# SYNOPSIS – PEACE-6 Vulnerable

## A) TRIAL IDENTIFICATION

**SPONSOR – PROTOCOL CODE NUMBER:** Unicancer - UC-GTG-2006

**VERSION (NUMBER & DATE):** 4.0 – 10Jan2023 MASTER

**TRIAL TITLE:**

A double-blind randomised phase III trial evaluating the efficacy of ADT +/- darolutamide in de novo metastatic prostate cancer patients with vulnerable functional ability and not elected for docetaxel or androgen receptor targeted agents

**PHASE (FOR TRIALS ON MEDICINAL PRODUCTS):** Phase 3

**TRIAL TITLE FOR LAY PEOPLE:** Randomised phase III trial of ADT +/- darolutamide in frail men with castration-naïve *de novo* metastatic prostate cancer

**ABBREVIATED TITLE:** PEACE 6 Vulnerable

**COORDINATING INVESTIGATORS:**

Dr Giulia Baciarello - Azienda Ospedaliera S. Camillo-Forlanini, Italy

Prof. Karim Fizazi - Gustave Roussy Cancer Campus, France

| | |
|---|---|
| **NUMBER OF SITES:** 100 | **NUMBER OF PATIENTS:** 300 |

## B) SPONSOR IDENTIFICATION

| | |
|---|---|
| **NAME:** | **Unicancer**<br>101, rue de Tolbiac<br>75654 Paris Cedex 13<br>(France) |
| **CONTACT PERSON:** | **Ms Isabelle RIEGER**<br>Project Manager<br>**R&D UNICANCER**<br>Tel: +33 (0) 1 80 50 15 99<br>email: i-rieger@unicancer.fr |

## C) TRIAL GENERAL INFORMATION

**INDICATION:** *De novo* metastatic Prostate Cancer

**TRIAL DESCRIPTION/DESIGN:**

This is a Phase III, international, multicentre, randomised, double-blinded placebo controlled trial, evaluating the efficacy and safety of ADT +/- darolutamide in castration-naïve *de novo* metastatic prostate cancer patients with vulnerable functional ability who have not elected for docetaxel or other androgen receptor pathway inhibitors.

The study plans to enrol 300 patients who will be randomised (1:1) to receive either:

- Experimental arm: ADT + darolutamide 600 mg po b.i.d

- Control arm: ADT + placebo po b.i.d

Patient participation is divided into 4 phases: Screening, Treatment, End of Treatment (EoT), and Long-Term Follow-up (LTFU).

Following signature of the informed consent form, prospective patients will enter the Screening period (max. 28 days prior to start of treatment) during which all examinations required to assess their eligibility will be performed, including demographic data collection, tumour evaluation and clinical and laboratory evaluations. Eligible patients will be randomised via an interactive web response system (IWRS). For patients who provide their additional consent, the availability of a suitable formalin-fixed, paraffin-embedded (FFPE) biopsy sample of a metastatic site or primitive tumour tissue will be verified during the screening period. France only: Blood samples will also be collected prior to the start of treatment.

Randomised patients will receive ADT plus the investigational product (IP, darolutamide 600 mg), or placebo equivalent as a tablet to be taken orally (po) twice a day (b.i.d). Patients will be asked to attend clinical visits to perform safety and efficacy assessments on Day 30 (±3 days), Day 60 (±3 days), Day 120 (±7 days), Day 180 (±7 days), Day 240 (±7 days) and then every 120 (±14) days for the first two years of treatment and every 180 (±14) days thereafter. Response to treatment will be assessed according to the Prostate Cancer Clinical Trials Working Group 3 (PCWG3) criteria by radiographic exams performed every 120 (±14) days after randomisation during the first 2 years and every 180 (±14) days thereafter.

Treatment will be continued until radiographic disease progression according to PCWG3 criteria. Treatment may also be terminated at the initiative of either the patient or the investigator for any reason that would be beneficial to the patient, including: unacceptable toxicity, intercurrent conditions that preclude continuation of treatment, or patient request.

An EoT visit will be performed within 30 (±3) days of study treatment discontinuation for any reason. After the EoT visit, patients will enter the LTFU period and will be followed for up to 10 years from the date of randomisation. During this time, information will be collected every 180 (±14) days regarding survival status, subsequent antineoplastic treatments, and the status of ongoing AEs and/or new IP related AEs. Patients who discontinue treatment for reasons other than disease progression (e.g. due to toxicity, patient or investigator decision) will continue to be assessed by clinical/laboratory exam and radiographic imaging according to the protocol schedule, until disease progression or initiation of a new antineoplastic treatment, or death.

