NCT02485691

AMENDED CLINICAL TRIAL PROTOCOL 05

COMPOUND: Jevtana®/cabazitaxel/XRP6258

A randomized, open label, multicenter study of Cabazitaxel versus an Androgen Receptor (AR)-targeted agent (abiraterone or enzalutamide) in mCRPC patients previously treated with Docetaxel and who rapidly failed a prior AR-targeted agent (CARD)

STUDY NUMBER: LPS14201

STUDY NAME: CARD

VERSION DATE / STATUS: 01-March-2019

CLINICAL STUDY DIRECTOR: [redacted]

Version number: 1	EudraCT and/or IND number:	2014-004676-29
	UTN number:	U1111-1166-5329
Date: 01-Mar-2019	Total number of page:	119

NAMES AND ADDRESSES OF

COORDINATING INVESTIGATOR	Name: Address: Tel: Fax: E-mail:	[redacted].
MONITORING TEAM'S REPRESENTATIVE	Name: Address: Tel: Fax: E-mail:	
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DOCUMENT HISTORY

Document	Country-specificity if applicable	Date, version
Amended protocol 05	All	01-Mar-2019, version 1 (electronic 6.0)
Amended protocol 04	All	08-Nov-2018, version 1 (electronic 5.0)
Amended protocol 03	All	11-May-2018, version 1 (electronic 1.0)
Amended protocol 02	FR	31-Mar-2016, version 1 (electronic 4.0)
Amended protocol 01	All	29-Oct-2015, version 1 (electronic 3.0)
Original Protocol		14-Apr-2015, version 2 (electronic 2.0)

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amended protocol 05 (01-Mar-2019)

This amended protocol (amendment 05) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

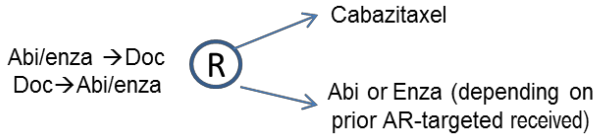
Based on approved label for both study comparators (ZYTIGA 500 mg, Xtandi 40mg) and Cabazitaxel IB edition 16 Amendment 2 which could significantly impacts the safety of female partner and/or future child of participants of the study, this amendment introduces mainly update of exclusion criteria in relation with pregnancy, lactation, and reproductive potential for IMPs, with changes in exclusion criteria E09.

Protocol amendment summary of changes table

Section # and Name	Description of change	Brief rationale
Clinical Trial Summary and section 7 of the protocol: study population, exclusion criteria E09.	Patients with reproductive potential who do not agree, in conjunction with their partner, to use accepted and effective method of contraception during the study treatment period and up to 6 months after the last administered dose. The definition of “effective method of contraception” described hereafter: oral contraceptives, combined hormonal intravaginal, transdermal, intra uterine device or condoms will be based on respective study treatment labelling and country-specific regulatory requirements, and are documented in the Informed Consent Form.	Inclusion criteria E09 has been updated and harmonized for the three arms of treatment, based on the approved label (for Abiraterone and Enzalutamide) and Cabazitaxel IB 16 Amendment 2.

CLINICAL TRIAL SUMMARY

COMPOUND: Jevtana®/cabazitaxel/XRP6258	**STUDY No: LPS14201 STUDY NAME: CARD**
TITLE	A randomized, open label, multicenter study of Cabazitaxel versus an AR-targeted agent (abiraterone or enzalutamide) in mCRPC patients previously treated with Docetaxel and who rapidly failed a prior AR-targeted agent (CARD)
INVESTIGATOR/TRIAL LOCATION	Multicenter/multinational
PHASE OF DEVELOPMENT	Phase IV
STUDY OBJECTIVE(S)	**Primary objective** • To compare the radiographic Progression-Free Survival (rPFS) [Using Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 for tumor lesions and Prostate Cancer Working Group 2 (PCWG2) criteria for bone scan lesions (1)(2)] or death due to any cause] with chemotherapy (Cabazitaxel plus prednisone) (Arm A) versus AR targeted therapy (enzalutamide or abiraterone acetate plus prednisone) (Arm B) in mCRPC patients who have been treated with docetaxel and who had disease progression while receiving AR targeted therapy within 12 months of AR treatment initiation (≤12 months)(either before or after docetaxel). **Secondary objectives** • To compare efficacy of cabazitaxel plus prednisone to enzalutamide or abiraterone acetate plus prednisone for: - PSA response rate. - Time to PSA progression (TTPP). - Progression-free survival. - Objective tumor response (RECIST1.1 criteria in patients with measurable disease). - Duration of tumor response. - Pain intensity palliation. - Time to pain progression. - Symptomatic Skeletal Events (SSEs) rate. - Time to occurrence of Symptomatic Skeletal Events (SSEs). - Overall survival (OS). • To compare Health-Related Quality Of Life (HRQOL) according to FACT-P questionnaire. • To compare Health status/utility (EQ-5D-5L). • To evaluate the correlation of a signature of resistance to AR targeted agents with clinical outcomes, via the analysis of Circulating Tumor Cells (CTCs) phenotypes as well as expression and localization of proteins including AR isoforms in CTCs. • To evaluate safety in the 2 treatment arms. **Exploratory Objectives** **Biomarkers:** • [redacted]

STUDY DESIGN	• Open-label randomized phase IV study. • All eligible Patients (after Abi or Enza →Doc. or Doc → Abi or Enza) are randomly assigned to either arm A or B in a 1:1 proportion by using an Interactive Voice/Web Response System (IVRS/IWRS). • Patients who rapidly failed a prior AR-targeted agent are defined as patients who have disease progression while receiving AR targeted therapy within 12 months of AR treatment initiation (≤12 months). • Each patient will be treated until radiographic disease progression, unacceptable toxicity, or patient's refusal of further study treatment. • A Steering Committee will be responsible for supervising the progress of the trial. This committee will include Study Chairmen's and Sponsor's representatives. • A translational Steering Committee will be responsible for supervising the biomarkers part. This committee will include Study Chairmen's and Sponsor's representatives. • Randomization will be stratified by: Eastern Cooperative Oncology Group (ECOG) performance status (0-1 Vs. 2), time from AR targeted agent initiation to progression ([0; 6 months] Vs. [6; 12 months]), timing of AR targeted agent (before Vs. after docetaxel). For patients who received docetaxel re-challenge, the last sequence of treatment must be considered for "the timing of AR targeted agent (before Vs. after docetaxel)" stratification factor. 
STUDY POPULATION **Main selection criteria**	**Inclusion criteria** I 01. Histologically confirmed prostate adenocarcinoma. I 02. Metastatic disease. I 03. Effective castration with serum testosterone levels <0.5 ng/mL(1.7 nmol/L). If the patient has been treated with LHRH agonists or antagonist (ie, without orchiectomy), then this therapy should be continued. I 04. Progressive disease by at least one of the following: a) Progression in measurable disease (RECIST 1.1 criteria). Patient with measurable disease must have at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded). Each lesion must be at least 10 mm when measured by computed tomography (CT) [CT scan thickness no greater than 5 mm] or magnetic resonance imaging (MRI). Lymph nodes should be ≥ 15 mm in short axis. As defined by PCWG2, if lymph node metastasis is the only evidence of metastasis, it must be ≥ 20 mm in diameter when measured by spiral CT or MRI. Previously irradiated lesions, primary prostate lesion and bone lesions will be considered non-measurable disease (see Appendix A) and/or b) Appearance of 2 or more new bone lesions (PCWG2). They must be confirmed by other imaging modalities (CT; MRI) if ambiguous results and/or

	c) Rising PSA defined (PCWG2) as at least two consecutive rises in PSA to be documented over a reference value (measure 1) taken at least one week apart. The first rising PSA (measure 2) should be taken at least 7 days after the reference value. A third confirmatory PSA measure is required (2nd beyond the reference level) to be greater than the second measure and it must be obtained at least 7 days after the 2nd measure. If this is not the case, a fourth PSA measure is required to be taken and be greater than the 2nd measure. The third (or the fourth) confirmatory PSA should be taken within 4 weeks prior to randomization (see Appendix B). I 05. Having received prior docetaxel for at least 3 cycles (before or after an AR targeted therapy). Docetaxel administration in combination with Androgen Deprivation Therapy (ADT) in metastatic hormone-sensitive disease is considered a prior exposure (3). Docetaxel re-challenge is allowed. I 06. Having progressive disease (PD) (according to I04) while receiving AR targeted therapy with abiraterone acetate or enzalutamide within 12 months of AR treatment initiation (≤12 months), even if treatment duration is longer than 12 months. Patients treated with Abiraterone Acetate + ADT in metastatic hormone-sensitive setting are eligible in the study if they have progressed within 12 months with the AR-targeted agent. Patients having PSA progression only (as per PCWG 2) within 12 months are eligible I 07. A PSA value of at least 2ng/mL is required at study entry. I 08. Prior AR targeted therapy (abiraterone acetate or enzalutamide) must be stopped at least 2 weeks before study treatment. I 09. Signed informed consent. **Exclusion criteria** **Related to methodology:** E 01. Prior chemotherapy other than docetaxel for prostate cancer except estramustine and except adjuvant/neoadjuvant treatment completed >3 years ago. E 02. Less than 28 days elapsed from prior treatment with chemotherapy, immunotherapy radiotherapy or surgery to the time of randomization. E 03. Adverse events (AEs) (excluding alopecia and those listed in the specific exclusion criteria) from any prior anticancer therapy of Grade >1 (National Cancer Institute Common Terminology Criteria [NCI CTCAE] v4.0) at the time of randomization (see Appendix C). E 04. Less than 18 years (or country's legal age of majority if the legal age is >18 years). E 05. Eastern Cooperative Oncology Group performance status (ECOG PS) >2 (ECOG 2 must be related to prostate cancer, not to other comorbidities) (see Appendix D). E 06. Prior malignancy. Adequately treated basal cell or squamous cell skin or superficial (pTis, pTa, and pT1) bladder cancer are allowed, as well as any other cancer for which treatment has been completed ≥5 years ago and from which the patient has been disease-free for ≥5 years. E 07. Participation in another clinical trial and any concurrent treatment with any investigational drug within 30 days prior to randomization.

	E 08. Acquired immunodeficiency syndrome (AIDS related illnesses) or known HIV disease requiring antiretroviral treatment. E 09. Patients with reproductive potential who do not agree, in conjunction with their partner, to use accepted and effective method of contraception during the study treatment period and up to 6 months after the last administered dose. The definition of "effective method of contraception" described hereafter: oral contraceptives, combined hormonal intravaginal, transdermal, intra uterine device or condoms will be based on respective study treatment labelling and country-specific regulatory requirements, and are documented in the Informed Consent Form. **Related to study treatments:** E 10. Known allergies, hypersensitivity or intolerance to prednisone or excipients of abiraterone acetate or enzalutamide or docetaxel or polysorbate 80. E 11. Known history of mineralocorticoid excess or deficiency. E 12. History of seizure, underlying brain injury with loss of consciousness, transient ischemic attack within the past 12 months, cerebral vascular accident, brain arteriovenous malformation, brain metastases or the use of concomitant medications that may lower the seizure threshold. E 13. Unable to swallow a whole tablet or capsule. E 14. Inadequate organ and bone marrow function as evidenced by: a) Hemoglobin <10.0 g/dL b) Absolute neutrophil count <1.5 x 10^9/L c) Platelet count <100 x 10^9/L d) AST/SGOT and/or ALT/SGPT >1.5 x ULN; e) Total bilirubin >1.0 x ULN f) Potassium <3.5 mmol/L g) Child-Pugh Class C E 15. Contraindications to the use of corticosteroid treatment. E 16. Symptomatic peripheral neuropathy Grade ≥2 (National Cancer Institute Common Terminology Criteria [NCI CTCAE] v.4.0). E 17. Uncontrolled severe illness or medical condition including uncontrolled diabetes mellitus, history of cardiovascular disease (uncontrolled hypertension, arterial thrombotic events in the past 6 months, congestive heart failure, severe or unstable angina pectoris, recent myocardial infraction within last 6 months or uncontrolled cardiac arrhythmia). E 18. Concomitant vaccination with yellow fever vaccine.
Total expected number of patients	N= 234 randomized patients (117 per arm) approximatively
STUDY TREATMENT(s)	CABAZITAXEL (XRP6258)
Investigational medicinal product(s) (IMP) **Formulation**	• Cabazitaxel is supplied as a sterile, non-pyrogenic, non-aqueous yellowish to brownish yellow concentrate for solution for infusion at 60 mg/1.5 mL and packaged in a 15 mL clear type I glass vial closed with a rubber closure. The rubber closure is crimped to the vial with an aluminum cap covered with a light green plastic flip-off cap. • Single-dose vial, containing a total of 60 mg of cabazitaxel expressed as anhydrous and solvent-free basis, per 1.5 mL of solution. The fill volume has been established to include an overfill (ie 1.5 mL [nominal

	volume] + 0.33 mL). This overfill was determined to ensure that a 10 mg/mL concentration is obtained in the premix and that 60 mg dose can be extracted. **Solvent:** • The diluent used for the preparation of the premix is a sterile, non-pyrogenic solution containing a 13% w/w ethanol solution in water for injection. This solution is contained in a 15mL clear glass vial, stoppered with a rubber closure. The rubber closure is crimped to the vial with either an aluminum cap covered with a light grey plastic flip-off cap or a gold-color aluminum cap covered with a colorless plastic flip-off cap. • Each vial of solvent is overfilled to ensure that a 10 mg/mL concentration is obtained in the Premix and that 60 mg dose can be extracted. (ie, 4.5 mL (nominal volume) + 1.17 mL]. • Each vial of cabazitaxel must be diluted with the ENTIRE content of one solvent vial. The solution is a clear colorless liquid. **ABIRATERONE ACETATE:** • 250 mg tablets, white to off-white, oval tablets debossed with AA250 on one side. Abiraterone acetate 250 mg tablets are available in high-density polyethylene bottles of 120 tablets. OR • 500 mg tablets, Film-coated tablet. Purple, oval-shaped, film-coated tablets debossed with “AA” on one side and “500” on the other side. Abiraterone acetate 500 mg tablets are available in:PVdC/PE/PVC/aluminum blister of 12 filmcoated tablets in a cardboard wallet. Each carton contains (60 filmcoated tablets) 5 wallets, or PVdC/PE/PVC/aluminum blister of 14 filmcoated tablets in a cardboard wallet. Each carton contains (56 filmcoated tablets) 4 wallets. **ENZALUTAMIDE:** • 40 mg capsules, white to off-white oblong soft capsules (approximately 20 mm x 9 mm) imprinted with "ENZ" in black ink on one side. Commercially available formulations will be used for the comparators (abiraterone acetate and enzalutamide).
Route(s) of administration	Cabazitaxel will be administered by IV route. Abiraterone acetate and enzalutamide will be administered by oral route
Dose regimen	**Arm A** Cabazitaxel 25 mg/m² intravenously in 1 hour (D1) every 3 weeks, plus prednisone 10 mg orally given daily. A cycle is defined as a 3 week period Primary prophylactic G-CSF is required for all patients in Cabazitaxel arm. **Arm B** Abiraterone acetate: Patients who were previously treated with enzalutamide before study entry, will receive abiraterone acetate at the dose of 1000 mg (4 tablets 250 mg or 2 tablets 500 mg) orally (PO) continuously once daily from D1 to D21. It must be taken on an empty stomach. No food should be consumed for at least 2 hours before the dose is taken and for at least 1 hour after the dose is taken. The tablets should be swallowed whole with water, plus prednisone 5 mg orally twice daily. A cycle is defined as a 3 week period. OR

	Enzalutamide: Patients who were previously treated with abiraterone acetate before study entry, will receive enzalutamide at the dose of 160 mg (4 capsules) PO continuously once daily from D1 to D21, with or without food, capsules should be swallowed whole. A cycle is defined as a 3 week period.
Non Investigational medicinal product(s) (IMP)	Prednisone or Prednisolone: Commercially available product will be used. Prednisone or Prednisolone will be administered by oral route. G-CSF in patients in Cabazitaxel arm: Commercially available products will be used. The choice of the product is left to the investigator's decision. For any G-CSF product, the package insert or summary of product characteristics for details on description, administration, and precautions for use will be used.
ENDPOINT(S)	**Primary endpoint** Radiographic Progression-Free Survival (rPFS) defined as the time from randomization to the occurrence of one of the following: • Radiological tumor progression using RECIST 1.1 • Progression of bone lesions using PCWG2 criteria • Death due to any cause **Secondary endpoints** **Efficacy** • **PSA response** defined as a reduction from baseline PSA level of at least 50%, maintained for at least 3 weeks. • **Time to PSA progression (TTPP)** defined as the time interval between the date of randomization and the date of first documented PSA progression. PSA progression is defined as (2) : - **If decline from baseline value**: an increase of ≥25% (at least 2 ng/mL) over the nadir value, confirmed by a second PSA value at least 3 weeks apart. - **If no decline from baseline value**: an increase of ≥25% (at least 2 ng/mL) over the baseline value after 12 weeks of treatment, confirmed by a second PSA value at least 3 weeks apart. Early increase in PSA within 12 weeks, when followed by subsequent decline, is ignored in determining this endpoint. • **Progression-free survival** defined as the time interval between the date of randomization and the date of the first documentation of any of the following events: - Radiological tumor progression by RECIST 1.1 and PCWG2, - Symptomatic progression, - Pain progression, - Or death due to any cause. • **Objective tumor response** in patients with measurable disease (RECIST 1.1). • Duration of tumor response. • **Pain intensity palliation** defined as a decrease by <30% from baseline in the BPI-SF pain intensity item scores observed at 2 consecutive evaluations ≥3 weeks apart without increase in analgesic usage score.

	• **Time to pain progression** defined as the time interval from randomization to the first date increase by ≥30% from baseline in the BPI SF pain intensity score observed at 2 consecutive evaluations ≥3 weeks apart without decrease in analgesic usage score or an increase in analgesic usage score ≥30%. Early increase in BPI-SF and analgesic usage within 12 weeks, when followed by subsequent decline, is ignored in determining this endpoint. • **SSE rate**, occurrence of SSE (by clinical evaluation) is defined as (4): - The occurrence of a new symptomatic pathological fracture, or - The use of external beam radiation to relieve bone pain, or - The occurrence of spinal cord compression, or - Tumor-related orthopedic surgical intervention. • **Time to occurrence of SSE** defined as the time interval between the date of randomization and the date of the occurrence of the first event defining a SSE. • **OS** (defined as the time interval from the date of randomization to the date of death due to any cause). **Health Related Quality of life:** • HRQOL as assessed by FACT-P. **Health status/utility:** • EQ-5D-5L. **Biomarkers:** • Evaluation of the correlation of a signature of resistance to AR targeted agents with clinical outcomes, via the analysis of Circulating Tumor Cells (CTCs) phenotypes as well as expression and localization of proteins including AR isoforms in CTCs. **Safety:** • Treatment Emergent Adverse Events (TEAE): Type according to MedDRA (Medical Dictionary for Regulatory Activities), frequency, severity according to NCI CTCAE V4.0, seriousness, and relationship of study treatment will be assessed. Laboratory abnormalities will be assessed according to the NCI CTCAE v.4.0. **Other endpoints** **Biomarkers:** [redacted]
ASSESSMENT SCHEDULE	• Screening will be performed within 4 weeks before randomization. • Clinical examinations (including height at baseline only, weight, ECOG PS, vital signs), laboratory tests (including complete blood counts and serum chemistry), concomitant medications and AEs (NCI CTCAE v.4.0) will be obtained prior to drug administration, at every cycle before treatment administration and up to 30 days after the last study treatment administration. • Electrocardiogram (ECG) will be obtained within 8 days prior to first drug administration and at the end of treatment visit only if clinically indicated or cardiac event during the treatment period. • ECOG PS will be collected until disease progression, start of another

	anticancer therapy or study cut-off and subsequent anti-cancer treatments administered will be collected until death or study cut-off date (see Section 6.2), whichever comes first. • Serum testosterone will be measured at baseline. • PSA will be determined at baseline, every 3 weeks at each visit before study treatment administration, at the end of treatment visit and every 12 weeks at each follow-up until the end of the first further anticancer therapy if any, or study cut-off whichever comes first. • Pain intensity evaluation will be obtained at baseline (within 3 days prior the first study treatment), every 3 weeks at each visit before study treatment administration, at the end of treatment visit and every 12 weeks at each follow-up until disease progression, start of another cancer therapy or study cut-off whichever comes first. • Patient's diary will be given to record the consumption of abiraterone acetate or enzalutamide and/or prednisone or prednisolone. • SSE assessment will be obtained at baseline, every 3 weeks at each visit before study treatment administration, at the end of treatment visit and every 12 weeks until occurrence of first SSE or study cut-off, whichever comes first. • HRQOL as assessed by FACT-P at baseline (within 3 days prior the first study treatment), at each visit before drug administration, at end of treatment visit and every 12 weeks during the follow-up period until disease progression, start of other anticancer treatment or study cut-off, whichever comes first. • Health status/utility (EQ-5D-5L) evaluation at baseline (within 3 days prior the first study treatment), at each visit before drug administration, at end of treatment visit and every 12 weeks during the follow-up period until disease progression, start of other anticancer treatment or study cut-off, whichever comes first. • Tumor radiological evaluation by CT or MRI of the whole body (chest, abdomen, and pelvis) and by bone scan for all patients at baseline, every 12 weeks (+/- 1 week) until radiological tumor progression is documented, start of another cancer therapy or study cut-off, whichever comes first, using the same method for each assessment. • 3 blood samples for CTCs analysis will be collected in patients at screening, at D1 of Cycle 2 and at relapse or EOT. • [redacted] • [redacted] • After study treatment discontinuation, patients will be followed every 12 weeks until death, study cut-off date or withdrawal of patients' consent. Details of any further anticancer therapy will be collected.
STATISTICAL CONSIDERATIONS	**Sample size determination:** In post-docetaxel setting, the HR for rPFS is 0.66 [0.58-0.76] between abiraterone/prednisone and prednisone in COU-AA-301(5) and 0.40 [0.35-0.47] between enzalutamide and placebo in AFFIRM (6). In pre-docetaxel setting, the Hazard ratio (HR) for rPFS is 0.53 [0.45 to 0.62] between abiraterone/prednisone and prednisone in COU-AA-302 (7) and 0.19 [0.15-0.23] between enzalutamide and placebo in PREVAIL (8). We thus consider that a HR of 0.67 should be considered as the smallest effect of clinical interest between cabazitaxel and an AR-targeted agent (abiraterone or

enzalutamide).

