UNICANCER Tumour Group: GETUG

Protocol n°: UC-GTG-2006 (GETUG-AFU 40)

EU CT number: 2022-502425-18-00

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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

Abbreviated title: PEACE 6 – Vulnerable

Version n° 6.0 – 17Dec2024_EU

Version history		
Submission	Version n° - Date	Part I Conclusion
Transition under Regulation n° 536/2014	V4.0 – 10 Jan 2023	12 May2023
CTIS – Amendment 1	V5.1 – 04 Mar 2024	19 Apr 2024
CTIS – Amendment 2	V6.0 – 17 Dec 2024	

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CURRENT AMENDMENT

Amendment Number	**Amendment # 2 under CTIS**	
Approximate Enrolled	**115/300 patients (global)**	
Reasons for Amendment	**Primary reasons for Amendment:** **Harmonization and correction of the statistical section, which referred to a 48-month inclusion period, to align it with the expected duration of inclusions, as reported in the rest of the protocol (60 months= 5 years).**	**Other reason(s) for Amendment:** **Updated protocol in line with the CTR** **The list of international coordinating investigators has been updated.** **A clarification has been added for the recommended imaging examinations (CT Scan or MRI and Bone Scan) that must be performed for the disease assessment according to PCWG3 recommendations.** **A section on the sponsor's responsibilities has been added.** **Section 11.1 "Independent data monitoring committee": IDMC meeting schedule has been updated to align with the approved IDMC charter.** **"G8 Screening tool" (Appendix 7) was updated: age range inconsistency corrected**
Summary of the Amendment	**Harmonization of the statistical section** **Clarification, updating and correction as specified above**	

CONTACT DETAILS

PROTOCOL N°: UC-GTG-2006

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

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APPROVAL AND SIGNATURE
FOR PROTOCOL N°: UC-GTG-2006

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

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TABLE OF CONTENT

LIST OF ABBREVIATIONS

Abbreviation	Definition
11C	Choline-11
4-IADL	Instrumental activities of daily living (4 question version)
ADL	Activities of daily living
ADT	Androgen deprivation therapy
AE	Adverse event
AR	Androgen receptor
ASAT	Aspartate aminotransferase
b.i.d	Twice a day (*bis in die*)
BMI	Body mass index
BP	Blood pressure
BPI-SF	Brief Pain Inventory - Short Form
BRC	Biological Resource Centre
CI	Confidence interval
CISR-G	Cumulative Illness Score Rating-Geriatrics
cPFS	Clinical progression-free survival
CRA	Clinical research associate
CRPC	Castrate resistant prostate cancer
CT	Computed tomography
CTC	Circulating tumour cells
CV	*Curriculum vitae*
DDI	Drug-Drug interaction
DILI	Drug-Induced Liver Injury
ECOG	Eastern cooperative oncology group
eCRF	Electronic case report form
EDTA	Ethylenediaminetetraacetic acid
EORTC	European organisation for research and treatment of cancer
EoT	End of Treatment
FCH	Fluorine-18 choline
FDG	Fluorine-18 fluorodeoxyglucose
FFPE	Formalin-fixed, paraffin-embedded
FIM	First in man
G-CODE	Geriatric Core Dataset
GCP	Good clinical practice
HR	Hazard ratio
HRD	homologous recombination deficiency
HSPC	Hormone-sensitive prostate cancer
ICF	Informed consent form
ICH	International conference on harmonisation

Abbreviation	Definition
IDMC	Independent data monitoring committee
INCa	*Institut National Du Cancer* – French National Cancer Institute
IRC	Independent review committee
IP	Investigational product
ITT	Intent-to-treat
IWRS	Interactive Web Response System
LTFU	Long-term follow-up
LFT	Liver Function Test
M1	*de novo* metastatic
mg	milligram(s)
mIBG	Metaiodobenzylguanidine
min	minute(s)
mL	millilitre(s)
MRI	magnetic resonance imaging
MSI	microsatellite instability
NCI-CTCAE	National cancer institute - Common terminology criteria for adverse events
nmol	nanomole
OS	Overall survival
PCWG 3	Prostate Cancer Working Group 3
PET	Positron emission tomography
PFS	Progression-free survival
PFS2	PFS after next line of treatment
PIS	Patient information sheet
PK	Pharmacokinetics
po	Oral administration (*Per os*)
PSA	Prostate specific antigen
QLQ	Quality of life questionnaire
QoL	Quality of life
RECIST	Response evaluation criteria in solid tumours
rPFS	Radiographic progression-free survival
SACT	Systemic anti-cancer therapy
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SNV	Single nucleotide variation
SOC	Standard of care
SST	Serum-separating tube
TEAE	Treatment emergent adverse event
TMF	Trial Master File

Abbreviation	Definition
TUG	Timed up and go test
WGA	Whole genome amplification

STATEMENT OF COMPLIANCE

UNICANCER, the trial sponsor, certifies that the trial PEACE 6 Vulnerable will be conducted in compliance with the protocol described in this document, and in accordance with the current Declaration of Helsinki (Appendix 1), the current International conference on harmonisation (ICH) Harmonized Tripartite Guideline for Good Clinical Practice (ICH-GCP, see Appendix 2), the Good Manufacturing Practices (in particular, Annex 13 on investigational medicinal products), Regulation (EU) no 536/2014 of the European Parliament and of the Council on clinical trials on medicinal products for human use,, Regulation (EU) 2016/679 (General Data Protection Regulation) and any national legal requirements.

PROTOCOL SUMMARY

A) TRIAL IDENTIFICATION

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

VERSION (NUMBER & DATE): *Version n° 6.0 – 17Dec2024 -EU*

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

INTERNATIONAL COORDINATING INVESTIGATOR:

Prof. Karim Fizazi - Gustave Roussy Cancer Campus, France

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

B) SPONSOR IDENTIFICATION

NAME:	**Unicancer** 101, rue de Tolbiac 75654 Paris Cedex 13 (France)
CONTACT PERSON:	**Ms Rachida KHERRAZ** Project Manager **R&D UNICANCER** Tel: +33 (0) 1 80 50 15 99 email: r-kherraz@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, or;
   b. 4-Instrumental activities of daily living (4-IADL) assessment score 2 or 3/4, or;
   c. A Grade 3 event on the Cumulative Illness Score Rating-Geriatrics (CISR-G) questionnaire, or;
   d. Body mass index (BMI) ≤21 kg/m^2 and/or >5% weight loss in the last 6 months, or;
   e. Timed up and go test (TUG) >14 sec.

Nota Bene: Regarding CISR-G assessment, more specifically genitourinary scoring, score N°4 is not applicable

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

   Nota Bene: (*Regarding CISR-G assessment, more specifically genitourinary scoring, score N°4 is not applicable)*.
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/curatorship/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:

General requirements for dose modifications

A patient who experiences a Grade 3 or 4 AE that is considered related to the study drug (darolutamide/placebo), should interrupt the study drug until the AE improves to Grade ≤2 or to baseline status. More specific guidance on how to proceed in the case of Grade 3-4 AEs is provided in the protocol in section 5.5 dose adaptation.

1- Study drug dose modifications for all AEs except for increases in ALT/AST

A patient who is experiencing a ≤ Grade 2 AEs (according to NCI-CTCAE v5.0), should keep receiving treatment as per protocol schedule. It is per investigator's decision to interrupt or to reduce study drug (darolutamide/placebo).

If a patient experiences a ≥ Grade 3 toxicity that is considered as related to the study drug (darolutamide/placebo):

- Treatment should be withheld until the AE improves to Grade ≤ 2 or to baseline status.
- When the severity is Grade ≤ 2, restart at a reduced dose of 300 mg b.i.d. Re-escalation to 600 mg b.i.d may be considered by the investigator when AE returns to baseline or is resolved.
- If there is no recovery after 28 consecutive days, treatment with darolutamide/placebo should be permanently discontinued.
- If, following a re-escalation to 600 mg b.i.d, a second Grade ≥ 3 AE occurs, a permanent dose reduction to 300 mg b.i.d is required.
- If a 3rd occurrence of Grade ≥ 3 AE occurs while the participant is on a dose of 300 mg b.i.d (following temporary or permanent dose reduction), the patient must be withdrawn from study treatment.