**PRIMARY OBJECTIVE:**

To compare the efficacy of ADT + darolutamide vs ADT + placebo in terms of radiographic progression-free survival (rPFS) in patients with castration-naïve *de novo* metastatic prostate cancer with vulnerable functional ability and not elected for docetaxel or other androgen receptor pathway inhibitors.

**SECONDARY OBJECTIVES:**

Key Secondary objectives:

- To assess the efficacy of ADT + darolutamide vs ADT + placebo in terms of:
  - Castration-resistant prostate cancer-free survival
  - Clinical progression-free survival (cPFS)
  - Overall survival

- To assess the safety profile of the ADT + darolutamide combination.

Other secondary objectives:

- Time to worsening in prostate cancer-related urinary symptoms
- Time to next symptomatic skeletal event
- Prostate specific antigen (PSA) response
- Prostate cancer-specific survival
- To assess the effect of ADT + darolutamide on subsequent lines of therapy
- To evaluate the evolution of quality of life and geriatric status in individuals during the treatment period
- To evaluate the impact of sarcopenia on survival and treatment response

**EXPLORATORY OBJECTIVES**

- To identify the oncogenic drivers of *de novo* metastatic prostate cancer

**DIAGNOSIS AND INCLUSION CRITERIA:**

To be eligible, patients must meet all of the following criteria:

1. Signed a written informed consent form prior to any trial specific procedures.

   ***Note:*** *If the patient is physically unable to provide their written consent, a trusted person of their choice, independent of the Investigator or the Sponsor, can confirm the patients consent in writing.*

2. Men with histologically or cytologically confirmed adenocarcinoma of the prostate.
3. Aged ≥18 years old at the time of signing informed consent.
4. *De novo* metastatic disease defined by clinical or radiographic evidence of metastases.

   ***Note:*** *For patients with nodal metastases only, only patients with extra-pelvic enlarged lymph nodes (lymph nodes located above the iliac bifurcation) can be included if they have either:*

   - *At least one extra-pelvic lymph node ≥ 2 cm*
   - *At least one extra-pelvic lymph node ≥ 1 cm if the patients also have at least one pelvic lymph node ≥ 2 cm*

5. Measurable disease or bone lesions that are evaluable according to PCWG3 criteria.
6. Ineligible for treatment with all of the following drugs: docetaxel, abiraterone, enzalutamide, apalutamide; AND meets at least one of the following frailty criteria:
   a. Activities of daily living (ADL) assessment (excluding urinary incontinence question) score 3 or 4/5;
   b. 4-Instrumental activities of daily living (4-IADL) assessment score 2 or 3/4;
   c. A Grade 3 event on the Cumulative Illness Score Rating-Geriatrics (CISR-G) questionnaire;

d. Body mass index (BMI) ≤21 kg/m$^2$ and/or >5% weight loss in the last 6 months;

e. Timed up and go test (TUG) >14 sec.

7. Adequate bone marrow function: haemoglobin ≥80 g/L, white blood cells ≥3.0 x10$^9$/L and platelets ≥80 x10$^9$/L.
8. Adequate liver function: alanine aminotransferase (ALT) <2 x upper limit of normal (ULN) and bilirubin <1.5 x ULN, (or if bilirubin is between 1.5-2 x ULN, they must have a normal conjugated bilirubin). For patients with documented liver metastasis, ALT <5 x ULN is acceptable.
9. Adequate renal function: calculated creatinine clearance >30 ml/min (using the MDRD or CKD EPI method).
10. For sexually active men, agreement to use adequate contraception for the duration of trial participation and up to 2 weeks after completing study treatment.
11. Affiliated to the social security system or in possession of equivalent private health insurance (according to local regulations for participation in clinical trials).
12. Willing and able to comply with the protocol for the duration of the trial including undergoing treatment and scheduled visits, and examinations including follow-up.