The following table presents how such a HR translates for a variety of envisaged median rPFS in the abiraterone acetate or Enzalutamide group (9) (10).

Hazard Ratio	median rPFS (month)	
	Abiraterone acetate or Enzalutamide group	Cabazitaxel group
0.67	4	6.0
0.67	5	7.5
0.67	6	9.0

A total of 196 patients with event is needed to achieve 80% power to demonstrate rPFS superiority of Cabazitaxel over abiraterone acetate/prednisone or enzalutamide by 2 sided log rank test at 0.05 type I error rate.

At the time of the cut-off date, when the primary analysis will be conducted, events will be censored in some patients either by end-of-study or by cut-off date. This phenomenon is estimated with [redacted]; 10% of patients are estimated to achieve the end-of-study (as currently censored either by events or by last contact in on-going patients) by 7.5 months.

The observed accrual rates, that have been lower than expected, have been considered for this new sample size calculation:

Period	Starting at time	Accrual rate (Patients per month)
1	Mid-November 2015 = M0	3
2	Mid-October 2016 = M11	8
3	Mid-February 2017 = M15	7
4	Mid-August 2017 = M25	12
5	Mid-December 2017=M29 (up to end of June 2018)	12

A total of 234 patients in 2 arms (117 patients per arm) are anticipated to be needed to reach the targeted number of patients with event. This new target should be achieved for an estimated constant accrual rate equal to 12 until the end of the recruitment expected in June 2018.

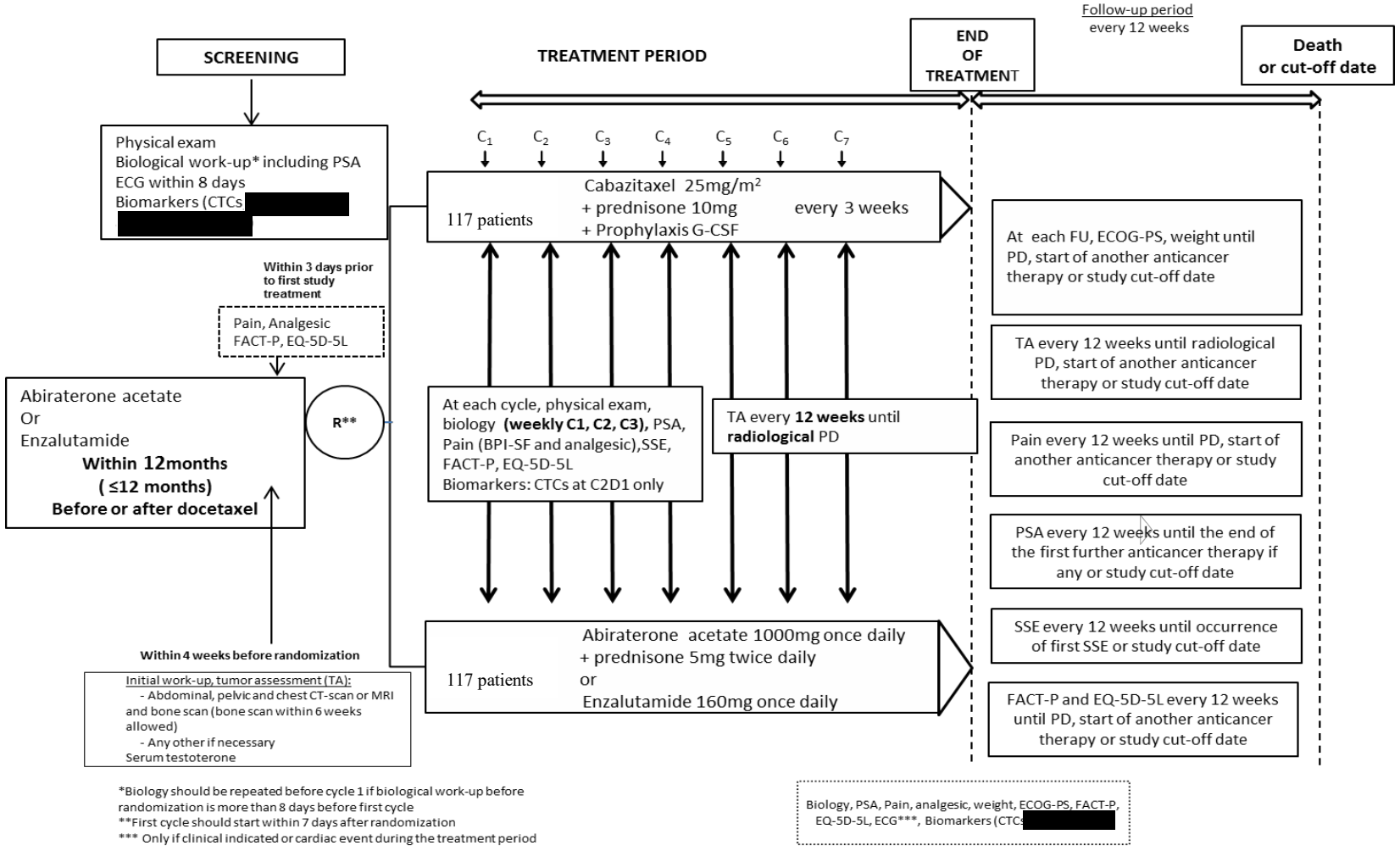
Analysis population:

- Intent-to-Treat (ITT) population: This population includes all randomized patients. It is the primary population for all efficacy parameters. All analyses using this population will be based on the treatment assigned by randomization.
- Safety population: This population includes all patients who will take at least one dose of the study drug. This population is for safety analyses. All analyses using this population will be based on the treatment actually received.
- Evaluable population: tumor response will be evaluated in patients

	with measurable disease at baseline. PSA response will be evaluated in patients with PSA value >2 ng/mL at baseline. Pain response will be evaluated using BPI-SF and WHO's analgesic ladder. • Health related quality of life population: subset of the safety population composed of patients with an evaluable FACT-P questionnaire at baseline and at least one post baseline evaluable FACT-P. • Health status population: subset of the Safety population composed of patients with an evaluable EQ-5D-5L at baseline and with at least one post-baseline evaluable EQ-5D-5L. **Primary analysis:** Primary analysis will consist of rPFS comparison between abiraterone acetate or enzalutamide group and cabazitaxel group through a 2 sided 5% log-rank adjusted for the stratification factors ECOG performance status (0-1 Vs. 2), time from AR targeted agent initiation to progression (]0; 6 months] Vs.]6; 12 months]), timing of AR targeted agent (before Vs. after docetaxel) as specified at the time of randomization. This analysis will be performed on the ITT population. If radiological progression or death is not observed during the study, data on rPFS 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 2 sided 5% Cox model adjusted for the stratification factors. Medians survival times and 95% confidence intervals will also be provided by treatment arm. The survival curves will be estimated using Kaplan-Meier estimates. **Analysis of secondary endpoints:** Time To event data will be analyzed as the primary efficacy endpoint. PSA response will be compared between groups using chi-square tests under evaluable population. Safety endpoints will be summarized by the frequency and percent in patients and by toxicity grade will be summarized by the frequency in patients and by toxicity grade.
DURATION OF STUDY PERIOD (per patient)	Patients will be treated until radiographic progressive disease, unacceptable toxicity, patient's refusal of further study treatment. All patients will be followed when on study treatment and after completion of study treatment during follow up period until death, the study cut-off date (see Section 6.2), or withdrawal of patients' consent whichever comes first.

1 FLOW CHARTS

1.1 GRAPHICAL STUDY DESIGN



1.2 STUDY FLOW CHART

Evaluation	Baseline		Treatment period First cycle within 7 days after randomization		Post- treatment follow-up period
	Prior to randomization		Every cycle	End of treatment (30 days after last treatment)	**Every 12 weeks (+/-1 week)**
Informed Consent	Before any study procedures				
Inclusion/Exclusion Criteria	Within 8 days				
Patient demography	Within 28 days				
Prior Medical/Surgical & Cancer History[a]	Within 28 days				
Clinical Examination[b]	Within 8 days	**R**	X	X	X (ECOG and weight only)
Laboratory Studies [c*]	Within 8 days	**A N**	X (Hematology/Biochemistry weekly during 3 first cycles)	X	
12 lead ECG [d]	Within 8 days	**D**		X[d]	
Study drug Administration [e]		**O**	X		
Adverse Events [f]		**M**	X	X	X
Prior/ Concomitant/ Post Medications [g]	Within 28 days	**I**	X	X	X(if indicated)[g]
Other investigations	As clinically indicated	**Z**	X	X	X
Symptomatic Skeletal Event[h]	Within 8 days	**A**	X	X	X
Tumor Assessment [i]	Within 28 days	**T**	every 12 weeks (+/- 1 week)	X	X
Serum Testosterone Measurement [j]	Within 28 days	**I**			
PSA Measurement [k**]	Within 8 days[k]	**O**	X	X	X
Analgesic & Pain [l]	Within 3 days[l]	**N**	X	X	X
HRQOL and Health status[m]	Within 3 days[m]	*r*	X	X	X
Patient's diary[n]			X		
Circulating Tumor Cells (CTCs)[o]	Within 8 days		D1 of Cycle 2	X[o]	
[redacted]	Within 8 days			X[p]	
[redacted]	Within 8 days				
Survival status[q]					X

* To be repeated if performed more than 8 days before the 1st infusion. ** Must be performed prior to registration for eligibility assessment.

a **Prior Medical/Surgical & Cancer History** Includes cancer diagnosis (primary tumor characteristics and metastatic sites), prior surgery for cancer, radiotherapy, systemic anticancer therapy, and concurrent illness.

b **Clinical Examination**: Includes examination of major body systems [blood pressure, heart rate, height (at baseline only), body weight, ECOG PS]. During the follow-up period, ECOG PS, weight will be collected every 12 weeks (+/- 1 week) from end of study treatment until disease progression, start of other anticancer therapy or study cut-off, whichever comes first.

c **Laboratory Studies** Includes, prior each cycle, hematology (White blood cell (WBC) with differential count, Absolute neutrophil count (ANC), hemoglobin, platelet count), blood biochemistry (sodium, potassium, calcium, phosphorus, blood urea nitrogen(BUN), magnesium, LDH, creatinine, total protein, albumin, Serum Glutamooxaloacétate Transférase (SGOT) (AST), Serum Glutamo-Pyruvate Transferase (SGPT) (ALT), alkaline phosphatase, total bilirubin, glucose). Only at baseline: serum Chromogranin A (CgA). In addition, hematology and biochemistry will be performed every week (D8 and D15) during the 3 first cycles and then within further cycles in case of fever or infection. Coagulation (prothrombin time at baseline, and then within further cycles if needed [expressed as international normalized ratio]).

d **12-lead ECG** to be performed at baseline, and end of treatment visit only if cardiac event during the treatment period.

e **Study drug Administration** Arm A: Cabazitaxel 25 mg/m² will be administered on Days 1 of each 21-day cycle + prednisone 10 mg daily per os (in countries where prednisone is not commercially available prednisolone 10 mg daily per os may be used). Primary prophylactic G-CSF is required at each cycle for all patients in cabazitaxel arm. Cycle administration will start within 7 days of randomization, and then repeated every 3 weeks. Arm B: Abiraterone acetate 1000 mg (4 tablets 250 mg or 2 tablets 500 mg) orally once daily plus prednisone 5 mg orally twice daily, continuously or enzalutamide 160 mg (4 capsules) orally once daily continuously.

f **Adverse Events** The period of safety observation starts from the time the patient gives informed consent. All AEs will be recorded until 30 days after the last administration of study drugs. During the follow-up period, only ongoing related or new related AEs will be recorded. Serious adverse events (SAEs) ongoing at the end of the study treatment will be followed during the follow-up period until resolution or stabilization regardless of relationship with study drugs. Adverse events will be recorded according to NCI-CTCAE version 4.0.

g **Prior/ Concomitant/ Post Medications** Concomitant medications and treatments will be recorded from 28 days prior to the start of study drug, before every cycle during the study treatment period and up to 30 days after the final dose of study drug. Once the patient has withdrawn from study treatment, concomitant medication should only be recorded if used to treat new or unresolved study treatment related AEs.

h **Symptomatic Skeletal Event**: The use of external beam radiation to relieve bone pain, or occurrence of a new symptomatic pathological fracture, or occurrence of spinal cord compression, or tumor-related orthopedic surgical intervention, until the occurrence of the first SSE or study cut-off date.

i **Tumor Assessment** Chest, abdomen, and pelvic CT-scan or MRI and bone scan to be performed to assess disease status at baseline (bone scan performed within 6 weeks prior to randomization is allowed) then every 12 weeks (+/- 1 week) until radiological tumor progression, whenever disease progression is suspected, using the same method for each assessment to follow all target and/ or non-target lesions present at baseline. In addition, bone scan will be repeated to confirm progression in case PD is diagnosed only on bone scan (6 weeks after initial documentation of progression); In case of doubtful lesions on bone scan, bone-centered X-ray or MRI scan should be performed to determine the nature of those lesions (metastatic or not). In post treatment follow up period, patients that have not radiographic progression or started another anticancer therapy, tumor assessment to be performed every 12 weeks (+/- 1 week).

j **Serum testosterone measurement**, to be performed at baseline only.

k **PSA measurements** to be performed at baseline (last PSA if progression is defined by rising PSA only should be done within 8 days prior randomization) and then repeated on pre dose of D1 of each cycle, approximately 30 days after the last study treatment administration (end of treatment visit), every 12 weeks (+/- 1 week). during the follow-up period until the end of the first further anticancer therapy if any or the study cutoff date, whichever comes first.

l **Analgesic and pain diary** (BPI-SF). The collection will be done at baseline (within 3 days prior to the first treatment administration), before each cycle, at the end of treatment and every 12 weeks (+/- 1 week). until disease progression, start of another anticancer therapy or study cut-off, whichever comes first.

m **HRQOL and Health status: FACT-P and EQ-5D-5L** to be completed by the patient at the center, at baseline (within 3 days prior the first study treatment), before each cycle, at the end of treatment visit and every 12 weeks (+/- 1 week). during the follow-up period until disease progression, start of another anticancer therapy or study cut-off, whichever comes first.

n **Patient's diary** to be used by all patients to record the consumption of abiraterone acetate or enzalutamide and/or prednisone or prednisolone.

o **Circulating Tumor Cells (CTCs)** - CTCs assays will be done by a central laboratory. 3 samples will be collected at screening (within 8 days during abiraterone acetate or enzalutamide washout), D1 of Cycle 2, and at relapse or EOT if any other reason of discontinuation.

p [redacted]

q **Survival status**: During the follow-up period, patients who went off study treatment prior to documented radiographic disease progression will be evaluated for tumor progression every 12 weeks (+/- 1 week). from end of study treatment until radiographic disease progression, start of other anticancer therapy or study cut-off date, whichever comes first. Further anticancer therapy data will be collected until death or study cutoff date.

r **Randomization** All eligible patients will be randomly assigned to one of the 2 treatment groups using an Interactive Voice Response System (IVRS/IWRS). Study treatment should be started within 7 calendar days from randomization.

2 TABLE OF CONTENTS

2.1 LIST OF TABLES

3 LIST OF ABBREVIATIONS

ACTH:	adrenocorticotropic hormone
ADT:	Androgen Deprivation Therapy
AE:	adverse event
AESI:	AE of special interest
ALT:	alanine aminotransferase
ANC:	absolute neutrophil count
AR:	androgen receptor
ASCO:	American Society of Clinical Oncology
AST:	aspartate aminotransferase
AUC:	area under the curve
BPI-SF:	Brief Pain Inventory-Short Form
BUN:	blood urea nitrogen
CBC:	complete blood count
CBZ:	cabazitaxel
CR:	complete responses
CRF:	case report form
CRPC:	castration-reistant prostate cancer
CT:	computer tomography
CTCs:	circulation tumor cells
DLT:	dose limiting toxicity
DRF:	Discrepancy Resolution Form
ECG:	electrocardiogram
ECOG:	Eastern Cooperative Oncology Group
EMEA:	European Medicines Agency
FDA:	Food and Drug Administration
GCP:	good clinical practice
G-CSF:	Granulocyte-Colony Stimulating Factors
GI:	gastrointestinal
HLGT:	high group level term
HLT:	high level term
HR:	hazard ratio
HRPC:	hormone refractory prostate cancer
HRQOL:	Health-Relatd Quality Of Life
ICH:	International Conference on Harmonisation
IMP:	investigational medicinal product
INR:	International Normalized Ratio
IRB/IEC:	Institutional Review Board/Independent Ethics Committee
ITT:	intent to treat
IV:	intra-venous
IVRS/IWRS:	Interactive Voice/Web Response System
LDH:	lactate deshydrogenase

mCRPC:	metastatic Castration Resistant Prostate Cancer
MedDRA:	Medical Dictionary for Regulatory Activities
MRI:	magnetic resonance imaging
MTD:	maximum tolerated dose
MTX:	mitoxantrone
NCI CTCAE:	National Cancer Institute Common Terminology Criteria
NIMP:	non investigational medicinal product
NSAIDs:	Nonsteroidal Antiinflammatory Drugs
OS:	overall survival
PCWG2:	Prostate Cancer Working Group criteria 2
PD:	Progressive Disease, Progressive Disease
PFS:	progression free survival
PI:	package insert
PO:	orally
PR:	partial response
PS:	performance status
PSA:	Prostate-Specific Antigen
PSA:	Prostate-Specific antigen
PT:	preferred term
rPFS:	radiographic Progression-Free Survival
SAE:	serious adverse event
SAP:	statistical analysis plan
SC:	Steering Committee
SGOT:	Serum Glutamooxaloacétate Transférase
SGPT:	Serum Glutamo-Pyruvate Transferase
SmPC:	summary of product characteristics
SOC:	System Organ Class
SSE:	symptomatic skeletal event
SUSAR:	Suspected Unexpected Serious Adverse Reactions
TEAE:	Treatment Emergent Adverse Events
TTPP:	Time to PSA progression
ULN:	upper limit of normal
WBC:	white blood cell
WHO:	World Health Organization

4 INTRODUCTION AND RATIONALE

Prostate cancer is the most frequently diagnosed cancer in men, and represents the third cause of male cancer-related death, after lung and colorectal cancers, in Europe (11).

Treatment of advanced prostate cancer is palliative. Androgen ablation remains the mainstay of treatment, producing a rapid decrease in bone pain, metastases, and prostate-specific antigen (PSA) levels. Nevertheless, in virtually all patients, the tumor becomes resistant to castration within a median of 18 months after castration (12).

Until 2010, chemotherapy with docetaxel (75 mg/m² every 3 weeks) associated with daily prednisone was the unique treatment option having demonstrated a survival benefit in mCRPC, based on results of two phase III trials (TAX 327 and SWOG 99-16) which included around 2000 patients (13, 14, 15). Docetaxel every 3 weeks reduced by 24% the risk of death compared to the active comparator mitoxantrone plus prednisone (hazard ratio [HR] of death 0.76 [95% CI 0.62-0.92]), with a concomitant improvement of pain and quality of life.

Since 2010, the medical management of mCRPC has changed dramatically with five new agents (cabazitaxel, abiraterone, enzalutamide, radium 223, sipuleucel T) having demonstrated a survival benefit in mCRPC patients (16, 17, 18, 5, 6, 19). The challenge for physicians is now to integrate this broad armamentarium rationally in daily practice and appropriately tailor therapy to optimize treatment outcomes.

4.1 INVESTIGATIONAL MEDICINAL PRODUCT

4.1.1 Preclinical data

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 either poorly active 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.

More information on the preclinical data is available in the clinical Investigator's brochure (20).

4.1.2 Summary of clinical data

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

4.1.2.1 Phase 1

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

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 diarrhea. 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 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.

4.1.2.2 Phase 2

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/m2 cabazitaxel every 3 weeks with the option to dose-escalate cabazitaxel based on favorable tolerability at Cycle 1. In 20 of 71 patients, the cabazitaxel dose was escalated from 20 to 25 mg/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%), diarrhea (39.4%), myalgia (25.4%), anorexia (25.4%), weight loss (25.4%), and vomiting (23.9%). The overall response rate was 14.1% with 2 complete responses (CR) and 8 partial responses (PR).