2- Study drug dose modifications for increases in ALT and/or AST

Cases of idiosyncratic Drug-Induced Liver Injury (DILI) with increases in ALT and/or AST to ≥5 and ≥ 20x ULN, including with concomitant bilirubin elevation > 2x ULN, have been reported with darolutamide.

Liver function test (LFT) abnormalities were reversible upon darolutamide discontinuation.

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. More specific guidance on how to proceed in the case of DILI is provided in the protocol in section 5.5 dose adaptation.

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.

Dose reduction below 300 mg b.i.d. is not recommended, because efficacy has not been established.

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.

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 at least 70% of the number of expected events (i.e. at least 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: +/-2.437)
- Final analysis (197 events, i.e. 100% expected events): p-value to reject $H_0 \leq 0.045$ (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?

De novo metastatic 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 objective: 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 (handgrip strength should be measured twice at each visit.)

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 15 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[(l)]				X		X	X	X	X	X[(b)]
Bone scan	X[(l)]				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[(m)]	X[(m)]		X[(m)]	X[(m)]	X[(m)]	X[(m)]	X[(m)]	X[(m)]	X[(m)]	X[(m)]	
GERIATRIC ASSESSMENT											
G8 screening test	X										
G-CODE	X				X		X	X	X	X	
CISR-G	X										
QUALITY OF LIFE ASSESSMENT											

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-C30		X[k]			X		X	X	X	X	
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.
(l) Paraclinical examination (CT scan or MRI and bone scan) to be performed within 12 weeks prior to randomization, but we strongly recommend that baseline imaging be performed within 28 days prior to randomization.
(m) handgrip strength should be measured twice at each visit.

1. INTRODUCTION

1.1. Background information

1.1.1. *Disease/pathology epidemiology*

Prostate cancer is the most commonly occurring cancer in men. In Europe approximately 450,000 new cases are diagnosed per year and prostate cancer remains the third-leading cause of cancer mortality in men, with approximately 107,000 deaths in 2018 (Ferlay, 2018). Although metastases are detected at diagnosis in only about 10% of cases in Europe, *de novo* metastatic (M1) prostate cancer is responsible for most of these deaths (Patrikidou, 2014).

1.1.2. *Prognosis*

The 5-year survival rate for patients diagnosed with M1 prostate cancer is 31%, compared with a survival rate approaching 100% for cancers diagnosed at a local or regional stage (Cancer Facts & Figures 2020).

1.1.3. *Investigational medicinal products (IMP)*

Darolutamide (or N-((S)-1-(3-(3-Chloro-4-cyanophenyl)-1H-pyrazol-1-yl)propan-2-yl)-5-(1-hydroxyethyl)-1H- pyrazole-3- carboxamide), is a novel nonsteroidal antagonist of the androgen receptor (AR), developed by the Orion Corporation Orion Pharma (Orion) and Bayer Healthcare.

Darolutamide, which is structurally distinct compared to other anti-androgens, potently inhibits androgen binding to AR and retains antagonistic properties in cells expressing increased AR levels. Darolutamide diminishes AR-signalling by inhibiting testosterone-mediated nuclear localization of AR.

Darolutamide shows anti-androgenic and anti-tumour activity in in vitro and in vivo models of castrate resistant prostate cancer (CRPC).

Darolutamide is a 1:1 mixture of two pharmacologically active diastereomers: (S,R)-darolutamide and (S,S)-darolutamide which shows no major differences in pharmacological activity in vitro. The major metabolite keto-darolutamide has similar high binding affinity for the AR and exhibits comparable activity in in vitro assays.

Darolutamide is provided as 300 mg tablets.

The product is currently approved by all major regulatory authorities including the United States of America, Food and Drug Administration (FDA), the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) and the European Medicines Agency (EMA) for the treatment of men with non-metastatic CRPC and is in clinical development in a phase 3 trial in metastatic hormone-sensitive prostate cancer (HSPC). A comprehensive set of primary and secondary pharmacodynamics, safety pharmacology, pharmacokinetics (PK) and metabolism, and toxicology studies was conducted to demonstrate the non-clinical safety and efficacy of darolutamide.

Until now, darolutamide has been studied in 12 company-sponsored clinical studies, of which six studies were conducted in prostate cancer patients and six studies were conducted in non-cancer subjects i.e. healthy volunteers and subjects with renal or hepatic impairment: a first-in-man (FIM) study with a Phase II cohort expansion (Study 17829 ARADES); a long-term safety extension study for the FIM study (Study 18035 ARADES EXT); a bioavailability study (Study 17830 ARAFOR); a mass balance and bioavailability study in healthy male subjects (Study 17831 ARIADME); a study to investigate the safety, tolerability, and PK of darolutamide in Japanese subjects with metastatic

CRPC (Study 17719); a study to investigate the PK, safety and tolerability in subjects with hepatic impairment, renal impairment, and normal hepatic and renal function (Study 17721); a Phase I Drug-Drug interaction (DDI) study in healthy male and female subjects (Study 17723) to investigate the effect of darolutamide on the PK of a probe substrate for the transporters BCRP, OATP1B1, OATP1B3, and OAT3; a Phase I DDI study in healthy male subjects (Study 17726) investigating the influence of CYP3A4/P-gp mediating agents on the PK of darolutamide, its diastereomers and major metabolite; and another Phase I DDI study in healthy male subjects (Study 18860) to assess the effect of darolutamide on the PK of probe substrates of CYP3A4 and P-gp; and a Phase I, randomised, placebo-controlled, open-label, three period crossover, study to investigate the effect of darolutamide and enzalutamide on cerebral blood flow in healthy male volunteers (Study 18426). In addition, it is currently being studied in two randomised double blind Phase III studies; in men with non-metastatic CRPC and a PSA doubling time of 10 months or less (ARAMIS 17712) and in men with metastatic HSPC (ARASENS 17777). The results of clinical studies indicate that darolutamide is well-tolerated, and demonstrates anti-tumour efficacy in patients with CRPC.

Refer to the current version of the darolutamide Investigator Brochure for a complete summary of non-clinical and clinical data including safety, efficacy, and pharmacokinetics data.

1.2. Trial rationale

For more than 7 decades, men with metastatic HSPC were treated with androgen deprivation therapy (ADT) alone, with no meaningful progress until 2013, when the French GETUG-15 trial showed that combining ADT with docetaxel improved progression-free survival (PFS) (Hazard ratio [HR]: 0.72, 95% confidence interval [CI]: 0.57–0.91; p=0.005), but not overall survival (OS) (Gravis, 2013; Gravis, 2016). Subsequently, two larger Phase III trials, CHAARTED and STAMPEDE showed that ADT + docetaxel also improved OS compared to ADT alone (median OS: 57.6 vs 47.2 months [HR: 0.72, 95%CI: 0.59-0.89, p=0.0018] and 65 vs. 43 months [HR: 0.73, 95%CI: 0.59–0.89; p=0.002] respectively) (Sweeney, 2015; James, 2016).

More recently, the combination of ADT with next-generation AR axis-targeted agents has also been demonstrated to confer a survival benefit to M1 prostate cancer patients, compared to ADT alone.

The LATITUDE and STAMPEDE trials compared the efficacy of combining abiraterone and prednisone with ADT. In the LATITUDE trial median OS was 53.3 with abiraterone, prednisone and ADT compared with 36.5 months with ADT alone (HR: 0.66, 95%CI: 0.56-0.78, p<0.0001) (Fizazi, 2017). The STAMPEDE trial also found a significant OS benefit in favour of the combination (HR: 0.61, 95%CI: 0.49-0.75) (James, 2017). Similar OS findings have also been reported for combinations of enzalutamide + ADT (ENZAMET trial: HR: 0.67, 95%CI: 0.52-0.86, p=0.002) and apalutamide + ADT (AXIS trial: HR: 0.67, 95%CI: 0.51-0.89, p=0.005) compared with ADT alone (Davis 2019, Chi 2019).

