.
- Throughout the treatment, adequate hydration of the patient needs to be ensured, in order to prevent complications like renal failure.
- Treatments with strong inhibitors or strong inducers of cytochrome P450 3A4/5 (see Appendix) are not authorized during the study.

7. PLAN OF THE STUDY

7.1 Pretreatment evaluation (within 30 days prior to inclusion)

- Patient information and signed informed consent
- Demography

- Disease history (date of diagnosis, initial Gleason score and stage, prior therapies duration of response to first hormonal therapy, PSA values, metastatic sites).
- Associated comorbidities (CISRG) (see appendix)
- Physical examination (including height, body weight)
- Vital signs(body temperature, blood pressure, pulse and respiratory rate)
- Health status: ECOG/PS, G8, dependence (ADL, IADL) - see appendix C
- Pain status (using the numerical rating scale from 0 to 10) – see appendix B
- Laboratory measurements:
    - Serum PSA
    - Serum testosterone
    - Hematology (within 3 days before): WBC with differential count, haemoglobin, platelet count.
    - Blood chemistry(within 3 days before): creatinine, SGOT (AST), SGPT (ALT), alkaline phosphatase, total bilirubin, LDH
    - Dipstick test
- Tumour assessment (within 30 days prior to enrolment)
    - CT-Scan (abdominal/pelvic/chest) or MRI whole body
    - Bone scan
- Inclusion and exclusion criteria
- Assessment of concomitant medications

7.2 Evaluation at Day 1 before the first cycle

- Review of inclusion and exclusion criteria
- Physical examination (including body weight)
- Vital signs(Body temperature, blood pressure, pulse and respiratory rate)
- ECOG/ PS
- Pain status (using the numerical rating scale from 0 to 10)
- FACT-P (see appendix D)
- Skeletal-Related Event (SRE)
- Adverse events
- Assessment of concomitant medications
- Laboratory measurements:
    - Serum PSA
    - Hematology: WBC with differential count, haemoglobin, platelet count (new cycles of therapy may not begin until Absolute Neutrophil Count (ANC) ≥1500/mm3, platelet count ≥75 000/mm^3)
    - Blood chemistry: creatinine, SGOT (AST), SGPT (ALT), alkaline phosphatase, total bilirubin, LDH
    - Dipstick test

7.3 Evaluation at Day 1 before each other cycle

- Vital signs (Body weight, temperature, blood pressure, pulse and respiratory rate) ECOG/PS
- Pain status (using the numerical rating scale from 0 to 10)
- FACT-P (see appendix D)
- Skeletal-Related Event (SRE)
- Adverse events
- Assessment of concomitant medications
- Laboratory measurements:
    - Serum PSA
    - Hematology: WBC with differential count, haemoglobin, platelet count (new cycles of therapy may not begin until Absolute Neutrophil Count (ANC) ≥1500/mm3, platelet count ≥75 000/mm^3)
    - Blood chemistry: creatinine, SGOT (AST), SGPT (ALT), alkaline phosphatase, total bilirubin, LDH
    - Dipstick test

7.4 Haematology

- Haematology test will be done every week until end of treatment.
- In case of grade ≥3 neutropenia, haematological test will be done every 3 days until grade ≤ 2.

7.5 Re-staging

- Bone scan, CT scan or MRI whole body or other disease assessment diagnostics every 3 months (±7 days) and if disease progression is suspected.

7.6 Assessment during End of treatment visit (Upon progression or 30 days after last cycle

- Physical examination (including body weight)
- Vital signs (Body temperature, blood pressure, pulse and respiratory rate)ECOG/PS
- Pain status (using the numerical rating scale from 0 to 10)
- FACT-P

7.7 Follow-up period

Patients will be followed for OS and for subsequent therapies taken (all randomized patients) until the End of Study.

-

7.8 Skeletal-Related Event (SRE)

- Adverse events
- Assessment of concomitant medications
- Laboratory measurements:

- Serum PSA
- Serum testosterone
- Hematology: WBC with differential count, haemoglobin, platelet count
- Blood chemistry: creatinine, SGOT (AST), SGPT (ALT), alkaline phosphatase, total bilirubin, LDH
- Dipstick test

- Tumour assessment (within±7 days):
  - CT-Scan (abdominal/pelvic/chest) or MRI whole body
  - Bone scan
- Subsequent antineoplastic therapies after the last cycle will be recorded until End of Study.

7.9 Patient Withdrawal

Patients may withdraw from the study at any time at their own request or may be withdrawn at the investigator's or sponsor's discretion for safety, behavioral or administrative reasons.

If a patient does not return for a scheduled visit, every effort should be made to contact the patient. In all circumstances, every effort should be made to document patient outcome. The investigator should inquire about the reason for withdrawal, ask the patient to return for the end-of-treatment visit, if applicable, and follow up the patient in relation to any unresolved adverse events.

If the patient withdraws from the study, 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 withdrawal of consent.

Patients will be withdrawn from the study in the following cases:

- Disease progression
- Unacceptable toxicity
- Patient non compliance
- Patient lost to follow-up
- Withdrawal of patient consent

8. CRITERIA FOR TREATMENT EVALUATION

8.1 Primary criterion

- Incidence of grade ≥ 3 neutropenia and/or neutropenic complications (febrile neutropenia, neutropenic infection, sepsis)

8.2 Secondary criteria

- Maximum PSA change from baseline at any time using waterfall plot (PCWG2) [26]. The percentage of patients with a ≥ 30% and ≥ 50% decrease from baseline will be derived from this waterfall plot.
- Time to PSA progression as per PCWG2 criterion (time to first PSA increase that is ≥ 25% and ≥2 ng/mL above the nadir, and which is confirmed by a second value) [26].

- Dose reductions and dose delays
- Radiological progression-free survival (rPFS) as per PCWG2 criterion (calculated from time to randomization and defined by modified RECIST criteria 1. or the appearance of 2 new lesions on a bone scan, confirmed by a bone scan 6 weeks later) [26].
- Time to first Skeletal-Related Event: time from randomization to the occurrence of the first skeletal-related event (radiation therapy or surgery to bone, pathologic bone fracture, spinal cord compression, or change of antineoplastic therapy to treat bone pain)
- Incidence of SREs (radiation therapy or surgery to bone, pathologic bone fracture, spinal cord compression)
- Time to opioid treatment: time from randomization to the first use of opioid treatment (if pertinent)
- FACT-P (Functional Assessment of Cancer Therapy – Prostate): 27 core items to assess patient function in four domains (physical, social/family, emotional, and functional wellbeing) and supplemented by 12 specific items to assess for prostate-related symptoms. Each item is rated on a 0 to 4 Likert-type scale, and then combined to produce subscale scores for each domain, as well as a global quality of life score. Higher scores represent better quality of life. Patients are defined as having a quality-of-life response if they have a 10-point improvement in their global FACT-P score, as compared with baseline, on two consecutive measurements obtained at least three weeks apart.
- Overall survival: time from randomization to death from any cause in the intent to treat population.
- Time to onset of grade ≥ 3 neutropenia
- Grade ≥3 neutropenia duration (from date of onset of grade ≥ 3 until grade ≤ 2)
- Incidence of grade ≥ 3 neutropenia and/or neutropenic complications by cycle
- Adverse events, serious adverse events and discontinuation for adverse events
- Exploratory (in selected sites): to evaluate the relationship between myeloid derived suppressor cells and NLR decline, neutropenia and cabazitaxel treatment schedule

8.3 Exploratory sub-study outcomes

Primary:

- Proportion of patients achieving a best objective response of SD, PR or CR according to RECIST 1.1 specifically comparing those achieving >30% and >50% decrease in MDSC post-induction compared to those who did not achieve this reduction.
- Proportion of patients achieving a >50% PSA response at 12 weeks and at any time specifically comparing those achieving >30% and >50% decrease in MDSC post-induction compared to those who did not achieve this reduction.
- Radiological progression-free survival (rPFS) according to PCWG2 criteria for all patients, in relation to percentage MDSC change (continuous) and those achieving >30% and >50% decrease in MDSC

Secondary:

- Proportion of patients achieving a best objective response and best PSA>50% response comparing those achieving NLR conversion (or remaining <3) compared to those who did not achieve this reduction
- Differences in peripheral blood immune populations (MDSCs, regulatory T-cells, T-effector and natural killer [NK] cells) with cabazitaxel responsiveness for Q2W and Q3W dosing schedule at week 6 and week 12
- Correlations between extent of MDSC (continuous) and NLR decline (continuous)
- Association between MDSC decline (>30% or >50%) with neutropenia (presence or absence)
- Associations between cabazitaxel exposure, presence of neutropenia (C1D8), NLR conversion (wk6 and wk12) and MDSC decline (wk6 and wk12)
- To evaluate changes in peripheral blood immune populations at failure on cabazitaxel with particular focus on CD38 positive MDSC subsets
- Associations between baseline MDSC and molecular background (from cfDNA, specifically studying MYCN amplification)

9. DETERMINATION OF SAMPLE SIZE AND STATISTICAL ANALYSIS

9.1 Determination of sample size

- The primary end-point of this phase 3 trial is the incidence of grade ≥3 neutropenia and/or neutropenic complications, measured at D7 and D14.
- Of 131 patients treated with cabazitaxel every 3 weeks at HEGP, 40% developed grade ≥3 neutropenia. In the two pilot studies conducted with cabazitaxel 16mg/m2 bi-weekly, the range of grade ≥3 neutropenia was 15% in the Finnish cohort [23] and 16.5% in HEGP cohort [24].
- A sample size of 77 to 90 evaluable patients per arm will achieve 80% power to detect a 20% difference in G3 neutropenia incidence between the two arms. The incidence of grade ≥3 neutropneia with cabazitaxel 25 mg/m2 q3w is assumed to be 32% versus 12% on bi-weekly cabazitaxel arm. The test used is a two-sided Fisher's exact test at 0.05 significance level. Assuming 10% non-evaluable patients, 85 to 100 patients should be included in each arm for a total of 170 to 200.
- Patients will be stratified according to G8 score (< 14 vs. ≥ 14), and age (< 70 vs. ≥ 70) before randomization.

9.2 Statistical methods

- The primary end-point will be the incidence of grade 3-4 neutropenia and/or neutropenic complications (febrile neutropenia, neutropenic infection) at D7 and D14 after cabazitaxel injection over the whole chemotherapy period (maximum of 10 cycles). More than 1 onset of grade 3 neutropenia for a given patient will be counted once.
- The incidence of grade ≥3 neutropenia and/or neutropenic complications will also be analysed by cycle
- A reasonable hypothesis is that baseline neutrophil levels should be correlated to the outcome. Hence, the comparison of incidence between the 2 arms will be

adjusted on the neutrophil level at baseline using an analysis of covariance (ANCOVA) taking into account stratification factors (G8 score and age (<70 vs. ≥ 70) to randomization).

- Extent of exposure will be assessed on the intent to treat population. Number of patients treated, number of cycles administered, duration of dosing (weeks), cumulative dose (mg/m²), dose intensity (mg/m²/3 weeks) and relative dose intensity (%) will be summarized.
- Dose delays and dose reductions will be analyzed.
- Radiological PFS in both arms will be compared through a two sided 5% log-rank adjusted for the stratification factors. This analysis will be performed on the ITT population. If radiological progression or death is not observed during the study, data on PFS will be censored at the last valid tumor assessment date or at the cut-off date, whichever comes first. The estimates of the hazard ratio and corresponding 95% confidence interval will also be provided using a Cox proportional hazard model stratified by the same stratification factors as those described above.
- Time to event (PSA progression, time to symptomatic *progression,* time to symptomatic skeletal events, time to opioid consumption if pertinent) will be compared between the 2 treatment arms using the same methodology as radiological PFS.
- Overall survival: a stratified log-rank test will be used to compare both arms. This comparison will be 2-sided test at the 0.05 level of significance. Patients alive at the end of study (will be censored for survival status and subsequent therapies
- The survival curves will be estimated using Kaplan-Meier estimates. Median times and associated 95% confidence intervals will also be provided by treatment. Hazard ratios and 95% confidence intervals will be provided using a Cox proportional hazard model.
- Continuous data will be summarized using number of available data, median, minimum, Q1, Q3 and maximum for each dose level. The 2 arms will be compared using either t-test or non-parametric Mann-Whitney U test (depending on the normality of the data, the SAP will detail which method will be used).
- Categorical data will be summarized using number and percentage of patients in each dose level (patients with missing data will not be included in the percentage calculation). The two arms will be compared using chi-square test of Fisher's exact test. Tumor, PSA, and pain response will be analyzed on their respective evaluable population.