4.1.2.3 Phase 3

One Phase 3 study was conducted in mCRPC patients previously treated with docetaxel containing regimen. This study compared cabazitaxel (CBZ) plus prednisone to mitoxantrone (MTX) plus prednisone (EFC6193). A total of 755 patients were randomized (378 patients in

CBZ arm and 377 patients in MTX arm). A statistically significant increase in OS was observed in patients treated with CBZ plus prednisone compared to patients treated with MTX plus prednisone, with a HR of 0.70 (95%CI: 0.59 – 0.83), a log-rank p-value of 0.0001. The median OS was 15.1 months (95%CI: 14.1 – 16.3) in CBZ arm versus 12.7 months (95%CI: 11.6 – 13.7) in MTX arm.

The secondary endpoints also demonstrated a net benefit in favor of CBZ treated patients compared with MTX treated patients. Progression-free survival, defined as the earliest date of radiological tumor progression, PSA progression, pain progression, or symptom deterioration or death due to any cause, was statistically significantly longer in the CBZ group compared with the MTX group ($p<0.0001$, HR = 0.74 [95% CI, 0.64 - 0.86]), and median progression-free survival was 2.8 months versus 1.4 months. Response rates for PSA and tumor assessments, as well as the time to PSA and tumor progression when defined as radiological progression or death were statistically significant in favor of CBZ. Pain response and time to pain progression were not statistically different between CBZ and MTX, for which the primary basis for approval was pain relief and control.

Treatment emergent AEs were experienced by 95.7% of patients in the CBZ group and 88.4% of patients in the MTX group; 57.4% of patients in the CBZ group and 39.4% of patients in the MTX group had at least one Grade 3-4 TEAE. In the CBZ group 39.1% of patients had at least 1 Serious Adverse Event (SAE) compared with 20.8% of patients in the MTX group. Study treatment discontinuation due to a TEAE was reported in 18.3% of patients in the CBZ group and 8.4% of patients in the MTX group.

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

Gastrointestinal disorders of all types (Grade 3-4) were more common in the CBZ group (12.4% CBZ, 1.6% MTX). Notably, Grade 3-4 diarrhea was more common on CBZ (6.2%) compared with MTX (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.

Adverse events in the renal and urinary disorders System Organ Class (SOC) (Grade 3-4) also were more common in the CBZ group (8.6% CBZ, 2.4% MTX). These events consisted of renal failure and impairment (3.2% CBZ, 0.3% MTX) as well as renal obstructive disorders (0.8% CBZ, 0.5% MTX). In the CBZ group, 15 patients were reported to have acute renal Adverse Events (AEs) Grade 3-4, the etiology 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 CBZ arm and 11.6%/0.5% in MTX. In addition, more hematuria was reported in CBZ arm versus MTX arm (62 patients/16.7% versus 14 patients/3.8%). In CBZ 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 hemorrhagic cystitis (3 cystitis

were documented with biopsy). Of note, in human the urinary excretion of cabazitaxel is about 3.7% of the dose with 2.3% excreted as unchanged drug.

Death within 30 days due to AE occurred in 18 patients (4.9%) in the CBZ group and 3 patients (<1.0%) in the MTX group. Of the 18 deaths in the CBZ group, 7 were the result of neutropenia and/or infection, 5 were due to cardiac events (2 cardiac arrest, 1 cardiac failure, 1 dyspnea 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 etiology and a death from a cerebral hemorrhage following a fall in a patient taking concomitant clopidrogrel.
Based on the results of this study, a dossier to register cabazitaxel in hormone refractory metastatic prostate cancer patients previously treated with Taxotere® containing regimen has been submitted in several countries worldwide Cabazitaxel in combination with prednisone or prednisolone is currently approved in the United States, the European Union, Canada, Switzerland, and numerous other countries in Latin America, Asia, and the Middle East.

4.2 STUDY RATIONALE

Metastatic CRPC is a heterogeneous disease and not all patients benefit from available treatments to the same extend. In COU AA 301 study, about 30% of patients experienced radiological progression with abiraterone acetate/prednisone at 3 months (18, 5). In AFFIRM, about 25% experienced radiological progression with enzalutamide at 3 months (6). Retrospective data based on a small number of patients suggest that 30% of patients treated with enzalutamide experience PSA progression at 3 months (21). Retrospective studies also suggest there is high level of cross-resistance between abiraterone and enzalutamide in post-docetaxel setting. Patients progressing on abiraterone (post-docetaxel) may have a marginal response to enzalutamide (22, 23, 24, 25) and vice-versa (26, 27). In contrast, retrospective studies suggest that cabazitaxel has a high anti-tumor activity in patients progressing on AR targeted agents (28, 29, 30).

Despite the retrospective data suggesting the cross-resistance between abiraterone acetate and enzalutamide, the switch to the second AR targeted agent before the use of chemotherapy is still part of the standard medical practice.

Docetaxel is the first-line chemotherapy in all international guidelines (31, 32, 20). However, many physicians currently use an AR targeted agent either before or after Docetaxel. It is not known if prescribing docetaxel between 2 AR targeted agents may restore some sensitivity to AR targeted agents.

Cabazitaxel is a novel taxane which has been developed to overcome docetaxel resistance. Cabazitaxel has been shown to be as effective as docetaxel but 10 fold more potent than docetaxel in chemotherapy-resistant cell lines and tumors (33). Furthermore, cabazitaxel, unlike paclitaxel and docetaxel, has been shown to pass the blood-brain barrier in vivo thereby being potentially active in patients with cerebral or leptomeningeal metastatic disease. The efficacy of cabazitaxel in mCRPC has been demonstrated in TROPIC trial, an international, open label Phase III trial in which 755 patients with mCRPC who progressed during or after docetaxel were randomized to receive either intravenous cabazitaxel 25 mg/m^2 over 1 h (N = 378) or mitoxantrone 12 mg/m^2

over 1530 min (N = 377) every 3 weeks for ten cycles, in combination with prednisone 10 mg daily (16). The trial met its primary endpoint, with a statistically significant ($p < 0.0001$) improvement in median OS in patients receiving cabazitaxel (15.1 months; 95% CI, 14.1-16.3 months) compared to patients receiving mitoxantrone (12.7 months; 95% CI, 11.6-13.7 months). The hazard ratio (HR) for death was 0.70 (95% CI, 0.59-0.83; $p < 0.0001$), corresponding to a 30% reduction in the risk of death with cabazitaxel compared to mitoxantrone. Median progression-free survival, a composite measure defined as the time between randomization and the date of disease progression (PSA or tumor or pain progression) or death, was 2.8 months (95% CI, 2.4-3.0) in the cabazitaxel group and 1.4 months (95% CI, 1.4-1.7) in the mitoxantrone group (HR, 0.74; 95% CI, 0.64-0.86; $p<0.0001$). PSA response and tumor response were also significantly higher with cabazitaxel than with mitoxantrone. An updated OS analysis of confirmed that the survival benefit of cabazitaxel was maintained in the long term with 15.9% of patients remaining alive over 2 years with cabazitaxel versus only 8.2% with mitoxantrone.

The biological heterogeneity of the mCRPC clearly indicates the importance of distinguishing patients with primary resistance to AR targeted therapy with appropriate monitoring during the treatment. Promising published data have shown that a biomarker signature (including presence of AR splice variant) in circulating tumor cells could predict resistance to AR targeted agents (34).

The aim of this randomized, open-label study is to compare the efficacy of cabazitaxel versus an AR targeted agent (abiraterone acetate or enzalutamide, depending on what was received first), in patients previously treated with docetaxel and rapidly progressing with an AR targeted agents (progression within 12 months on abiraterone acetate or enzalutamide, before or after docetaxel).

5 STUDY OBJECTIVES

5.1 PRIMARY

To compare the radiographic Progression-Free Survival (rPFS) [Using Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 for tumor lesions and Prostate Cancer Working Group 2 (PCWG2) criteria for bone scan lesions (1, 2) or death due to any cause] with chemotherapy (Cabazitaxel plus prednisone) (Arm A) versus AR targeted therapy (enzalutamide or abiraterone acetate plus prednisone) (Arm B) in mCRPC patients who have been treated with docetaxel and who had disease progression while receiving AR targeted therapy within 12 months of AR treatment initiation (≤12 months)(either before or after docetaxel).

5.2 SECONDARY

- To compare efficacy of cabazitaxel plus prednisone to enzalutamide or abiraterone acetate plus prednisone for:
  - PSA response rate,
  - Time to PSA progression (TTPP),
  - Progression-free survival,
  - Objective tumor response (RECIST1.1 criteria in patients with measurable disease),
  - Duration of tumor response,
  - Pain intensity palliation,
  - Time to pain progression,
  - Symptomatic Skeletal Events (SSEs) rate,
  - Time to occurrence of Symptomatic Skeletal Events (SSEs),
  - OS.
- To compare Health-Related Quality Of Life (HRQOL) according to FACT-P questionnaire.
- To compare Health status/utility (EQ-5D-5L).
- To evaluate the correlation of a signature of resistance to AR targeted agents with clinical outcomes, via the analysis of Circulating Tumor Cells (CTCs) phenotypes as well as expression and localization of proteins including AR isoforms in CTCs.
- To evaluate safety in the 2 treatment arms.

5.3 EXPLORATORY

- [redacted]
- [redacted]

6 STUDY DESIGN

This is a prospective, multicenter, multinational, randomized, open label phase IV study, comparing the efficacy of cabazitaxel at 25 mg/m² plus prednisone (Arm A) versus either enzalutamide at 160 mg once daily or abiraterone acetate at 1000 mg once daily plus prednisone (Arm B). Patients who rapidly failed a prior AR-targeted agent are defined as patients who have disease progression while receiving AR targeted therapy within 12 months of AR treatment initiation (≤12 months), (either before or after docetaxel).

6.1 DESCRIPTION OF THE PROTOCOL

Treatment allocation will be performed by an Interactive Voice/Web Response System (IVRS/IWRS). All eligible patients will be randomly assigned to either Arm A or B in a 1:1 proportion.

Randomization will be stratified by: ECOG performance status (0-1 Vs. 2), time from AR targeted agent initiation to progression (]0; 6 months] Vs.]6; 12 months]), timing of AR targeted agent (before Vs. after docetaxel).

For patients who received docetaxel re-challenge, the last sequence of treatment must be considered for “the timing of AR targeted agent (before Vs. after docetaxel)” stratification factor.

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

Each patient will be treated until radiographic disease progression, unacceptable toxicity, or patient’s refusal of further study treatment. The study period will include the screening phase, the study treatment period (until 30 days after last cabazitaxel or abiraterone acetate or enzalutamide administration) and the follow-up period. Cabazitaxel will be administered every 3 weeks. The comparators will be given orally continuously. The first study treatment should be administered within 7 calendar days after randomization. The time between biological work-up and first cycle should not exceed 8 days. If it is the case, hematology and biochemistry should be done again before first cycle in order to check that eligibility criteria are still met. After study treatment discontinuation, patient will be followed every 12 weeks (+/-1 week) until death, cut-off date or withdrawal of patient’s consent, whichever comes first. During the follow-up period, ongoing related AEs at end of treatment and all (serious or non-serious) new AEs related to study treatment will be collected and followed until resolution or stabilization.

Patients still on study treatment at the main analysis cut-off date can continue treatment until at least 1 treatment discontinuation criterion as defined in Section 10.3.2 is met.

All efforts should be made to document radiographic progression before initiation of further therapy. In case of treatment discontinuation due to reason other than radiographic progressive disease (for example discontinuation due to adverse event), the choice of further therapy, if any, is let to investigator, and data concerning first further therapy must be documented.

6.2.2 Determination of end of clinical trial (all patients)

The study is event driven and the final cut-off date will be when 196 rPFS events have occurred (expected to occur around 12 months after the last patient in).

The end of clinical trial will be last patient last visit.

6.3 INTERIM ANALYSIS

No interim analysis is planned.

6.4 STUDY COMMITTEES

- A Steering Committee (SC), including Study Chairmen and sponsor representatives, will be responsible for:
  - Supervising the progress of the trial towards its overall objectives,
  - Reviewing at regular intervals relevant information that may affect the study conduct.
- A translational SC will be responsible for supervising the biomarkers part. This committee will include Study Chairmen and Sponsor representatives.

7 SELECTION OF PATIENTS

Eligible patients with mCRPC will be recruited by the appropriate service at each participating institution. Participation is voluntary. The consenting physician will inform patients of their diagnosis, current treatment options, including standard treatment, and the risks, benefits and experimental nature of this treatment program.

7.1 INCLUSION CRITERIA

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

I 01. Histologically confirmed prostate adenocarcinoma.

I 02. Metastatic disease.

I 03. Effective castration with serum testosterone levels < 0.5 ng/mL (1.7 nmol/L). If the patient has been treated with LHRH agonists or antagonist (ie, without orchiectomy), then this therapy should be continued.

I 04. Progressive disease by at least one of the following:

a) Progression in measurable disease (RECIST 1.1 criteria). Patient with measurable disease must have at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded). Each lesion must be at least 10 mm when measured by CT [CT scan thickness no greater than 5 mm] or MRI. Lymph nodes should be ≥15 mm in short axis. As defined by PCWG2, if lymph node metastasis is the only evidence of metastasis, it must be ≥ 20 mm in diameter when measured by spiral CT or MRI. Previously irradiated lesions, primary prostate lesion and bone lesions will be considered non-measurable disease (see Appendix A), and/or

b) Appearance of 2 or more new bone lesions (PCWG2). They must be confirmed by other imaging modalities (CT; MRI) if ambiguous results and/or

c) Rising PSA defined (PCWG2) as at least two consecutive rises in PSA to be documented over a reference value (measure 1) taken at least one week apart. The first rising PSA (measure 2) should be taken at least 7 days after the reference value. A third confirmatory PSA measure is required (2nd beyond the reference level) to be greater than the second measure and it must be obtained at least 7 days after the 2nd measure. If this is not the case, a fourth PSA measure is required to be taken and be greater than the 2nd measure. The third (or the fourth) confirmatory PSA should be taken within 4 weeks prior to randomization (see Appendix B).

I 05. Having received prior docetaxel for at least 3 cycles (before or after an AR targeted therapy). Docetaxel administration in combination with Androgen Deprivation Therapy (ADT) in metastatic hormone-sensitive disease is considered a prior exposure (3). Docetaxel re-challenge is allowed.

I 06. Having progressive disease (PD) (according to I04) while receiving AR targeted therapy with abiraterone acetate or enzalutamide within 12 months of AR treatment initiation (≤12 months) even if treatment duration is longer than 12 months. Patients treated with Abiraterone acetate + ADT in metastatic hormone-sensitive setting are eligible for CARD if they have progressed within 12 months with the AR-targeted agent. Patients having PSA progression only (as per PCWG 2) within 12 months are eligible.

I 07. A PSA value of at least 2 ng/mL is required at study entry.

I 08. Prior AR targeted therapy (abiraterone acetate or enzalutamide) must be stopped at least 2 weeks before study treatment.

I 09. Signed informed consent.

7.2 EXCLUSION CRITERIA

Patients who have met all the above inclusion criteria listed in Section 7.1 will be screened for the following exclusion criteria which are sorted and numbered in the following 2 subsections:

7.2.1 Exclusion criteria related to study methodology

E 01. Prior chemotherapy other than docetaxel for prostate cancer, except estramustine and except adjuvant/neoadjuvant treatment completed >3 years ago.

E 02. Less than 28 days elapsed from prior treatment with chemotherapy, immunotherapy, radiotherapy or surgery to the time of randomization.

E 03. Adverse events (excluding alopecia and those listed in the specific exclusion criteria) from any prior anticancer therapy of Grade >1(National Cancer Institute Common Terminology Criteria [NCI CTCAE] v4.0) at the time of randomization (see Appendix C).

E 04. Less than 18 years (or country's legal age of majority if the legal age is >18 years).

E 05. Eastern Cooperative Oncology Group performance status (ECOG PS)>2 (ECOG 2 must be related to prostate cancer, not to other comorbidities (see Appendix D).

E 06. Prior malignancy. Adequately treated basal cell or squamous cell skin or superficial (pTis, pTa, and pT1) bladder cancer are allowed, as well as any other cancer for which treatment has been completed ≥5 years ago and from which the patient has been disease-free for ≥5 years.

E 07. Participation in another clinical trial and any concurrent treatment with any investigational drug within 30 days prior to randomization.

E 08. Acquired immunodeficiency syndrome (AIDS-related illnesses) or known HIV disease requiring antiretroviral treatment.

E 09. Patients with reproductive potential who do not agree, in conjunction with their partner, to use accepted and effective method of contraception during the study treatment period and up to 6 months after the last administered dose. The definition of "effective method of contraception" described hereafter: oral contraceptives, combined hormonal intravaginal, transdermal, intra uterine device or condoms will be based on respective study treatment labelling and country-specific regulatory requirements, and are documented in the Informed Consent Form.

7.2.2 Exclusion criteria related to study treatments

E 10. Known allergies, hypersensitivity or intolerance to prednisone or excipients of abiraterone acetate or enzalutamide or docetaxel or polysorbate 80.

E 11. Known history of mineralocorticoid excess or deficiency.

E 12. History of seizure, underlying brain injury with loss of consciousness, transient ischemic attack within the past 12 months, cerebral vascular accident, brain arteriovenous malformation, brain metastases or the use of concomitant medications that may lower the seizure threshold.

E 13. Unable to swallow a whole tablet or capsule

E 14. Inadequate organ and bone marrow function as evidenced by:

a) Hemoglobin <10.0 g/dL
b) Absolute neutrophil count <1.5 x 10^9/L
c) Platelet count <100 x 10^9/L
d) AST/SGOT and/or ALT/SGPT >1.5 x ULN;
e) Total bilirubin >1.0 x ULN
f) Potassium <3.5 mmol/L
g) Child-Pugh Class C

E 15. Contraindications to the use of corticosteroid treatment.

E 16. Symptomatic peripheral neuropathy Grade ≥2 (National Cancer Institute Common Terminology Criteria [NCI CTCAE] v.4.0).

E 17. Uncontrolled severe illness or medical condition including uncontrolled diabetes mellitus, history of cardiovascular disease (uncontrolled hypertension, arterial thrombotic events in the past 6 months , congestive heart failure, severe or unstable angina pectoris, recent myocardial infraction within last 6 months or uncontrolled cardiac arrhythmia).

E 18. Concomitant vaccination with yellow fever vaccine.

8 STUDY TREATMENTS

Name and formulation details of drugs used in study are summarized in Table 1 below.

Table 1 • Study treatments

Drug code	**XRP6258**	**-**
INN	**cabazitaxel**	**prednisone or prednisolone**
Formulation	Cabazitaxel is supplied as a sterile, non-pyrogenic, non-aqueous yellowish to brownish yellow concentrate for solution for infusion at 60 mg/1.5 mL and packaged in a 15 mL clear type I glass vial closed with a rubber closure. The rubber closure is crimped to the vial with an aluminum cap covered with a light green plastic flip-off cap. Single-dose vial, containing a total of 60 mg of cabazitaxel expressed as anhydrous and solvent-free basis, per 1.5 mL of solution. The fill volume has been established to include an overfill, [i.e., 1.5 mL (nominal volume) + 0.33 mL]. This overfill was determined to ensure that a 10 mg/mL concentration is obtained in the premix and that 60 mg dose can be extracted. The solvent used for the preparation of the premix is a sterile, non-pyrogenic solution containing a 13% w/w ethanol solution in water for injection. This solvent is supplied in a 15 mL clear type I glass vial closed with a rubber closure. The rubber closure is crimped to the vial with either an aluminum cap covered with a light grey plastic flip-off cap or a gold-color aluminum cap covered with a colorless plastic flip-off cap. Each vial of solvent 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]. The solution is a clear colorless liquid.	Commercially available formulation (refer to the local labeling)
Storage conditions	Do not store above 30°C. Do not refrigerate. The solvent was also shown to be stable under these conditions. All vials must be kept in their box until use.	Refer to the local labeling.
Drug code INN	**Abiraterone Acetate**	prednisone or prednisolone
Formulation	250 mg tablets, white to off-white, oval tablets debossed with AA250 on one side. Abiraterone acetate 250 mg tablets are available in high-density polyethylene bottles of 120 tablets or 500 mg tablets, Film-coated tablet. Purple, oval-shaped, film-coated tablets debossed with “AA” on one side and “500” on the other side. Abiraterone acetate 500 mg tablets are available in: PVdC/PE/PVC/aluminum blister of 12 filmcoated tablets in a cardboard wallet. Each carton contains (60 filmcoated tablets) 5 wallets, or PVdC/PE/PVC/aluminum blister of 14 filmcoated tablets in a cardboard wallet. Each carton contains (56 filmcoated tablets) 4 wallets.	Commercially available formulation (refer to the local labeling)
Storage	Refer to the local labeling	Refer to the local labeling
Drug code INN	**Enzalutamide**	
Formulation	40 mg capsules, white to off-white oblong soft capsules (approximately 20 mm x 9 mm) imprinted with "ENZ" in black ink on one side	
Storage	Refer to the local labeling	

8.1 INVESTIGATIONAL MEDICINAL PRODUCT

CABAZITAXEL

8.1.1 Preparation and administration of cabazitaxel

The preparation of the cabazitaxel (XRP6258) infusion solution for administration requires **two** dilutions prior to administration, the preparation of a premix solution at 60 mg/6 mL (nominal concentration). This must be done with a 13% w/w ethanol solution in water for injection (the "solvent") supplied with the cabazitaxel concentrate for solution for infusion ("preparation of the premix solution"). Then the premix solution must be diluted in an infusion vehicle ("preparation of the infusion solution") prior to administration.

An improper preparation may lead to overdose.