The ongoing PEACE-1 trial is currently investigating whether adding abiraterone or local radiotherapy to men receiving ADT + docetaxel can further improve OS beyond that seen with the doublet therapy: the planned accrual of 1173 men was completed in December 2018 and first read outs are expected in 2021.

The PEACE-6 umbrella programme

Previous trials of M1 prostate cancer treatment combinations described above were open to all comers. Our hypothesis is that tailoring treatment based on clinical and molecular characteristics is now required to keep improving outcomes.

The PEACE 6 programme represents a collaborative network of investigators from 14 European countries (Belgium, France, Germany, Ireland, Italy, The Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Spain, Sweden, and Switzerland). Under the PEACE 6 umbrella program, M1 prostate cancer patients will be oriented to a specific randomised comparative trial of combination therapy versus standard of care (SOC) according to patient and disease characteristics. Four trials have been defined initially and patients will be allocated to one of these trials according to the following ranking:

1. PEACE-6 Oligo: Will evaluate the addition of metastases-directed radiotherapy to SOC in patients with oligo-metastatic prostate cancer: approximately 30% of patients;
2. PEACE-6 Vulnerable: Will evaluate the combination of darolutamide with SOC in “unfi” elderly M1 prostate cancer patients (defined by geriatric scales): approximately 20% of patients;
3. PEACE-6 PARPi-IO: Will evaluate the combination of a PD-1 inhibitor plus a PARP inhibitor with SOC in M1 prostate patients with either homologous recombination deficiency positive (HRD+), microsatellite instability (MSI-high), or cdk12-/- cancers: approximately 15% of patients;
4. PEACE-6 PSMA: Will evaluate the benefit of prostate-specific membrane antigen (PSMA) targeted therapy for M1 prostate cancer patients who do not fit in previous subgroups and who respond poorly to SOC (i.e. PSA >0.1 ng/mL, 6-8 months after initiation of systemic treatment, with no evidence of cancer progression, including no rising PSA): approximately 35% of patients.

Additional trials may be added at a later date according to changes in the treatment landscape and state of the art.

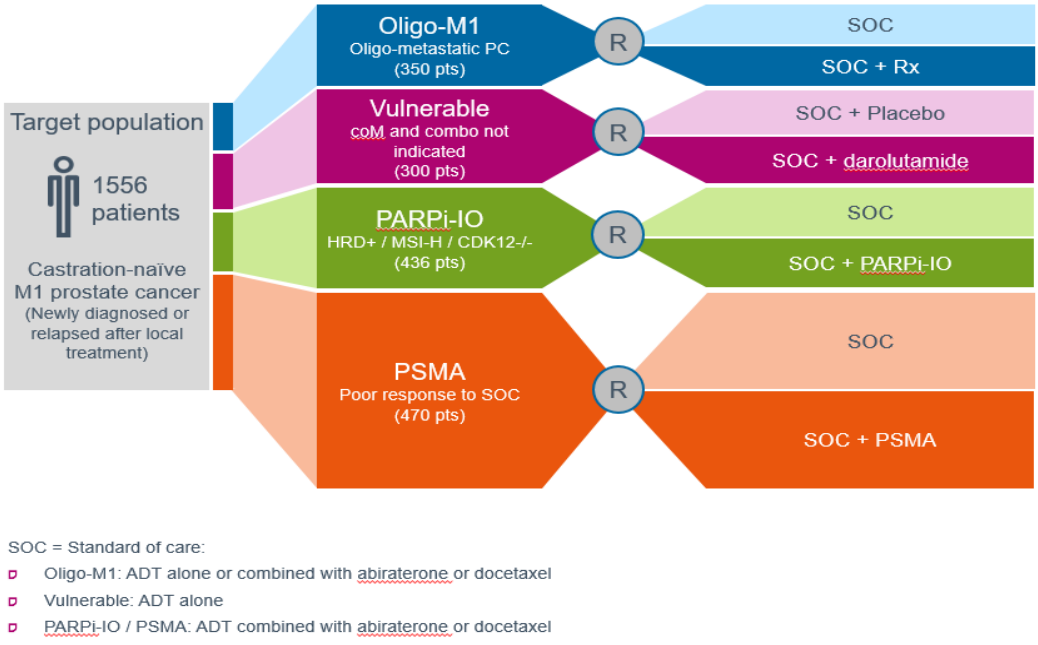


Figure 1. Schematic of the PEACE 6 programme of clinical trials in *de novo* metastatic prostate cancer

PEACE-6 Vulnerable

The health status of men over 70 years old can vary widely. Some elderly patients may have no comorbidity and remain autonomous, while others must deal with polypharmacy, severe comorbidities, or impaired cognitive or physical function. The former are usually eligible to receive standard treatments but for the latter group of men, who are usually excluded from clinical trials, the best treatment options remains to be tested. With the aging of the European population, we believe that clinical trials with the specific aim of optimizing treatments in the unfit population are a top priority.

In recent years, several attempts have been made to define frailty, but so far there is no consensus on how to identify this population. Balducci defined frailty as a condition of dependence and vulnerability, which is reflected in abnormalities in one or more activities of daily living (ADL), severe comorbidity and cognitive deterioration (Balducci, 2000).

The current SOC for vunerable men with M1 prostate cancer remains ADT alone. This subgroup is unfit to receive currently available systemic ADT combination regimen: docetaxel because of its multiple side effects; abiraterone due to the need for concomitant steroids, related muscle loss and other side effects; and enzalutamide or apalutamide due to their central nervous system-related adverse events including increased risk of falls and fractures and potential for important drug-drug interactions. Moreover, both abiraterone and enzalutamide significantly increase the incidence of cardiovascular events.

Darolutamide is a next-generation AR antagonist with a different chemical structure to apalutamide and enzalutamide. It was previously studied in two Phase I-II trials (ARADES and ARAFOR) and both trials supported strong activity and minimal toxicity (with no clear drug-related side effect detected) in patients with various stages of metastatic CRPC (Fizazi, 2014; Massard, 2016).

Darolutamide has low penetration of the blood-brain barrier, a property that may reduce the risk of fatigue and seizure, and does not require concomitant steroids. Darolutamide does not bind significantly to cytochrome CYP 3A4. Thus, it is hypothesized that combining ADT with darolutamide will improve patients' outcomes compared to ADT alone, with an acceptable toxicity. Indeed, darolutamide + ADT was recently shown to improve metastases-free survival over ADT alone in patients with non-metastatic CRPC (median: 40.4 vs 18.4 months, HR: 0.41, 95%CI: 0.34-0.50, p<0.001). In the final analysis of the ARAMIS trial, darolutamide with ADT demonstrated a significant decrease in risk of death by 31% vs ADT alone (HR 0.69, p=0.003) and a remarkable safety profile, with almost no significant side effects compared to ADT alone (Fizazi, 2019). This very favourable efficacy/safety profile makes darolutamide a perfect candidate for this vulnerable M1 prostate cancer population.

PEACE-6 Vulnerable will compare the efficacy and safety of ADT + darolutamide versus ADT + placebo in this "frail" (defined by geriatric scales) elderly castration-naïve M1 prostate cancer population.

1.3. Justification for the therapeutic regimens and treatment durations

Previous Phase 2 and Phase 3 studies have demonstrated that darolutamide administrated orally (*per* os, po) at a dose of 600 mg twice a day (b.i.d) to patients with non-metastatic CRPC improved OS with a good safety profile (Fizazi, 2019).

In this trial, darolutamide 600 mg, or a placebo control will be administered po, b.i.d to patients with castration-naive prostate cancer in combination with standard ADT. Treatment will be continued until disease progression according to Prostate Cancer Working Group 3 (PCWG3) criteria (Scher, 2016).

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.

1.4. Potential risks and benefits

1.4.1. *Known potential risks*

Foreseeable risks of study participation therapy include a lack of response to treatment, and potential side effects related to darolutamide as outlined in the Investigator's Brochure.