All AE will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTC-AE v 4.0) and summarized using MedDRA terminology v19.

- Summary tables of AE, TEAE, serious adverse events and withdrawals for adverse events will be provided by treatment period. Adverse events will be summarized by worst severity grade. AEs.

9.3 Sub- study statistical methods

The trial is powered on a clinical endpoint, namely to detect a 20% difference in G3 neutropenia incidence between arms (32% arm A vs 12% arm B; power 80% with two-sided alpha of 5%, correcting for 10% non-evaluable patients (=17 patients).

From the 153 to 180 evaluable patients, we have 76 to 90 patients in each arm, of which we expect 40-60 evaluable patients for translational studies (calculations performed on 25 per arm).

In arm A, we expect 8 patients (32% of patients) with G3 neutropenia, and 17 patients that do not. In arm B, we expect 3 patients (12% of patients) with G3 neutropenia, and 22 patients that do not. For the MDSC analyses, we therefore will be comparing 11 patients with G3 neutropenia to 39 patients.

For all continuous variables, including all immune subpopulations present in blood, mean and standard deviation (sd) will be presented if the distribution seems to be symmetric and in case of a skewed distribution the median and IQR. For categorical data, number and percentage will be presented. For comparison of continuous data linear regression analyses or correlation (Spearman or Pearson) will used. For comparison of continuous data with categorical data logistic regression analysis will be used. For comparison of two sets of categorical data the chi-square test of Fisher's exact test will be utilized. For the radiological PFS analyses the estimates of the hazard ratio and corresponding 95% confidence interval will be tested using a Cox Proportional hazard model. For the overall survival, a stratified log-rank test will be used to compare between groups.

9.4 Interim analysis

There will be no interim analysis

10. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

10.1 Definitions

10.1.1 Adverse Event (AE)

An Adverse Event (AE) is any new untoward medical occurrence or worsening of a preexisting medical condition in a patient or clinical investigation subject administered an investigational (medicinal) product. An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory findings for example), symptom, or disease temporally associated with the use of a medical product, whether or not a causal relationship (i.e. related/not related) with the treatment is suspected.

10.1.2 Serious Adverse Event (SAE)

A **Serious Adverse Event (SAE)** is any untoward medical occurrence that at any dose:

- is fatal (results in death)
- is life-threatening
    - the term 'life-threatening' in the definition of 'serious' refers to an event in which the patient 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
- requires or prolongs in-patient hospitalization
- results in persistent or significant disability / incapacity
- is a congenital anomaly / birth defect

- is medically significant, defined as any clinical event or laboratory result that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment,
    - may jeopardize the subject or
    - may require intervention (eg, medical, surgical) to prevent one of the other serious outcomes listed in the definition above.
    - Examples of such events include but are not limited to, allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasia or convulsions that do not result in inpatient hospitalization, development of drug dependency or drug abuse, transmission of an infectious agent.

Although overdose (defined by more than 30% over intended dose) and cancer are not always serious by regulatory definitions, these events should be reported on a SAE report form and sent to the sponsor in an expedited manner.

The following are not considered to be serious adverse events (SAE):

- Death consecutive to disease progression
- a visit to the emergency room or other other hospital department for less than 24 hours that does not result in admission (unless considered an “important medical event” or a life-threatening event)
- outpatient or same-day or ambulatory procedures
- observation or short-stay units
- Hospitalization due to diagnostic procedures or standard supportive care (e.g. implant of central venous catheter)
- A pre-planned hospitalization for a condition which existed at the start of study drug and which did not worsen during the course of study drug treatment
- Social admission (e.g., subject has no place to sleep; hospice facilities)
- Administrative admission (e.g., for yearly physical examinations)
- Protocol-specified admission during a clinical trial (e.g., for a procedure required by the study protocol or for clinical research)
- Optional admission not associated with a precipitating clinical AE (e.g., for elective cosmetic surgery)

10.1.3 Expected Serious Adverse Event

An expected SAE is an event already mentioned in the most recent version of the investigator brochure for drugs with a market authorization.

10.1.4 Unexpected Serious Adverse Event

An unexpected SAE is an event not mentioned or different by its nature, intensity and/or, evolution with respect to the investigator brochure summary, for drugs with a market authorization.

10.1.5 Intensity criteria

Intensity criteria must not be confused with criteria for seriousness, which serve as guidelines for definition of obligations for declaration.

Intensity of events will be estimated according to the NCI-CTCAE classification, version 4.0 (toxicity score grade 1 to 5); see Appendix H. Intensity of adverse events not listed in this classification will be evaluated according to the following terms:

- Mild (grade 1): does not affect the patient's usual daily activity
- Moderate (grade 2): perturbs the patient's usual daily activity
- Severe (grade 3): prevents the patient carrying out his usual daily activities
- Very Severe (grade 4): necessitates intensive care or is life-threatening
- Death (grade 5)

10.2 Safety reporting

10.2.1 Adverse events

- All AEs regardless of seriousness or relationship to investigational product (IP), spanning from the signature of the informed consent form, until the end of the study treatment up to 30 days after last study treatment administration as defined by the protocol for that patient, are to be recorded on the corresponding page(s) or screen(s) included in the CRF.
- Whenever possible, diagnosis or single syndrome should be reported instead of symptoms. The Investigator should specify the date of onset, intensity, action taken with respect to IP, corrective treatment/therapy given, additional investigations performed, outcome and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the IP.
- Laboratory and vital sign are to be recorded as AEs only if:
    - leading to IP discontinuation or modification of dosing, and/or
    - fulfilling a seriousness criterion

10.2.2 Serious adverse events

- Any SAE which occurs or comes to the attention of the investigator at any time during the study since consent is given and within 30 days after the last administration of study drugs, independent of the circumstances or suspected cause, must be reported immediately, within one working day of awareness (at latest on the next working day) by E-mail or by fax via a SAE report form to:

PV mailbox

safety@fordrugconsulting.fr

Fax: (+33) 1 47 46 18 48

- All late Serious Adverse Events (occurring after this period of 30 days) considered to be reasonably related to the study treatment(s) or the research must be reported within one working day of awareness (no time limit).
- Information collected in the SAE form is crucial to assess the case. For this reason diligence in collecting as much verifiable and reliable information is needed: both, quality and timeliness are key factors. If known, the diagnosis of the underlying illness or disorder should be recorded, rather than its individual symptoms. The following information should be captured for all SAEs: onset, duration, intensity, and seriousness, relationship to study drugs, action taken and treatment required.
- The investigator must also attach the following to the serious adverse event report form, wherever possible:

- A copy of the summary of hospitalization or prolongation of hospitalization
- A copy of the post-mortem report(if applicable)
- A copy of all relevant laboratory examinations and the dates on which these examinations were carried out, including relevant negative results, as well as normal laboratory ranges.
- All other document that he judges useful and relevant.

- All these documents will remain anonymous.
- Further information can be requested (by fax, telephone or when visiting) by the monitor and/or the safety manager.

Follow-up information

- The investigator is responsible for the appropriate medical follow-up of patients until resolution or stabilization of the adverse event or until the patient's death. **This may mean that follow-up should continue once the patient has left the trial.**
- Follow up information about a previously reported serious adverse event must be reported by the investigator to the Pharmacovigilance Unit within 24 hours of receiving it (on the serious adverse event report form, by ticking the box marked Follow-up N°…). The investigator also transmits the final report at the time of resolution or stabilization of the SAE.
- He retains the documents concerning the supposed adverse event so that previously transmitted information can be completed if necessary.

10.3 Responsibilities of the coordinating Sponsor

The coordinator sponsor will assess the SAE in terms of seriousness, severity (NCI-CTCAE v4.0), relationship to the study drugs and expectedness. All SAEs will be coded using MedDRA v19.

The coordinating Sponsor shall be responsible for ensuring submission of required expedited and periodic reports to National Competent Authorities and to the National Ethics Committee as per local regulation.

Suspected Unexpected Serious Adverse Reactions (SUSARs)

To comply with regulatory requirements, the sponsor will report all SAEs that are related to the investigational medicinal product and unexpected (ie, not previously described in the investigator brochure or in the Summary of Product Characteristics) to the competent authority and national ethic committee of each participating country. In the European Union, an event meeting these criteria is termed as suspected Unexpected Serious Adverse Reaction (SUSAR).

Sanofi will provide HeCOG with all DILs (SUSARs) that are linked with cabazitaxel from cases and clinical trials.

All SAEs regardless of causality must be sent in English to the Sanofi-Aventis Group pharmacovigilance contact within one working day. Any safety-related finding or communications with Health Authorities are to be likewise sent to the Sanofi-Aventis Group Pharmacovigilance contact

Periodic reports (DSUR & Semi Annual Safety reports)

The coordinating sponsor will issue and submit once a year/6 months throughout the clinical trial, or on request, the DSUR/SASR of the study, in accordance with the detailed guidance issued by the European Commission on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use (CT-3).

11. STUDY DISCONTINUATION

The study could be interrupted or terminated by the sponsor in agreement with the coordinator and with the competent authority for the following reason:

- frequency and/or unexpected severity of the toxicity,
- recruitment of patients too low,
- poor quality of the data collected,
- request of the Data Monitoring Committee (if applicable)

12. ETHICAL AND REGULATORY ASPECTS

12.1 Ethical principles

- This Clinical Trial will be conducted in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies, and the ICH guidelines for Good Clinical Practice (GCP).

12.2 Laws and regulations

- This Clinical Trial will be conducted in compliance with all international guidelines, and national laws and regulations of the country(ies) in which the Clinical Trial is performed, as well as any applicable guidelines.

12.3 Informed consent

- The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator, and under the Investigator's responsibility, should fully inform the Patient of all pertinent aspects of the Clinical Trial including the written information giving approval/favourable opinion by the Ethics Committee (IRB/IEC). All participants should be informed to the fullest extent possible about the study, in language and terms they are able to understand.
- Prior to a patient’s participation in the Clinical Trial, the written Informed Consent Form should be signed, name filled in and personally dated by the patient or by the patient’s legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written Informed Consent Form will be provided to the patient.
- The Informed Consent Form used by the Investigator for obtaining the patient's informed consent must be reviewed and approved by the Sponsor prior to submission to the appropriate Ethics Committee (IRB/IEC) for approval/favorable opinion.

12.4 Institutional review board/independent Ethics Committee (IRB/IEC)

- As required by local regulation, the Investigator or the Sponsor must submit this Clinical Trial Protocol to the appropriate Ethics Committee (IRB/IEC), and is required to forward to the respective other party a copy of the written and dated

approval/favorable opinion signed by the Chairman with Ethics Committee (IRB/IEC) composition.

- The Clinical Trial (study number, Clinical Trial Protocol title and version number), the documents reviewed (Clinical Trial Protocol, Informed Consent Form, Investigator's Brochure, Investigator's curriculum vitae [CV], etc.) and the date of the review should be clearly stated on the written (IRB/IEC) approval/favorable opinion.
- IP will not be released at the study site and the Investigator will not start the study before the written and dated approval/favorable opinion is received by the Investigator and the Sponsor.
- During the Clinical Trial, any amendment or modification to the Clinical Trial Protocol should be submitted to the Ethics Committee (IRB/IEC) before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the IRB/IEC should be informed as soon as possible. It should also be informed of any event likely to affect the safety of patients or the continued conduct of the Clinical Trial, in particular any change in safety. All updates to the Investigator's Brochure will be sent to the Ethics Committee (IRB/IEC).
- A progress report is sent to the Ethics Committee (IRB/IEC) at least annually and a summary of the Clinical Trial's outcome at the end of the Clinical Trial.

13. STUDY MONITORING

13.1 Responsibilities of the investigator(s)

- The Investigator(s) and delegated Investigator staff undertake(s) to perform the Clinical Trial in accordance with this Clinical Trial Protocol, ICH guidelines for Good Clinical Practice and the applicable regulatory requirements.
- The Investigator is required to ensure compliance with all procedures required by the Clinical Trial Protocol and with all study procedures provided by the Sponsor (including security rules).The Investigator agrees to provide reliable data and all information requested by the Clinical Trial Protocol (with the help of the CRF, Discrepancy Resolution Form [DRF] or other appropriate instrument) in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents by Sponsor representatives.
- If any circuit includes transfer of data particular attention should be paid to the confidentiality of the patient's data to be transferred.
- The Investigator may appoint such other individuals as he/she may deem appropriate as Sub-Investigators to assist in the conduct of the Clinical Trial in accordance with the Clinical Trial Protocol. All Sub-Investigators shall be appointed and listed in a timely manner. The Sub- Investigators will be supervised by and work under the responsibility of the Investigator. The Investigator will provide them with a copy of the Clinical Trial Protocol and all necessary information.