Both the Cabazitaxel Injection and supplied diluent vials contain an overfill to compensate for liquid loss during preparation. This overfill ensures that after dilution with the **entire contents** of the accompanying diluent, there is an initial diluted solution containing 10 mg/mL Cabazitaxel.

8.1.1.1 Preparation of the premix solution under aseptic conditions

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

- Using a syringe fitted with a needle, aseptically withdraw the ENTIRE CONTENTS of the solvent vial and inject it into the corresponding vial of cabazitaxel.
- The addition of the ENTIRE CONTENTS of 1 solvent vial ensures a minimal extractable volume of the premix solution of 6 mL, containing 10 mg/mL of cabazitaxel.
- Remove the syringe and needle and gently mix the reconstituted solution by repeated inversions for at least 45 seconds. Do not shake.
- Allow the premix solution to stand for 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.

The premix solution contains 10 mg/mL of cabazitaxel. Then the premix solution must be diluted in an infusion vehicle so as to obtain the required dose for administration.

8.1.1.2 Preparation of the infusion solution under aseptic conditions

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

- Aseptically, with a syringe and needle, withdraw the volume of the premix solution containing 10 mg/mL of cabazitaxel that corresponds to the required dose (mg) for administration of cabazitaxel.
- Inject the required premix volume into a 125 to 500 mL infusion container (containing either 5% glucose solution or 0.9% sodium chloride solution).

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

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

8.1.1.3 Infusion conditions

- The recommended infusion duration is 1 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 1 hour infusion time).
- The infusion solution should be administered at room temperature under normal lighting conditions.
- Do not use polyvinyl chloride (PVC) infusion containers or polyurethane infusion sets for cabazitaxel preparation and administration.
- Glass bottles could also be used.
- Use and in-line filter of 0.22 µm nominal pore size (also referred to as 0.2 µm) during cabazitaxel administration.

8.1.1.4 Storage period of premix and infusion solution

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

8.1.1.5 Recommendation for safe handling

- Cabazitaxel is an anti-neoplastic 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.

8.1.2 Dosage and schedule

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 m^2 = wgt in kg $^{0.425}$ x hgt. in cm $^{0.725}$ x 0.007184.

The treatment should continue for at least 12 weeks (4 cycles) in the absence of radiological evidence of disease progression defined in Section 9.1 **or unacceptable toxicity or patient refusal of further treatment**. Subsequently, no decision of treatment discontinuation should be

made in case of PSA increase ALONE or pain increase ALONE, within the first 12 weeks, see Section 9.2.1.2.

Each patient will be treated until radiographic progressive disease, unacceptable toxicity, patient's refusal of further study treatment or any other discontinuation criteria as defined in Section 10.3.2.

In case of patient discontinues study treatment due to reason other than radiological progressive disease, the investigator may consider not to initiate further anticancer therapy before radiological progression is documented (as defined in Section 9.1), in case study treatment discontinuation occurs within the 4 first cycles the decision is left to investigator judgment.

Dose adjustment will be permitted for subsequent treatment cycles based on individual patient tolerance (see Section 8.1.2.3) Treatment will continue unless any of the Withdrawal Criteria are met as described in Section 10.3.2.

8.1.2.1 Study treatments

Cabazitaxel 25 mg/m² in dextrose 5% or NaCl 0.9% (for volume see Section 8.1.1.2) intravenously on D1 every 3 weeks, plus prednisone (or prednisolone) 10 mg orally given daily.

8.1.2.2 Premedication

For cabazitaxel premedication will include an antihistamine (dexchlorpheniramine 5 mg, diphenhydramine 25 mg, or other antihistamine), steroid (dexamethasone 8 mg or equivalent steroid), and H2 antagonist (ranitidine 50 mg or other H2 antagonist). These premedications will be administered by IV infusion, at least 30 minutes prior to each dose of cabazitaxel. For countries where IV antihistamines are not available, oral instead of IV antihistamines can be used according to the local practice.

For cabazitaxel appropriate prophylactic antiemetic therapy is left to current hospital practices.

Primary prophylactic G-CSF at each cycle is required for all patients in Cabazitaxel arm.

8.1.2.3 Dose modification and dose delay

8.1.2.3.1 General Rules

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 diarrhea, and antipyretics, and/or antihistamines for drug fever.

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. Up to a maximum of 2 dose reductions will be allowed per patient. If a third dose reduction is required per the modifications below, the patient should discontinue study treatment. Dose levels in case of dose reduction are described in Table 2 below.

Table 2 • Cabazitaxel dose reduction levels

	Initial dose (mg/m²)	Dose reduction 1		Dose Reduction 2
Cabazitaxel	25	20	→	15

Chemotherapy Delay

A treatment delay ≥ 4 days should be justified (ie, to be reported in the case report form (CRF)). Treatment may be delayed no more than 2 weeks to allow recovery from acute toxicity. In case of treatment delay greater than 2 weeks, patient should discontinue study treatment, unless there is strong evidence of clinical benefit to justify continuation of dosing with study treatment, and the investigator must discuss the rationale with the Sponsor before a decision is taken.

8.1.2.3.2 Dose modification and dose delay

The dose cabazitaxel could be modified in case of toxicity. Dose modifications are summarized in Table 3.

Table 3 • Dose modifications for cabazitaxel*

Toxicity	Grade 2	Grade 3	Grade 4
Neutropenia	If not recovered on D21, delay** next infusion until recovery to Grade ≤1 (neutrophil ≥1.5 x 10^9/L). - 1st episode: No dose reduction required. - 2nd episode; reduce by 1 dose level	No dose reduction if isolated and duration ≤7 days. If duration more than 7 days or not recovered on D21 despite prophylactic G-CSF: Delay** next infusion until ANC ≥1.5 x 10^9/L and: - 1st episode: Reduce dose by 1 dose level and continue prophylactic G-CSF treatment in subsequent cycles. - 2nd episode after first dose reduction: Reduce dose by 1 dose level (dose reduction level 2) and continue prophylactic G-CSF treatment in subsequent cycles. - 3rd episode: 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: reduce the dose and continue prophylactic G-CSF treatment in subsequent cycles. - 2nd episode: Withdraw from study treatment	

Toxicity	Grade 2	Grade 3	Grade 4
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 dose by 1 dose level. - 2nd episode: Reduce dose by 1 more dose level. - 3rd episode: Withdraw from study treatment in case of recurrence.	
Diarrhea	Delay** next infusion until recovery (grade ≤1) No dose reduction required.	Delay** next infusion until recovery (Grade ≤1): - 1st episode: Reduce dose by 1 dose level. - 2nd episode: Reduce dose by 1 more dose level. - 3rd episode: Withdraw from study treatment.	
Stomatitis	Delay** next infusion until recovery (Grade ≤1) No dose reduction required.	Delay** next infusion until recovery (Grade ≤1): - 1st episode: Reduce dose by 1 dose level. - 2nd episode: Reduce dose by 1 more dose level. - 3rd episode: Withdraw from study treatment.	
Cutaneous Reactions	Delay** next infusion until recovery (Grade ≤1) No dose reduction required.	Delay** next infusion until recovery (Grade ≤1): - 1st episode: Reduce dose by 1 dose level. - 2nd episode: Withdraw from study treatment.	Withdraw from study treatment.
Creatinine increase	Withdraw from study treatment in case of any degradation of renal function to renal failure ≥ CTCAE Grade 3 (>3.0 baseline; >3.0 - 6.0 x ULN)		
Neurological toxicity* **	No delay Reduce by 1 dose level	Withdraw from study treatment.	
Total Bilirubin Elevation	In case of bilirubin > 1.0 x UNL Delay** until recovery to bilirubin ≤1.0 x UNL and reduce dose: If > 1 to ≤ 1.5 x (ULN), reduce dose to dose reduction 1 If > 1.5 to ≤ 3 x ULN, reduce dose to dose reduction 2 If > 3 X ULN, withdraw from study treatment		
Transaminases Elevation	In case of AST/ALT > 1.5 x ULN, delay** until recovery to AST/ALT ≤1.5 x UNL and reduce dose by 1 dose level (2 dose reductions are allowed).	Withdraw from study treatment.	
Hypersensitivity	No dose reduction. See Table 4 for management of hypersensitivity due to study drug. Withdraw from study treatment in case of 2nd Grade 3 episode.		Withdraw from study treatment.

* Dose reduction levels provided in Table 2
** maximum of 2 weeks delay, otherwise the patient will be withdrawn from study treatment, unless discussed and accepted by sponsor
*** Including hearing disorders

8.1.2.3.3 Specific recommendations

8.1.2.3.3.1 Hypersensitivity

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 first and the second 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 (ie, 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 (eg, 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 below.

Table 4 • Interventions in case of hypersensitivity reaction

Symptom Severity	Intervention Recommendation
Mild symptoms: Localized cutaneous reaction such as mild pruritus, flushing, rash	Consider decreasing the rate of infusion until recovery of symptoms, stay at bedside, Then, complete study drug infusion at the initial planned rate
Moderate symptoms: Any symptom such as generalized pruritus, flushing, rash, dyspnea, back pain during infusion, hypotension with systolic blood pressure (BP) >80 mm Hg not listed above (mild symptoms) or below (severe symptoms).	Stop study drug infusion, Give diphenhydramine 50 mg i.v. and/or i.v. dexamethasone 10 mg, Resume study drug infusion within 3 hours following recovery of hypersensitivity reaction. Administer study drug over 2 hours for all subsequent treatments.
Severe symptoms, such as: Bronchospasm, generalized urticaria, systolic BP ≤80 mm Hg, angioedema	• Stop study drug infusion; • Give IV diphenhydramine 50 mg and/or i.v. dexamethasone 10 mg and/or epinephrine as needed. • 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 (Grade 4 reaction)	NO FURTHER PROTOCOL THERAPY.

Management of subsequent cycles

The recommended pretreatment for subsequent infusions is 50 mg diphenhydramine i.v. or other i.v. H1 antihistaminic agent and 10 mg dexamethasone i.v. 30 minutes prior to study drug infusion. For patients who experience moderate or severe hypersensitivity reactions, the study

drug should be administered over 2 hours for subsequent treatment courses in addition to premedication as noted above. These patients must be informed of the potential risk of recurrent allergic reactions and must be carefully monitored.

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

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

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

8.1.2.3.3.2 Hematological toxicities

Blood counts will be performed in case of fever or infection. Blood counts should be monitored weekly for the first 3 cycles to determine if dosage modification is needed. Study treatment should not be given to patients with neutrophil counts <1,500 cells/mm3.

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 according to ASCO guidelines (35). Infections concomitant with Grade 3-4 neutropenia should be reported with the term “neutropenic infection” in the eCRF.

No dose modification will be made for anemia. Caution is recommended in patients with haemoglobin <10 g/dl, and appropriate measures should be taken as clinically indicated. Patients will be supported appropriately by the treating physician (the investigator can refer to ASCO guidelines (36).

8.1.2.3.3.3 Gastrointestinal disorders and diarrhea:

Nausea, vomiting and severe diarrhea, at times, may occur. Death related to diarrhea and electrolyte imbalance occurred in the randomized clinical trial.

Gastrointestinal (GI) hemorrhage and perforation, ileus, enterocolitis, neutropenic enterocolitis, including fatal outcome, have been reported. Risk may be increased with neutropenia, age, steroid use, concomitant use of NSAIDs, anti-platelet therapy or anti-coagulants, and patients with prior history of pelvic radiotherapy, adhesions, ulceration and GI bleeding.

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

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

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

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

Diarrhea ≥Grade 3 associated with neutropenia ≥Grade 3:

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

8.1.2.3.3.4 Urinary disorders

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). Therefore, in case of hematuria with no clear possible explanation any efforts should be done to document the cause (eg, urine cultures, urinary tract ultrasonography, and if no cause identified cystoscopy plus or minus biopsy). Hematuria should be confirmed by microscopic examination.

8.1.2.3.3.5 Other toxicities

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

8.2 OTHER IMP(S)

Commercially available formulation of abiraterone acetate and enzalutamide will be used.

8.2.1 Administration

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

8.2.2 Dosage and schedule

Abiraterone acetate: Patients who were previously treated with enzalutamide before study entry, will receive abiraterone acetate at the dose of 1000 mg (4 tablets 250 mg or 2 tablets 500 mg) PO continuously once daily from D1 to D21. It must be taken on an empty stomach. No food should be consumed for at least 2 hours before the dose is taken and for at least 1 hour after the dose is taken. The tablets should be swallowed whole with water, plus prednisone 5 mg orally twice daily. A cycle is defined as a 3 week period.

OR

Enzalutamide: Patients who were previously treated with abiraterone acetate before study entry, will receive enzalutamide at the dose of 160 mg (4 capsules) PO continuously once daily from D1 to D21, with or without food, capsules should be swallowed whole. A cycle is defined as a 3 week period.

8.2.2.1 Dose Reductions and Delay due to Toxicity related to Abiraterone Acetate

In clinical studies, Abiraterone acetate was generally tolerated without dose interruptions or reductions. The most common Abiraterone acetate-related AEs include fatigue (cortisol reduced by CYP17 inhibition) and mineralocorticoid-related hypertension, fluid retention, and hypokalemia (compensatory adrenocorticotrophic hormone [ACTH] drive). In this study, prednisone is expected to mitigate these effects through cortisol supplementation and abrogation of the ACTH drive.

Table 5 • Abiraterone dose reduction level

	Initial dose (mg)		Dose Reduction (mg)
Abiraterone	1000 (4 tablets 250 or 2 tablets 500)	→	500 (2 tablets 250 or 1 tablet 500)

One dose reduction is allowed for AEs. At dose reduction, the dose will be reduced by either 2 tablets of 250 mg, (from 4 tablets 250 mg (1000 mg) to 2 tablets 250 (500 mg)), or by 1 tablet 500 mg (from 2 tablets 500 mg (1000 mg) to 1 tablet 500 mg). An Abiraterone acetate dose of lower than 500 mg/D is not allowed. Study drug should not be resumed until resolution of the AE is documented.

Treatment may be delayed no more than 2 weeks to allow recovery from acute toxicity.

8.2.2.2 Management of Toxicity related to Abiraterone Acetate

For additional information refer to the ZYTIGA (abiraterone acetate) package insert for details on description, preparation, administration, and precautions for use.

8.2.2.2.1 Management of Hypokalemia

At the initial observation of Grade 1 or 2 hypokalemia (serum potassium <3.5 mmol/L or below lower limit of normal range, but ≥3.0 mM), oral potassium supplement will be initiated. The dose of potassium supplement must be carefully titrated to maintain serum potassium from 3.5 to 5.0 mmol/L, inclusive. Any subject with low potassium during the study or a history of hypokalemia from a preexisting or concurrent medical condition will undergo at least weekly laboratory electrolyte evaluation until recovery to the range ≥3.0 mmol/L. The investigator should consider maintaining potassium ≥4.0 mmol/L in these subjects Table 6.

If any subject experiences Grade 3 symptomatic hypokalemia (serum potassium levels <3.0 to 2.5 mM, NCI CTCAE version 4.0) or life-threatening hypokalemia with potassium levels <2.5 mM (NCI CTCAE version 4.0, hypokalemia Grade 4), Abiraterone acetate treatment will be withheld and the subject will be hospitalized for IV potassium replacement and cardiac monitoring. Re initiation of Abiraterone acetate treatment after normalization of potassium levels must be discussed with and approved by the Sponsor's medical monitor Table 6.

Table 6 • Management of Hypokalemia

Serum K+	Grade of Hypokalemia	Action	Further Action or Maintenance
Low potassium or history of hypokalemia		Weekly (or more frequent) laboratory electrolyte evaluations	Titrate dose to maintain a serum potassium ≥3.5 mM ≤5.0 mM (maintenance of subjects at ≥4.0 mM is recommended)
<3.5 mM to 3.0mM	Grade 1 or 2	Initiate oral or IV potassium supplementation Consider monitoring magnesium and replacement if needed	Titrate dose to maintain a serum potassium ≥3.5 mM to ≤5.0 mM (maintenance of subjects at ≥4.0 mM is recommended)
<3.0 mM to 2.5 mM	Grade 3	Withhold Abiraterone acetate (and initiate oral or IV potassium and cardiac monitoring Consider monitoring magnesium and replacement if needed	Call the Sponsor's medical monitor prior to re-initiating study drug
<2.5 mM	Grade 4	Withhold Abiraterone acetate and initiate oral or IV potassium and cardiac monitoring Consider monitoring magnesium and replacement if needed	Call the Sponsor's medical monitor prior to re-initiating study drug

IV=intravenous; mM=millimolar.

8.2.2.2.2 Management of Hypertension

- If Grade 1 or 2 AEs occur, management per investigator. No Abiraterone acetate dose reduction.
- If Grade 3 or 4 AEs occur, withhold Abiraterone acetate. Adjust or add medications to mitigate the toxicity or consider the specific mineralocorticoid receptor blocker, eplerenone (the dose not to exceed 200 mg/D). When hypertension resolves to ≤Grade 1, resume study drug at full dose.
- If toxicity recurs, withhold Abiraterone acetate, and adjust or add medications to mitigate the toxicity. When toxicity resolved to ≤ Grade 1, resume Abiraterone acetate with the dose level reduction (2 tablets, 250 mg or 1 tablet 500 mg of Abiraterone acetate).
- If toxicity recurs despite optimal medical management and the dose reduction, discontinue Abiraterone acetate.

8.2.2.2.3 Management of Fluid Retention/ Edema

- If lower limbs edema occurs, supportive management per investigator. No Abiraterone acetate dose reduction.
- If Grade 3 pulmonary edema requiring supplemental oxygen occurs, withhold Abiraterone acetate. Adjust or add medications to mitigate the toxicity and consider the specific mineralocorticoid receptor blocker, eplerenone (the dose not to exceed 200 mg/D). When toxicity resolves to ≤ Grade 1, resume Abiraterone acetate at full dose.
- If toxicity recurs, withhold Abiraterone acetate, and adjust or add medications to mitigate the toxicity. When toxicity resolved to ≤ Grade 1, resume Abiraterone acetate with the dose level reduction (2 tablets, 250 mg or 1 tablet 500 mg of Abiraterone acetate).
- If toxicity recurs despite optimal medical management and the dose reduction, discontinue Abiraterone acetate.

8.2.2.2.4 Management of Abnormal Liver Function Tests

For patients who develop hepatotoxicity during treatment (alanine aminotransferase [ALT] increases or aspartate aminotransferase [AST] increases above 5 times the upper limit of normal [ULN]), treatment should be withheld immediately. Re-treatment following return of liver function tests to the patient's baseline may be given at a reduced dose of 500 mg (two tablets 250 mg or 1 tablet 500 mg) once daily. For patients being re-treated, serum transaminases should be monitored at a minimum of every two weeks for three months and monthly thereafter. If hepatotoxicity recurs at the reduced dose of 500 mg daily, treatment should be discontinued. If patients develop severe hepatotoxicity (ALT or AST 20 times the ULN) anytime while on therapy, treatment should be discontinued and patients should not be re-treated.

8.2.2.2.5 Management of Non-Mineralocorticoid Based Side Effects

- If Grade 1 to 2 toxicities occur, give supportive care per institutional guidelines. No Abiraterone acetate dose reduction.
- If Grade 3 or higher toxicities occur, including headache (interferes with activities of daily living), nausea (total parenteral nutrition/IV fluids), vomiting (6 or more episodes in 24 hours, total parenteral nutrition/IV fluids), diarrhea (IV fluids, hospitalization, hemodynamic collapse), or any other toxicity judged related to Abiraterone acetate is observed where the subjects safety is jeopardized, hold Abiraterone acetate.
- When toxicity resolves to ≤ Grade 1, resume Abiraterone acetate at full dose.
- If toxicity recurs, withhold Abiraterone acetate, and adjust or add medications to mitigate the toxicity. When toxicity resolved to ≤ Grade 1, resume Abiraterone acetate with the dose level reduction (2 tablets 250 mg or 1 tablet 500 mg of Abiraterone acetate).
- If toxicity recurs despite aggressive medical management and dose level reduction, discontinue Abiraterone acetate.

8.2.2.3 Drug interactions related to abiraterone acetate

(see Appendix I).

Co-administration of a strong CYP3A4 inducer, decreases exposure of abiraterone by 55%. Avoid concomitant strong CYP3A4 inducers during abiraterone acetate treatment.

Abiraterone acetate is an inhibitor of the hepatic drug-metabolizing enzyme CYP2D6. Avoid co-administration of abiraterone acetate with substrates of CYP2D6 with a narrow therapeutic index.

8.2.2.4 Dose Reductions and Delay due to Toxicity related to enzalutamide

For additional information refer to the XTANDI (enzalutamide) package insert for details on description, preparation, administration, and precautions for use.

If a patient experiences a ≥ Grade 3 toxicity or an intolerable adverse reaction, dosing should be withheld for one week or until symptoms improve to ≤ Grade 2, then resumed at the same or a reduced dose (120 mg or 80 mg) if warranted. Up to two (2) dose reductions are allowed for AEs.

Treatment may be delayed no more than 2 weeks to allow recovery from acute toxicity.

In case of seizure, the patient must discontinue from treatment.

Table 7 • Enzalutamide dose reduction levels

	Initial dose (mg)		Dose reduction 1		Dose Reduction 2
Enzalutamide	160 (4 capsules)	→	120 (3 capsules)	→	80 (2 capsules)

8.2.2.5 Drug interactions related to enzalutamide

(see Appendix I).