The overall safety profile of darolutamide is based on data from 1508 patients of whom 954 received at least one dose of darolutamide in the Phase 3 Study 17712 (ARAMIS). The incidence of treatment emergent adverse events (TEAE) leading to permanent discontinuation of study treatment was comparable in both darolutamide (8.9%) and placebo (8.7%) treatment arms. The adverse drug reactions (ADRs) observed with darolutamide are rash, pain in extremity (common) and fatigue (very common). Laboratory test abnormalities related to darolutamide treatment and reported more frequently in darolutamide-treated patients compared to placebo-treated patients in the ARAMIS study were neutrophil count decreased, bilirubin increased, and aspartate aminotransferase (ASAT) increased.

As darolutamide shares a mode of action with the ADT and with the novel anti-androgens, the key risks associated with ADT and with the novel anti-androgens such as osteoporosis/fractures, decrease in lean body weight/sarcopenia, insulin resistance, dyslipidaemia and cerebrovascular disorders are considered as potential risks of darolutamide.

The primary endpoint of the study is radiographic progression-free survival (rPFS). Measurement of this endpoint requires a regular evaluation of the disease by computed tomography (CT) scan, or magnetic resonance imaging (MRI) and bone scan. Radiographic exams are generally performed at 4-12 month intervals or to confirm a suspected evolution of the disease.

The risk associated with radiographic examination are those associated with an increased exposure to radiation.

1.4.2. *Known potential benefits*

The benefit of participation in the trial is access to a potentially efficacious experimental combination which has been shown to provide a better survival rate that current standard of care in similar settings (see Section 1.2).

1.5. Trial population

The trial population is to be composed of adult men, diagnosed with castration-naïve *de novo* metastatic prostate cancer, and who are ineligible to receive currently available systemic ADT combination regimen (docetaxel, abiraterone, or enzalutamide) and are considered as frail (defined by standard geriatric scales).

2. TRIAL OBJECTIVES

2.1. Primary objective

To compare the efficacy of ADT + darolutamide vs ADT + placebo in terms of radiographic progression-free survival 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.

2.2. Secondary objective(s)

The key secondary objectives of PEACE-6 Vulnerable are:

- 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.

2.3. Exploratory objective(s)

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

3. TRIAL DESIGN AND ENDPOINTS

3.1. Description of the trial design

This is a Phase III, international, multicentre, randomised, double-blinded placebo controlled trial, evaluating the efficacy and safety of ADT +/- darolutamide in vulnerable men with castration-naïve *de novo* metastatic prostate cancer.

3.2. Trial Endpoints

3.2.1. *Primary endpoint*

Radiographic progression-free survival, defined as time from randomisation to radiographic progression as assessed by the investigator according to PCWG3 criteria (Scher, 2016; Appendix 3), 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; Eisenhauer, 2009). The date of radiographic progression will be the date of the first reported event meeting the above definition (see Appendix 3 & Appendix 4 for further details).

3.2.2. *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 withdraw consent.
- Toxicity will be evaluated according to version 5 of the National Cancer Institut - 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.

3.3. Progression of the trial

Patients participating in the trial will comply with the protocol for an estimated 12 months of treatment and subsequent follow-up for up to 10 years from the date of randomisation.

The end of the study corresponds to the last visit of the last patient.

The investigation/examination schedule is defined by the trial schedule of activities in Section "Schedule of visits and activities" of the protocol summary.

3.4. Inclusion and randomisation procedure

Patients written informed consent is to be obtained before any study related procedures are performed. Candidates who consent to study participation will then 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 (see Section 7.1). 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. Blood samples will also be collected prior to the start of treatment.

Eligible patients will be randomised via the interactive web response system (IWRS, https://ecrf.euraxipharma.fr/csonline/) and registered on the Unicancer electronic case report form (eCRF, https://ecrf.icm.unicancer.fr/csonline) with a unique identification number. This number must be used as the sole patient identifier throughout the study.

It is the responsibility of the investigator to verify and confirm that all inclusion and non-inclusion criteria are met prior to randomisation.

Eligible patients will be randomised (1:1) via a specific Interactive Web Response System (IWRS) to receive either:

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

Randomisation will be blinded, and stratified according to LATITUDE risk criteria (high risk versus low risk) and ECOG performance status score (0 or 1 vs. 2) using a system of different sized random permuted blocks to ensure the treatment arms are balanced for all combinations of stratification factors. A patient is considered as high risk according to the LATITUDE criteria if he has at least two of the three following high-risk factors associated with poor prognosis: a Gleason score of 8 or more (on a scale of 2 to 10, with higher scores indicating more aggressive disease), at least three bone lesions, and the presence of measurable visceral metastasis. He is otherwise considered as low risk (Fizazi, 2017).

E-mail confirmation of the randomisation and assigned treatment number will be sent to the Investigator, Statistician, Sponsor and Data Manager.

Instructions for the use of the IWRS will be provided to all investigators during the trial initiation visit at each site.

3.5. Procedure for breaking the randomisation code (unblinding)

Except in case of necessity to implement an immediate treatment for a serious adverse event (SAE), breaking the randomisation code may be authorised only in case of absolute necessity (in instances when the nature of the treatment allocated is necessary for patient management) or after approval from the sponsor.

Unblinding is performed via the IWRS. Instructions for the use of the IWRS will be provided to all investigators during the trial initiation visit at each site.

3.6. Premature Trial Terminations and Suspension

The trial may be suspended or stopped by the sponsor after meeting with the coordinating investigators or following a request by the respective regulatory authority and/or the responsible Ethics Committee for the following reasons:

- High frequency and/or unexpected severity of toxicity
- Insufficient patient enrolment
- Lack of significant results («futility»)
- Insufficient quality of data collection

3.7. Patient's trial withdrawal and discontinuation

Patient withdrawal concerns patients who stop treatment and all other protocol-defined procedures. Please note that treatment discontinuation without consent withdrawal from a patient is not

considered as a trial withdrawal. For treatment discontinuation only, please refer to Section 5.6. This can occur under the following circumstances:

- Patient withdraws consent
- The principal investigator may terminate a patient's participants from the trial, if this is in the interest of the patient.

Trial patients may withdraw their consent at any time without justification, irrespective of the reason(s). In the case of withdrawal, the investigator should attempt to obtain as much information as possible. This information should be noted in the patient's medical file. The patient's withdrawal of consent does not impact the patient's right to receive medical treatment.

4. PATIENT SELECTION

4.1. 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 (Scher, 2016; Appendix 3).
6. Ineligible for treatment with all of the following drugs: docetaxel, abiraterone, enzalutamide, apalutamide; AND meets at least one of the following frailty criteria:
   - Activities of daily living (ADL) assessment (excluding urinary incontinence question) score 3 or 4/5 (Katz, 1970; Appendix 8), or;
   - 4-Instrumental activities of daily living (4-IADL) assessment score 2 or 3/4 (Lawton, 1969; Appendix 8), or;
   - A Grade 3 event on the Cumulative Illness Score Rating-Geriatrics (CISR-G) questionnaire (Miller, 1992; Appendix 9), or;
   - Body mass index (BMI) ≤21 kg/m2 and/or >5% weight loss in the last 6 months, or;
   - Timed up and go test (TUG) > 14 sec (Podsiadlo, 1991; Appendix 8).

Nota Bene: Regarding CISR-G assessment, more specifically genitourinary scoring, score N°4 is not applicable

7. Adequate bone marrow function: haemoglobin ≥80g/L, white blood cells ≥ 3.0 x10^9/L and platelets ≥80 x10^9/L.
8. Adequate liver function: alanine aminotransferase (ALT) < 2 xULN and bilirubin < 1.5 xULN, (or if bilirubin is between 1.5-2x ULN, they must have a normal conjugated bilirubin). For patients with documented liver metastasis ALT < 5 xULN 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.

4.2. 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.

   Nota Bene: Regarding CISR-G assessment, more specifically genitourinary scoring, score N°4 is not applicable

2. Eastern Cooperative Oncology Group (ECOG) performance status score ≥3 (Appendix 5).
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/curatorship/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.