**NON-INCLUSION CRITERIA:**

Patients are not eligible to participate in the trial if they meet any of the following criteria:

1. Three or more Grade 3, or any Grade 4 events on the CISR-G questionnaire.
2. Eastern Cooperative Oncology Group (ECOG) performance status score ≥3.
3. Hypertension not controlled by an anti-hypertensive treatment (systolic blood pressure [BP] ≥160 mmHg or diastolic BP ≥95 mmHg; 3 consecutive measures taken 5 minutes apart).
4. Acute toxicities of prior treatments and procedures not resolved to grade ≤1 or baseline before randomisation, with the exception of hot flushes and erectile dysfunction.
5. Previous systemic treatment for prostate cancer, except less than 12 weeks of ADT and/or an old-generation AR inhibitor.
6. Severe or uncontrolled concurrent disease, infection or co-morbidity.
7. Known hypersensitivity to the study treatment or any of its ingredients.
8. Major surgery within 28 days before randomisation.
9. Any of the following within 6 months before randomisation: stroke, myocardial infarction, severe/unstable angina pectoris, coronary/peripheral artery bypass graft; congestive heart failure New York Heart Association (NYHA) Class III or IV.
10. Prior malignancy ≤3 years before study enrolment. Adequately treated basal cell or squamous cell carcinoma of skin or superficial bladder cancer that has not spread behind the connective tissue layer (i.e., pTis, pTa, and pT1) is allowed, as well as any localized cancer for which treatment has been completed ≥6 months before randomisation and from which the subject has been disease-free, or for which the risk of relapse is less than 30%, as well as early stage chronic lymphocytic leukaemia that does not require any specific treatment.
11. Inability to swallow oral medications.

12. Gastrointestinal disorder or procedure that can be expected to interfere significantly with the absorption of study treatment.
13. Known to have active viral hepatitis, active human immunodeficiency virus (HIV) or chronic liver disease at screening.
14. Treatment with any investigational product within 28 days before randomisation.
15. Concurrent participation in another clinical trial involving an investigational product (patients enrolled in non-experimental trials with no modification of the standard of care can be included).
16. Individual of full age deprived of liberty or placed under a legal protection measure (tutorship/temporary guardianship).
17. Significantly altered mental status prohibiting the understanding of the study or with psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule or any condition that, in the opinion of the investigator, would preclude participation in this trial.

**PRIMARY ENDPOINT:**

Radiographic progression-free survival, defined as time from randomisation to radiographic progression as assessed by the investigator according to PCWG3 criteria, or death, whichever occurs first.

*According to the PCWG3 recommendations, radiographic progression is defined as either the appearance of two or more new bone lesions on bone scan or a nodal or visceral progression according to Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST v1.1). The date of radiographic progression will be the date of the first reported event meeting the above definition.*

**SECONDARY ENDPOINT(S):**

**Key secondary endpoints:**

- Castration-resistant prostate cancer (CRPC)-free survival, defined as the time from randomisation to onset of CRPC according to PCWG3 criteria, or death, whichever occurs first.
- Clinical progression-free survival, defined as time from randomisation to first occurrence of any one of the following:
  - Cancer pain deterioration (2-point deterioration from baseline according to the Brief Pain Inventory - Short Form [BPI-SF] questionnaire, or initiation of opioid therapy, or a ≥30% increase in opiate use),
  - Any deterioration of physical function measured using the 4-IADL assessment tool,
  - A deterioration in ECOG performance status of at least 2 points from baseline,
  - Death from any cause.
- Overall survival, defined as the time from randomisation to the time of death from any cause. For subjects alive at the time of analysis, data will be censored on the last date the subject was known to be alive or lost to follow-up or to have withdrawn consent.
- Toxicity will be evaluated according to version 5.0 of the National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE v5.0).

**Other secondary endpoints:**

- Time to worsening in prostate cancer-related urinary symptoms, defined as an increase from baseline of greater or equal to 8 points in the urinary symptom scale/score (PRURI), measured using the prostate cancer module of the European organisation for research and treatment of cancer (EORTC) quality of life questionnaire (QLQ) (EORTC-QLQ-PR25).
- Time to next symptomatic skeletal event, defined as the time from randomisation until first occurrence of one of the following: a symptomatic fracture, radiation or surgery to bone or a spinal cord compression (PCWG3 criteria).