13.2 Responsibilities of the sponsor

- The Sponsor of this Clinical Trial is responsible to Health Authorities for taking all reasonable steps to ensure the proper conduct of the Clinical Trial Protocol as regards ethics, Clinical Trial Protocol compliance, and integrity and validity of the data recorded on the CRFs. Thus, the main duty of the Monitoring Team is to

help the Investigator and the Sponsor maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the Clinical Trial.

- At regular intervals during the Clinical Trial, the site will be contacted, through monitoring visits, letters or telephone calls, by a representative of the Monitoring Team to review study progress, Investigator and patient compliance with Clinical Trial Protocol requirements and any emergent problems. These monitoring visits, will include but not be limited to review of the following aspects: patient informed consent, patient recruitment and follow-up, SAE documentation and reporting, AEs with pre-specified monitoring documentation and reporting, AE documentation, IP allocation, patient compliance with the IP regimen, IP accountability, concomitant therapy use and quality of data.

13.3 Source of document requirements

- According to the ICH guidelines for Good Clinical Practice, the Monitoring Team must check the CRF entries against the source documents, except for the pre-identified source data directly recorded in the CRF. The Informed Consent Form will include a statement by which the patient allows the Sponsor's duly authorized personnel, the Ethics Committee (IRB/IEC), and the regulatory authorities to have direct access to original medical records which support the data on the CRFs (e.g., patient's medical file, appointment books, original laboratory records, etc.). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

13.4 Use and completion of case report forms (CRFs) and additional request

- It is the responsibility of the Investigator to maintain adequate and accurate CRFs (according to the technology used) designed by the Sponsor to record (according to Sponsor instructions) all observations and other data pertinent to the clinical investigation in a timely manner. All CRFs should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of data.
- Should a correction be made, the corrected information will be entered in the e-CRF overwriting the initial information. An audit trail allows identifying the modification.
- Data are available within the system to the sponsor as soon as they are entered in the e-CRF.
- The computerized handling of the data by the Sponsor when available in the e-CRF may generate additional requests (DRF) to which the Investigator is obliged to respond by confirming or modifying the data questioned. The requests with their responses will be managed through the e-CRF.

13.5 Use of computerized systems

- Procedures shall be employed and controls designed to ensure the confidentiality of electronic records. Such procedures and controls shall include validation of systems to ensure accuracy and reliability, ability to generate accurate and complete copies of records, protection of records to enable retrieval, use of secure, computer-generated, time-stamped entries, use of operational system checks, use of device checks to determine validity of source data input, determination that person who develop, maintain, or use such systems have adequate education and training, the establishment and adherence of written policies to deter record falsification, the use of appropriate controls over systems documentation including the distribution of or use of documentation for system operation and maintenance, and revision and change control procedures which

document time-sequenced development and modifications of systems documentation

14. ADMINISTRATIVE RULES

14.1 Curriculum vitae

- A current copy of the curriculum vitae describing the experience, qualification and training of each Investigator and Sub-Investigator will be signed, dated and provided to the Sponsor prior to the beginning of the Clinical Trial

14.2 Record retention in study site (s)

- The Investigator must maintain confidential all study documentation, and take measures to prevent accidental or premature destruction of these documents.
- The Investigator should retain the study documents at least fifteen (15) years after the completion or discontinuation of the Clinical Trial.
- However, applicable regulatory requirements should be taken into account in the event that a longer period is required.
- The Investigator must notify the Sponsor prior to destroying any study essential documents following the Clinical Trial completion or discontinuation.
- If the Investigator's personal situation is such that archiving can no longer be ensured by him/her, the Investigator shall inform the Sponsor and the relevant records shall be transferred to a mutually agreed upon designee.

15. CONFIDENTIALITY

- All information disclosed or provided by the Sponsor (or any company/institution acting on their behalf), or produced during the Clinical Trial, including, but not limited to, the Clinical Trial Protocol, the CRFs, the Investigator's Brochure and the results obtained during the course of the Clinical Trial, is confidential, prior to the publication of results. The Investigator and any person under his/her authority agree to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor.
- However, the submission of this Clinical Trial Protocol and other necessary documentation to the Ethics Committee (IRB/IEC) is expressly permitted, the IRB/IEC members having the same obligation of confidentiality.
- The Sub-Investigators shall be bound by the same obligation as the Investigator. The Investigator shall inform the Sub-Investigators of the confidential nature of the Clinical Trial.
- The Investigator and the Sub-Investigators shall use the information solely for the purposes of the Clinical Trial, to the exclusion of any use for their own or for a third party's account.
- Furthermore, the Investigator and the Sponsor agree to adhere to the principles of personal data confidentiality in relation to the patients, Investigator and its collaborators involved in the study.

16. DATA PROTECTION

- The patient's personal data, which are included in the Sponsor database shall be treated in compliance with all applicable laws and regulations;
- When archiving or processing personal data pertaining to the Investigator and/or to the patients, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.
- The Sponsor also collects specific data regarding Investigator as well as personal data from any person involved in the study which may be included in the Sponsor's databases, shall be treated by both the Sponsor and the Investigator in compliance with all applicable laws and regulations.

17. INSURANCE COMPENSATION

- The Sponsor certifies that it has taken out a liability insurance policy covering all clinical trials under its sponsorship. This insurance policy is in accordance with local laws and requirements.
- The insurance of the Sponsor does not relieve the Investigator and the collaborators from maintaining their own liability insurance policy. An insurance certificate will be provided to the Ethics committees/IRB or Health Authorities in countries requiring this document.

18. AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

- The investigators should understand that source documents for this trial should be made available to authorized trial-monitors or health authority inspectors after appropriate notification. The verification of the Case Report Form data must be made by direct inspection of source documents.

19. PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE OUT OF A SITE

- The study could be interrupted or terminated by the sponsor in agreement with the coordinator and with the competent authority for the following reason:
    - frequency and/or unexpected severity of the toxicity,
    - recruitment of patients too low,
    - poor quality of the data collected.

20. CLINICAL TRIAL RESULTS

- The Sponsor will be responsible for preparing a Clinical Study Report and to provide a summary of study results to the Investigator.

21. PUBLICATION AND COMMUNICATIONS

- The investigator promises, on his/her behalf as well as that of all the persons involved in the conduct of the trial, to guarantee the confidentiality of all the information provided by the Sponsor until the publication of the results of the trial.

- All publications, abstracts or presentations including the results of the trial require prior approval of the Sponsor.
- The manufacturer of cabazitaxel has the right to read manuscripts before they are submitted for publication
- All oral presentations, manuscripts must include a rubric mentioning the Sponsor, the investigators / institutions that participated in the trial, the cooperative groups, learned societies which contributed to the conduct of the trial and the bodies which funded the research.
- The study will be published in clinicaltrial.gov

22. CLINICAL TRIAL PROTOCOL AMENDMENTS

- All appendices attached hereto and referred to herein are made part of this Clinical Trial Protocol.
- The Investigator should not implement any deviation from, or changes of the Clinical Trial Protocol without agreement by the Sponsor and prior review and documented approval/favourable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to Clinical Trial Patients, or when the change(s) involves only logistical or administrative aspects of the trial. Any change agreed upon will be recorded in writing, the written amendment will be signed by the Investigator and by the Sponsor and the signed amendment will be filed with this Clinical Trial Protocol.
- Any amendment to the Clinical Trial Protocol requires written approval/favorable opinion by the Ethics Committee (IRB/IEC) prior to its implementation, unless there are overriding safety reasons.
- In some instances, an amendment may require a change to the Informed Consent Form. The Investigator must receive an IRB/IEC approval/favorable opinion concerning the revised Informed Consent Form prior to implementation of the change and patient signature should be recollected if necessary.

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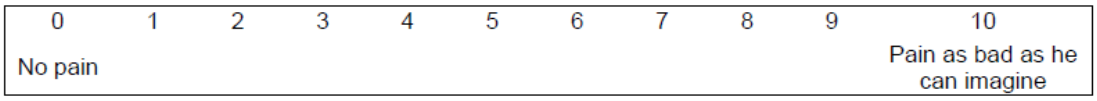
24. APPENDIX A: ECOG /PERFORMANCE STATUS(PS)

ECOG performance score/PS

0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction
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).
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% waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

25. APPENDIX B: THE PAIN NUMERICAL SCALE

Using the Pain Numerical Scale, please rate the patient's pain by indicating the number that best describes his pain on average in the last 12 hours.



26. APPENDIX C: HEALTH STATUS EVALUATION/DEPENDANCE STATUS/COMORBIDITY= G8

	Items	Score for possible responses
A	Has food intake declined over the past 3 months owing to loss of appetite, digestive problems, difficulties with chewing or swallowing?	0=severe decrease in food intake 1=moderate decrease in food intake 2=no decrease in food intake
B	Weight loss during the past 3 months	0=weight loss of more than 3 kg 1=does not know 2=weight loss between 1 kg and 3 kg 3=no weight loss
C	Mobility	0=bed or chair bound 1=able to get out of bed or chair but does not go out 2=goes out
E	Neuropsychological problems	0=severe dementia or depression 1=mild dementia 2=no psychological problems
F	Body-mass index	0=<19·0 kg/m² 1=19·0–20·9 kg/m² 2=21·0–22·9 kg/m² 3=≥23·0 kg/m²
G	Does the patient take more than three prescribed drugs per day?	0=yes 1=no
H	By comparison with other people of the same age, how does the patient consider his health status?	0=not as good 0·5=does not know 1·0=as good 2·0=better
I	Age	0=>85 years 1=80–85 years 2=<80 years
Total score		0–17

Adapted from Bellera and colleagues[16] by permission of Oxford University Press.

DEPENDANCE STATUS

Instrumental activities of daily living (IADL)

Do you take your own medecine (or could you take it) without help?	❑1 Yes ❑2 No
Can you manage your own money and mail without help?	❑1 Yes ❑2 No
Can you use the telephone without help?	❑1 Yes ❑2 No
Can you get to places out of walking distance without help?	❑1 Yes ❑2 No

Activities of daily living (ADL)

Is your patient independent in main activities of daily leaving (bathing, dressing, going to the toilets, moving out of bed or chair,continence, feeding)?	❑1 Yes ❑2 No

COMORBIDITY

CUMULATIVE ILLNESS SCORE RATING- FOR GERIATRICS (CISR-G)

Rating strategy:

[0] No problem
[1] Current mild problem or past significant problem
[2] Moderate disability or morbidity / requires "first line" therapy
[3] Severe/constant significant disability / "uncontrollable" chronic problems
[4] Extremely severe/ immediate treatment required/ end organ failure/ severe impairment in fonction

	Maximum score (0 to 4)				
Heart *(ischemic heart disease, chronic heart failure, arrhythmias, valvular disease, pericardial pathology…)*	❑0	❑1	❑2	❑3	❑4
Vascular *(Hypertension, peripheral atherosclerotic disease, intracranial vascular event, aortic aneurysm…)*	❑0	❑1	❑2	❑3	❑4
Haematopoietic *(Malignancy, anaemia, leucopoenia…)*	❑0	❑1	❑2	❑3	❑4
Respiratory *(Chronic bronchitis, asthma, emphysema, pneumonia…)*	❑0	❑1	❑2	❑3	❑4
Eyes, ears, nose, throat and larynx *(Impaired vision, hearing impairment, vertigo/dizziness…)*	❑0	❑1	❑2	❑3	❑4
Upper GI (esophagus, stomach, duodenum) *(Hiatal hernia, ulcers, cancer…)*	❑0	❑1	❑2	❑3	❑4
Lower GI (intestine, hernias) *(Constipation, bleeding, cancer, diverticular disease…)*	❑0	❑1	❑2	❑3	❑4
Liver *(Gallbladder disease, hepatitis, pancreatic disease, carcinoma…)*	❑0	❑1	❑2	❑3	❑4
Renal *(Renal disease, renal failure…)*	❑0	❑1	❑2	❑3	❑4
Genitourinary (ureters, bladder, urethra, prostate, genitals) *(Urinary incontinence, urinary infections, prostate problems…)*	❑0	❑1	❑2	❑3	❑4
Musculosquelettal/integument (muscle, bone and skin) *(Skin cancers, arthritis, osteoporosis, osteomyelitis, cancer…)*	❑0	❑1	❑2	❑3	❑4
Neurological *(Headaches, transient ischemic attack, strokes, neurodegenerative disease…)*	❑0	❑1	❑2	❑3	❑4
Endocrine/metabolic and breast *(Diabetes mellitus, thyroid, obesity, breast pathology…)*	❑0	❑1	❑2	❑3	❑4
Psychiatric illness *(Dementia, depression, delirium, psychiatric illness…)*	❑0	❑1	❑2	❑3	❑4