5. TRIAL TREATMENTS/INTERVENTIONS

5.1. Description of trial treatments/interventions

Patients who have signed the informed consent form and are eligible for inclusion will be randomised to receive the following treatments:

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

Androgen-deprivation therapy

All patients will receive continuous ADT. Intermittent ADT will not be used in this trial, except if severe intolerance to ADT occurs.

The choice of ADT is left to the discretion of the investigator, to be administered according to local standard procedures but should consist in either:

- A bilateral orchiectomy
- A luteinizing hormone-releasing hormone (LHRH) agonists associated, during the first weeks, with an androgen receptor (AR) inhibitor (e.g. bicalutamide or flutamine). All formulations of LHRH agonists (monthly, 3 monthly, 6 monthly, etc) are acceptable as long as treatment is used continuously.

  Note: *If the patient has been receiving LHRH + AR inhibitor for more than 4 weeks prior to randomisation, the androgen receptor inhibitor should be discontinued at randomization*.

- A LHRH antagonist.

Patients may have initiated ADT therapy up to 12 weeks prior to randomization.

Darolutamide/placebo

Patients are to take two 300 mg tablets of darolutamide or placebo twice daily, (i.e equivalent to a total daily dose of 1200 mg) with food and a glass of water. This dose may be adjusted in the event of adverse toxicity (see Section 5.5).

Treatment observance will be recorded in the eCRF, and the patients will be asked to complete a personal logbook daily.

5.2. Acquisition, reception, and storage

The investigational product (IP) darolutamide and placebo control will be provided by the sponsor. It will be distributed to the pharmacy at the investigational site via a dedicated courier (Eurofins) in accordance with the current Good Distribution Practices guidelines.

The pharmacist of the trial site will receive numbered treatment and will acknowledge receipt of all deliveries by sending the necessary completed documents to the distributor.

The pharmacist is responsible for a safe and proper handling and storage of the IP at the investigational site. The IP must be stored in a locked facility with access restricted to the pharmacist and authorized personnel, and under environmental conditions consistent with the drug manufacturer recommendations (Investigator's Brochure).

- Darolutamide and placebo must be stored below 30°C.

Up to date temperature logs must be maintained by the pharmacist/investigator to document adequate storage during the trial. These logs must be available at the site during monitoring visits, and in the event of an audit or inspection.

If the storage conditions as indicated above are exceeded (e.g. temperature excursion), the pharmacist/investigator must place the corresponding treatments in quarantine and immediately notify the sponsor who will indicate the procedure to follow. Under no circumstances should these treatments be delivered to trial patients without prior authorization by the sponsor.

5.3. Trial treatments accountability, return and destruction

Patients will return unused and used treatments to the physician-investigator or to the pharmacy. The pharmacist (or investigator) of each investigational site will count the returned tablets and accurately keep record of them. These records will be made available to the clinical research associate (CRA) mandated by the sponsor.

The investigator/pharmacist must ensure that the IP is administrated only to patients randomised in this trial. The IP must not to be used outside the context of the trial protocol.

The pharmacist or authorized staff must document the receipt, dispensation, return and destruction of all IP received during this trial. Records of IP delivery to the site, the inventory at the site, the use by each patient, and the return to the sponsor or destruction by the site must be implemented and maintained by the pharmacist or another appropriately trained individual at the investigational site. The following minimum information must be present: all relevant dates (delivery dates, dispensation, returns, and destruction), quantities, and IP batch numbers. Accountability form will be provided by the sponsor to ensure trial treatment accountability.

The pharmacist will implement an accounting of IP dispensed, used, unused, returned by the patients. The accountability of the IP returned by patients will be systematically done by the pharmacist of the site.

This process will be monitored by the Unicancer CRA during the trial. The CRA will check that the accountability documentation has been filled in and signed by the pharmacist before the IP, used and unused, are destroyed.

All remaining IP, used and unused, shall be collected and returned for destruction. The destruction will take place at the investigator sites under the responsibility of their pharmacist in accordance with national regulatory requirements, and with prior formal agreement from the sponsor. A certificate of destruction, identifying the numbered products concerned, will be provided to the sponsor.

5.4. Formulation, appearance, packaging, and labelling

Darolutamide and the placebo control are formulated as blue film-coated immediate-release 0.3 g tablet for oral application.

The tablets are provided in a high-density polyethylene white opaque plastic bottle.

The darolutamide and placebo control will be provided by the Sponsor and labelled appropriately as IP for this study in accordance with the specific requirements of this study, applicable Good Manufacturing Practices, and national regulations.

Packaging will be performed by Bayer. Relabelling will be performed by Eurofins.

5.5. Dose adaptation

General requirements for dose modifications

A patient who experiences a Grade 3 or 4 AE that is considered related to the study drug (darolutamide/placebo), should interrupt the study drug until the AE improves to Grade ≤2 or to baseline status. Specific guidance on how to proceed in the setting of Grade 3-4 AEs is provided in Table 1 Study drug dose modifications for all AEs except for increases in ALT/AST" and Table 2 Study drug dose modifications for increases in ALT and/or AST" .

5.5.1. *Study drug dose modifications for all AEs except for increases in ALT/AST*

Table 1 Study drug dose modifications for all AEs except for increases in ALT/AST

Severity grade (NCI-CTCAE v5.0)	**Dose modifications**	**Study treatment withdrawal**
Grade 0 – 2	Treat on time Per investigator's decision to interrupt or reduce study drug[a,b]	Not applicable
Grade 3 – 4	Interrupt until Grade ≤2 or baseline[a],	If Grade ≥ 3 study drug-related AE occurs while the participant is on a

	When the severity is Grade ≤2, restart at a reduced dose 300 mg b.i.d[b,c]	dose of 300 mg b.i.d (following temporary or permanent dose reduction), the participant must be withdrawn from treatment with study drug

Excludes clinically non-significant and asymptomatic laboratory abnormalities

AE = Adverse Event; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; b.i.d = Twice daily; NCI-CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0;

[a]: If there is no recovery after 28 consecutive days, treatment with study drug should be permanently discontinued.

[b]: when AE returns to baseline or is resolved, re-escalation to 600 mg b.i.d may be considered by the investigator.

[c]: If, following a re-escalation to 600 mg b.i.d, a second Grade ≥ 3 study drug-related AE occurs, a permanent dose reduction to 300 mg b.i.d is required. A third occurrence of a Grade ≥ 3 study drug-related AE requires permanent discontinuation of treatment with study drug.

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.

Dose reduction below 300 mg b.i.d is not recommended because efficacy has not been established. The maximum efficacious daily dose is the recommended dose of 600 mg b.i.d.

5.5.2. *Study drug dose modifications for increases in ALT and/or AST*

Cases of idiosyncratic Drug-Induced Liver Injury (DILI) with increases in ALT and/or AST to ≥5 and ≥ 20x ULN, including with concomitant bilirubin elevation > 2x ULN, have been reported with darolutamide.

Liver function test (LFT) abnormalities were reversible upon darolutamide discontinuation. Participants who experience hepatic transaminase elevations suggestive of idiosyncratic DILI considered to be causally related to study drug, should discontinue study drug.

Additional laboratorytests monitoring is recommended for Grade ≥ 2 ALT and/or AST increase (ALT/AST >3 x ULN) as show in Table 2

Table 2 Study drug dose modifications for increases in ALT and/or AST

Severity grade (NCI CTCAE v.5.0)	**ALT/AST increase**
Grade 0 – 1	- Treat on time. - Per investigator's decision to interrupt or reduce study drug[a]
Grade 2 - 4	If ALT or AST rise to >3 ULN: - Per investigator's decision to interrupt or reduce study drug,

	- Monitor LFT (ALT, AST, total and direct bilirubin, ALP) and INR within 72 hours after the onset and then as frequently as needed according to investigator's clinical judgment, until ALT and/or AST returns to baseline or normal values. - Participants must be discontinued from the study treatment in case of hepatic transaminase elevations suggestive of idiosyncratic DILI considered to be causally related to study drug. DILI should be suspected after other causes of liver injury, have been excluded. A further guidance for diagnostic and laboratory evaluation for suspected DILI, is provided in Appendix 14 - The criteria for darolutamide discontinuation (FDA 2009) are: o ALT or AST > 8xULN o ALT or AST> 5xULN for more than 2 weeks o ALT or AST> 3xULN and (TBL> 2xULN or INR> 1.5) o ALT or AST> 3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).
For all grades:	Further recommendations: - If ALT and AST return to normal values or to baseline after study drug interruption, study drug may be restarted at the reduced dose of 300 mg b.i.d. - If, at the reduced dose, there is no increase of ALT or AST in the subsequent 2 weeks, full dose may be resumed. - If, at the reduced or full dose, ALT or AST values rise again, stud drug should be permanently discontinued. Monitor LFTs until ALT and/or AST return to baseline or normal values.