  ***Note**: The occurrence of these events will be determined by investigator evaluation. No systematic X-Ray will be performed.*
- Complete PSA response (defined as PSA ≤ 0.2 ng/ml) at 6 months.
- Prostate cancer-specific survival, defined as the time from randomisation to the date of death due to prostate cancer (deaths due to other causes will be censored).
- Time to deterioration for EORTC QLQ-PR25 symptom subscales, defined as the first decline in the HRQoL score from baseline equal to or greater than the minimally important difference (MID; a measure of clinical significance) defined as half the standard deviation of the baseline value for each subscale.
- Time to first subsequent systemic anti-cancer therapy (SACT) defined as the time from randomisation to the date of initiation of any SACT for CRPC, following initiation of the study treatment.
- Efficacy of subsequent SACT will be assessed according to rPFS, OS, and PFS after next line of treatment (PFS2); defined as the time from randomisation to second objective disease progression, or death from any cause, whichever first.
- Health related quality of life will be evaluated using the EORTC-QLQ-C30, EORTC-QLQ-PR25 and BPI-SF questionnaires.
- Geriatric status will be evaluated using the Geriatric Core Dataset (G-Code) assessment.
- Impact of sarcopenia on overall survival will be evaluated by comparing the distribution of overall survival between sarcopenic and non-sarcopenic patients.
- Impact of sarcopenia on treatment response will be evaluated by comparing rate of response in sarcopenic and non-sarcopenic patients.

## D) INVESTIGATIONAL MEDICINAL PRODUCTS

**PRODUCT NAMES AND ADMINISTRATION:**

| Drug name (INN) | Registered name(1) | Pharmaceutical form | Administration route | Posology |
|---|---|---|---|---|
| Nubeqa | Darolutamide | 300 mg tablets | oral | 600 mg b.i.d |

(1) When any generic drug can be is used indicate only the international nonproprietary name (INN). The choice of the registered name or brand name used in the trial is at the investigators discretion.

**THERAPEUTIC REGIMENS:**

- Experimental arm: ADT + darolutamide 600 mg po b.i.d
- Control arm: ADT + placebo po b.i.d.

The choice of ADT is left to the discretion of the investigator, to be administered according to local standard procedures.

**TREATMENT DURATION:**

Treatment will be continued until radiographic disease progression. Treatment may also be terminated at the initiative of either the patient or the investigator for any reason that would be beneficial to the patient, including: unacceptable toxicity, intercurrent conditions that preclude continuation of treatment, or patient request.

**DOSE MODIFICATION:**

If a patient experiences a ≥ Grade 3 toxicity (according to NCI-CTCAE v5.0) or an intolerable adverse reaction, treatment should be withheld or reduced to 300 mg b.i.d. until symptoms improve. Treatment may then be resumed at a dose of 600 mg b.i.d.

In the event of treatment interruption due to toxicity of more than 56 days, the decision to restart treatment or not should be discussed and agreed between the Investigator and Sponsor.

If a ≥ Grade 3 toxicity reoccurs after 1 dose reduction despite medical intervention, the patient must be withdrawn from study treatment. Dose reduction below 300 mg b.i.d. is not recommended, because efficacy has not been established.

In case of hepatic transaminase elevations suggestive of idiosyncratic Drug Induced Liver Injury (DILI) considered to be causally related to darolutamide, treatment with darolutamide should be permanently discontinued.

## E) STATISTICAL ANALYSIS PLAN

**REQUIRED NUMBER OF PATIENTS TO BE SCREENED/INCLUDED:**

Assuming a median rPFS of 12 months for the control group (based on data from the control arm of the LATITUDE trial (Fizazi, 2017), and taking into account that 1) patients with oligo-metastatic disease (low risk patients) will not be in this group, and 2) some patients are expected to die from other causes before they reach a progression endpoint, making the median rPFS probably shorter than what it was in the LATITUDE trial), a planned sample size of 300 subjects will be required to provide an 85% power to detect at least a HR of 0.65 (median rPFS 12 months in the standard arm versus 18.5 months in the experimental arm) at a 2-tailed significance level of 0.05 and a drop-out hazard rate in both arms of 0.014 (i.e. a maximum 19.3% drop-out rate at the end of study corresponding to non-evaluable or study withdrawal patients).

The number of **randomised patients will be 300 patients** (150 patients per arm). The dropout rate will be monitored during the study and in case of increased drop-out the sample size may be adjusted accordingly.The number of **randomised patients will be 300 patients** (150 patients per arm). The dropout rate will be monitored during the study and in case of increased drop-out the sample size may be adjusted accordingly.