27. APPENDIX D: FACT-P

FACT-P_ENG_Final_Ver4_19Nov07.pdf

28. APPENDIX E: STRONG INHIBITORS OR STRONG INDUCERS OF CYTOCHROME P450 3A4/5

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

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

List of moderate CYP 3A inducers

Inducers	% AUC decrease	Substrate for the observed % AUC decrease	Inducer Classification
Ritonavir and St John's wort	77.2	midazolam	Moderate
Efavirenz	76	alfentanil	Moderate
Tipranavir and ritonavir	75.6	saquinavir	Moderate
Bosentan	69	sildenafil	Moderate
Genistein**	13.7	midazolam	Moderate
Thioridazine	68.7	quetiapine	Moderate
Nafcillin	62.6	nifedipine	Moderate
Lopinavir	59.7	amprenavir	Moderate
Modafinil	57.6	triazolam	Moderate
Estravirine	56.7	sildenafil	Moderate
Lersivirine	51.4	midazolam	Moderate

** Food product

Strong CYP 2C8 inhibitor

Gemfibrozil

Strong and moderate CYP 2C8 inducers

Rifampin, flucloxacillin

List of strong CYP2D6 substrates with a narrow therapeutic index

Thioridazine, pimozide

List of moderate CYP3A substrates with a narrow therapeutic index

Alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine

List of CYP2C9 substrates with a narrow therapeutic index

Warfarin, phenytoin

List of CYP2C19 substrates with a narrow therapeutic index

S-mephenytoin

29. APPENDIX F: NATIONAL CANCER INSTITUTE - COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

National Cancer Institute - Common Terminology Criteria for Adverse Events

(NCI-CTCAE, Version 4.0)

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

http://ctep.cancer.gov/

30. APPENDIX G: RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (FROM EUROPEAN JOURNAL OF CANCER 4 5 (2 0 0 9) 2 2 8 –2 4 7)

RECIST CRITERIA v1.1: SUMMARY

1. Measurability of tumour at baseline

1.1. Definitions

At baseline, tumour lesions/lymph nodes will be categorised measurable or non-measurable as follows:

1.1.1. Measurable

Tumour lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

• 10mm by CT scan (CT scan slice thickness no greater than 5 mm; see Appendix II on imaging guidance).

• 10mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15mm 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 (see Schwartz et al. in this Special Issue[15]). See also notes below on 'Baseline documentation of target and non-target lesions' for information on lymph node measurement.

1.1.2. Non-measurable

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

1.1.3. Special considerations regarding lesion measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment: Bone lesions:.

• Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

• Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

• Blastic bone lesions are non-measurable.

Cystic lesions:.

• 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.

Lesions with prior local treatment:

• Tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

1.2. **Specifications by methods of measurements**

1.2.1. Measurement of lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

1.2.2. Method of assessment

The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than 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 and ≥10mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

: Chest CT is preferred over, particularly when progression is an important endpoint, since CT is

more sensitive than, particularly in identifying new lesions. However, lesions on may be considered measurable if they are clearly defined and surrounded by aerated lung. See Appendix II for more details.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5mm or less. As is described in Appendix II, when 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). More details concerning the use of both CT and MRI for assessment of objective tumour response evaluation are provided in Appendix II. 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 (described in greater detail in Appendix II). 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 utilisation of these techniques for objective tumour evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumour markers: Tumour markers alone cannot be used to assess objective tumour response. If markers are initially above the upper normal limit, however, they must normalise for a patient to be considered in complete response. Because tumour markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer), have been published.[16–18] In addition, the Gynaecologic Cancer Intergroup has developed CA125 progression criteria which are to be integrated with objective tumour assessment for use in first-line trials in ovarian cancer.

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumour types such as germ cell tumours, where known residual benign tumours can remain).When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumour has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

2. **Tumour response evaluation**

2.1. **Assessment of overall tumour burden and measurable disease**

To assess objective response or future progression, it is necessary to estimate the overall tumour burden at baseline and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included in protocols where objective tumour response is the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion (as detailed above in Section 3). In studies where the primary endpoint is tumour progression (either time to progression or proportion with progression at a fixed date), the protocol must specify if entry is restricted to those with measurable disease or whether patients having non-measurable disease only are also eligible.

2.2. **Baseline documentation of 'target' and 'non-target'lesions**

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and

measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded). For evidence to support the selection of only five target lesions, see analyses on a large prospective database in the article by Bogaerts et al.[10].

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. To illustrate this point see the example in Fig. 3 of Appendix II.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumour. As noted in Section 3, pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of P15mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumour. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20mm· 30mm has a short axis of 20mm and qualifies as a malignant, measurable node. In this example, 20mm should be recorded as the node measurement (See also the example in Fig. 4 in Appendix II). All other pathological nodes (those with short axis P10mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10mm are considered non-pathological and should not be recorded or followed.

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 as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterise any objective tumour regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

2.3. **Response criteria**

This section provides the definitions of the criteria used to determine objective tumour response for target lesions.

2.3.1. 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 diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of 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 progression).

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.

2.3.3. Evaluation of non-target lesions

This section provides the definitions of the criteria used to determine the tumour response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol. Complete Response (CR): Disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological in size (<10mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

2.3.4. Special notes on assessment of progression of non-target disease

The concept of progression of non-target disease requires additional explanation as follows:

When the patient also has measurable disease. In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy (see examples in Appendix II and further details below). A modest 'increase' in the size of one or more non-target lesions is usually not

sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare. When the patient has only non-measurable disease. This circumstance arises in some phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PDf or measurable disease: i.e.an increase in tumour burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localised to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. Some illustrative examples are shown in Figs. 5 and 6 in Appendix II. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

2.3.5. New lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline. If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan. 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.

2.4. **Evaluation of best overall response**

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomised trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the 'best overall response'. This is described further below.

2.4.1. Time point response

It is assumed that at each protocol specified time point, a response assessment occurs. Table 1 on the next page provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

2.4.2. Missing assessments and invaluable designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

2.4.3. Best overall response: all time points

The best overall response is determined once all the data for the patient is known.

Best response determination in trials where confirmation of complete or partial response IS NOT required: Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered invaluable.

Best response determination in trials where confirmation of complete or partial response IS required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later). In this circumstance, the best overall response can be interpreted as in Table 3.

Table 1 – Time point response: patients with target (+/– non-target) disease.

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

Table 2 – Time point response: patients with non-target disease only.

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease, and NE = inevaluable.

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

Table 3 – Best overall response when confirmation of CR and PR required.

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.
a If a CR is *truly* met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Table 3 – Best overall response when confirmation of CR and PR required.

31. APPENDIX H : CRITERIA FOR PROGRESSION PCWG2

(FROM JOURNAL OF CLINICAL ONCOLOGY 10.1200/JCO.2007.12.4487)

Table 5. Suggested Outcome Measures for Phase II Clinical Trials in Prostate Cancer

Variable	PCWG1 (1999)[1]	PCWG2 (2007)
PSA	Monitor PSA ≥ 1/month	Recognize that a favorable effect on PSA may be delayed for 12 weeks or more, even for a cytotoxic drug
		Monitor PSA by cycle but plan to continue through early rises for a minimum of 12 weeks unless other evidence of progression
		Ignore early rises (prior to 12 weeks) in determining PSA response
	PSA response:	**For control/relieve/eliminate end points:**
	Defined a PSA partial response as a > 50% decline from baseline (measured twice 3 to 4 weeks apart)	Record the percent change from baseline (rise or fall) at 12 weeks, and separately, the maximal change (rise or fall) at any time using a waterfall plot[32]*
	Progression:	**Progression:**
	After decline from baseline: progression = 50% increase from nadir and an increase of at least 5 ng/mL, or back to baseline, whichever was lowest	**Decline from baseline**: record time from start of therapy to first PSA increase that is ≥ 25% and ≥ 2 ng/mL above the nadir, and which is confirmed by a second value 3 or more weeks later (ie, a confirmed rising trend)†
		The requirement of an increase of 5 ng/mL is decreased to 2 ng/mL, and the requirement for a 50% increase is reduced to 25%
	Record duration of PSA decline	Recording the duration of PSA decline of little value
		No decline from baseline:
		PSA progression ≥ 25% and ≥ 2 ng/mL after 12 weeks
Soft-tissue lesions	Change in size of lymph nodes or parenchymal masses on physical exam or x-ray	**For control/relieve/eliminate end points:**
		Use RECIST with caveats
		Only report changes in lymph nodes that were ≥ 2 cm in diameter at baseline
		Record changes in nodal and visceral soft tissue sites separately
		Record complete elimination of disease at any site separately
		Confirm favorable change with second scan
		Record changes using waterfall plot
		For delay/prevent end points:
		Use RECIST criteria for progression, with additional requirement that progression at first assessment be confirmed by a second scan 6 or more weeks later‡
		Note that for some treatments, a lesion may increase in size before it decreases
Bone	No definition for response provided	**For control/relieve eliminate end points:**
		Record outcome as new lesions or no new lesions
		First scheduled reassessment:
		No new lesions: continue therapy
		New lesions: perform a confirmatory scan 6 or more weeks later
		Confirmatory scan:
		No new lesions: continue therapy
		Additional new lesions: progression
		Subsequent scheduled reassessments:
		No new lesions: continue
		New lesions: progression
	Progression:	**For prevent/delay end points (progression):**
	> 1 new lesion	The appearance of ≥ 2 new lesions, and, for the first reassessment only, a confirmatory scan performed 6 or more weeks later that shows a minimum of 2 or more additional new lesions§
	Worsening scan = progressive disease, regardless of PSA	The date of progression is the date of the first scan that shows the change
Symptoms	Not addressed	Consider independently of other outcome measures
		Document pain and analgesia at entry with a lead in period and measure repeatedly at 3- to 4-week intervals
		Perform serial assessments of global changes in HRQOL, urinary or bowel compromise, pain management, additional anticancer therapy
		Ignore early changes (≤ 12 weeks) in pain or HRQOL in absence of compelling evidence of disease progression
		Confirm response or progression of pain or HRQOL end points ≥ 3 weeks later

Abbreviations: PCWG1, Prostate-Specific Antigen Working Group 1; PCWG2, Prostate Cancer Clinical Trials Working Group 2; PSA, prostate-specific antigen; HRQOL, health-related quality of life.
*See Figure 3.
†See Figure 4.
‡Particularly important when anticipated effect on PSA is delayed or for biologic therapies.
§See Figure 5.