AE = Adverse Event; ALP = Alkaline phosphatase; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; b.i.d = Twice daily; DILI = Drug-Induced Liver Injury; INR= International Normalised Ratio; LFT = Liver Function Test; NCI-CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0; TBL = Total Biribulin; ULN = Upper Limit of Normal

[a] : If there is no recovery after 28 consecutive days, treatment with study drug would be permanently discontinued.

If the patient discontinues darolutamide/placebo due to toxicity, ADT should be continued.

If the patient experiences intolerable side effects due to ADT then the ADT may be substituted with another ADT at the discretion of the investigator. If the patient refuses the ADT, the investigator will ask the sponsor what steps to take.

5.6. Patients' discontinuations of treatment

Patients can discontinue the trial treatment for the following reasons:

- Unacceptable toxicity.
- Patients decline further treatment/therapy but accept to continue with protocol.
- Investigator's decision.

- Radiographic disease progression

After discontinuation of trial treatment, subsequent therapy decisions are left to the physician's discretion.

Patients who discontinue trial treatment will continue with the trial and the protocol-defined procedures, unless they specifically withdraw their consent and indicate that they do not want to perform any further trial-related visits or assessments (for patient withdrawals see Section 3.7).

5.7. Concomitant medications and therapies

All medications (including herbal preparations) and therapies taken by the patients or administered to the patients from the onset of trial and given in addition to the IP during the trial are considered as concomitant medications. Any concomitant medication(s) trial will be recorded in the eCRF.

5.7.1. *Authorized concomitant treatments*

All symptomatic treatments/therapies required for the patients' comfort (antiemetic, anti-diarrhoeic, antibiotics, and corticosteroid cream) are authorized with the exception of those treatments specified in Section 5.7.2 below. The posology and duration of administration are at the investigator's discretion, as per standard of care.

5.7.2. *Prohibited concomitant treatments*

Prohibited medication/class of drug:	**Usage:**
Any investigational anticancer therapy other than those under investigation in this trial	Should not be given concomitantly whilst the patient is on trial treatment
Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment (prostate or second cancer) other than those under investigation in this trial	Should not be given concomitantly whilst the patient is on trial treatment. (Concurrent use of hormones for non-cancer-related conditions [e.g., insulin for diabetes and hormone replacement therapy] is acceptable. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable [e.g., by local surgery or radiotherapy])
CYP450 enzyme inducers	Use of strong CYP3A4 inducers and P-gp inducers (e.g., carbamazepine, phenobarbital, St. John's Wort) during treatment with darolutamide is not recommended, unless there is no therapeutic alternative. Selection of an alternate concomitant medicinal product, with no or weak potential to induce CYP3A4 or P-gp, should be considered.
BCRP substrates	Co-administration of darolutamide may increase the plasma concentrations of BCRP substrates (e.g., rosuvastatin, methotrexate, sulfasalazine, fluvastatin, atorvastatin). Therefore, the related recommendation in the product information of the BCRP substrate should be followed when co-administered with darolutamide.

Non-anticancer concomitant medication should be handled as recommended by the valid professional information for darolutamide unless otherwise specified in this protocol or the investigator brochure.

5.7.3. *Drug-drug Interactions*

5.7.3.1. Effects of other medicinal products on darolutamide

CYP3A4 and P-glycoprotein inducers

Darolutamide is a substrate of CYP3A4 and P-glycoprotein (P-gp).

Use of strong and moderate CYP3A4 inducers and P-gp inducers (e.g. carbamazepine, phenobarbital, St. John's Wort, phenytoin, and rifampicin) during treatment with darolutamide is not recommended, unless there is no therapeutic alternative. Selection of an alternate concomitant medicinal product, with no or weak potential to induce CYP3A4 or P-gp should be considered.

Repeated administration of rifampicin (600 mg), a strong CYP3A4 and a P-gp inducer, with a single dose of darolutamide (600 mg) together with food, resulted in a decrease of 72% in mean exposure (AUC0-72) and a decrease of 52% in C_{max} of darolutamide.

CYP3A4, P-glycoprotein and breast cancer resistance protein inhibitors

Darolutamide is a substrate of CYP3A4, P-gp and breast cancer resistance protein (BCRP).

No clinically relevant drug-drug interaction is expected in case of CYP3A4, P-gp or BCRP inhibitor administration. Darolutamide may be given concomitantly with CYP3A4, P-gp or BCRP inhibitors. Concomitant use of darolutamide with a combined P-gp and strong CYP3A4 inhibitor increases darolutamide exposure which may increase the risk of darolutamide adverse reactions. It is recommended to monitor patients more frequently for darolutamide adverse reactions and modify darolutamide dose as needed.

Administration of itraconazole (200 mg twice daily on day 1 and once daily on the following 7 days), a strong CYP3A4, P-gp and BCRP inhibitor, with a single dose of darolutamide (600 mg on day 5 together with food) resulted in a 1.7-fold increase in mean exposure (AUC0-72) and a 1.4-fold increase of C_{max} of darolutamide.

UGT1A9 inhibitors

Darolutamide is a substrate of UGT1A9.

No clinically relevant drug-drug interaction is expected in case of UGT1A9 inhibitor administration.

Darolutamide may be given concomitantly with UGT1A9 inhibitors.

A population pharmacokinetic analysis showed that co-administration of UGT1A9 inhibitors with darolutamide resulted in a 1.2-fold increase in exposure (AUC0-72) of darolutamide.

5.7.3.2. Effects of darolutamide on other medicinal products

Breast cancer resistance protein, organic anion transporting polypeptide substrates

Darolutamide is an inhibitor of BCRP and organic anion transporting polypeptides (OATP) 1B1 and 1B3.

Co-administration of rosuvastatin should be avoided unless there is no therapeutic alternative. Selection of an alternative concomitant medicinal product with less potential to inhibit BCRP, OATP1B1 and OATP1B3 should be considered.

Administration of darolutamide (600 mg twice daily for 5 days) prior to co-administration of a single dose of rosuvastatin (5 mg) together with food resulted in approximately 5-fold increase in mean exposure (AUC) and C_{max} of rosuvastatin.

Co-administration of darolutamide with other BCRP substrates should be avoided where possible.

Co-administration of darolutamide may increase the plasma concentrations of other concomitant BCRP, OATP1B1 and OATP1B3 substrates (e.g. methotrexate, sulfasalazine, fluvastatin, atorvastatin, pitavastatin). Therefore, it is recommended to monitor patients for adverse reactions of BCRP, OATP1B1 and OATP1B3 substrates. In addition, the related recommendation in the product information of these substrates should be followed when co-administered with darolutamide.

P-gp substrates

No clinically relevant drug-drug interaction is expected in case of P-gp substrate administration. Darolutamide may be given concomitantly with P-gp substrates (e.g. digoxin, verapamil or nifedipine). Co-administration of darolutamide together with the sensitive P-gp substrate dabigatran etexilate did not reveal any increase in exposure (AUC and C_{max}) of dabigatran.

CYP3A4 substrates

Darolutamide is a mild inducer of CYP3A4.

No clinically relevant drug-drug interaction is expected in case of CYP substrate administration. Darolutamide may be given concomitantly with CYP substrates (e.g. warfarin, L-thyroxine, omeprazole).

Administration of darolutamide (600 mg twice daily for 9 days) prior to co-administration of a single dose of the sensitive CYP3A4 substrate midazolam (1 mg) together with food, decreased the mean exposure (AUC) and C_{max} of midazolam by 29% and 32%, respectively.