**STATISTICAL ANALYSIS:**

For primary and secondary efficacy endpoints, the analysis will be performed on the ITT population, i.e. all randomised patients will be included, whether eligible or not, compliant or not. Patients will be analysed according to their randomisation arm, regardless of the actual treatment received.

Analysis of the primary endpoint will be event-driven. Time to event endpoints will be reported using the Kaplan-Meier method with Rothman's 95% confidence intervals. A log-rank test will provide the statistical significance of the randomised treatment effect. Additionally a Cox model will provide an estimate of the randomised treatment effect (hazard ratio).

Stratification factors will include: LATITUDE risk criteria (high risk versus low risk, Fizazi, 2017) and ECOG performance status score (0 or 1 vs. 2).

Qualitative data will be expressed as percentages and compared between the treatment groups using the chi-square test (or the Fisher exact test). Quantitative data will be expressed as means and standard deviation (or medians and range) and compared between the treatment groups using the Student t-test (or the Wilcoxon test).

The analysis of the secondary endpoints will be performed using a formal adjustment for multiple testing.

One interim analysis will be performed after observing 70% of the number of expected events (i.e. 138 events). Stopping rules using the spending function approach of Lan and DeMets with O'Brien-Fleming type spending function will be followed to conclude at each sequential analysis.

Nominal p values for overall type I error of 0.05 Lan-DeMets boundaries are:

- Efficacy interim analysis (138 events, i.e. 70% expected events): p-value to reject $H_0 \leq 0.015$ (equivalent to the stopping boundaries Z-Scale: +/-2.438)
- Final analysis (197 events, i.e. 100% expected events): p-value to reject $H_0 \leq 0.046$ (equivalent to the stopping boundaries Z-Scale: +/-2.0)

The results of the interim analyses will be given only to the IDMC members.

Safety analysis will be summarized on the Safety Population (i.e. all patients who receive any part of investigational treatment). Incidence of AEs will be summarized by system organ class and preferred term according to MedDRA coding, and will be presented by treatment groups and overall. AEs will be summarized by grade (NCI CTCAE v5.0), according to the worst grade experienced.

## F) OPTIONAL TRANSLATIONAL RESEARCHES

### 1. Samples

Blood samples and tumour tissues will be collected to conduct a translational program to address two current critical questions:

(i) What are the oncogenic drivers of *de novo* metastatic prostate cancer?
(ii) What is the underlying biology of oligometastatic prostate cancer?

M1 patients have a poor prognosis and contribute to at least 50% of prostate cancer-related deaths. The landscape of genomic alterations in M1 prostate cancer remains uncharacterized. Specifically, we hypothesize that molecular drivers usually found later during disease evolution when patients develop resistance to castration may be already present in M1 prostate cancer.

**Tumour samples**

The following samples will be collected from all patients who provide their additional consent:

- Archived Formalin fixed / paraffin embedded (FFPE) biopsy material obtained at time of diagnosis as part of the standard medical care will be collected at study entry.
- Where feasible, a biopsy will be performed at time of disease progression to collect a treatment-resistant tumour sample.

**Blood samples (France only)**

Blood samples will be collected prospectively during the study from patients who provide their additional consent, in order to study tumour clonal evolution. At Day 1, prior to initiating IP treatment, blood will be collected from each patient and processed to obtain circulating tumour cells (CTCs) and plasma. An additional sample of whole blood will also be collected for genomic analysis.

Additional blood samples will be collected and processed to obtain CTCs and plasma at Day 30 (plasma), Day 60 (CTCs), Day 120 (plasma), and at disease progression (CTCs and plasma).

**Exome analysis**

Host and cell-free tumour DNA will be extracted from baseline blood samples (whole blood and plasma). Archival FFPE biopsy samples will be used to extract somatic tumour DNA.

Both normal and somatic DNA will be then used for whole-exome sequencing in order to investigate (a) the genomic landscape (single nucleotide variation [SNV], copy number variation [CNV]) of M1 prostate cancer (b) the tumour clonal evolution in a subset of patients in whom paired biopsies (baseline – resistant tumour) are available. Cell-free DNA collected at baseline and at progression will be analysed in order to assess clonal evolution.