Randomized multicenter, phase III trial evaluating the safety of 2 schedules of cabazitaxel (bi-weekly *versus* tri-weekly) plus prednisone in elderly men (≥ 65 years) with metastatic castration-resistant prostate cancer (mCRPC) previously treated with a docetaxel-containing regimen

Abbreviated Title of Protocol: CABASTY

EudraCT N° 2016-001179-60

Version 7 – 17-SEPT-2021

STATISTICAL ANALYIS PLAN

Product:	CABAZITAXEL
Study No:	1688
Author:	Euraxipharma
Date:	November 30th, 2021
Version:	Final 1.0

Version History

Version	Description
Draft 0.1	Initial version
Draft 0.2	Consideration of Sanofi's comments and corrections
Draft 0.3	Consideration of Sanofi's comments and corrections
Final 1.0	Consideration of Sanofi's comments and corrections

SIGNATURE PAGE

Statistical Analysis Plan

<table>
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 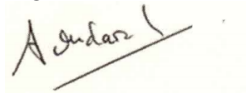 </td></tr>
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 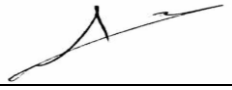 </td></tr>
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Table of contents

List of Abbreviations

ADL	Activities of daily living
ADT	Androgen deprivation therapy
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BOR	Best overall response
BMI	Body Mass Index
CI	Confidence Interval
CISR-G	Cumulative Illness Score Rating-Geriatrics
CS	Clinically Significant
DBP	Diastolic blood pressure
DI	Dose intensity
ECOG	Eastern Cooperative Oncology Group
EWB	Emotional well-being
FACT-P	Functional Assessment of Cancer Therapy-Prostate
FU	Follow-up
FWB	Functional well-being
HR	Hazard Ratio
IADL	Instrumental activities of daily living
LHRH	Luteinizing Hormone Releasing Homone
mCRPC	Metastatic castration resistant prostate cancer
MedDRA	Medicinal Dictionary for Regulatory Activities
NCS	Not Clinically Significant
ORR	Objective response rate
OS	Overall survival
PCS	Prostate cancer subscale
PCWG2	Prostate Cancer Working Group 2
PFS	Progression-free survival
PSA	Prostate-specific antigen
PS	Performance status
PT	Preferred Term
PWB	Physical well-being

RDI	Relative dose intensity
RECIST	Response Evaluation Criteria In Solid Tumors
rPFS	Radiological progression-free survival (rPFS)
SAE	Serious Adverse Event
SIOG	International Society of Geriatric Oncology,
SRE	Skeletal-Related Event
SOC	System Organ Class
SWB	Social/Family well-being
TEAE	Treatment-emergent adverse event
TOI	Trial Outcome Index
VAS	Visual analog scale

1. DESCRIPTION OF THE STUDY

1.1 Study Objectives

1.1.1 Primary objective

To evaluate the incidence of grade ≥ 3 neutropenia (measured at Day 7 and Day 14) and/or neutropenic complications (febrile neutropenia, neutropenic infection) with two schedules of cabazitaxel (bi-weekly versus tri-weekly) plus prednisone in elderly men (≥ 65 years) with mCRPC previously treated with a docetaxel-containing regimen.

1.1.2 Secondary objectives

- To compare efficacy of cabazitaxel biweekly versus triweekly, plus prednisone for the following main secondary end-points:
  - Radiological progression-free survival (rPFS)
  - Overall survival (OS)
  - PSA response rate
  - Objective response rate (ORR) in measurable lesions (RECIST criteria 1.1)

- To compare efficacy of cabazitaxel biweekly versus triweekly, plus prednisone for other secondary end-point:
  - Time to PSA progression
  - Time to first symptomatic Skeletal-Related Event (SRE) and incidence of SREs
  - Time to opioid treatment (if relevant)

- To compare Health-Related Quality Of Life (HRQL) according to Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire between arms

- To evaluate factors influencing the occurrence of grade ≥ 3 neutropenia and/or neutropenic complications: age (<70 (reference) vs ≥ 70-74 vs 75+), ECOG (0-1 [ref] vs 2+), moderate or severe pain at randomization (no [ref] vs yes), number of cycles of prior docetaxel (<10 (ref) vs 10+), neutrophils/lymphocytes ratio at randomization (<median vs ≥ median [ref])

neutrophil count at randomization (<median [ref] vs ≥ median), lymphocyte count at randomization (<median [ref] vs ≥ median), LDH at randomization (<median [ref] vs ≥ median), ALK at randomization (<median [ref] vs ≥ median) geriatric assessment G8 (>14 [ref] vs ≤14), treatment schedule (biweekly versus tri-weekly [ref]),

- To evaluate factors influencing survival: age (<70 (reference) vs ≥ 70), ECOG (0-1 [ref] vs 2+), duration of response to first ADT (<12 months [ref] vs ≥ 12 months), M1 disease at diagnosis (no [ref] vs yes), Gleason at diagnosis (<8 [ref] vs 8-10), visceral metastases at randomization (no [ref] vs yes), moderate or severe pain at randomization (no [ref] vs yes) serum testosterone at randomization (< median vs ≥ median [ref]), cumulative dose of cabazitaxel (<median vs ≥ median [ref]), neutrophils/lymphocytes ratio at randomization (<median vs ≥ median [ref]) neutrophil count at randomization (<median [ref] vs ≥ median), lymphocyte count at randomization (<median [ref] vs ≥ median), LDH at randomization (<median [ref] vs ≥ median), ALK at randomization (<median [ref] vs ≥ median), PSA value log 10 (<median (ref) vs ≥ median), geriatric assessment G8 (>14 [ref] vs ≤14), grade ≥3 neutropenia during therapy (yes [ref] vs no), treatment schedule (biweekly versus tri-weekly [ref]),

- To evaluate safety in both treatment arms:
  - Adverse events, serious adverse events, and discontinuation for adverse events
  - Analysis of grade ≥3 neutropenia and/or neutropenia by cycle
  - Time to onset of grade ≥3 of neutropenia
  - Grade ≥3 neutropenia duration (from date of onset of grade ≥ 3 until grade ≤ 2)

1.2 Study Design

1.2.1 Description

Randomized, open-label, phase 3 trial comparing cabazitaxel 25 mg/m^2 on Day 1 of a 3-week cycle plus daily prednisone versus cabazitaxel 16 mg/m^2 on Day 1 and Day 15 of a 4-week cycle in mCRPC patients aged ≥ 65 years.

This study consists of three phases: screening, treatment, and follow-up.

1.2.2 Schedule of assessments and study procedures

Data were collected at the following visits:

- Screening (D-30 to D-1)
- Randomization visit (C1D1)
- every 3 weeks (arm A) or 2 weeks (arm B)
- end of study (30 days after last cycle or disease progression and death.

Hematology parameters were collected every week.

CT-Scan or MRI Whole body and Bone scan results were collected every 3 months.

Study procedures are presented in table 1 below:

Table 1- Study procedures	Screening	Randomization visit	Each subsequent visit (±2 days)	End of study 30 days after last cycle Or upon progression
Week	D-30 to D-1	C1D1[d]	Every 3 weeks (arm A) or 2 weeks (arm B)	
Data collection				
Informed consent	X			
Inclusion/exclusion criteria	X	X		
Medical/oncologic history	X			
Concomitant medications	X	X	X	X
Physical examination	X	X		X
Vital signs	X	X	X	X
ECOG/PS	X	X	X	X
G8	X			
ADL, IADL, CISRG	X			
FACT-P		X	X	X
Skeletal-Related Events		X	X	X
Pain status (VAS)	X	X	X	X
Hematology	X	X[a]	Every week	X
Biochemistry	X	X[a]	X	X
Dipstick test	X	X	X	X
Serum PSA	X	X	X	X
Serum Testosterone	X			X
CT-Scan (abdominal/pelvic/chest) or MRI Whole body [b]	X		Every 3 months (±7 days)	X
Bone scan[b]	X		Every 3 months (±7 days)	X
Cabazitaxel		X	X	
Toxicity				
Adverse events	X			
Treatment				
Cabazitaxel		X	X	
G-CSF[c]		X	X	

[a] Blood tests (hematology and biochemistry): within 3 days prior to enrolment

[b]Tumour assessment (CT-Scan (abdominal/pelvic/chest) or whole-body MRI and Bone scan):

- within 30 days prior to the date of randomization
- every 3 months (±7 days)

- within 7 days prior to End of Study or upon progression

[c]G-CSF (GRANOCYTE) to be injected from Day 3 to Day 7(5 days) after every administration of cabazitaxel.

[d] First dose to be administered within 3 days following randomization.

1 cycle tri-weekly (Arm A) = D1-D21

1 cycle bi-weekly (Arm B) = D1-D14 (equal to two administrations of cabazitaxel)

1.3 Study treatments

1.3.1 Treatments arms, dosage, and schedule

- Arm A: cabazitaxel 25 mg/m² intravenously over 1 hour on Day 1of a 3-week cycle, plus prednisone (or prednisolone) 10 mg orally given daily for a maximum of 10 cycles (i.e., 30 weeks of treatment)
- Arm B: cabazitaxel 16 mg/m2 on Day 1 and Day 15 of a 4-week cycle plus prednisone (or prednisolone) 10 mg per day, up to 10 cycles (i.e., 40 weeks of treatment)
- Treatment should be continued for a maximum of 10 cycles in each arm unless there is confirmed disease progression or unacceptable treatment toxicity.
- Prophylactic G-CSF (GRANOCYTE) will be injected from Day 3 to Day 7 (5 days) after every administration of cabazitaxel.
- Treatment with LHRH should not be discontinued.
- Dose can be reduced for cabazitaxel when necessary, in case of hematological toxicity (neutropenia, grade ≥ 3, febrile neutropenia or neutropenic infection, grade ≥ 3 thrombocytopenia).
    - The dose, which has been reduced for toxicity, must not be re-escalated.
    - Only one dose reductions will be allowed per patient. If a second dose reduction is required per the modifications below, the patient should discontinue study treatment.
- Treatment with cabazitaxel may be delayed no more than 2 weeks to allow recovery from acute toxicity (neutropenia, grade ≥ 2, febrile neutropenia and/or neutropenic infection, grade ≥ 2 thrombocytopenia). In case of treatment delay greater than 2 weeks, patient should discontinue cabazitaxel.

1.3.2 Treatment duration

Treatment duration in arm A will be 30 weeks and in arm B will be 40 weeks.

1.4 Randomization

The randomization will occur after control of the whole inclusion and exclusion criteria.

The following information will be required:

- Name of the center and principal investigator,
- Date of screening
- Patient's initial, age and file number,
- G8 score,

The randomization will be stratified by G8 score (< 14 vs. ≥ 14) and age (< 70 vs. ≥ 70). An adaptive randomization will be used to insure timely balance of stratification factors within strata.

The site will be informed of the allocated treatment arm for the patient to be included:

- Arm A: cabazitaxel 25 mg/m² on Day 1 of a 3-week cycle plus daily prednisone
  or
- Arm B: cabazitaxel 16 mg/m² on Day 1 and Day 15 of a 4-week cycle plus daily prednisone.

First dose to be administered within 3 days following randomization.

1.5 Sample size determination

- The primary endpoint of this phase 3 trial is the incidence of grade ≥3 neutropenia and/or neutropenic complications, measured at D7 and D14.
- Of 131 patients treated with cabazitaxel every 3 weeks at HEGP, 40% developed grade ≥3 neutropenia. In the 2 pilot studies conducted with cabazitaxel 16 mg/m^2 bi-weekly, the range of grade ≥3 neutropenia was 15% in the Finnish cohort and 16.5% in HEGP cohort.
- A sample size of 77 to 90 evaluable patients per arm will achieve 80% power to detect a 20% difference in G3 neutropenia incidence between the two arms. The incidence of grade ≥3 neutropenia with cabazitaxel 25 mg/m^2 given every 3 weeks is assumed to be 32% versus 12% with cabazitaxel given bi-

weekly. The test used is a two-sided Fisher's exact test at 0.05 significance level. Assuming 10% non-evaluable patients, approximately 85 to 100 patients should be included in each arm for a total of 170 to 200.

2. ANALYSIS POPULATIONS

The screened population includes all patients with a date of screening visit who signed an informed consent form.

Patients treated without being randomized will not be considered randomized and will not be included in any efficacy population.

The randomized population includes any patient who has been allocated to a randomized treatment regardless of whether the treatment kit was used.

2.1 Intent-to-treat population

All randomized patients will be included in the Intent-to-treat (ITT) population.

The primary efficacy analysis population will be the ITT population.

2.2 Safety population

All randomized patients having received at least one study treatment dose will be included in the Safety population.

2.3 Other populations

- Tumor response will be evaluated in the ITT patients with RECIST evaluation and with at least one post baseline assessment.
- PSA response will be evaluated in the ITT patients with a PSA level at baseline, with at least one post-baseline assessment
- Pain status will be evaluated in patients with a pain evaluation at baseline and at least one post-baseline assessment. The quality-of-life population based on the ITT population, taking into account patients who have at least one evaluable subscale of FACT-P questionnaire at baseline and at least one post baseline evaluable FACT-P.

3. CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

3.1 PROTOCOL AMENDMENTS

Document	Date of issue	Summary of changes

Original protocol version 01	29/07/2016	Not applicable
Amendment n°1 (local)	25/10/2017	New sites added
Amendment n°2 (local)	19/03/2018	Change of Principal Investigator at site 250-018
Amendment n°3 Revised protocol version 02	16/07/2018	• Extension of recruitment period • Recruitment to patients aged ≥65 years (instead of ≥70 years) with stratification by age (<70 and ≥70) at randomization • Progressive disease at enrollment according to PCWG3 (instead of investigator judgment) • G-CSF administration homogenized (G-CSF to be given from Day 3 to Day 7 (5 days) in all patients • Window for visit dates added • Addition of new sites
Amendment n°4 Revised protocol version 03	25/01/2019	• Exploratory substudy added (in selected sites) to evaluate the relationship between myeloid derived suppressor cells and NLR decline, neutropenia and cabazitaxel treatment schedule. • Management of hypersensitivity updated per updated Jevtana investigator brochure (version 16) • New sites added
Amendment n°5 Revised protocol version 04	23/08/2019	Additional information regarding primary and secondary objectives of the sub-study (in selected sites) has been added.
Amendment n°6 Revised protocol version 05	13/11/2019	Extension of the study timelines
Amendment n°7 Revised protocol version 06	02/07/2020	Extension of recruitment period
Amendment n°8 Revised protocol version 07	29/09/2021	Patient status (alive or dead) at last follow-up to be collected for all patients

3.2 CHANGES IN THE STATISTICAL ANALYSIS PLAN

Rationale	Description of statistical changes	Date
Patients ≥ 65 years allowed to be included to speed up recruitment	Stratification factor added: age < 70 vs ≥ 70; no change for G8 stratification (< 14 vs. ≥ 14)	23/11/2021
3.3.6.2 Other analyses of primary endpoint The comparison method of the incidence of grade 3-4 neutropenia between the 2 arms has been modified compared to the protocol because ANCOVA is not suitable for this type of criterion (binary)	*3.3.6.2 Other analyses of primary endpoint* ANCOVA has been removed and replaced by a logistic regression.	23/11/2021
3.3.8.3 PSA response and time to PSA progression No analysis was planned to compare percentages of responders between the treatmnent arms	*3.3.8.3 PSA response and time to PSA progression* Comparison will be added using Chi² test or Fisher exact test.	23/11/2021
3.3.8.5 Quality of life (FACT-P) No analysis is specified in the protocol	*3.3.8.5 Quality of life (FACT-P)* Some analyses have been added: Comparison of change from baseline on HRQL scores between treatments arms using mixed linear repeated measures model. 4 main FACT-P responder analyses: - FACT-P total score responders - PWB, SWB, EWB and FWB subscale scores responders - Pain PCS summary score responders - FACT-G total and FACT-P TOI responders Analysis of time to definitive deterioration using a Cox proportional hazard model adjusted to the stratification factors.	23/11/2021
3.3.8.6 Objective response rate (ORR) in measurable lesions (RECIST criteria 1.1) This criterion appeared only in the synopsis of the protocol but not in §8.2 Secondary criteria. No analysis was planned to compare percentages of responders between the treatmnent arms.	*3.3.8.6 Objective response rate (ORR) in measurable lesions (RECIST criteria 1.1)* Comparison will be added using Chi² test or Fisher exact test.	23/11/2021
3.3.8.8 To evaluate factors influencing the occurrence of grade ≥ 3 neutropenia and/or neutropenic complications This analysis was not planned in the protocol.	*3.3.8.8 To evaluate factors influencing the occurrence of grade ≥ 3 neutropenia and/or neutropenic complications* This analysis has been added in the SAP.	23/11/2021
3.3.9.2 Adverse events No subgroups analyses were planned.	*3.3.9.2 Adverse events* Analyses according to the age at	23/11/2021

	inclusion (<70, [70-74[, ≥ 75) and G8 score (<14 and ≥ 14) have been added.	
3.3.9.4 Extent of exposure For Arm B, unit of dose intensity was incorrect (mg/m²/3 weeks)	*3.3.9.4 Extent of exposure* Unit of dose intensity has been added according to the treatment arm.	23/11/2021

3.3 STATISTICAL ANALYSES

3.3.1 Generalities

Statistical analyses will be performed by Euraxipharma. Analyses will be conducted with SAS® software, version 9.4 (SAS Institute, North Caroline, USA).

All statistical tests will be two-sided and type I error (alpha) set to 5%.

Quantitative variables will be summarized in summary tables indicating, for each treatment group and for the overall population, the number of non missing observations (n), the mean and standard deviation, the median, the minimum and maximum.

Qualitative variables will be summarized in summary tables indicating, for each treatment group and for the overall population, the number of non missing observations (n), frequency and percentage of each modality.

For all parameters, the number of missing values will also be reported in the tables, but they will not be counted for the percentage calculation (qualitative data).

Time-to-event endpoints will be summarized in terms of probability of occurrence and confidence interval using the Kaplan-Meier method and estimated survival curves will be displayed graphically when appropriate.

Unless otherwise specified, quantitative parameters will be compared between groups using the following methods. First, the normality assumption of parameter distribution will be checked graphically, and using Skewness and Kurtosis, and Shapiro-Wilk's statistic as well. If the normality assumption of parameter distribution can be accepted, then treatment groups will be compared using Student's t test. Otherwise, Wilcoxon ranks sum test will be used.

For non-ordered qualitative variables, treatment groups will be compared using Chi-square test (or Fisher's exact test in case of expected frequencies of less than 5).

For ordered qualitative variables, treatment groups will be compared using Cochran-Mantel-Haenszel test, with modified ridit scores 'row mean score differ' option.
For counting qualitative variables, treatment groups will be compared using Cochran-Mantel-Haenszel test, with tables scores 'row mean score differ' option.

3.3.2 Interim analyses

There will be no interim analysis.

3.3.3 Handling of Missing Data and derived variables

Missing data handling

For time calculations, if the day is missing for one or both dates among treatment start date and event or censoring date, the following rules will be applied: if the day of the treatment start date is missing, it will be replaced by the first day of the month, if the day of the date of death is missing it will be replaced by the day of the date of last contact or the first day of the month. If the month (or the date) is missing, the date of death will be replaced by the date of last contact. If the day of the date of another event is missing, it will be replaced by the first day of the month. For an AE, if the start date is completely missing, it will be estimated by the first administration date.
For calculation of treatment duration, if the day of the treatment start date is missing, it will be replaced by the first day of the month. If the day of the treatment stop date, it will be replaced by the last day of the month. If the month of one of the 2 dates is missing, the date will be considered as missing. If one or both dates are completely missing, the treatment duration will be considered as missing.

<u>FACT-P</u>

The FACT-P is summed to give a FACT-P total score in the range of 0-156, where higher values represent better HRQL (Functional Assessment of Chronic Illness Therapy (FACIT.org). Questionnaires, Cancer Specific Measures, Scoring and Interpretation Materials, FACIT Administration and Scoring Guidelines, Scoring the FACT-G. [Online]. 2015 [cited 2015 Nov 24]; [1-3]. Available from: URL: http://www.facit.org/FACITOrg/Questionnaires.

To achieve this, the FACT-P scoring guide identifies those items which must be reversed before being added to obtain subscale totals. Negatively stated items are reversed by subtracting the response from "4" (i.e., 4 - item score). After reversing proper items, all subscale items are summed to a total, which is the subscale score (see ref in yellow)

Handling of missing data for FACT-P

If there are missing items, subscale scores can be prorated. This is done by multiplying the sum of the subscale by the number of items in the subscale, then dividing by the number of items actually answered. When there are missing data, prorating by subscale is acceptable as long as more than 50% of the items in a domain were answered (e.g., a minimum of 4 of 7 items, 4 of 6 items, 7 of 12 items, etc.) (see ref in yellow).

This can be done by using the formula below:
Prorated subscale score = [Sum of item scores] x [N of items in subscale] ÷ [N of items answered]

Derived variables

1. Baseline for laboratory results (including PSA), vital signs and physical examination will be defined as value at randomization or at screening if missing.

2. Age (years) = Integer(screening visit date – birth date) / 365.25,

   Note: The day of the birth date will be replaced by the 1st of the month for calculation.

3. Time since the initial diagnosis (years) = (randomization date – diagnosis date) / 365.25 (rounded to 1 decimal),

   Note: if day and month of diagnosis date are missing, only year of diagnosis date and year of randomization will be used for calculation and if only the day of the diagnosis date is missing, it will be replaced by the 15 of the month.

4. Time since metastatic disease (years) = (randomization date – metastatic disease date) / 365.25 (rounded to 1 decimal),

<u>Note</u>: if day and month of metastatic disease date are missing, only year of diagnosis date and year of randomization will be used for calculation and if only the day of the metastatic disease is missing, it will be replaced by the 15 of the month.

5. BMI (kg/m²) = weight (kg) / (height (cm) / 100) ² (rounded to 1 decimal),

6. BSA (m²) $= \sqrt{\frac{Weight\ (kg)\ x\ Heigth\ (cm)}{3600}}$

7. G8 Score = Sum of the 8 items of G8score – Questionnaire,

8. Quality of life: FACT-P

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9. IADL Score = Sum of the 4 items of IADL – Questionnaire,

10. CISR-G Score = Sum of the 14 items of CISR-G – Questionnaire,

11. Duration of study (months) = ((date of end of study or date of discontinuation - screening visit date) + 1) / (365.25/12),

12. Treatment duration (weeks) =
    Arm A: (last treatment administration – first treatment administration + 21) / 7,
    Arm B: (last treatment administration – first administration + 14) / 7.

13. Actual dose received (mg/m²) by cycle = Actual dose (mg) collected / BSA (m²),

14. Cumuative dose (mg/m²) = Sum of all actual doses received,

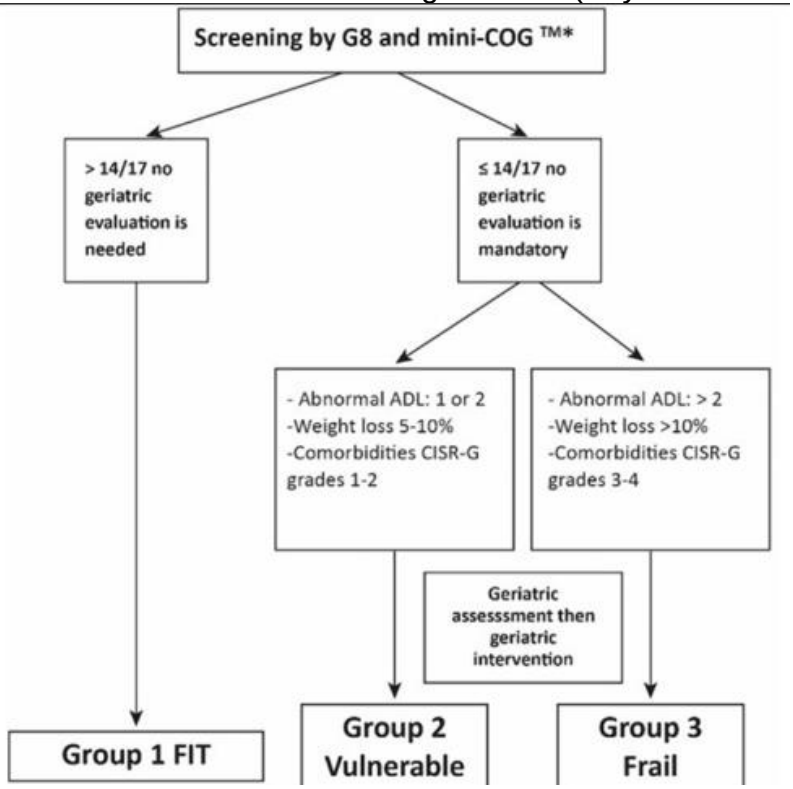
15. Dose intensity (DI) =
    Arm A (mg/m²/3 weeks): (Cumulative dose (mg/m²) / Treatment duration (weeks)) * 3,
    Arm B (mg/m²/4 weeks): (Cumulative dose (mg/m²) / Treatment duration (weeks)) * 4.

16. Relative dose intensity (RDI) (%) = DI / (planned dose intensity),
    - Where, planned dose intensity =

      Arm A (mg/m²/3 weeks): Theorical dose of 25 mg/m² x number of cycles x 3 / treatment duration,

      Arm B (mg/m²/4 weeks): Theorical dose of 16 mg/m² x 2 x number of cycles x 4 / treatment duration,

17. Time to onset of AE (days) = AE start date - first treatment administration date date,
18. Duration of AE (days) = (AE resolution date – AE start date) + 1,
19. Duration of first ADT (months) = ((End date - start date) + 1) / (365.25/12),
20. CISR-G: classification according to SIOG (Boyle E et al. Eur J Cancer 2019):



19. Number of cycles of docetaxel = (End date of docetaxel – start date of docetaxel) / 3 + 1,

For survival analyses, times were calculated and expressed in months, e.g.

Time to death (month) = (date of death – randomization date + 1) / (365.25/12)

3.3.4 Multiple comparisons and multiplicity

No multiplicity adjustment will be conducted.