Darolutamide did not inhibit the metabolism of selected CYP substrates *in vitro* at clinically relevant concentrations.

Medicinal products that prolong the QT interval

Since androgen deprivation treatment may prolong the QT interval, the co-administration with medicinal products known to prolong the QT interval or medicinal products able to induce Torsades de pointes should be carefully evaluated. These include medicinal products such as class IA (e.g. quinidine, disopyramide) or class III (e.g., amiodarone, sotalol, dofetilide, ibutilide) antiarrhythmic medicinal products, methadone, moxifloxacin, and antipsychotics (e.g. haloperidol).

5.7.4. *Treatment at radiographic disease progression*

Following radiographic progression, subsequent treatment will be prescribed at the investigator's discretion.

5.7.5. *Contraception during the trial*

Non-sterilized males who are sexually active with a female partner of childbearing potential must use a male condom plus spermicide during the treatment phase and for 2 weeks after the last trial treatment administration. Male patients should refrain from sperm donation throughout this period.

Definitions

Females of childbearing potential are those who are not surgically sterile (i.e., bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or post-menopausal (for the definition of post-menopausal see below).

Women will be considered post-menopausal if they have been amenorrhea for 12 months without an alternative medical cause. The following age-specific requirements apply:

- Women <50 years of age would be considered post-menopausal if they have been amenorrhea for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy or hysterectomy).
- Women ≥50 years of age would be considered post-menopausal if they have been amenorrhea for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

6. EVALUATION OF TREATMENT EFFICACY AND SAFETY

6.1. Efficacy evaluation

Treatment efficacy will be evaluated by measuring changes in tumour size/number of lesions (see Section 7.3.8) and serum PSA levels in response to treatment; according to PCWG3 criteria (Scher, 2016; Appendix 3).

Patient's disease will be assessed at "baseline" (during the screening period) and then every 120 (±14) days after randomisation during the first 2 years and every 180 (±14) days thereafter, until documented radiographic progression, or death, whichever occurs first. For patients who discontinue study treatment for reasons other than radiographic progression, death, or consent withdrawal, investigators will continue to perform disease evaluations during the follow-up period until progression.

The primary evaluation endpoint is radiographic progression-free survival, defined as time from randomisation to radiographic progression according to PCWG3 criteria or death, whichever occurs first.

For secondary evaluation endpoints see Section 3.2.2.

6.1.1. *Centralized review*

The final analysis of the primary endpoint (rPFS) will be analysed according to the investigators' assessment of response. If the results meet the pre-specified hypothesis (see Section 10.1), an additional sensitivity analysis of rPFS will be performed using the results of a centralised disease evaluation by an independent review committee (IRC).

The IRC will be provided with recordings of each scheduled CT scan or magnetic resonance imaging (MRI) exam (DICOM format), bone scan, and any other clinical, biological, or radiographic disease assessments performed. Disease evaluation will be performed according to the schedule and methods described in a separate IRC charter.

***Note**: Treatment decisions are to be made by the investigator, based on their assessment of patient response.*

6.2. Safety evaluation

Evaluation of the safety of study treatment will be based on adverse event (AE) occurrence, the use of concomitant treatments, changes occurring in the course of treatment, observed during physical examination, in the vital signs (artery pressure, pulse, body temperature), and biological and clinical examinations (biochemistry, haematology). Safety criteria will be assessed according to NCI-CTCAE v5.0 (Appendix 6).

In case of emergency, the patient, a patient's relative or the patient's general practitioner should inform the investigator about the occurrence of an AE. The possibility of interruption or dose adaptation (decrease) of the investigational product will be considered as well as adequate concomitant treatment if necessary.

6.3. Evaluation of quality of life study & geriatric status

Quality of life

Patient reported outcomes will be captured through the use of three validated self-reported questionnaires: the EORTC-QLQ-C30, the EORTC-QLQ-PR25, and the BPI-SF.

- The EORTC-QLQ-C30 questionnaire (Appendix 10) is a 30-item questionnaire developed to assess the quality of life of cancer patients. It has been translated and validated into over 100 languages and is used in each year in more than 5,000 studies worldwide
- The EORTC QLQ-PR25 questionnaire (Appendix 11) is a 25-item questionnaire for assessing the quality of life of prostate cancer patients with various stages of disease and treatment modality (i.e. surgery, chemotherapy, radiotherapy, etc.)
- The Brief Pain Inventory is a tool to assess the severity of pain and the impact of pain on daily functions in patients with chronically painful diseases or conditions such as cancer, osteoarthritis and low back pain, or with pain from acute conditions such as postoperative pain. The Short Form of the questionnaire (BPI-SF; Appendix 12) has been specifically developed for clinical trials.

Geriatric status

Patient geriatric status will be evaluated using the G8 screening tool, G-CODE assessment tool and CISR-G comorbidity assessment tool.

- The G8 screening tool (Soubeyran, 2008; Appendix 7) was developed to separate fit older cancer patients who were able to receive standard treatment from those that should undergo a geriatric assessment to guide tailoring of therapy. It consists of a short, nurse-administered survey of eight questions to establish: appetite, weight loss, BMI, mobility, mood and cognition, number of medications, patient-related health, age categories.
- The G-CODE (Paillaud, 2018; Appendix 8) is a core set of commonly used tools/items for geriatric assessment which has been validated for the collection of geriatric data in clinical cancer trials of older adults, enabling comparison across trials. The tools/items proposed in G-CODE are:

    (i) Social assessment: living alone or support requested to stay at home;

(ii) Functional autonomy: Activities of Daily Living (ADL) questionnaire and short instrumental ADL questionnaire (4-IADL);

(iii) Mobility: Timed Up and Go test;

(iv) Nutrition: weight loss during the past 6 months and body mass index;

(v) Cognition: Mini-Cog test;

(vi) Mood: mini-Geriatric Depression Scale;

(vii) Comorbidity: updated Charlson Comorbidity Index.

- The CISR-G (Miller, 1992; Appendix 9) is a nurse administered questionnaire to record and score the medical and psychiatric impairment of older patients to quantify the overall burden of disease (comorbidity)

7. DESCRIPTION OF VISITS AND INVESTIGATIONS

The study is divided into four phases: a Screening phase of up to 28 days, a Treatment phase, an End of Treatment (EoT) visit, and a long-term follow-up (LTFU) phase.

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. Blood samples will also be taken and the availability of a suitable FFPE biopsy sample of a metastatic site or primitive tumour tissue will be verified during the screening period.