Co-administration of a strong CYP2C8 inhibitor (gemfibrozil) increased the composite area under the plasma concentration-time curve (AUC) of enzalutamide plus N-desmethyl enzalutamide by 2.2-fold in healthy volunteers. Avoid concomitant strong CYP2C8 inhibitors during enzalutamide treatment.

Co-administration of enzalutamide with strong or moderate CYP2C8 inducers (e.g., rifampin) may alter the plasma exposure of enzalutamide and should be avoided.

Co-administration of a strong CYP3A4 inhibitor (itraconazole) increased the composite AUC of enzalutamide and should be avoided.

Co-administration of enzalutamide with strong CYP3A4 inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine) may decrease the plasma exposure of enzalutamide and should be avoided. Moderate CYP3A4 inducers (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin) and St. John's Wort may also reduce the plasma exposure of enzalutamide and should be avoided.

Concomitant use of enzalutamide with narrow therapeutic index drugs that are metabolized by CYP3A4 (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus and tacrolimus), CYP2C9 (e.g., phenytoin, warfarin) and CYP2C19 (e.g., S-mephenytoin) should be avoided, as enzalutamide may decrease their exposure.

8.3 NON INVESTIGATIONAL MEDICINAL PRODUCT

Prednisone or prednisolone as associated product during treatment with cabazitaxel and abiraterone:

Commercially available products will be used (oral route). The choice of the product is left to the investigator's decision. The package insert or summary of product characteristics for details on description, administration and precautions for use will be used.

G-CSF in patients in Cabazitaxel arm:

Commercially available products will be used. The choice of the product is left to the investigator's decision. For any G-CSF product, the package insert or summary of product characteristics for details on description, administration, and precautions for use will be used.

8.4 BLINDING PROCEDURES

8.4.1 Methods of blinding

Not applicable.

8.5 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

8.5.1 Patient number and treatment number

Patients who meet all inclusion criteria and none of the exclusion criteria are deemed eligible for randomization.

Randomization and treatment allocation(s) will be performed centrally by an interactive voice/Web response system (IVRS/IWRS). A randomized patient is a patient with a patient number and a treatment allocated by the IVRS/IWRS.

8.5.2 Allocation of treatment(s)

Treatment will be allocated by the IVRS/IWRS to either arm in a 1:1 ratio.

Randomization will be stratified by:

- ECOG performance status (0-1 Vs. 2);
- Time from AR targeted agent initiation to progression (]0; 6months] Vs.]6; 12 months]);
- Timing of AR targeted agent (before Vs. after docetaxel).

For patients who received docetaxel re-challenge, the last sequence of treatment must be considered for “the timing of AR targeted agent (before Vs. after docetaxel)” stratification factor.

8.6 PACKAGING AND LABELING

This is an open label study. The Investigational Medicinal Product (cabazitaxel) will be packaged in:

- Sterile, single-use vials.

Packaging is in accordance with the administration schedule. The content of the labeling is in accordance with the local regulatory specifications and requirements.

For infusion conditions, see Section 8.1.1.3.

For abiraterone acetate and enzalutamide, the content of the labeling is in accordance with the local regulatory specifications and requirements.

8.7 STORAGE CONDITIONS AND SHELF LIFE

Cabazitaxel (concentrate for solution for infusion) as packaged should not be stored above 30°C. Do not refrigerate.

The solvent was also shown to be stable under these conditions.

All vials must be kept in their box until use.

Abiraterone acetate and Enzalutamide: refer to the package insert (PI) or the summary of product characteristics (SmPC).

8.8 RESPONSIBILITIES

The Investigator, the hospital pharmacist, or other personnel allowed to store and dispense the IMP will be responsible for ensuring that the IMP used in the clinical trial is securely maintained as specified by the Sponsor and in accordance with applicable regulatory requirements.

All IMPs will be dispensed in accordance with the Investigator's prescription and it is the Investigator's responsibility to ensure that an accurate record of IMP issued and returned is maintained.

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) should be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure.

A potential defect in the quality of IMP may be subject to initiation of a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall IMP and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP to a third party, allow the IMP to be used other than as directed by this clinical trial protocol, or dispose of IMP in any other manner.

8.8.1 Treatment accountability and compliance

The investigator or pharmacist will inventory and acknowledge receipt of all shipments of the IMP. The study drug must be kept in a locked area with restricted access. The study drug must be stored and handled in accordance with the manufacturer's instructions. The investigator or pharmacist will also keep accurate records of the quantities of the study drugs dispensed and used by each patient. The study monitor will periodically check the supplies of study drugs held by the investigator or pharmacist to verify accountability of all study drugs used. At the conclusion of the study, all unused study drugs and all medication containers will preferably be destroyed at the investigational site (at a locally authorized facility) according to local regulation unless other arrangements have been approved by the Sponsor. Destruction of unused vials will occur only after drug accountability has been performed and written permission for destruction has been obtained. Used medication vials may be destroyed during the conduct of the study as required by the institution.

The investigator or sub-investigator will supervise administration of the investigational drug. Any delegation of this responsibility must follow Section 13.1.

The person responsible for drug dispensing is required to maintain adequate records of all study drugs. These records (eg, drug inventory form) include the date the study medication is received from the Sponsor, dispensed for patient, and destroyed or returned to the Sponsor as detailed in Section 8.8.2). The fixed label portions of all the cabazitaxel vials administered to patients must be completed (patient number, date of infusion). The batch number/Kit number on the vial must be recorded on the CRF/drug accountability form.

The person responsible for drug administration to the patient will record precisely the dose, date, and time the drug is administered to the patient.

8.8.2 Return and/or destruction of treatments

Partially used cabazitaxel, abiraterone acetate and enzalutamide (when applicable) will be destroyed on site according to standard practices of the site.

Unused Cabazitaxel, abiraterone acetate and enzalutamide (when applicable) will be destroyed on site after final batch accountability has been validated by the sponsor monitoring team representative and only after having received written authorization from the sponsor.

In the event of a potential defect in the quality of IMP, it may be necessary for the Sponsor to initiate a recall procedure. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall IMP and eliminate potential hazards.

8.9 CONCOMITANT MEDICATION

Concomitant medications should be kept to a minimum during the study. However, if these are considered necessary for the patient's welfare and are unlikely to interfere with the IMP, they may be given at the discretion of the investigator and recorded in the e-CRF.

The following concomitant treatments are not permitted during this study:

- Concurrent treatment with other investigational drugs.
- Concurrent treatment with any other anticancer therapy including immunotherapy, targeted therapy or biological therapies.
- Concurrent treatment with strong inhibitors of cytochrome P450 3A4, such as ketoconazole, itraconazole, clarythromycin. For patients who were receiving treatment with such agents, a one-week washout period is required prior to randomization (see Appendix I).
- Concurrent treatment with potent strong or moderate inducers of cytochrome P450 3A4, such as the antiepileptic drugs carbamazepine, phenytoin, phenobarbital, and St John Wort (millepertuis). For patients who were receiving treatment with such agents, a two-week washout period is required prior to randomization (see Appendix I).
- Concurrent treatment with CYP2D6 substrates and that have a narrow therapeutic window (see Appendix I).
- Concurrent treatment with strong or moderate inducers or strong inhibitors of CYP2C8 (see Appendix I).
- Concurrent treatment with CYP3A4, CYP2C9 and CYP2C19 with a narrow therapeutic index (see Appendix I).

The following concomitant treatments are permitted during this study:

- LH-RH agonists that are ongoing prior to study entry. In addition, patients who are treated with LH-RH agonists (ie, without orchiectomy) should continue this therapy during the study treatment period.
- The use of bisphosphonates and denosumab are allowed, however the dose must be stable for 4 weeks prior to enrollment and during the study treatment period (though bisphosphonate treatment may be discontinued during the study treatment period).
- Ancillary treatment must be given as medically indicated; they must be specified in the CRF.
- Primary prophylactic G-CSF is required at each cycle for all patients in Cabazitaxel arm.
- Patients with severe diarrhea should be carefully monitored and given fluid and electrolyte replacement if they become dehydrated. Standard antidiarrheal treatments (eg, loperamide) are recommended.
- Supportive treatment as medically indicated for the patient's well-being (including hyperalimentation and blood transfusion) may be prescribed at the investigator's discretion. Every medication or treatment taken by the patient during the trial and the reason for its administration must be recorded on the CRF.
- Use of erythropoietin for chemotherapy-related anemia.

9 ASSESSMENT OF IMP

9.1 PRIMARY ENDPOINT

Radiographic Progression-Free Survival (rPFS) defined as the time from randomization to the occurrence of one of the following:

- Radiological tumor progression using RECIST 1.1 (see Appendix A). except for lymph nodes: if lymph node metastasis is the only evidence of metastasis at baseline, it must be ≥ 20 mm in diameter when measured by spiral CT or MRI (as defined by PCWG2).
- Progression of bone lesions using PCWG2 criteria:
  - The first bone scan with ≥2 new lesions compared to baseline is observed <12 weeks from randomization and is confirmed by a second bone scan taken ≥6 weeks later showing ≥ 2 additional new lesions compared to previous bone scan (a total of ≥4 new lesions compared to baseline);
  - The first bone scan with ≥2 new lesions compared to baseline is observed ≥12 weeks from randomization and these ≥2 new lesions are verified on the next bone scan ≥6 weeks later (a total of ≥2 new lesions compared to baseline).
- Death due to any cause.

9.2 SECONDARY ENDPOINTS

9.2.1 PSA endpoints

PSA-derived efficacy endpoints in this study will include PSA response, duration of PSA response and Time to PSA progression. For each patient, PSA will be assessed at baseline, every 3 weeks during study treatment, and in case of study treatment discontinuation without PSA progression every 12 weeks until the end of the first further anticancer therapy if any or study cut-off, whichever comes first. Two PSA determinations are needed to define PSA progression.

9.2.1.1 PSA response

PSA response defined as a decline of serum PSA from baseline of ≥50% confirmed at least 3 weeks later. It will be calculated among patients with a baseline PSA ≥2 ng/mL. Increases (of any magnitude) in PSA during the first 12 weeks should be ignored in determining PSA response.

9.2.1.2 Time to PSA progression (TTPP)

Time to PSA progression is defined as the time interval between the date of randomization and the date of first documented PSA progression.

PSA progression is defined as (see Appendix B):

- If decline from baseline value: an increase of ≥25% (at least 2 ng/mL) over the nadir value, confirmed by a second PSA value at least 3 weeks apart.
- If no decline from baseline value: an increase of ≥25% (at least 2 ng/mL) over the baseline value after 12 weeks of treatment, confirmed by a second PSA value at least 3 weeks apart.

Early increase in PSA within 12 weeks, when followed by subsequent decline, is ignored in determining this endpoint. Early rise in PSA only indicates progression if it is associated with another sign of disease progression or if it continues beyond 12 weeks. Progression will only be dated prior to 12 weeks if there is continued increase in PSA beyond that time point or if it was associated with another sign of disease progression.

9.2.2 Progression free survival

Progression free survival (PFS), excluding PSA progression, will be evaluated from the date of randomization to the date of the first documentation of any of the following events:

- Radiological tumor progression using RECIST 1.1 except for lymph nodes: if lymph node metastasis is the only evidence of metastasis at baseline, it must be ≥ 20 mm in diameter when measured by spiral CT or MRI (as defined by PCWG2).
- Progression of bone lesions using PCWG2 criteria (see Section 9.1 for details).
- Symptomatic progression is defined as:
  - Developing urinary or bowel symptoms related to prostate cancer,
  - Needing to change anti-cancer therapy (most commonly, needing to administer radiation therapy for palliating an osseous or epidural lesion).
- Pain progression.
- Or death due to any cause.

9.2.3 Tumor endpoints

9.2.3.1 Tumor response

Tumor response will be analyzed using (RECIST 1.1), in patients with measurable disease.

Tumor response is defined as either a partial response (PR) or complete response (CR) according to the RECIST 1.1 criteria (see Appendix A).

9.2.3.2 Duration of tumor response

Duration of tumor response is defined as the time between the first evaluation at which the response criteria (PR-CR as per RECIST 1.1) are met and the first documentation of tumor progression.

9.2.4 Pain endpoints

Diary will be utilized to collect pain scores in all patients (see Appendix E). The Brief Pain Inventory-Short Form (BPI-SF) will be utilized to assess pain. Pain scores (WHO Analgesic Ladder (see Appendix F) and BPI-SF) will be assessed in all patients at baseline, before each cycle, at the end of treatment and then every 12 weeks until disease progression, start of another anticancer therapy or study cut-off, whichever comes first.

9.2.4.1 Pain response

Pain response is defined as:

- a decrease by <30% from baseline in the average of BPI-SF pain intensity score observed at 2 consecutive evaluations ≥3 weeks apart without increase in analgesic usage score.

Either criterion has to be maintained for two consecutive evaluations at least 3 weeks apart.

Increases in pain during the first 12 weeks should be ignored in determining pain response.

9.2.4.2 Time to pain progression

Time to pain progression is defined as the time interval between the date of randomization and the date of either first documented pain progression.

Pain progression, in patients with no pain or stable pain at baseline, is defined as:

- an increase by ≥30% from baseline in the BPI-SF pain intensity score observed at 2 consecutive evaluations ≥3 weeks apart without decrease in analgesic usage score OR increase in analgesic usage score ≥ 30%.

Either criterion has to be maintained for two consecutive evaluations at least 3 weeks apart.

Early rise in pain (within the first 12 weeks) only indicates progression if it is associated with another sign of disease progression or if it continues beyond 12 weeks. Progression will only be dated prior to 12 weeks if there is continued increase in pain beyond that time point or if it was associated with another sign of disease progression.

9.2.5 Symptomatic Skeletal Events

9.2.5.1 SSE rate

SSE assessment will be performed by clinical evaluation. Occurrence of SSE is defined as:

- The occurrence of a new symptomatic pathological fracture, or
- The use of external beam radiation to relieve bone pain, or
- The occurrence of spinal cord compression, or
- Tumour-related orthopeadic surgical intervention

SSE is not a criterion of progression.

9.2.5.2 Time to occurrence of SSE

Time to SSE is defined as the time interval between the date of randomization and the date of the occurrence of the first event defining a SSE, whichever is earlier. For each patient, SSE will be assessed at baseline, every 3 weeks during study treatment, at the end of treatment visit and every 12 weeks during follow-up until occurrence of first SSE or study cut-off, whichever comes first.

9.2.6 Overall Survival

The OS is defined as the time interval from the date of randomization to the date of death due to any cause.

9.2.7 Health-Related Quality Of Life and Health status/utility

- Health-related Quality of Life (HRQOL) as assessed by FACT-P within 3 days prior the first study treatment, the first day of each cycle prior to treatment administration, at the end of treatment visit and every 12 weeks during the follow-up period until disease progression, start of another anticancer therapy or study cut off, whichever comes first.

  The core questionnaire and prostate modules have been tested for reliability and validity (37, 38, 39). Questionnaires will be self-administered, it takes approximately 10 minutes to complete.

  The FACT-P scale, developed by Cella et al. (37), before each cycle administration and at the end of study treatment. It consists of 5 (4 core + additional concerns) subscales:
  - physical well-being (PWB): 7 questions
  - social/family well-being (SWB): 7 questions
  - emotional well-being (EWB): 6 questions
  - functional well-being (FWB): 7 questions
  - prostate-specific concerns (PSC): 12 questions

  The FACT-P is summed to give a score in the range of 0-156, where higher values represent better HRQL.

- Health status evaluation will be performed using EQ-5D-5L questionnaire.

  A generic measure, the 5-Level EuroQol Group's 5-Dimension (EQ-5D-5L) questionnaire will be evaluated within 3 days prior the first study treatment, the first day of each cycle prior to treatment administration, at the end of treatment visit and every 12 weeks during the follow-up period until disease progression, start of another anticancer therapy or study cut-off, whichever comes first.

9.2.8 Biomarkers

[redacted]

9.3 SAFETY ENDPOINT

9.3.1 Adverse events

Treatment-emergent adverse events: Type according to MedDRA (Medical Dictionary for Regulatory Activities), frequency and severity according to NCI CTCAE V4.0, seriousness, and relationship to study treatment will be assessed.

Refer to Section 10.4 to Section 10.7 for details.

9.3.2 Laboratory safety variables

The clinical laboratory data consist of blood analysis (including hematology, clinical chemistry and urinalysis). Clinical laboratory values will be analyzed after conversion into standard international units. International units will be used in all listings and tables.

Laboratory abnormalities will be assessed according to the NCI CTCAE v.4.0.

9.3.3 Vital signs

Vital signs include: blood pressure, heart rate.

9.3.4 ECG variables

ECG data will be assessed by the Investigator based on the automatic device reading.

ECG parameters include: normal or abnormal.

9.4 OTHER ENDPOINTS

Additional Exploratory Collaborative End-Points include:

- [redacted]
- [redacted]

Special procedure for collection, storage and shipping of samples will be described in the laboratory manual.

9.5 FUTURE USE OF SAMPLES

Not all of the blood samples obtained during this study may be used for the tests that are part of the clinical trial. Following the conclusion of the study, the samples may be used for additional research. This research will help to understand disease subtypes, drug response, and toxicity, and possibly to identify new drug targets or biomarkers that predict subject response to treatment. The use of the samples for internal research will be done in accordance with the guidelines defined by the Food and Drug Adminstration (FDA) document “Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable” (issued 25 April 2006) and European Medicines Agency’s (EMEA’s) “Reflection Paper on Pharmacogenetic Samples, Testing, and Data Handling” (EMEA 2007). If a subject requests destruction of their blood samples, and the samples have not yet been de-identified, the sponsor (or central laboratory) will destroy the samples as described in this FDA guidance. The sponsor (or central laboratory) will notify the investigator in writing that the samples have been destroyed.

10 STUDY PROCEDURES

10.1 VISIT SCHEDULE

All patients entering the study must be evaluated according to the schedule outlined in the study Flow Chart (see Section 1.2) and described below. The results of the evaluation will be recorded on the appropriate e-CRF pages until the patients are not followed any longer (End of Study).

10.1.1 Screening

Each potential patient will be examined before the start of the study to determine his eligibility for participation. These tests are to be performed within 4 weeks prior to study randomization, with the exception of physical examination, biological tests, PSA measurement and ECG that must be performed no more than 8 days before randomization. If the time between biological baseline work-up and first administration of study treatment is more than 8 days, biological tests should be done again to check that eligibility criteria are still met. The written informed consent will have to be signed by the patient before any protocol specific procedures.

The following examinations will be performed:

- **Inclusion/Exclusion criteria** within 8 days prior randomization.
- **Demographic characteristics** within 4 weeks prior randomization.
- **Physical examination** within 8 days prior randomization including major body systems exam, height and weight, ECOG performance status (PS), and vital signs (blood pressure, heart rate).
- **Medical, surgical and oncological history** including significant prior and concurrent illnesses, primary diagnosis and prior antitumor therapy. Renal medical history which should include co-morbidities at risk of renal impairment (eg, diabetes) and medication at risk of renal function impairment (such as bisphosphonates, non-steroids anti-inflammatory drugs, aminoglycosides antibiotics, etc.) should be documented before randomization.
- **Concomitant medications** will be recorded from 4 weeks prior to randomization.
- **Pain assessment and analgesic for cancer pain**: diary information should be collected using the BPI-SF (see Appendix E) and WHO Analgesic Ladder will be evaluated (see Appendix F) based on the analgesic consumption at baseline within 3 days prior to the first treatment administration.
- **Symptomatic Skeletal Events** within 8 days before randomization: The use of external beam radiation to relieve bone pain, or occurrence of a new symptomatic pathological fracture, or occurrence of spinal cord compression, or tumor-related orthopedic surgical intervention.
- **12-lead ECG** within 8 days prior randomization.

- **Hematology** within 8 days prior D1 cycle 1 (time between hematological work-up and D1 cycle 1 should not exceed 8 days; if time exceed 8 days, hematological work-up should be repeated): WBC with differential count, hemoglobin, platelet count. To be repeated before cycle 1 if the time between baseline biological work-up and first administration of study treatment is more than 8 days, to check that eligibility criteria are still met.
- **Blood Chemistry and Coagulation tests** within 8 days prior D1 cycle 1 (time between biochemistry work-up and D1 cycle 1 should not exceed 8 days; if time exceed 8 days, biochemistry work-up should be repeated): sodium, potassium, calcium, phosphorus, BUN, magnesium, creatinine, total protein, albumin, SGOT (AST), SGPT (ALT), alkaline phosphatase, total bilirubin, glucose, lactate dehydrogenase (LDH), and INR (at baseline, and then within further cycles if needed). To be repeated before cycle 1 if the time between baseline biological work-up and first administration of study treatment is more than 8 days, to check that eligibility criteria are still met. In addition and only at baseline: serum Chromogranin A (CgA).
- **Blood sample for CTCs assay:** 1 sample will be taken within 8 days prior randomization.

[redacted]

- **PSA** (last PSA if progression is defined by rising PSA) within 8 days prior randomization: in case of rising PSA alone 2 sequential increases above the previous lowest reference value obtained at least 1-week apart are required. A PSA value at study entry of at least 2 ng/mL is required.
- **Serum testosterone** measurement within 4 weeks prior to randomization
- **Tumor assessment** within 4 weeks prior to randomization (6 weeks for bone scan): whole body (abdominal/pelvic/chest) CT-Scan or MRI, bone scan and all other exams as clinically indicated (e.g. brain CT-Scan or MRI in case of clinical suspicion of central nervous system involvement) to assess all TARGET or NON TARGET lesions (measurable and non-measurable). CT-Scan/MRI will be preferred to X-Ray for the purposes of efficacy assessment. To ensure comparability, the imaging should be performed using identical techniques throughout the study period (ie, CT-scan or MRI, scans performed immediately following bolus contrast administration using a standard volume of contrast, the identical contrast agent, and preferably the same scanner). When available, spiral CT acquisition should be done. Slice thickness should be adapted to the anatomical area and presumed size of the lesions. Slice thickness of 5 to 8 mm should be favored rather than 10 mm, especially during spiral acquisition.