3.3.5 Description of the study population

3.3.5.1 Patient Disposition

Screened patients are defined as patients with a date of screening visit and a signed informed consent.

Randomized patients include any patient who has been allocated to a randomized treatment regardless of whether the treatment kit was used.

Patients' disposition will be described for each treatment arm and for the overall population.

The number and percentage of patients in each one of the following categories will be presented in the clinical study report using a summary table:

- Screened patients
- Patients treated but nonrandomized (if pertinent)
- Patients randomized but not treated (if pertinent)
- Patients randomized and treated
- Randomized patients by stratification factors distribution (stratification factors to be specified)
- Patients still on treatment (i.e., patients who did not discontinue study treatment)
- Patients who discontinued study treatment by main reason for permanent treatment discontinuation (adverse event, poor compliance to protocol, disease progression, lost of follow-up, investigator decision, patient's request, other reason. [will be specified in a separate listing])

The number of patients screened but not randomized will be specified and reasons for non-inclusion will be described.

Number of screened patients, randomized patients, treated patients and patients who discontinued study treatment will be displayed by country and by site.

Following data will be described on ITT:

- The number of patients per centre,
- The number of patients at each cycle,

- The number of patients who completed the study,
- The number of patients who were prematurely withdrawn from the study, the main reasons for withdrawal and the time to study discontinuation,
- Duration of study (months).

3.3.6 Demographics and Other Baseline Characteristics

Summary statistics of demographic and other baseline characteristics will be given by randomization arm and on overall ITT population.

The following variables will be presented:

- Demographic data: age (years) in continuous and in classes (< 70 years / ≥ 70 years), < 70, [70-75[years, ≥75 years *(screening visit)*
- Disease history, medical and oncology history: time since initial diagnosis (histology) (years), type of diagnosis (biopsy / prostectomy), time since metastatic disease (years), Gleason score at prostate cancer diagnosis (Gleason <7, 7, 8-10, missing), M1 disease at diagnosis (yes/no), prior curative therapies (None, radical prostatectomy, radiation therapy, brachytherapy, other), rising PSA at study entry, metastasis location, *(screening visit)*
- Duration of first ADT, *(screening visit)*
- Number (1 or 2 or 3 or > 3) of prior life extending therapies (will be considered as life extending therapies: docetaxel, abiraterone, enzalutamide, apalutamide, darolutamide, radium 223, Lu-PSMA) and patients with prior docetaxel, *(screening visit)*
- Number (1 or 2 or 3+) of prior novel hormonal therapies (abiraterone enzalutamide, apalutamide, darolutamide), *(screening visit)*
- Number of patients with prior radium-223, *(screening visit)*
- Analgesic use at baseline (none, non-opioid analgesic, opioid for moderate pain, opioid for severe pain),
- Comorbidities: hypertension, diabetes, ischemic cardiac disease, cardiac failure, *(screening visit)*
- Clinical assessment: ECOG performance status (PS) (0-1, 2, > 2), vital signs [Height (cm), weight (kg), BMI (kg/m²) in continuous and in classes (Underweight: BMI < 18.5 kg/m² / Normal weight : 18.5 kg/m² ≤ BMI < 25

kg/m² / Pre-obesity : 25 kg/m² ≤ BMI < 30 kg/m² / Obesity : BMI ≥ 30 kg/m²), *(screening and randomization visits)*

- Health status: G8 score in continuous and in classes (<14 / ≥ 14), *(screening visit)*
- Tumor markers (below or above median): Alkaline phosphatase, LDH, neutrophil to lymphocyte ratio (NLR), lymphocyte count, neutrophil count, anemia, serum PSA and testosterone values, *(screening and/or randomization visits)*
- Cancer pain severity using visual analog scale (VAS) at baseline: percentage of patients with no pain (VAS=0), mild pain (VAS=1-3), moderate pain (VAS= 4-6), severe pain (VAS = 7-10), *(screening and randomization visits)*
- Prior radical prostatectomy (yes or no), *(screening visit)*
- Quality of life: FACT-P (FACT-P TOI / FACT-G Total score / FACT-P Total score), *(randomization visit)*
- Dependance status:
    - Instrumental activities of daily living (IADL): percentage of patients with one abnormality in IADL, % with 2 abnormalities, % with > 2 abnormalities
    - Activities of daily living (ADL), *(screening visit):* percentage of patients with one abnormality in ADL
- Associated comorbidities: Cumulative Illness Score Rating-Geriatrics (CISR-G), *(screening visit)*:
    - % patients with CISRG grade 1 or 2 only
    - % patients with at least one CISRG grade 3
    - % patients with at least one CISRG grade 4
- Percentage of patients classified as fit, vulnerable or frail according to SIOG (Boyle E et al. Eur J Cancer 2019*), (screening visit)*
- Skeletal Related Events (Yes/No), type (pathological fracture / requirement to initiate radiotherapy / spinal cord compression / requirement for bone surgery), *(randomization visit)*

3.3.7 Primary analyses

3.3.7.1 Primary endpoint analysis

The primary endpoint analysis will be conducted primarily in the ITT population.

The primary endpoint will be the incidence of grade ≥ 3 neutropenia and/or neutropenic complications (febrile neutropenia, neutropenic infection or sepsis) over the whole chemotherapy period (for up to 10 cycles). More than 1 onset of grade ≥ 3 neutropenia for a given patient will be counted once.

The incidence of grade ≥3 neutropenia and/or neutropenic complications will be described on the whole chemotherapy period by randomization arm with 95% confidence interval associated and will be compared between the 2 arms using a Chi-square or a fisher's exact test.

3.3.7.2 Other analyses of primary endpoint

The incidence of grade ≥ 3 neutropenia and/or neutropenic complications on the whole chemotherapy period will be also compared between the 2 arms using a logistic regression with Firth-type penalized maximum likelihood with randomisation arm, neutrophil level at baseline (below or above median), SIOG health status (fit, vulnerable or frail) and stratification factors (G8 score (<14 / ≥ 14) and age (<70 years / ≥ 70 years)) as fixed factors.

Results will be presented in terms of odd ratio with 95% confidence interval associated and p-value.

3.3.8 Secondary analyses

Secondary criteria will be analyzed on ITT population.

3.3.8.1 Dose reductions and dose delays

Number and percentage of patients with at least one dose reduction will be presented by randomization arm.

Number and percentage of patients with at least one dose delays will be presented by randomization arm.

3.3.8.2 Radiological progression-free survival (rPFS)

Radiological progression-free survival (rPFS), expressed in months, will be defined as the time between randomization and the date of radiological progression or death from any cause. It will be analyzed using Kaplan-Meier method. Patients without radiological progression and still alive at the end of the study will be censored at the last valid tumor assessment date or date of last follow-up visit.

The number of patients with radiological progression or death, the number of censored patients, the median time to radiological progression months and the corresponding 95% confidence interval will be presented by treatment arm. The Kaplan-Meier survival curve will be also provided. Treatment arms will be compared with the log-rank test. Hazard ratios (HR) and 95% CIs will be provided using Cox's proportional hazards model. Cox's regression proportionality hazard assumptions will be tested.

A stratified Cox's proportional hazard model will be also used with stratification factors.

3.3.8.3 PSA response and time to PSA progression

Relative PSA change from baseline will be derived at each time from baseline. In case of PSA value of 0 ng/ml at baseline, a value of 0.1 ng/ml will be considered for calculation.

- PSA response

  Relative maximum PSA change from baseline at any time and the number and percentage of patients with a PSA decrease ≥ 30 % and ≥ 50 % from baseline will be described by randomization arm. These percentages will be compared between the two treatment arms using a Chi^2 test or Fisher exact test.

  A waterfall plot of best PSA response at any time during treatment will be provided.

- PSA Progression

  If decline from baseline, PSA progression is defined as the time from randomization to PSA increase ≥ 25% and ≥ 2 ng/mL above the nadir, confirmed by a second value.

  If no decline from baseline, Time to PSA progression is defined as the time from randomization to first PSA increase ≥ 25% and ≥ 2 ng/mL.

Time to PSA progression will be analyzed using the same method as radiological PFS.

3.3.8.4 Time to first symptomatic Skeletal-Related Event (SRE) and incidence of SREs

Time to first Skeletal-Related Event: time from randomization to the occurrence of the first skeletal-related event (radiation therapy or surgery to bone, pathologic bone fracture, spinal cord compression, or change of antineoplastic therapy to treat bone pain).

Time to SRE progression will be analyzed using the same method as radiological PFS.

3.3.8.5 Quality of life (FACT-P)

Each subscale score will be calculated:

- Physical well-being (PWB) (score range: 0-28)
- Social/family well-being (SWB) (score range: 0-28)
- Emotional well-being (EWB) (score range: 0-24)
- Functional well-being (FWB) (score range: 0-28)
- Prostate cancer subscale (PCS) (score range: 0-48)

Total scores and TOI will be also derived:

- FACT-P Trial Outcome Index (TOI) (score range: 0-104)
- FACT-G total score (score range: 0-108)
- FACT-P total score (score range: 0-156)

For all FACT-G and FACT-P subscale scores and symptom indices, the higher the score the better the HRQL.

The FACT-P total score is calculated as the sum of the un-weighted subscale scores and is evaluable when more than 80% of the items are answered (e.g., at least 22 of 27 FACT-G items completed, at least 21 of 26 TOI items completed). This is not to be confused with individual subscale item response rates, which allows a subscale

score to be prorated for missing items if greater than 50% of items are answered. Additionally, a subscale score should be completed if the component subscales have valid scores.

Analyses by cycles will be done up to the cycle (or follow-up visit) for which at least 20% of HRQL population will be reached in each treatment group, end-of treatment summary will be provided anyway.

Descriptive summary of the FACT-P evaluable scores (each subscale score from a domain, FACT-G, TOI, Pain PCS and total FACT-P scores will be calculated) for each visit and change from baseline at each visit will be provided.

The comparison of change from baseline on health-related quality-of-life scores (FACT-P total scores, subscale scores, summary measure scores: TOI and FACT-G total score and Pain PCS) between treatment arms will be performed by using MIXED linear repeated measures model where treatment is a fixed effect variable and subject is a random effect variable. The baseline stratification variables will be included in the model as covariates as well as the interaction treatment*visit. The least square means by treatment group with their 95% CIs obtained from mixed model will be presented graphically. These analyses will be conduct up to the cycle (or follow-up visit) for which at least 20% of HRQL population will be reached in each treatment group, and will include the end-of treatment visit.

The “robust” empirical estimator will be used to estimate the covariance structure for the estimator of model parameters. Compound symmetry will be the assumed covariance structure based on periods for the error terms.

The HRQL secondary analysis will include 4 main FACT-P responder analyses:

For those who improve and for those who deteriorate across 5 categories of FACT-P scales/summary scores (1. FACT-P total; 2. FACT-P subscales summary scale; 3. Pain PCS and 4. FACT-G and FACT TOI). These analyses are based on the MIDs for the FACT-P. The MIDS for each scale and summary score of the FACT-P can be found in Appendix.

The first responder analysis is for the FACT-P total score responders.

- Improvement in FACT-P total scores is defined as an increase of ≥ 10-points in FACT-P total scores from baseline on 2 consecutive evaluations ≥ 3 weeks apart during on-treatment period.
- Deterioration in FACT-P total scores is defined as a decrease of ≥10-points in FACT-P total scores from baseline on two consecutive evaluations ≥ 3 weeks apart during on-treatment period.

The 2nd responder analysis is for the physical, social, emotional, and functional well being (PWB, SWB, EWB and FWB) scales responders.

- Improvement in PWB, SWB, EWB and FWB scales is defined as an increase of ≥3 points in FACT-P PWB, SWB, EWB, FWB subscale scores from baseline on two consecutive evaluations ≥3 weeks apart.
- Deterioration in PWB, SWB, EWB and FWB scales scores is defined as a decrease of ≥ 3 points in FACT-P PWB, SWB, EWB, FWB subscales scores from baseline on 2 consecutive evaluations ≥3 weeks apart.

The 3rd responder analysis is for Pain PCS summary score responders.

- Improvement in Pain PCS summary score is defined as an increase ≥2 points from baseline in Pain PCS scores observed at two consecutive evaluations ≥3 weeks apart.
- Deterioration Pain PCS summary score is defined as a decrease of at least 2 points from baseline Pain PCS scores observed at 2 consecutive evaluations ≥3 weeks apart.

The fourth and final responder analysis is for the FACT-G Total and FACT-P TOI responders.