**Transcriptome analysis**

RNA will be extracted and analysed using TruSeq RNA/exome technology (Illumina) for mRNA profiling. TruSeq RNA/exome technology which generate RNA sequencing libraries from degraded samples that focus on the RNA coding regions. The TruSeq RNA/exome system isolates the high-value content regions to maximize discovery power with low input requirements and is extensively validated.

***Immunohistochemistry***

Immunohistochemistry staining will be performed on serial FFPE tumour tissue slides. Eleven markers will be assessed to identify key phenotypes of prostate cancer (AR, PSA, ERG, synaptophysin, chromogranin A, CD56, PTEN, p53, Rb, Ki67, SPOP).

***Circulating tumour cells***

Given the risk of tumour heterogeneity, samples from biopsy may not capture all tumour characteristics. Blood assays thus will be developed to investigate tumour-based biomarkers on CTCs. The objectives of this ancillary CTC analysis are to:

- Develop and validate a non-invasive and multiparametric assay to predict response to androgen receptor inhibitor through the detection and monitoring of neuroendocrine and genome instability markers-positive CTCs.
- Evaluate the relevance of this assay for patient stratification according to rPFS and OS.

Whole blood samples will be processed to obtain CTCs and control white blood cells by hematopoietic blood-cell depletion and cell sorting. Whole-genome amplification (WGA) will be performed and copy number alterations analysed on CTC and control white blood cell WGA samples using the LowPassGenome technique.

**2. Sarcopenia**

Additional data will be collected for consenting patients in order to answer the following secondary objectifve: what is the impact of sarcopenia on survival and treatment response?

A complementary clinical evaluation will be performed by investigators and recorded in the eCRF at each timepoint, from Screening to End of treatment:

- Abdominal circumference, weight and height and body mass index (BMI)
- Maximum handgrip strength using a hand dynamometer

In addition, CT images from centres participating in the ancillary study will be used to measure skeletal muscle index.

## G) TRIAL DURATIONS

**INCLUSION PERIOD:** 5 years

**TRIAL TREATMENT PERIOD:** Treatment will be continued until radiographic disease progression. Treatment may also be terminated early by the investigator for any reason that would be beneficial to the patient, (e.g. unacceptable toxicity, intercurrent conditions that preclude continuation), or patient request.

**FOLLOW-UP:** 10 years per patient, from date of randomisation

**DURATION UNTIL PRIMARY ENDPOINT EVALUATION:**

Approximately 13 months after inclusion of the last patient

**OVERALL TRIAL DURATION (INCLUDING FOLLOW-UP):** 15 years

# SCHEDULE OF VISITS AND ACTIVITIES

| VISIT # | SCN | V1 | V2 | V3 | V4 | V5 | V6 | Vn (if <2y) | Vn (if> 2y) | EOT | LTFU |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Days | D-28 – D0 | D1 | D30 | D60 | D120 | D180 | D240 | Q120d | Q180d | | Q180d |
| Written informed consent | X | | | | | | | | | | |
| Inclusion / exclusion criteria | X | X | | | | | | | | | |
| Randomisation | | X | | | | | | | | | |
| Study treatment (*according to IWRS)* | | X | X | X | X | X | X | X | X | | |
| *CLINICAL EXAMINATIONS* | | | | | | | | | | | |
| Weight and height | X | | X | X | X | X | X | X | X | X | |
| Complete clinical examination & vital signs | X | | X | X | X | X | X | X | X | X | |
| ECOG performance status | X | | X | X | X | X | X | X | X | X | X[(b)] |
| Collection of toxicities / AEs / symptoms | X | X | X | X | X | X | X | X | X | X | X[(a)] |
| Collection of concomitant therapies | X | X | X | X | X | X | X | X | X | X | X[(b)] |
| *PARACLINICAL EXAMINATIONS* | | | | | | | | | | | |
| Scanner (CT/MRI) | X | | | | X | | X | X | X | X | X[(b)] |
| Bone scan | X | | | | X | | X | X | X | X | X[(b)] |
| PCWG3 disease assessment | X | | | | X | | X | X | X | X | X[(b)] |
| Electrocardiogram [(c)] | X[(c)] | | | X[(c)] | X[(c)] | X[(c)] | X[(c)] | X[(c)] | X[(c)] | X[(c)] | |
| *LABORATORY EXAMINATIONS* | | | | | | | | | | | |
| Haematology [(d)] | X[(e)] | | X | X | X | X | X | X | X | X | |
| Serum chemistry [(f)] | X[(e)] | | X | X | X | X | X | X | X | X | |
| PSA, testosterone | X | | X | X | X | X | X | X | X | X | X[(b)] |
| *BIOLOGICAL SAMPLE COLLECTION* | | | | | | | | | | | |
| Tumour biopsy (if available)[(g)] | X[(h)] | | | | | | | | | X[(i)] | |
| Blood samples – *French sites only*[(g)] | | X | X | X | X | | | | | X[(i)] | |
| *TRANSLATIONAL STUDY ON SARCOPENIA* | | | | | | | | | | | |
| Abdominal circumference, body mass index | X | | X | X | X | X | X | X | X | X | |
| Maximum handgrip strength | X | | X | X | X | X | X | X | X | X | |
| *GERIATRIC ASSESSMENT* | | | | | | | | | | | |
| G8 screening test | X | | | | | | | | | | |
| G-CODE | X | | | | X | | X | X | X | X | |
| CISR-G | X | | | | | | | | | | |
| *QUALITY OF LIFE ASSESSMENT* | | | | | | | | | | | |
| EORTC-QLQ-C30 | | X[(k)] | | | X | | X | X | X | X | |