  If limitations appear in volume acquisition, it is encouraged to choose a 1.5 pitch and thin slices, rather than a 1 pitch with thick slices. A centimeter scale should appear on films.
- **HRQOL and Health status questionnaires**: FACT-P and EQ-5D-5L questionnaires will be completed within 3 days prior to the first study administration (see Appendix G; Appendix H).
- **Other investigations** if clinically indicated.

10.1.2 Randomization

Randomization will take place once the consented patient has completed all the necessary screening procedures and is deemed eligible for study entry by the investigator or designee. All eligible patients must be randomized by contacting the IVRS/IWRS (see Section 8.5).

The results of the screening examinations will be recorded in each randomized patient's CRF. Source documentation to support the screening results must be maintained in the patient's medical record. Treatment should begin within 7 days after randomization.

10.1.3 During study treatment

- **Physical examination** before each cycle including major body systems exam, weight, ECOG performance status (PS), and vital signs (blood pressure, heart rate).
- **Adverse events** assessment: at each cycle
- **Pain assessment and analgesic for cancer pain**: diary information should be collected using the BPI-SF (see Appendix E) and WHO Analgesic Ladder will be evaluated (see Appendix F) based on the analgesic consumption at D1 prior each cycle.
- **Symptomatic Skeletal events**: The use of external beam radiation to relieve bone pain, or occurrence of a new symptomatic pathological fracture, or occurrence of spinal cord compression, or tumor-related orthopedic surgical intervention.
- **Concomitant medications** will be recorded at every cycle.
- **Hematology** will be done before each study treatment administration (-3 days window is allowed) and in case of fever or infection: WBC with differential count, hemoglobin, platelet count.

  In addition, hematology will be performed every week (D8 and D15) during the 3 first cycles (+/- 1 day window is allowed) and then within further cycles in case of fever or infection.
- **Blood Chemistry** will be done before each study treatment administration (-3 days window is allowed): sodium, potassium, calcium, phosphorus, BUN, magnesium, creatinine, total protein, albumin, SGOT (AST), SGPT (ALT), alkaline phosphatase, total bilirubin, glucose, LDH.

  In addition, blood chemistry (sodium, potassium, calcium, BUN, magnesium, creatinine, SGOT (AST), SGPT (ALT), total bilirubin) will be performed every week (D8 and D15) during the 3 first cycles (± 1 day window is allowed).
- **Blood sample for CTCs**: 1 sample will be taken at Cycle 2D1.
- **PSA**: before each next cycle.
- **Tumor assessment** every 12 weeks (+/- 1 week) after first study treatment administration: whole body (abdominal/pelvic/chest) CT-Scan or MRI, bone scan and all other exams as clinically indicated (e.g. brain CT-Scan or MRI in case of clinical suspicion of central nervous system involvement) to assess all TARGET or NON TARGET lesions should be

assessed. To ensure comparability, the imaging should be performed using identical techniques throughout the study period (ie, scans performed immediately following bolus contrast administration using a standard volume of contrast, the identical contrast agent, and preferably the same scanner).

- **HRQOL and Health status questionnaires**: FACT-P and EQ-5D-5L questionnaires will be completed before each cycle administration (see Appendix G; Appendix H).
- **Patient's diary** to record the consumption of abiraterone acetate or enzalutamide and/or prednisone or prednisolone.
- **Other investigations** if clinically indicated.

10.1.4 End of treatment

All patients must continue to be observed for at least 30 days after the final dose of study treatment. The following procedures should be performed within the 22-30 days following the final dose of study treatment:

- **Physical exam:**
  ECOG PS, weight, examination of major body systems, including vital signs (blood pressure, heart rate).
- **12-lead ECG** only if clinically indicated or cardiac event during the treatment period.
- **Adverse events** assessments.
- **Pain assessment and analgesic** for cancer pain.
- **Symptomatic Skeletal events**: The use of external beam radiation to relieve bone pain, or occurrence of a new symptomatic pathological fracture, or occurrence of spinal cord compression, or tumor-related orthopedic surgical intervention.
- **Hematology**: WBC with differential count, hemoglobin, platelet count.
- **Blood Chemistry**: sodium, potassium, calcium, phosphorus, BUN, magnesium, creatinine, total protein, albumin, SGOT (AST), SGPT (ALT), alkaline phosphatase, total bilirubin, glucose, LDH.
- **Blood sample for CTCs assay**: 1 sample will be taken at relapse or EOT.
- [redacted]
- **Concomitant medications** assessments.
- PSA.
- Tumor assessment, if end of treatment visit occurs at the time of a planned tumor assessment:

  whole body (abdominal/pelvic/chest) CT-Scan or MRI, bone scan and all other exams as clinically indicated (eg, brain CT-Scan or MRI in case of clinical suspicion of central nervous system involvement) to assess all TARGET or NON TARGET lesions (measurable and non-measurable).

- **HRQOL and Health status questionnaires:** FACT-P and EQ-5D-5L (see Appendix G; Appendix H).
- **Other investigations** if clinically indicated.

10.1.5 Follow-up period

All patients will be followed every 12 weeks (+/- 1 week) (after end of treatment visit):

- Survival status.
- ECOG PS, weight until disease progression, start of another anticancer therapy or cut-off date, whichever comes first.
- All SAEs and/or related to study treatment AEs ongoing at the end of the study, or new related to study treatment AE which occur during the follow-up period will be recorded until recovery, or stabilization of patient's condition.
- Concomitant medications if correspond to treatment of related AEs.
- Pain and analgesic for cancer pain: until disease progression, start of another anticancer therapy or cut-off date, whichever comes first. The diary information should be collected at each scheduled visit.
- Symptomatic Skeletal events: The use of external beam radiation to relieve bone pain, or occurrence of a new symptomatic pathological fracture, or occurrence of spinal cord compression, or tumor-related orthopedic surgical intervention, until the occurrence of first SSE or study cut-off date, whichever comes first.
- PSA: until the end of the first further anticancer therapy if any or the study cut-off date, whichever comes first.
- Tumor assessment until radiological PD, start of another anticancer therapy or study cut-off if patient discontinued study treatment without radiological progressive disease:

  whole body (abdominal/pelvic/chest) CT-Scan or MRI, bone scan and all other exams as clinically indicated (eg brain CT-Scan or MRI in case of clinical suspicion of central nervous system involvement) to assess all TARGET or NON TARGET lesions should be assessed. To ensure comparability, the imaging should be performed using identical techniques throughout the study period (ie, scans performed immediately following bolus contrast administration using a standard volume of contrast, the identical contrast agent, and preferably the same scanner).
- **HRQOL and Health status questionnaire:** FACT-P and EQ-5D-5L (see Appendix G; Appendix H), until disease progression, start of another anticancer therapy or study cut-off, whichever comes first.
- **Further anticancer therapy:** All efforts should be made to document radiographic progression before initiation of further therapy. In case of treatment discontinuation due to reason other than radiographic progressive disease (for example discontinuation due to adverse event), The choice of further therapy, if any, is let to investigator, and data concerning first further therapy must be documented.

10.1.6 Post study cut-off date

Patients still on study treatment at the cut-off date can continue study treatment until at least 1 treatment discontinuation criterion as defined in Section 10.3.2 is met. The following information will be collected during the study treatment administration:

- IMP administration.
- All SAEs regardless of relationship to study treatment and AEs considered related to study treatment.
- End of treatment reason.
- No follow-up information will be collected after these patients discontinue study treatment except all SAEs still ongoing at the end of study treatment and all AEs considered as related to study treatment still ongoing or occurring after the end of study treatment, which will be followed until resolution/stabilization.

10.2 DEFINITION OF SOURCE DATA

Source data includes all information in original records and certified copies of original records of clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents.

Source documents are original documents, data and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, patient diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcripts certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at the pharmacy, at the laboratories, and at medical-technical departments) involved in the clinical study. Source documentation must be maintained to support information provided within a CRF.

The results of certain examinations or evaluations recorded in the CRF may be considered to be source data (such as patient's BPI-SF, WHO Analgesic Ladder...).

10.3 HANDLING OF PATIENT TEMPORARY OR PERMANENT TREATMENT DISCONTINUATION AND OF PATIENT STUDY DISCONTINUATION

The IMP should be continued whenever possible. In case the IMP is stopped, it should be determined whether the stop can be made temporarily; permanent IMP discontinuation should be a last resort. Any IMP discontinuation should be fully documented in the CRF. In any case, the patient should remain in the study as long as possible.

Patients will be followed up according to the study procedures as specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last.

If possible, and after the permanent discontinuation of treatment, the patients will be assessed using the procedure normally planned for the last dosing day with the IP.

All permanent treatment discontinuation should be recorded by the Investigator in the appropriate pages when considered as confirmed.

10.3.1 Permanent treatment discontinuation with IMP(s)

Permanent treatment discontinuation is any treatment discontinuation associated with the definitive decision from the Investigator or the patient not to re-expose the patient to the IMP at any time.

10.3.2 List of criteria for permanent treatment discontinuation

The patients may withdraw from treatment with the IMP if they decide to do so, at any time and irrespective of the reason, or this may be the Investigator's decision. All efforts should be made to document the reasons for treatment discontinuation and this should be documented in the e-CRF.

- The patients may withdraw from treatment if they decide to do so, at any time and irrespective of the reason or at the request of their legally authorized representative. "Legally authorized representative" means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective patient to the patient's participation in the procedure(s) involved in the research.
- If, in the investigator's opinion, continuation of the treatment would be detrimental to the patient's well-being, such as:
  - Radiographic disease progression as defined in Section 9.1,
  - Unacceptable AE(s) not manageable by symptomatic therapy, dose delay or dose modification (see Section 8.1.2.3),
  - Intercurrent illness that prevents further administration of study treatment,
  - Non-compliance to the study protocol or logistic consideration.
- Patient is lost to follow-up.

In all cases, the reason for and date of withdrawal must be recorded in the e-CRF and in the patient's medical records. The patient must be followed up to establish whether the reason was an AE, and, if so, this must be reported in accordance with the procedures in Section 10.4.

Any abnormal laboratory value or ECG parameter will be immediately rechecked for confirmation after 24 hours for making a decision of permanent discontinuation of the IMP for the concerned patient.

10.3.3 Handling of patients after permanent treatment discontinuation

Patients will be followed-up according to the study procedures as specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last.

If possible, and after the permanent discontinuation of treatment, the patients will be assessed using the procedure normally planned for the last dosing day with the IMP.

All cases of permanent treatment discontinuation should be recorded by the Investigator in the appropriate pages of the CRF when considered as confirmed.

10.3.4 Procedure and consequence for patient withdrawal from study

The patients may withdraw from the study before study completion if they decide to do so, at any time and irrespective of the reason. Withdrawal of consent for treatment should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-patient contact follow-up, eg, medical records check. Patients requesting withdrawal should be informed that withdrawal of consent for follow-up may jeopardize the public health value of the study.

If possible, the patients are assessed using the procedure normally planned for the end-of-study visit.

Patients who withdraw should be explicitly asked about the contribution of possible AEs to their decision to withdraw consent, and any AE information elicited should be documented. Preferably the patient should withdraw consent in writing and, if the patient or the patient's representative refuses or is physically unavailable, the site should document and sign the reason for the patient's failure to withdraw consent in writing.

All study withdrawals should be recorded by the Investigator in the appropriate screens of the e-CRF and in the patient's medical records when considered as confirmed. In the medical record, at least the date of the withdrawal and the reason should be documented.

For patients who fail to return to the site for the EOT visit, unless the patient withdraws the consent for follow-up, the Investigator should make the best effort to contact the patient (e.g., contacting patient's family or private physician, reviewing available registries or health care databases), and to determine his/her health status, including at least his/her vital status. Attempts to contact such patients must be documented in the patient's records (e.g., times and dates of attempted telephone contact, receipt for sending a registered letter).

The statistical analysis plan will specify how these patients lost to follow-up for their primary endpoints will be considered.

Patients who have withdrawn from the study cannot be re-randomized (treated) in the study. Their inclusion and treatment numbers must not be reused.

10.4 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.4.1 Definitions of AEs

10.4.1.1 AE

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

10.4.1.2 SAE

A SAE is any untoward medical occurrence that at any dose:

- Results in death, or
- Is life-threatening, or;

Note: 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 inpatient hospitalization or prolongation of existing hospitalization, or
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect
- Is a medically important event:

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention (ie, specific measures or corrective treatment) to prevent one of the other outcomes listed in the definition above.

Note: The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered as a medically important event. The list is not intended to be exhaustive:

- Intensive treatment in an emergency room or at home for:
  - Allergic bronchospasm
  - Suspected transmission of an infectious agent because it is applicable as administration route is IV.
  - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc),
  - Convulsions (seizures, epilepsy, epileptic fit, absence, etc).
  - Development of drug dependence or drug abuse
  - ALT >3 x ULN + total bilirubin >2 x ULN or asymptomatic ALT increase >10 x ULN
  - Suicide attempt or any event suggestive of suicidality
  - Syncope, loss of consciousness (except if documented as a consequence of blood sampling)
  - Bullous cutaneous eruptions
  - Cancers diagnosed during the study or aggravated during the study (only if judged unusual/significant by the Investigators in oncology studies)
  - Chronic neurodegenerative diseases (newly diagnosed) or aggravated during the study (only if judged unusual/significant by the Investigators in studies assessing specifically the effect of a study drug on these diseases).

10.4.1.3 Adverse event of special interest

An AE of special interest (AESI) is an AE (serious or non-serious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added or removed during a study by protocol amendment.

- Pregnancy occurring in a female partner of a male subject entered in a study with IMP/NIMP;
  - Pregnancy occurring in a female partner of a male patient entered in the clinical trial. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Section 10.4.1.2).
  - Follow-up of the pregnancy is mandatory until the outcome has been determined.
- Symptomatic overdose (serious or non-serious) with IMP/NIMP

An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the patient and defined as increase of at least 30% of the highest dose of cabazitaxel (ie, 30% of 25 mg/m²) to be administered.

Of note, asymptomatic overdose has to be reported as a standard AE.

10.4.2 General guidelines for reporting AEs

- All AEs, regardless of seriousness or relationship to IMP/NIMP, spanning from the signature of the informed consent form until the end of the treatment period (defined as: until 30 days after the last administration of study drugs), are to be recorded on the corresponding page(s) or screen(s) of the CRF. During the follow-up period, only ongoing related or new related AEs (ie, regardless of seriousness) will be recorded on the corresponding page(s) or screen(s) of the CRF. Serious adverse events (SAEs) ongoing at the end of the study treatment will be followed during the follow-up period until resolution or stabilization regardless of relationship with study drugs.
- 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 IMP, 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 IMP or by the study procedure(s).
- The Investigator should take appropriate measures to follow all AEs until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized, or until death, in order to ensure the safety of the patients. This may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the monitoring team up to as noticed by the Sponsor.
- When treatment is prematurely discontinued, the patient's observations will continue until the end of the study as defined by the protocol for that patient.

- Laboratory, vital signs or ECG abnormalities are to be recorded as AEs only if:
  - Symptomatic and/or
  - Requiring either corrective treatment or consultation, and/or
  - Leading to IMP discontinuation or modification of dosing, and/or
  - Fulfilling a seriousness criterion, and/or

10.4.3 Instructions for reporting SAEs

In the case of occurrence of an SAE, the Investigator must immediately:

- ENTER (within 24 hours) the information related to the SAE in the appropriate screens of the e-CRF; the system will automatically send a notification to the monitoring team after approval of the Investigator within the e-CRF or after a standard delay.
- SEND (preferably by fax or e-mail) a photocopy of all examinations carried out and the dates on which these examinations were performed, to the representative of the monitoring team whose name, fax number, and email address appear on the clinical trial protocol. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the clinical trial are properly mentioned on any copy of a source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.
- All further data updates should be recorded in the e-CRF as appropriate, and further documentation as well as additional information (for laboratory data, concomitant medications, patient status, etc) should be sent (by fax or e-mail) to the monitoring team within 24 hours of knowledge of the SAE. In addition, every effort should be made to further document any SAE that is fatal or life threatening within a week (7 days) of the initial notification.
- A back-up plan (using a paper CRF process) is available and should be used when the e CRF system does not work.

Any SAE brought to the attention of the Investigator at any time after the end of the study for the patient and considered by him/her to be caused by the IMP with a reasonable possibility, should be reported to the monitoring team.

10.4.4 Guidelines for reporting AEs of special interest

For AESIs, the Sponsor must be informed immediately (ie, within 24 hours), as per SAE notification guidelines described in Section 10.4.3, even if not fulfilling a seriousness criterion, using the corresponding pages of the CRF (to be sent) or screens in the e-CRF.

10.5 OBLIGATIONS OF THE SPONSOR

During the course of the study, the Sponsor will report in an expedited manner:

- All SAEs that are both unexpected and at least reasonably related to the IMP (SUSAR), to the regulatory authorities, IECs/IRBs as appropriate and to the Investigators.
- All SAEs that are expected and at least reasonably related to the IMPs to the regulatory authorities, according to local regulations.

In this study, some AEs are considered related to the underlying condition and thus will not be considered unexpected (40).

Any other AE not listed as an expected event in the Investigator's Brochure (40) or in this protocol will be considered unexpected.

The Sponsor will report all safety observations made during the conduct of the trial in the clinical study report.

10.6 SAFETY INSTRUCTIONS

10.6.1 Physical examination

Physical examination will include, but not limited to the examination of major body systems:

- Vital signs (blood pressure, heart rate),
- Height (screening only), body weight,
- ECOG performance status (see Appendix D).

If abnormal findings emerge or worsen or become serious from the baseline assessment, then the AE page of the CRF should be completed for these findings. If a finding meets the criteria for a SAE, then the appropriate procedures for reporting such events should be followed as described in Section 10.4.3. Height will be recorded at baseline only. Body weight and ECOG PS will be recorded at baseline, prior to the start of each treatment cycle (every 3 weeks (+/- 1 week)) and every follow up visit (every 12 weeks) (+/- 1 week)) until death or cut-off date whichever comes first.

Every attempt should be made to have the same study personnel to perform the assessment throughout the study for any given patient for consistency of grading.

10.6.2 Laboratory variables

Hematology panel and blood chemistry profile will be performed by a local laboratory. Baseline results must be available for eligibility determination. At the start of each new treatment cycle, results must be available prior to treating the patient with the study drug. In addition, hematological test will be performed every week (D8 and D15) during the 3 first cycles and then within further cycles only in case of fever or infection.

10.7 ADVERSE EVENTS MONITORING

All events will be managed and reported in compliance with all applicable regulations, and included in the final clinical study report.

11 STATISTICAL CONSIDERATIONS

11.1 DETERMINATION OF SAMPLE SIZE

In post-docetaxel setting, the HR for rPFS is 0.66 [0.58-0.76] between abiraterone/prednisone and prednisone in COU-AA-301 (5) and 0.40 [0.35-0.47] between enzalutamide and placebo in AFFIRM (6).

In pre-docetaxel setting, the HR for rPFS is 0.53 [0.45 to 0.62] between abiraterone/prednisone and prednisone in COU-AA-302 (7) and 0.19 [0.15-0.23] between enzalutamide and placebo in PREVAIL (8). We thus consider that a HR of 0.67 should be considered as the smallest effect of clinical interest between cabazitaxel and an AR-targeted agent (abiraterone or enzalutamide).

The following table presents how such a HR translates for a variety of envisaged median rPFS in the abiraterone acetate or Enzalutamide group (9)(10).

Hazard Ratio	median rPFS (month)	
	Abiraterone acetate or Enzalutamide group	Cabazitaxel group
0.67	4	6.0
0.67	5	7.5
0.67	6	9.0

A total of 196 patients with event is needed to achieve 80% power to demonstrate rPFS superiority of Cabazitaxel over abiraterone acetate/prednisone or enzalutamide by 2 sided log rank test at 0.05 type I error rate.

At the time of the cut-off date, when the primary analysis will be conducted, events will be censored in some patients either by end-of-study or by cut-off date. This phenomenon is estimated with [redacted]; 10% of patients are estimated to achieve the end-of-study (as currently censored either by events or by last contact in on-going patients) by 7.5 months.

The observed accrual rates, that have been lower than expected, have been considered for this new sample size calculation:

Period	Starting at time	Accrual rate (Patients per month)
1	Mid-November 2015 = M0	3
2	Mid-October 2016 = M11	8
3	Mid-February 2017 = M15	7
4	Mid-August 2017 = M25	12
5	Mid-December 2017=M29 (up to end of June 2018)	12

A total of 234 patients in 2 arms (117 patients per arm) are anticipated to be needed to reach the targeted number of patients with event. This new target should be achieved for an estimated constant accrual rate equal to 12 until the end of the recruitment expected in June 2018.

11.2 DISPOSITION OF PATIENTS

The total number of patients for each of the following categories will be provided into a summary table:

- Intent to Treat (ITT) patients.
- Safety population patients.
- Evaluable patients for tumor response, for PSA response, as well as for pain response.
- HRQOL and Health status populations.

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

For any patient randomized more than once, only the data associated with the first randomization will be used in any analysis population. The safety experience associated with any later randomization will be assessed separately.