- Improvement in FACT-G Total and FACT-P TOI scores is defined as an increase of ≥9 points from baseline in the FACT-G Total and the FACT-P TOI summary scores observed at two consecutive evaluations ≥ 3 weeks apart.
- Deterioration in FACT-G Total and FACT-P TOI summary scores is defined as a decrease of ≥9 points from baseline in the FACT-G Total and the FACT-P

TOI summary scores observed at 2 consecutive evaluations ≥3 weeks apart.

For all four types of responders analyses the response rate during on-treatment will be descriptively summarized up to the cycle (or follow-up visit) for which at least 20% of HRQL population will be reached in each treatment group, end-of treatment summary will be provided anyway.

The time to definitive deterioration (in months), will be analyzed by using a Cox proportional hazard model adjusted for the stratification factors. HRs and corresponding 95% confidence intervals will be provided. Kaplan-Meier estimates and the log-rank test will be performed if appropriate.
Deterioration will be considered definitive if there is no subsequent improvement above the defined threshold before further anticancer therapy is administered. If a definitive deterioration is observed after a scheduled visit with a missing value, it will be assumed that the deterioration occurred at the time of the scheduled visit.

Death will be considered an event in the absence of definitive deterioration if it occurred within 30 days of the last drug administration. Otherwise, the patient will be considered lost to follow-up and censored at the date of last assessment. Patients receiving further antitumor therapy before definitive deterioration will be censored at the date of their last assessment before therapy.

3.3.8.6 Cancer pain severity using visual analog scale (VAS)

The summary statistics of pain status will be described by randomization arm at baseline, each follow-up visit and EOS visit.

3.3.8.7 Objective response rate (ORR) in measurable lesions (RECIST criteria 1.1)

ORR is defined as the proportion of ITT patients who achieve a best overall response (BOR) of complete response (CR) or partial response (PR) using RECIST 1.1 criteria.
ORR at end of study will be described and compared between randomization arms using a Chi-square or Fisher exact test.

3.3.8.8 Overall survival (OS)

OS is defined as the time from the date of randomization to the date of death from any cause. Patients still alive at the end of the study or lost to follow-up will be censored at the last date they are known to be alive (i.e., max (date last contact, date of loss to follow-up)).

OS will be analyzed using the same method as radiological PFS.

3.3.8.9 To evaluate factors influencing the occurrence of grade ≥ 3 neutropenia and/or neutropenic complications: age (<70 (reference) vs ≥ 70-74 vs 75+), ECOG (0-1 [ref] vs 2+), moderate or severe pain at randomization (no [ref] vs yes), number of cycles of prior docetaxel (<10 (ref) vs 10+), cumulative dose of cabazitaxel (<median vs ≥ median [ref]), neutrophils/lymphocytes ratio at randomization (<median vs ≥ median [ref]) neutrophil count at randomization (<median [ref] vs ≥ median), lymphocyte count at randomization (<median [ref] vs ≥ median), LDH at randomization (<median [ref] vs ≥ median), ALK at randomization (<median [ref] vs ≥ median) geriatric assessment G8 (>14 [ref] vs ≤14), treatment schedule (biweekly versus tri-weekly [ref]),

3.3.8.10 To evaluate factors influencing survival (age (<70 (reference) vs ≥ 70), ECOG (0-1 [ref] vs 2+), duration of response to first ADT(<12 months [ref] vs ≥ 12 months), M1 disease at diagnosis (no [ref] vs yes), Gleason at diagnosis (<8 [ref] vs 8-10), visceral metastases at randomization (no [ref] vs yes), moderate or severe pain at randomization (no [ref] vs yes), serum testosterone at randomization (< median vs ≥ median [ref]),, cumulative dose of cabazitaxel(<median vs ≥ median [ref]),, neutrophils/lymphocytes ratio at randomization (<median vs ≥ median [ref]) neutrophil count at randomization (<median [ref] vs ≥ median), lymphocyte count at randomization (<median [ref] vs ≥ median), LDH at randomization (<median [ref] vs ≥ median), ALK at randomization (<median [ref] vs ≥ median), PSA value log 10 (<median (ref) vs ≥ median), geriatric assessment G8 (>14 [ref] vs ≤14), grade ≥3, , grade ≥3 neutropenia during therapy (yes [ref] vs no), treatment schedule (biweekly versus tri-weekly [ref]),

Factors favoring grade 3 neutropenia and/or neutropenic infection and factors influencing survival will be performed using Cox regression model.

Each parameter will be analyzed in a univariate model where the hypothesis of proportional risks will be tested. A p-value close to 0 for this test means that the proportional hazard assumption is not respected. Significant parameters at a 15%-level will be retained for the multivariate model.

Associations between significant parameters will be tested in order to keep only non correlated variables in the multivariate model. Associations between quantitative variables will be studied using the Pearson correlation coefficient and associations between qualitative variables will be studied using Chi-Square or Fisher's exact tests. The association between a qualitative and a quantitative variable will be performed using an in-class form of the quantitative variable. Associations will be considered as statistically significant if $p<0.05$. In the case of a substantial number of parameters retained after this first step (more than 5 retained parameters), a stepwise selection method will be used to select parameters in order to build a final model without interaction (significance level for entry = 10%, significance level for removal = 5%).

Forest plots will be provided to illustrate all significant prognostic factors in final models (one for survival criteria).

3.3.8.11 Time to onset of grade ≥3 of neutropenia

Time to onset of grade ≥3 of neutropenia: time from randomization to the occurrence of the grade ≥ 3 neutropenia and/or neutropenic complications (febrile neutropenia, neutropenic infection or sepsis).

Time to onset of grade ≥3 of neutropenia will be analyzed using the same method as radiological PFS.

3.3.8.12 Grade ≥ 3 neutropenia duration (from date of onset of grade ≥ 3 until grade ≤ 2

Grade ≥ 3 neutropenia duration will be defined as the time between date of onset of grade ≥ 3 until grade ≤ 2 (weeks). This duration will be described and compared between randomization arms using a Student's t test or Wilcoxon ranks sum test.

3.3.8.13 Analysis of grade ≥ 3 neutropenia and/or neutropenia by cycle

The incidence of grade ≥3 neutropenia and/or neutropenic complications will also be described by cycle by randomization arm

3.3.9 Safety analyses

3.3.9.1 General common rules

All safety analyses will be performed on safety population using the following common rules:

- Safety data in patients who do not belong to the safety population (e.g., exposed but not randomized) will be listed separately.
- The baseline value is defined as the last value or measurement taken before the first dose in the study.
- The analysis of the safety variables will be essentially descriptive and no systematic testing is planned.
- Selected safety analyses will be summarized by age at inclusion (<70, [70 74 [or ≥75) and G8 (<14 and ≥ 14).

3.3.9.2 Adverse events

All adverse events will be graded according to the NCI CTCAE version 4.0. All adverse events occurring between first administration of study treatment and 30 days after last administration of study treatment, i.e., Treatment Emergent Adverse Events (TEAEs) will be analyzed.

Note: If the day of start date is missing and the month is after the month of the first study treatment administration date and before the last study treatment administration + 30 days, adverse event will be analyzed. Else, the event will be considered as prior.

The table of all TEAEs will present the number (n) and percentage (%) of patients experiencing an AE by SOC (sorted by internationally agreed order) and PT (sorted in alphabetical order) for each treatment group.

For a given TEAE, the worst NCI grade will be considered.

The following TEAE summaries will be generated for the safety population.

- Overview of TEAEs, summarizing number (%) of patients with any
  - TEAE
  - Grade 3-4 TEAE
  - Grade 3-4 related TEAE
  - Serious TEAE
  - Serious related TEAE
  - TEAE leading to death (fatal outcome)
  - TEAE leading to permanent treatment discontinuation

- The same overview will be provided by age at inclusion (<70, [70 74 [or ≥75) and G8 (<14 and ≥ 14)

- Analysis of all treatment emergent serious adverse event(s)
  - All serious TEAEs by primary SOC and PT, showing the number (%) of patients with at least one serious TEAE, sorted by the internationally agreed SOC order. PT level will be presented in alphabetical order.

- All serious TEAEs regardless of relationship and related to IMP, by primary SOC and PT, showing the number (%) of patients with at least one serious TEAE, sorted by the internationally agreed SOC order. The other level (PT) will be presented in alphabetical order.

- Analysis of all TEAEs leading to treatment discontinuation
  - All TEAEs leading to treatment discontinuation, by primary SOC, PT, showing the number (%) of patients sorted by the internationally agreed SOC order. The other level (PT) will be presented in alphabetical order.

- Analysis of all TEAEs leading to dose modification
  - All TEAEs leading to dose reduction, by primary SOC and PT (worst grade by patient), showing the number (%) of patients, sorted by the sorting order defined above.
  - All TEAEs leading to dose delay, by primary SOC and PT (worst grade by patient), showing the number (%) of patients, sorted by the sorting order defined above.

3.3.9.3 Deaths

The following summaries of deaths will be generated for the safety population:

- Number (%) of patients who died by study period (on-study, on-treatment, post-study) and cause of death.
- TEAEs leading to death by primary SOC and PT showing number (%) of patients sorted by internationally agreed SOC order, with PT presented in alphabetical order within each SOC.
- All TEAEs leading to death and related TEAEs leading to death will be also summarized in one table. This table will include a tabular summary of all TEAEs leading to death with a column for the related TEAEs leading to death.

In addition, a listing of AEs (including deaths) beginning before the first administration of study treatment will be displayed and a listing of AEs beginning more than 30 days after the last administration of study treatment will be displayed.

3.3.9.4 Extent of exposure

Number of cycles administered, duration of dosing (weeks), cumulative dose (mg/m²), dose intensity (DI) (mg/m²/3 weeks) or (mg/m²/4 weeks), according to the treatment arm and relative dose intensity (RDI) (%) will be summarized. Premedication and prophilaxis will be also described.

3.3.9.5 Concomitant medication

Number and percentage of patients receiving G-CSF as prophylaxis during the 3 first cycles and at all cycles will be summarized.

3.3.9.6 Laboratory tests

- Hematological and clinical biochemistry toxicities will be assessed from laboratory test parameters. Worst NCI CTCAE grades, whenever applicable will be calculated according to the NCI common terminology criteria (NCI CTCAE version 4.0).
- For AST, ALT, Bilirubin, Alkaline phosphatase, LDH and creatinine, the classification Normal / Abnormal NCS and Abnormal CS will be used.
- In addition to creatinine levels, estimations of the renal function will be made by calculating the glomerular filtration rate (GFR) using the abbreviated Modification of Diet in Renal Disease (aMDRD) formula if the creatinine at baseline is 1.0-1.5xULN:

  GFR(mL/min/1.73m2)=k x 186 x[SCR]-1.154 x [age]-0.203

  With k=1 (men) and SCR=Serum creatinine

  CrCl categories (≥90, [60 to 90[, [45 to 60[, [30 to 45[and, [15 to 30[, <15 mL/min/1.73m²) and number of patients with renal function abnormalities on Creatinine clearance will be splitted and provided for both, when creatinine ≤1 x ULN and when creatinine >1xULN

- The number of patients with abnormal laboratory tests at baseline (all grades, grade 1, grade 2, grade 3 and grade 4) will be presented by grade. The frequency of patients in each grade (all grades, grade 1, grade 2, grade 3 and grade 4) of laboratory tests during treatment will be summarized. For patients

with multiple occurrences of the same laboratory variable during the treatment, the maximum grade (worst) per patient will be used. When appropriate, the summary table will present the frequency of patients with any grade of abnormal laboratory tests and with Grade 3-4 abnormal laboratory tests.

3.3.9.7 Vital signs and ECOG/PS

For vital signs (Height, Weight, BMI, Temperature, SBP, DBP, HR, Respiratory rate) and ECOG/PS, summary statistics at baseline, each follow-up visit and EOS visit will be presented by randomization arm.

3.3.9.8 Physical examination

The summary statistics of physical examination will be described by randomization arm at baseline and at EOS visit.

Appendix

FACT-P Scoring Information and MIDs for each Scale and Summary Score

5 Scales 5 Summary Scores	# of items	Scoring range	MID
PWB	7	0-28	3
SWB	7	0-28	3
EWB	6	0-24	3
FWB	7	0-28	3
PCS	12	0-48	3
FACT-P Total	PWB + SWB + EWB + FWB + PCS	0-156	10
FACT-G Total	PWB + SWB + EWB + FWB	0-108	9
FACT-P TOI	PWB + FWB + PCS	0-104	9
PCS-Pain	4 items (P1, P2, P3, GP4)	0-16	2