| VISIT # | SCN | V1 | V2 | V3 | V4 | V5 | V6 | Vn (if <2y) | Vn (if> 2y) | EOT | LTFU |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Days | D-28 – D0 | D1 | D30 | D60 | D120 | D180 | D240 | Q120d | Q180d | | Q180d |
| EORTC-QLQ-PR25 | | X[k] | | | X | | X | X | X | X | |
| BPI-SF | | X[k] | | | X | | X | X | X | X | X[b] |
| *SURVIVAL STATUS* | | | | | | | | | | | |
| Survival status | | | | | | | | | | | X[j] |
| Subsequent antineoplastic therapy | | | | | | | | | | | X[j] |
| Subsequent progression / relapse | | | | | | | | | | | X[j] |

AE: Adverse event; BPI-SF: Brief Pain Inventory - Short Form; CISR-G: Cumulative Illness Score Rating-Geriatrics; CT: Computated tomography scan; D: Day(s); ECOG: Eastern Cooperative Oncology Group; EORTC-QLQ: European Organisation for Research and Treatment of Cancer – Quality of Life Questionnaire; EOT: End of treatment visit; G-CODE: Geriatric Core Dataset; IWRS: Interactive web response system; LTFU: Long-term follow-up visit; MRI: Magnetic resonance imaging; PCWG3: Prostate Cancer Working Group 3 (Scher, 2016); PSA: Prostate specific antigen; Q: Every; SCN: Screening period (up to 28 days prior to randomisation); V: Visit

(a) Status of ongoing adverse events and/or new treatment-related adverse events
(b) If patient discontinued study treatment for a reason other than radiographic disease progression, procedure is to be performed according to the protocol schedule until disease progression.
(c) Mandatory at the screening visit, to be repeated at subsequent visits only in case of abnormal results or if clinically indicated by patient symptoms
(d) Haematology: Haemoglobin, Haematocrit, Platelet count, Red blood cell count, White blood cell count (total and differential), Absolut neutrophil count, Lymphocytes
(e) To be performed within 7 days prior to the first administration of study treatment
(f) Serum chemistry: Alanine aminotransferase (ALAT), Albumin, Alkaline phosphatase, Aspartate aminotransferase (ASAT), Blood urea nitrogen, Calcium, Chloride, C-reactive protein , Creatinine (With estimated GFR [MDRD or CKI EPI method]), Direct Bilirubin (If total bilirubin is elevated above the upper limit of normal), Gamma-glutamyl transferase (GGT), Glucose, Lactate dehydrogenase, Magnesium, Phosphorus, Potassium, Sodium, Total Bilirubin (+ Direct Bilirubin if total bilirubin is elevated above the upper limit of normal), Total protein, Urea, Uric Acid
(g) Optional: To be performed only for patients who provide additional informed consent to translational analysis
(h) Archived Formalin fixed / paraffin embedded (FFPE) biopsy material obtained at time of diagnosis as part of the standard medical care will be collected at study entry.
(i) At the time of disease progression, if medically feasible.
(j) This information may be collected during onsite visits (as part of patients continued treatment at the site), via communication with the patients treating physician or via telephone contact with the patient.
(k) The questionnaires must be completed before the initiation of treatment.