The safety experience of patients treated and not randomized will be reported separately, and these patients will not be in the safety population.

11.3 ANALYSIS POPULATIONS

Screened patients are defined as patients who meet the inclusion criteria.

Allocation of randomized treatment to eligible patients (patients who meet all inclusion/exclusion criteria) will be centrally performed using an IVRS/IWRS. A patient is considered as randomized as soon as there is confirmation of successful allocation of a randomization number through the IVRS/IWRS.

Patients allocated outside the IVRS/IWRS will not be taken into account in any of the analyses.

11.3.1 Efficacy populations

11.3.1.1 Intent–to-treat population

The primary efficacy population is the Intent-To-Treat (ITT) population which includes all randomized patients. The patients will be analyzed in the treatment group to which they will be allocated by the IVRS/IWRS (i.e. “as randomized” regardless of treatment actually received).

11.3.1.2 Evaluable populations

The following evaluable patient populations are defined for some selected efficacy endpoints.

- Tumor response will be evaluated in patients with measurable disease at baseline, with at least one post baseline assessment.
- PSA response will be evaluated in patients with PSA level >2 ng/mL at baseline, with at least one post baseline assessment.
- Pain response will be evaluated in patients using BPI-SF score and WHO Analgesic Ladder based on analgesic consumption that will be recorded in the eCRF (only patients with baseline assessment and at least one post baseline assessment will be considered).

Those populations are subsets of the ITT population, and patients are considered in the group "as randomized".

11.3.1.2 Health-Related Quality Of Life and Health status populations

The health related quality of life population is composed of patients who received at least one dose of the study drug and with an evaluable FACT-P questionnaire at baseline and at least one post baseline evaluable FACT-P.

The health status population is composed of patients who received at least one dose of the study drug and with an evaluable EQ-5D-5 L at baseline and with at least one post-baseline evaluable EQ-5D-5L.

Those populations are a subset of the Safety population, and patients are considered in the group "as treated".

11.3.2 Safety population

This population includes all patients who received at least one dose of the study drug. This population is for all Safety analyses. All analyses using this population will be based on the treatment actually received (i.e. "as treated").

In addition:

- Non randomized but treated patients will not be part of the safety population, but their safety data will be presented separately.
- Randomized patients for whom it is unclear whether they took the study medication will be included in the safety population as randomized.
- For patients receiving more than 1 study treatment during the trial, as soon as a patient will receive any study drug injection of Cabazitaxel, he/she is considered as a Cabazitaxel treated patient.

11.4 STATISTICAL METHODS

11.4.1 Extent of study treatment exposure

Extent of exposure will be assessed on the Safety population as follows:

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 also be analyzed.

Further details of the statistical evaluation of the extent of exposure will be provided in the SAP.

11.4.2 Analyses of efficacy endpoints

11.4.2.1 Analysis of primary efficacy endpoint(s)

Primary analysis will consist of rPFS comparison between abiraterone acetate or enzalutamide group and cabazitaxel group through a 2 sided 5% log-rank adjusted for the stratification factors ECOG performance status (0-1 Vs. 2), time from AR targeted agent initiation to progression ([0; 6 months] Vs. [6; 12 months]), timing of AR targeted agent (before Vs. after docetaxel) as specified at the time of randomization. This analysis will be performed on the ITT population. If radiological progression or death is not observed during the study, data on rPFS 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.

HR will also be provided on the subpopulations defined by the stratification factors.

The survival curves will be estimated using Kaplan-Meier estimates. Median survival times and associated 95% confidence intervals will also be provided by treatment.

Finally, the 2 arms will also be compared (sensitivity analysis) using a 2-sided 5% un-stratified log-rank test.

11.4.2.2 Analyses of secondary efficacy endpoints

Time To event endpoints will be compared between the 2 treatment arms using the same methodology as the primary efficacy endpoint primary analysis.

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, mean, standard deviation, 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 2 arms will be compared using chi-square test. Tumor, PSA, and pain response will be analyzed on their respective evaluable population.

11.4.2.3 Multiplicity considerations

Not applicable.

11.4.3 Analyses of safety data

The summary of Safety results will be presented by treatment group. Analysis of AEs and laboratory data will be descriptive and conducted on the Safety population. Summary of safety data will also be performed by patient and by cycle. For each of the Safety parameters, a baseline value will be defined as the last value or measurement taken up to the first dose in the study. Similar analysis will be presented for SAEs and AEs that cause dose reduction, dose relay and treatment discontinuation.

Adverse events will be considered as treatment-emergent if they first occur or worsen after the first day of dosing and up to 30 days after the last administration of study drug.

Adverse event incidence tables will present by system organ class (SOC) (sorted by internationally agreed order), High group level term (HLGT), High level term (HLT) and preferred term (PT) sorted in alphabetical order for each treatment group, the number (n) and percentage (%) of patients experiencing an AE. Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment phase. The denominator for computation of percentages is the safety population within each treatment group.

The grade and cycle will be taken into account in the summary. For patients with multiple occurrences of the same event, the maximum grade is used. The denominator used for the summary by cycle is the total number of cycles administered in a treatment group. For a given event, a patient contributes 1 to the numerator for each cycle in which an episode occurred (i.e., if the date of onset is on or after the first day of the cycle, but prior to the first day of the next cycle).

The following deaths summaries will be generated:

- Number (%) of patients who died by study period (TEAE, on-study) and reasons for death summarized on the safety population by treatment received.
- Death in non-randomized patients or randomized and not treated patients.
- TEAE leading to death (death as an outcome on the AE CRF page as reported by the Investigator) and related TEAEs leading to death by primary SOC, HLGT, HLT and PT

showing number (%) of patients sorted by internationally agreed order of SOC and alphabetic order of HLGT, HLT, and PT.

- 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.

Hematological toxicities will be assessed from laboratory parameters. Worst NCI CTCAE Grades of leukopenia, neutropenia, thrombocytopenia, and anemia will be calculated according to the NCI common terminology criteria.

Qualitative and quantitative results will be summarized for hematological toxicities. Qualitative data (worst NCI CTCAE V4.0 Grade) will be summarized by cycle and by patient.

Biochemistry will be analyzed using the worst NCI CTCAE V4.0 Grade, whenever applicable (laboratory normal ranges, otherwise) calculated from laboratory values.

11.4.4 Analyses of pharmacogenetic variables

Not applicable.

11.4.5 Analyses of HRQOL and of Health status

The Health-related Quality of Life assessment (FACT-P) will be obtained at baseline, at each visit before study treatment administration, at the end of treatment visit and every 12 weeks during the follow-p period until disease progression, start of other anticancer treatment or study cut-off, whichever comes first.

The FACT-P will compose of 5 categories: physical well-being, social/family well-being, emotional well-being, functional wellbeing, and additional concerns. The repeated measures of FACT-P will analysis by a Mixed model where treatment is a fixed variable and subject is a random variable. Responder of FACT-P is defined as 10-point (41) improvement in the total score on treatment.

Sub-domains of FACT-P will be analyzed separately. The time to a decline in functional status is defined as the months from randomization to the first date a patient has a decrease of 10 points or more on the Functional Assessment of Cancer Therapy–Prostate (FACT-P) instrument (range, 0 to 156, with higher scores indicating better overall quality of life). They will be compared between the groups.

The analyses of HRQoL will be detailed in the Statistical Analysis Plan.

The analyses of the health status questionnaire will be descriptive in nature; they will be detailed in the Statistical Analysis Plan.

11.4.6 Analyses of Biomarkers

The analyses will be detailed in the separate Statistical Analysis Plan.

11.5 INTERIM ANALYSIS

No interim analysis is planned.

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 ETHICAL AND REGULATORY STANDARDS

This clinical trial will be conducted by the Sponsor, the Investigator, delegated Investigator staff and Subinvestigator, 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), all applicable laws, rules and regulations.

This clinical trial will be recorded in a free, publicly accessible, internet-based registry, no later than 21 days after the first patient enrollment, in compliance with applicable regulatory requirements and with Sanofi public disclosure commitments.

12.2 INFORMED CONSENT

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. 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 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 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.

IMP 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 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 IRB/IEC.

A progress report is sent to the 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 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 Subinvestigators to assist in the conduct of the clinical trial in accordance with the clinical trial protocol. All Subinvestigators shall be appointed and listed in a timely manner. The Subinvestigators 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 regulatory authorities for taking all reasonable steps to ensure the proper conduct of the clinical trial 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, AESI documentation and reporting, AE documentation, IMP allocation, patient compliance with the IMP regimen, IMP accountability, concomitant therapy use and quality of data.

13.3 SOURCE DOCUMENT REQUIREMENTS

According to the ICH GCP, 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 (eg, 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 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 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

The complete list of computerized systems used for the study is provided in a separate document which is maintained in the Sponsor and Investigator study files.

14 ADDITIONAL REQUIREMENTS

14.1 CURRICULUM VITAE

A current copy of the curriculum vitae describing the experience, qualification and training of each Investigator and Subinvestigator will be signed, dated and provided to the Sponsor prior to the beginning of the clinical trial.

14.2 RECORD RETENTION IN STUDY SITES

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 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.

14.3 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, personal data in relation to the patients, 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 Subinvestigators shall be bound by the same obligation as the Investigator. The Investigator shall inform the Subinvestigators of the confidential nature of the clinical trial.

The Investigator and the Subinvestigators 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.

14.4 PROPERTY RIGHTS

All information, documents and IMP provided by the Sponsor or its designee are and remain the sole property of the Sponsor.

The Investigator shall not and shall cause the delegated Investigator staff /Subinvestigator not to mention any information or the Product in any application for a patent or for any other intellectual property rights.

All the results, data, documents and inventions, which arise directly or indirectly from the clinical trial in any form, shall be the immediate and exclusive property of the Sponsor.

The Sponsor may use or exploit all the results at its own discretion, without any limitation to its property right (territory, field, continuance). The Sponsor shall be under no obligation to patent, develop, market or otherwise use the results of the clinical trial.

As the case may be, the Investigator and/or the Subinvestigators shall provide all assistance required by the Sponsor, at the Sponsor's expense, for obtaining and defending any patent, including signature of legal documents.

14.5 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.

14.6 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 any obligation to maintain their own liability insurance policy. An insurance certificate will be provided to the IECs/IRBs or regulatory authorities in countries requiring this document.

14.7 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

For the purpose of ensuring compliance with the clinical trial protocol, Good Clinical Practice and applicable regulatory requirements, the Investigator should permit auditing by or on the behalf of the Sponsor and inspection by regulatory authorities.

The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that these personnel is bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

As soon as the Investigator is notified of a planned inspection by the authorities, he will inform the Sponsor and authorize the Sponsor to participate in this inspection.

The confidentiality of the data verified and the protection of the patients should be respected during these inspections.

Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the Sponsor.

The Investigator shall take appropriate measures required by the Sponsor to take corrective actions for all problems found during the audit or inspections.

14.8 PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE-OUT OF A SITE

14.8.1 By the Sponsor

The Sponsor has the right to terminate the participation of either an individual site or the study at any time, for any reason, including but not limited to the following:

- The information on the product leads to doubt as to the benefit/risk ratio;
- Patient enrollment is unsatisfactory;
- The Investigator has received from the Sponsor all IMP, means and information necessary to perform the clinical trial and has not included any patient after a reasonable period of time mutually agreed upon;
- Non-compliance of the Investigator or Subinvestigator, delegated staff with any provision of the clinical trial protocol, and breach of the applicable laws and regulations or breach of the ICH GCP;
- The total number of patients are included earlier than expected;

In any case the Sponsor will notify the Investigator of its decision by written notice.

14.8.2 By the Investigator

The Investigator may terminate his/her participation upon thirty (30) days' prior written notice if the study site or the Investigator for any reason becomes unable to perform or complete the clinical trial.

In the event of premature discontinuation of the study or premature close-out of a site, for any reason whatsoever, the appropriate IRB/IEC and regulatory authorities should be informed according to applicable regulatory requirements.

14.9 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.

14.10 PUBLICATIONS AND COMMUNICATIONS

The Investigator undertakes not to make any publication or release pertaining to the study and/or results of the study prior to the Sponsor's written consent, being understood that the Sponsor will not unreasonably withhold its approval.

As the study is being conducted at multiple sites, the Sponsor agrees that, consistent with scientific standards, a primary presentation or publication of the study results based on global study outcomes shall be sought. However, if no multicenter publication is submitted, underway or planned within twelve (12) months of the completion of this study at all sites, the Investigator shall have the right to publish or present independently the results of this study in agreement with other Investigators and stakeholders. The Investigator shall provide the Sponsor with a copy of any such presentation or publication for review and comment at least 30 days in advance of any presentation or submission for publication. In addition, if requested by the Sponsor, any presentation or submission for publication shall be delayed for a limited time, not to exceed 90 days, to allow for filing of a patent application or such other justified measures as the Sponsor deems appropriate to establish and preserve its proprietary rights.

The Investigator shall not use the name(s) of the Sponsor and/or its employees in advertising or promotional material or publication without the prior written consent of the Sponsor. The Sponsor shall not use the name(s) of the Investigator and/or the collaborators in advertising or promotional material or publication without having received his/her and/or their prior written consent(s).

The Sponsor has the right at any time to publish the results of the study.

15 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/favorable 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 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 re-collected if necessary.

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17 APPENDICES

Appendix A Modified Response Evaluation Criteria in Solid Tumors (RECIST1.1)

Detailed information is provided in reference (1).

Definitions

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

Measurable:

- Tumor 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:
- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm).
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest X-ray.
- Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed (see Special Issue 15). See also notes below on "Baseline documentation of target and non-target lesions" for information on lymph node measurement.

Non-measurable

- All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with 10 to <15 mm 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.

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.

Methods of measurement

- 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.

- Method of assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation 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 10 mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color 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 X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.
- 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 5 mm or less. 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).

- Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.
- Endoscopy, laparoscopy: The 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. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer), have been published. In addition, the Gynecologic 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.

Tumor response evaluation

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 1 measurable lesion. 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.

For baseline documentation of target and non-target lesions, see Section 9.1 in reference (1).

Response Criteria

For special notes on the assessment of target and non-target lesions in reference (1).

Table 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.s
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

Table 2

Evaluation of non-target lesions	
Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non-CR/non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumor 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).

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

New lesions: the appearance of new malignant lesions denotes disease progression in reference (1).

Evaluation of best overall response (1)

It is assumed that at each protocol specified time point, a response assessment occurs. The following table provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

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 inevaluable.

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 4.

Table 3

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

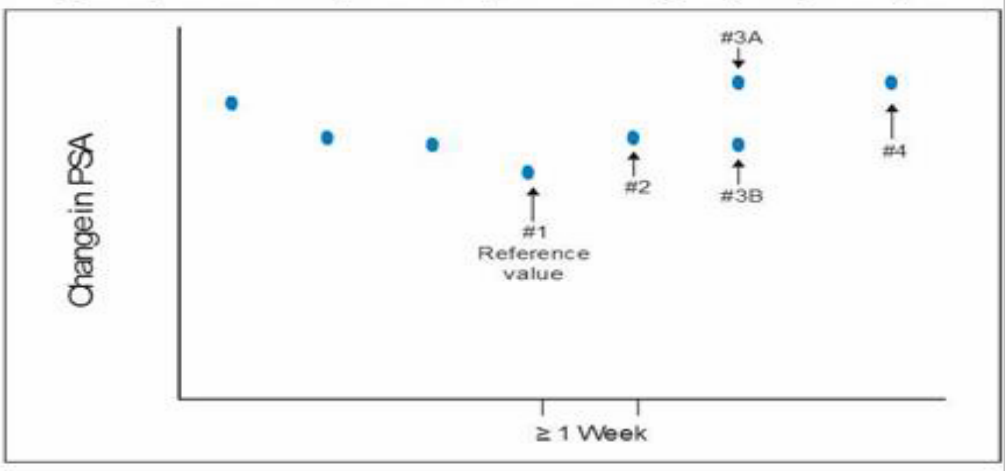
Table 4

Overall response	Overall response	BEST overall response
First time point	Subsequent time point	
CR	CR	CR
CR	PR	SD, PD or PRa
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

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.

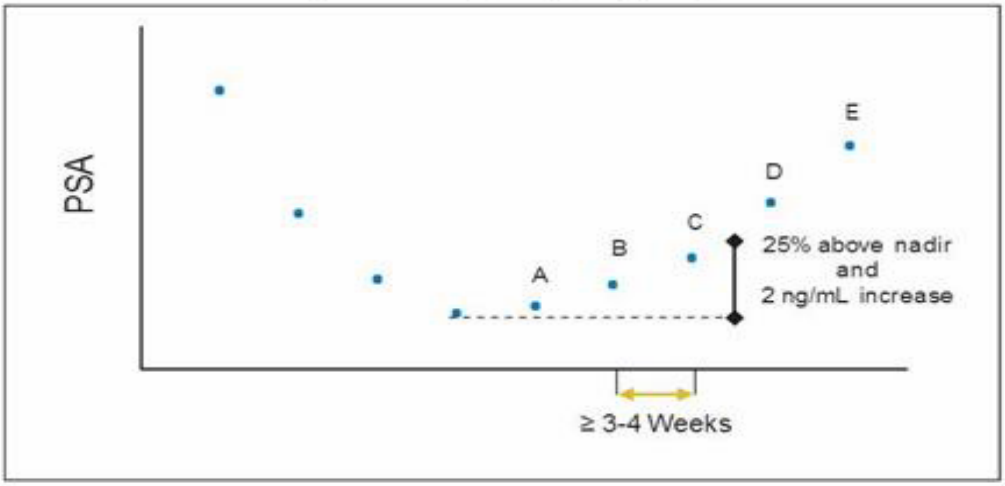
Appendix B PSA eligibility changes and progression

Eligibility based on prostate-specific antigen (PSA) changes.



The reference value (#1) is the last PSA measured before increases are documented, with subsequent values obtained a minimum of 1 week apart. If the PSA at time point 3 (value #3A) is greater than that at point 2, then eligibility has been met. If the PSA is not greater than point 2 (value #3B), but value #4 is, the patient is eligible assuming that other criteria are met, if values 3A or #4 are 2 ng/mL or higher.

Prostate-specific antigen (PSA) progression.



An increase of 25% and absolute increase of 2 ng/mL or more above the nadir. Values A, B, and C show rising PSA values that do not meet the criteria. Value D is the first PSA value that is greater than 25% and more than 2 ng/mL above the nadir, confirmed with a further rise in PSA shown by value E. For reporting purposes, PSA progression would be recorded on the date value D was obtained.

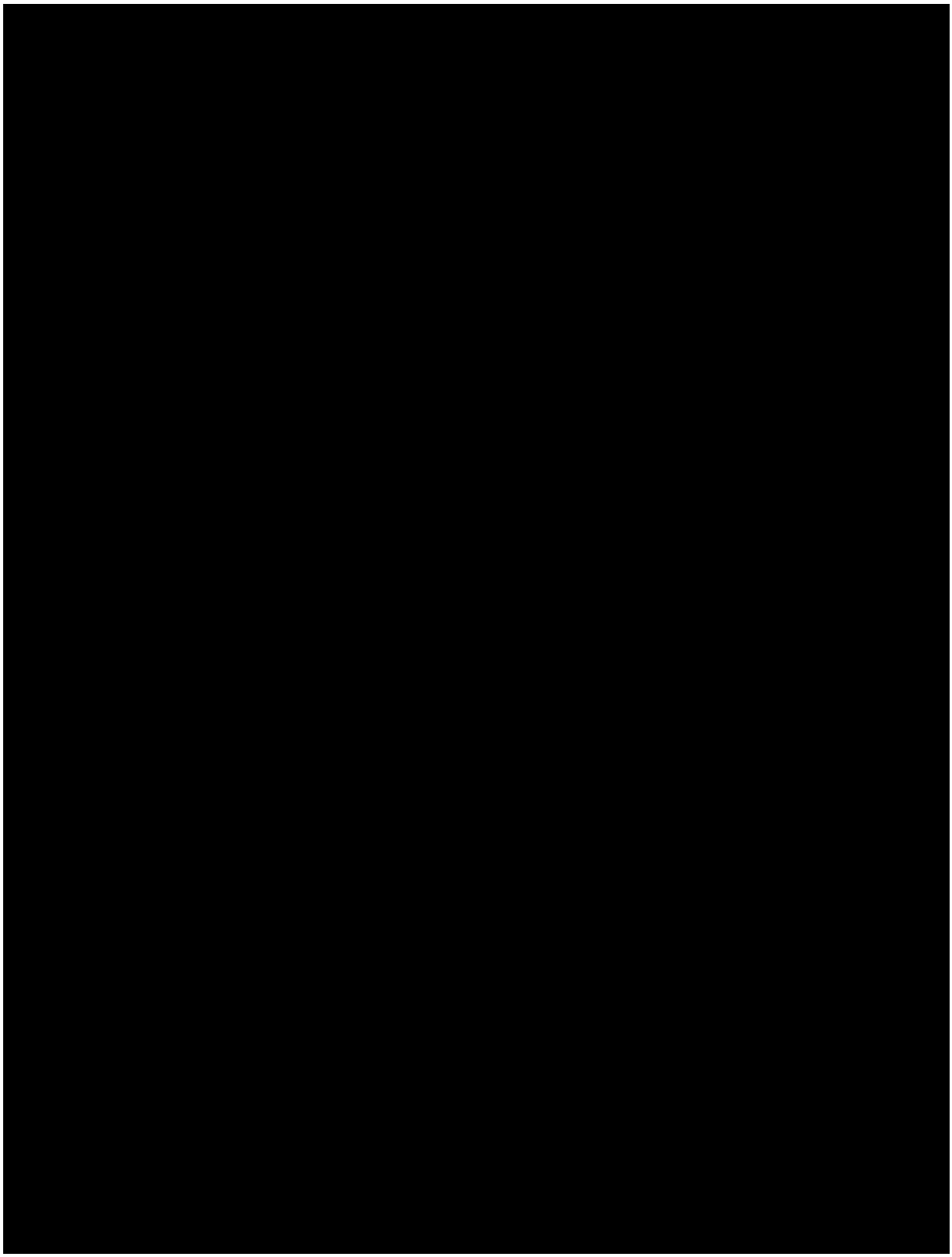
Appendix C National Cancer Institute Common Terminology Criteria for Adverse Events (9)

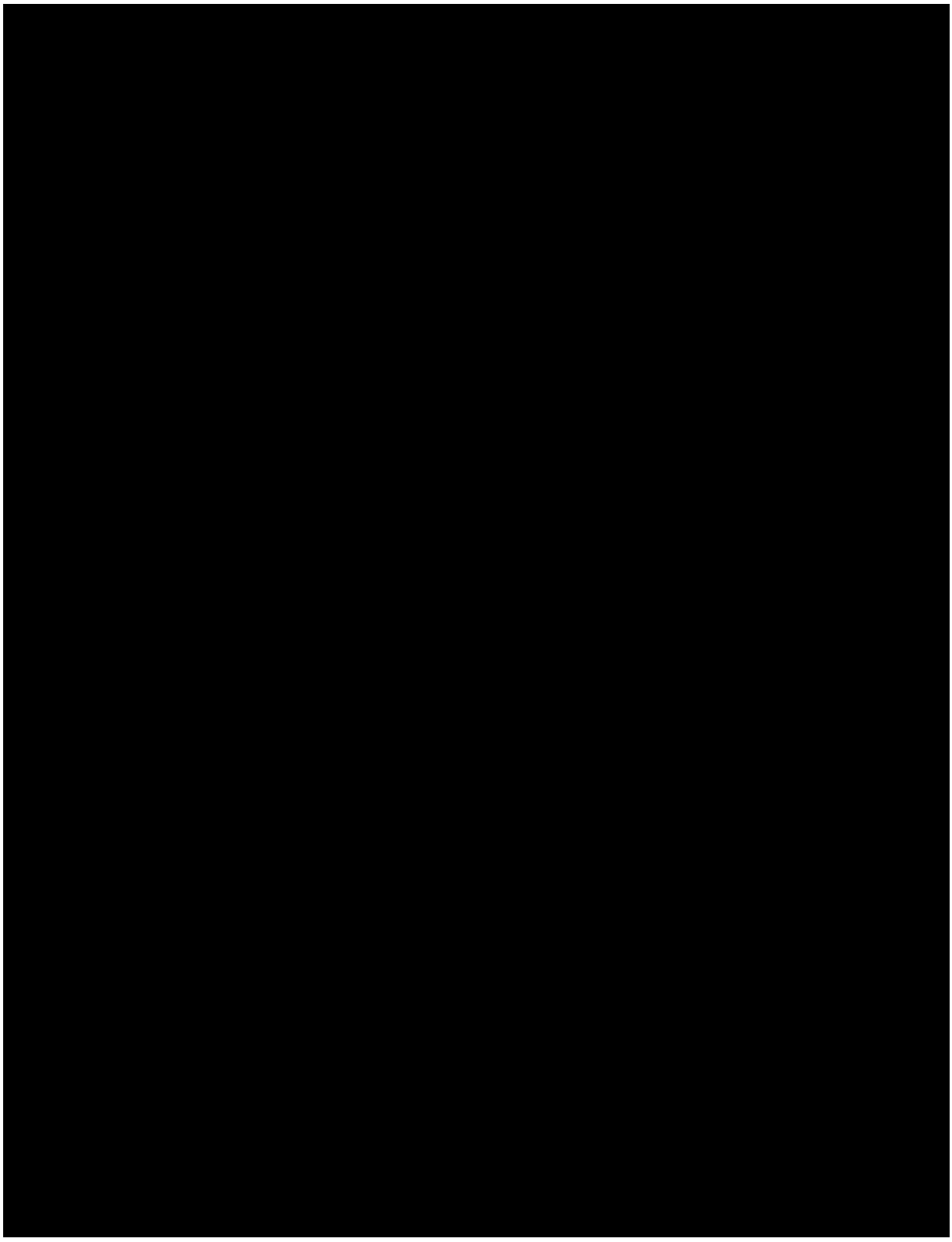
1. Toxicity grade should reflect the most severe degree occurring during the evaluated period, not an average.
2. When 2 criteria are available for similar toxicities, the one resulting in the more severe grade should be used.
3. The evaluator must attempt to discriminate between disease / treatment and related signs / symptoms.
4. An accurate baseline prior to therapy is essential.

Appendix D ECOG performance status scale

Grade	Description
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

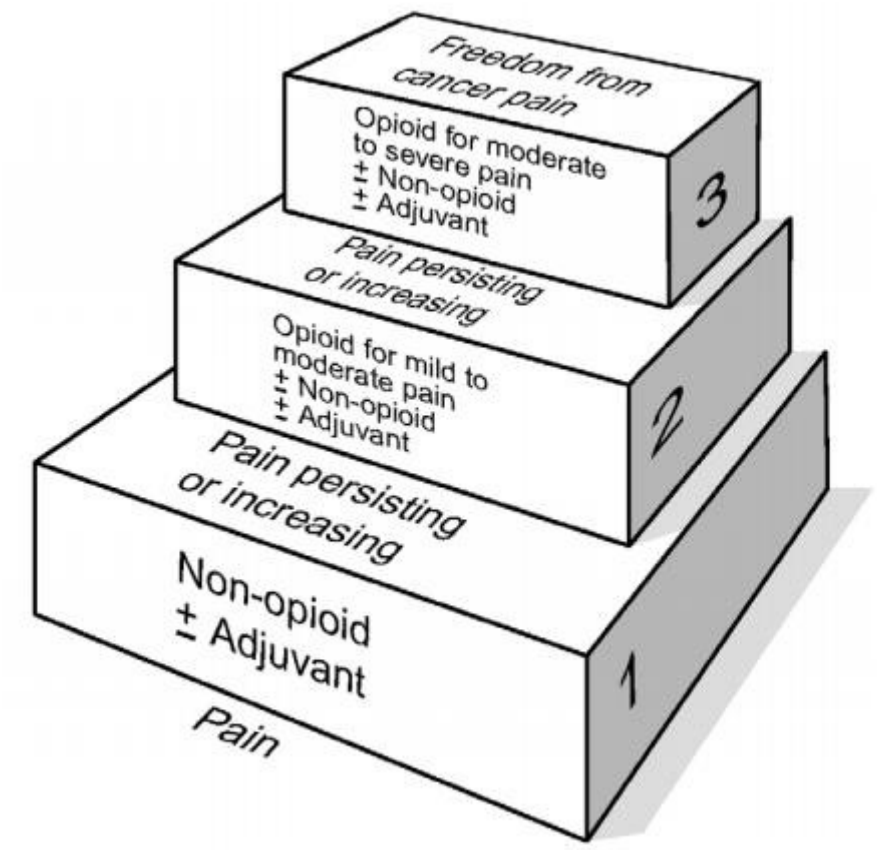
Appendix E Brief Pain Inventory (Short Form)





Appendix F WHO analgesic ladder for cancer pain

(http://www.who.int/cancer/palliative/painladder/en/index.html).



Adjuvant: To help calm fears and anxiety, adjuvant analgesics may be added at any step of the ladder

WHO analgesic ladder step	Score on numerical rating scale	Analgesics of choice
1 (mild pain)	<3 out of 10	paracetamol and NSAIDs
2 (mild to moderate pain)	3 to 6 out of 10	weak opioids(eg codeine or dihydrocoideine) plus paracetamol and NSAIDs
3 (severe pain)	> 6 out of 10	strong opioids (eg morphine, alfentanil, diamorphine, fentanyl, hydromorphone or oxycodone) plus paracetamol and NSAIDs

Appendix G EVALUATION OF QUALITY OF LIFE BY FACT-P (version 4 – 19 November 2007)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

By circling one (1) number per line, please indicate how true each statement has been for you during the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

By circling one (1) number per line, please indicate how true each statement has been for you during the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
C2	I am losing weight	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
P1	I have aches and pains that bother me	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
P3	My pain keeps me from doing things I want to do	0	1	2	3	4
P4	I am satisfied with my present comfort level	0	1	2	3	4
P5	I am able to feel like a man	0	1	2	3	4
P6	I have trouble moving my bowels	0	1	2	3	4
P7	I have difficulty urinating	0	1	2	3	4
BL2	I urinate more frequently than usual	0	1	2	3	4
P8	My problems with urinating limit my activities	0	1	2	3	4
BL5	I am able to have and maintain an erection	0	1	2	3	4

Appendix H EQ-5D-5L QUESTIONNAIRE

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

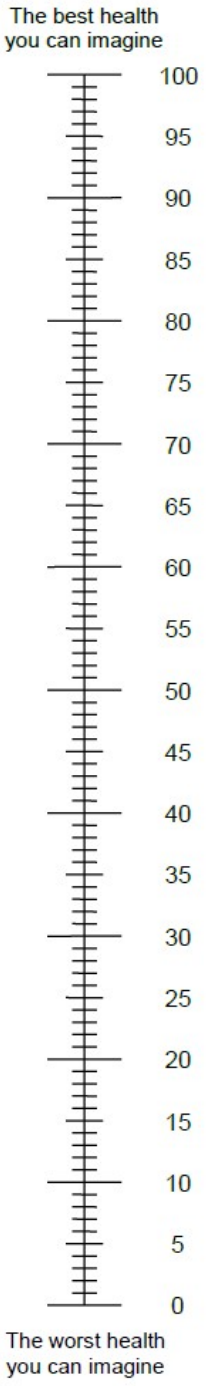
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix I CYP 3A4 inhibitors and CYP 3A4 inducers (Updated November 2011)

List of strong CYP 3A inhibitors

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

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

Appendix J COUNTRY-SPECIFIC REQUIREMENTS

Amendment 02 – France (31 March 2016)

Rationale:

The following modifications are made as per French Health Authorities (ANSM) request.

- **I01.** Has been modified in order to enroll patients with only histologically confirmed prostate adenocarcinoma and not cytologically according to French guidelines.
- **I03.** Has been clarified/added in order to continue an effective castration with LHRH agonists or antagonists for patients without surgical castration (orchiectomy).

No impact on the Written Subject Information.

In Section Clinical Trial Summary
Study Population – Inclusion criteria

I01. Histologically confirmed prostate adenocarcinoma

I03. Effective castration with serum testosterone levels < 0.5 ng/mL (1.7 nmol/L). If the patient has been treated with LHRH agonists or antagonist (ie, without orchiectomy), then this therapy should be continued.

Appendix K PROTOCOL AMENDMENT HISTORY

Amendment 01 – 29 October 2015

Reason for amendment:

- **Change to secondary objectives**

  Rationale: In addition to Health status assessed by EQ-5D-5L, Health-Related Quality Of Life assessed by FACT-P questionnaire is added as it is the most appropriate questionnaire in prostate cancer.

- **Change to exploratory objectives**

  [redacted]

- **Change to the inclusion/Exclusion criteria**

  Rationale:

  - In I05, the minimum dose exposure to docetaxel is specified. At least 3 cycles are needed to consider a prior treatment with docetaxel. It is also specified that docetaxel administration in combination with ADT in metastatic hormone-sensitive disease is considered a prior exposure. As per ESMO guidelines, ADT plus docetaxel is recommended as first-line treatment of metastatic hormone-naive disease in men fit enough for chemotherapy [1, A] (Parker C et al. Ann Oncol. 2015;26 (Suppl 5):v69-v77).
  - In I06, time to disease progression with a first AR-targeted agent has been extended from 6 to 12 months. Published retrospective data suggest that patients with acquired resistance to AR-targeted agents poorly respond to another targeted agent ((Loriot et al. Annals Oncol 2013, 24: 1807–1812; Bianchini et al. Eur J Cancer 2014, 50: 78–84). In addition, unpublished retrospective data suggest that patients having disease progression within 6-12 months with a first AR-targeted agent in post-docetaxel setting may poorly respond to another AR-targeted agent. In pre-docetaxel setting, patients having disease progression within 6-12 months with abiraterone or enzalutamide are considered 'rapid progressors' and may also poorly respond to another AR-targeted agent. Consequently, time to progression with a first AR-targeted agent has been extended from 6 to 12 months (with a stratification]0; 6 months] Vs.]6; 12 months]) to evaluate the optimal management of such patients.
  - In E02, was clarified for immunotherapy. Previous immunotherapy is allowed.
  - In E09, was modified as per NoMA (Norwegian Medicines Agency) request to give more details about the method of contraception.

- In E14 (h), creatinine clearance < 50 mL/min has been removed according to the last Smpc update. Cabazitaxel is minimally excreted through the kidney. No dose adjustment is necessary in patients with renal impairment, not requiring hemodialysis.
- In E16, was clarified in order to exclude patients with symptomatic peripheral neuropathy Grade 2 as well as patients with Grade > 2 according to the Smpc (dose modifications).
- In E18, concomitant vaccination with yellow fever vaccine, was added according to the Smpc and as per NoMA (Norwegian Medicines Agency) request.

- **Change to stratification factors**

  Rationale: to replace a stratification factor (metastatic Spread (Low Vs. High) by time from AR targeted agent initiation to progression (]0; 6 months] Vs.]6; 12 months]) due to the extent of the study population who has disease progression within 12 months of AR targeted treatment initiation instead of 6 months.

- [redacted]

- **Change to dose modification and dose delay**

  Rationale: Table 3 has been modified for creatinine increase, bilirubin elevation and transaminases elevation according to the last Smpc update (July 24th, 2015) regarding patients with renal and hepatic impairment.

- **Change to assessment schedule**

  Rationale: To add data collection regarding the response to first further anticancer therapy to better document the treatment sequences. To delete urine dipstick according to the last Smpc update regarding patients with renal impairment. Cabazitaxel is minimally excreted through the kidney. No dose adjustment is necessary in patients with renal impairment, not requiring hemodialysis.

- **Change to procedure and consequence for patient withdrawal from study**

  Rationale: FDA recommendation on withdrawal of consent for follow-up should be accompanied by documentation of the reason for withdrawal. Withdrawal of consent for treatment should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-patient contact follow-up, e.g., medical records checks. Subjects requesting withdrawal should be informed that withdrawal of consent for follow-up will jeopardize the public health value of the study.
  In addition, other minor changes are listed in the description of changes (next section).

  Written Subject Information has been updated to reflect the modifications related to the description of the study, the pregnancy, the biomarker testing and the utilization and protection of personal data.

Amendment 02 France – 31 March 2016

Reason for amendment:

Rationale:

The following modifications are made as per French Health Authorities (ANSM) request.

- **I01.** Has been modified in order to enroll patients with only histologically confirmed prostate adenocarcinoma and not cytologically according to French guidelines.
- **I03.** Has been clarified/added in order to continue an effective castration with LHRH agonists or antagonists for patients without surgical castration (orchiectomy).

No impact on the Written Subject Information.

Amendment 03 – 11 May 2018

Reason for amendment:

- **To introduce name and address of: Coordinating Investigator and Sponsor in cover page**
- **Clarification of the definition of rPFS in the Primary Objective and Primary Endpoint sections**

  Rationale:

  The definition of radiological Progression-Free Survival (rPFS) has to be consistent throughout the protocol. The definition of primary objective and corresponding primary endpoint in the tabulated clinical trial summary has thus been aligned with definition of primary endpoint provided in section 9.1 of the protocol.

  Moreover, in section 9.1, definition of rPFS has been clarified to reflect the PCWG2 with regards to progression of bone lesions and definition of measurability of lymph node.

- **Clarification of the definition of PFS**

  Rationale:

  Progression Free survival comprises currently the Radiological tumor progression event using RECIST 1.1. Definition of this event is updated and detailed to be in line with section 9.1.

- **To clarify and adapt the Inclusion criteria based on recent guidelines updates**

  Rationale:

  - In I 01, as per ESMO guidelines (Ann Oncol 2015, 26 (suppl 5) V69-V77), prostate cancer diagnosis has to be confirmed by histology, (cytology is not mentioned). This point was already modified in local French amendment 2.
  - In I 03, the sentence: “If the patient has been treated with LHRH agonists or antagonist (ie, without orchiectomy), then this therapy should be continued” is added. This clarification will be added to be in accordance with ESMO guidelines on management

of metastatic CRPC (ESMO guidelines. Annals of Oncology 26 (Supplement 5):v69–v77, 2015). LHRH agonists or antagonists were already allowed in section concomitant treatments 8.9, but to avoid any ambiguity and add clarity, it is now also specified in I03. This point was already modified in local French amendment 2.

- In I06, abiraterone acetate + androgen deprivation therapy (ADT) is now indicated in Europe for the treatment of metastatic hormone-sensitive prostate cancer. Such patients are thus eligible in CARD if they have progressed within 12 months with this regimen. It has also been clarified that patients having PSA progression only (as per PCWG 2) within 12 months, were eligible, even if total treatment duration with the AR-targeted agent was more than 12 months.

- **Revision of statistical power and accrual rates assumptions, and as a consequence reduction of the sample size**

  Rationale:

  Recruitment rate in the trial is lower than planned. Since statistical hypotheses for sample size calculation are still valid (HR of 0.67 between both arms), the Clinical Steering Committee agrees to reduce the study power from 90% to 80%. A power of 80% is indeed acceptable as per ICH step 9 and was used by important randomized trials in metastatic prostate cancer (CHAARTED: CJ Sweeney, YH Chen, M Carducci, G Liu, DF Jarrard, M Eisenberger and al. Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer. N Engl J Med. 2015;373:737-46) and (PROSELICA: M Eisenberger, AC Hardy-Bessard, CS Kim, L Géczi, D Ford, L Mourey and al. Phase III Study Comparing a Reduced Dose of Cabazitaxel (20 mg/m^2) and the Currently Approved Dose (25 mg/m^2 in Postdocetaxel Patients With Metastatic Castration-Resistant Prostate Cancer – PROSELICA. J Clin Oncol. 2017;35:3198-206). The number of patients to be randomized and number of patients with rPFS events needed for a power of 80% has been re-calculated precisely. Calculation were based on observed accrual rate so far and the further accrual rate expected up to the end of recruitment, and censored rate estimation. With a power of 80%, 196 rPFS events are needed and 234 patients should be randomized (117 per arm).

- **To introduce the 500mg dosage of the Investigational Medicinal Product(s) (IMP) – abiraterone acetate (Zytiga), and adapt dose modification and dose delay accordingly and to align dose adaptation rules with revised abiraterone acetate European labeling**

  Rationale:

  A new dosage for abiraterone acetate was launched by Janssen-Cilag: abiraterone acetate 500 mg currently available across Europe. In some countries, only 500 mg dosage is available. In order to deal with this new situation and to be in accordance with new European labelling of abiraterone acetate 250 and 500 mg, modifications throughout the protocol have been made . These modifications have been discussed and agreed by the Clinical Steering Committee.

  Description and formulation of tablet 500 mg abiraterone acetate have been added and monitoring instructions for dose reduction have been adapted accordingly.

In addition, management of abiraterone acetate adverse events have been aligned on new abiraterone acetate European labelling, in particular with regards to:

Dose reduction to 750 mg which has been deleted, and management of hypertension, fluid retention/ edema and non-mineralocorticoid based side effects have been revised.

- **To allow a time window of + or – 1 week for the tumor assessment scheduled every 12 weeks and the follow up visits for the Body Weight and ECOG PS scheduled prior to the start of each treatment cycle**

  Rationale: time window of + or - 1 week is introduced for tumor assessment during treatment and in follow up if applicable, as well as all follow up visit to increase compliance and flexibility for patients.

- **To clarify Change to procedure and consequence for patient withdrawal from study**

  Rationale:

  CARD study is an event driven study, (section 9.1) and all efforts should be made to document radiographic progression before initiation of further therapy.

  In case of treatment discontinuation due to reason other than radiographic progressive disease (or example discontinuation due to adverse event), the choice of further therapy, if any, is let to the investigator, and data concerning further therapy will be documented. Accordingly, section 6.2.1 has been modified.

- **To correct inconsistencies throughout the protocol with regards to general guidelines for reporting AEs**

  Rationale:

  As mentioned in the flowchart, the period of safety observation starts from the time the patient gives informed consent. All AEs will be recorded until 30 days after the last administration of study drugs. During the follow-up period, only ongoing related or new related AEs will be recorded. Serious Adverse Events (SAEs) ongoing at the end of the study treatment will be followed during the follow-up period until resolution or stabilization regardless of relationship with study drugs.

- **Change in appendices**

  Rationale:

  The version in initial protocol was not the most recent version used and released to patients. The correct version is inserted.

Amendment 04 – 08 November 2018

Reason for amendment:

This amendment has introduced mainly a new format of Abiraterone acetate 500 mg tablets (available in two formats (wallets 60 or 56 tablets, previously only 60 tablets), with no changes concerning the immediate packaging or daily dose), and introduced the new address of coordinating investigator.

Signature Page

lps14201-16-1-1-amended-protocol05

Approve & eSign	[redacted] Clinical [redacted]

Approve & eSign	[redacted] Clinical [redacted]