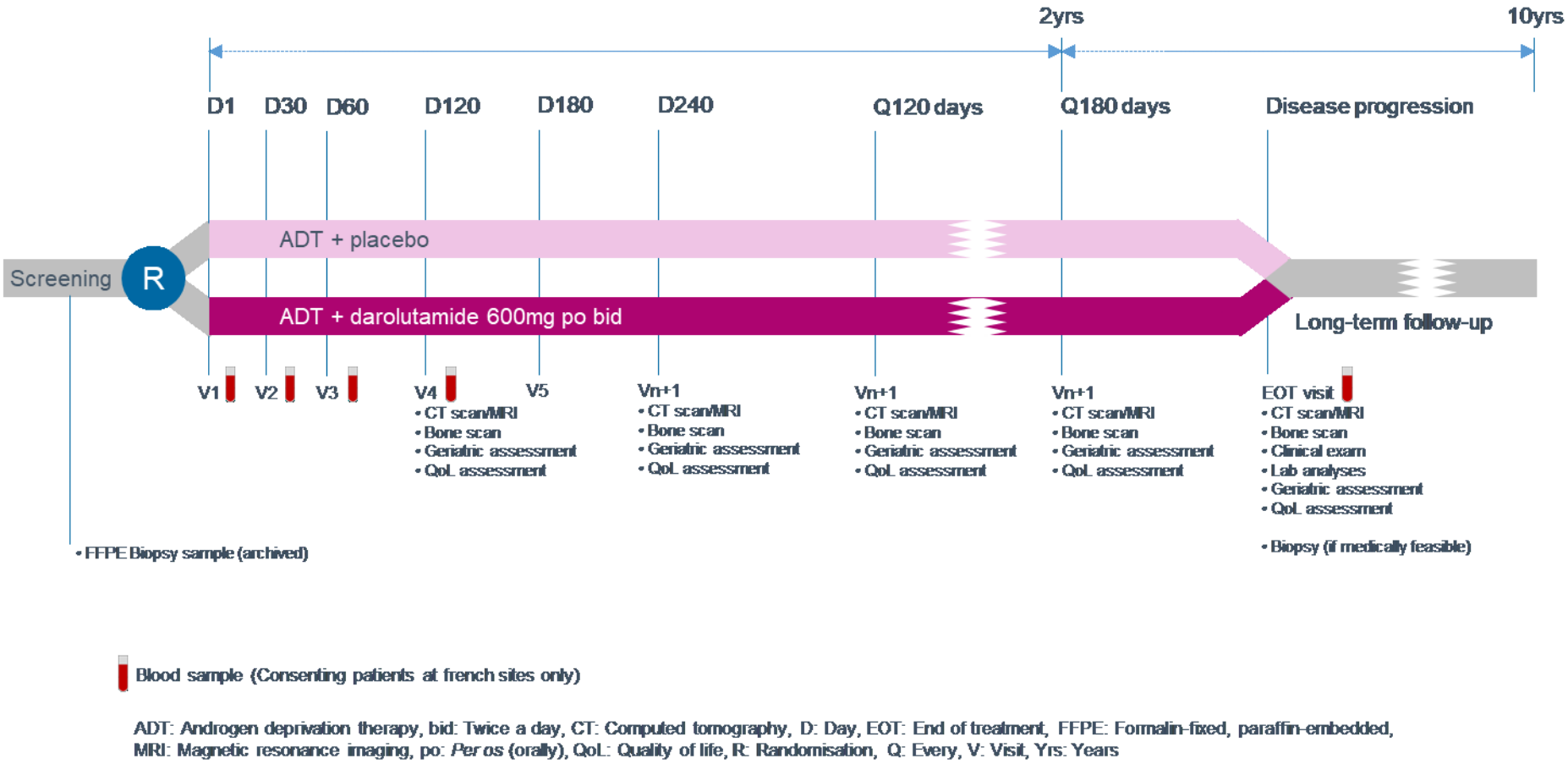
Eligible patients will be randomised by IWRS and enrolled through Unicancer's online eCRF (see Section 3.4).

During the treatment phase, included patients will receive ADT plus the IP (darolutamide), or placebo equivalent depending on the randomly assigned treatment arm. Patients will be asked to attend clinical visits to perform safety and efficacy assessments after 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 PCWG3 recommendations (Scher, 2016).

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 up for a maximum of 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 radiographic progression, or death.

A table summarizing the examination/visit schedule is provided in the "Schedule of visits and activities" section of the protocol summary.



ADT: Androgen deprivation therapy, bid: Twice a day, CT: Computed tomography, D: Day, EOT: End of treatment, FFPE: Formalin-fixed, paraffin-embedded, MRI: Magnetic resonance imaging, po: *Per os* (orally), QoL: Quality of life, R: Randomisation, Q: Every, V: Visit, Yrs: Years

Figure 2. Schema of patient visits and investigations

7.1. Screening visit

Written informed consent is to be obtained before any study related procedures are performed. However, if a protocol required screening procedure or assessment has been performed as part of the routine standard of patient care within the study timeframe, the procedure or assessment does not need to be repeated, unless clinically indicated.

The following should be performed **within 28 days** prior to the first administration of study treatment:

- Patient's written informed consent obtained.
- Collection of demographic data: age, height and body weight.
- Collection of cancer history (including verification of pathological diagnosis, date of diagnosis, stage at diagnosis, dates and sites of recurrent disease) and prior therapy (including name of agents, date of initiation, setting, date of last dose).
- Collection of other relevant medical history, and concomitant therapies.
- Complete clinical examination (major body systems).
- Measurement of vital signs (blood pressure, seated heart rate, body temperature).
- Assessment of ECOG performance status.
- Electrocardiogram
- Assessment of ongoing toxicities including pre-existing symptoms.
- Disease evaluation, including:
    - Clinical assessment of palpable or visual lesions.
    - Measurement of serum PSA and testosterone levels.
    - CT scan or MRI, for baseline disease assessment (paraclinical examination (CT scan or MRI and bone scan) to be performed within 12 weeks prior to randomization, but we strongly recommend that baseline imaging be performed within 28 days prior to randomization.).
    - Bone scan (paraclinical examination (CT scan or MRI and bone scan) to be performed within 12 weeks prior to randomization, but we strongly recommend that baseline imaging be performed within 28 days prior to randomization.).
    - Documentation of baseline tumour status including identification of all measurable and non-measurable lesions as per PCWG3/RECIST v1.1 (see Appendix 3 & Appendix 4)

  ***Note**: The same diagnostic method(s) must be used to evaluate disease status throughout the study. The results of all radiographic assessments (DICOM format) must be provided for central review by the IRC (Section 6.1.1).*

  *According to PCWG3 recommendations, the recommended imaging examinations for disease assessment are as follows: CT Scan or MRI (to assess Visceral lesion/lymph nodes) and Bone scan (to assess bone lesions). If bone scan is not available, PET scan or plain films can be used to confirm the presence or disappearance of bone lesions. Please refer to **appendix 3** - The Prostate Cancer Working Group 3 – Recommendations for castration-resistant prostate cancer trials.*

Other appropriate radiographic assessment (e.g. choline-11 [11C]-, fluorine-18 choline [FCH]-, or fluorine-18 fluorodeoxyglucose [FDG]-labelled positron emission tomography [PET]/CT, ultrasonography), to be performed at the investigator's discretion.

- Verification that a medically acceptable form of contraception (e.g. condoms) is being used by all sexually active patients or that complete abstinence is practiced.
- Assessment of patient geriatric status using the following tools:
  - G8 screening tool (Appendix 7).
  - G-CODE (Appendix 8).
  - CISR-G (Appendix 9).
- ***Patients who provide additional informed consent only:*** Verification of availability of a suitable FFPE biopsy sample of a metastatic site, or primitive tumour tissue.
- ***Patients who provide additional informed consent only:*** Abdominal circumference, body mass index (BMI) and maximum handgrip strength using a hand dynamometer. Handgrip strength should be measured twice.

The following should be performed within **7 days prior** to the first administration of study treatment:

- Haematology analysis (see Table 3).
- Serum chemistry analysis (see Table 3).

Table 3. Safety Laboratory Analyses to be Performed During the Trial

Haematology(1)	Serum chemistry(1)
Haemoglobin	ALAT
Haematocrit	Albumin
Platelet count	Alkaline phosphatase
Red Blood Cell Count	ASAT
WBC (total and differential)	Blood urea nitrogen
ANC	Calcium
Lymphocytes	Chloride
	C-reactive protein
	Creatinine(2)
	Direct Bilirubin(3)
	GGT
	Glucose
	LDH
	Magnesium
	Phosphorus
	Potassium
	Sodium
	Total Bilirubin
	Total protein
	Urea
	Uric Acid

ALAT= Alanine aminotransferase, ASAT=Aspartate aminotransferase, ANC= Absolute Neutrophil Count GGT= gamma-glutamyl transferase, LDH= Lactate dehydrogenase, PSA= Prostate specific antigen, WBC= White blood cell
(1) To be performed at screening visit (within 7 days prior to the first administration of study treatment) and at each subsequent clinical visit. For subsequent visits, blood draw is to be performed within 2 days before the date of the visit.
(2) With estimated GFR (MDRD or CKI EPI method)
(3) If total bilirubin is elevated above the upper limit of normal

Note: *Investigators should ensure that all study enrolment criteria have been met at randomisation. If a patients status changes (including laboratory results or receipt of additional medical records) during the screening period prior to randomisation such that he no longer meets all eligibility criteria, then the patient should be excluded from participation in the study. Patients who fail to meet the inclusion and exclusion criteria (i.e., screen failures) may be rescreened once, if their condition changes. Rescreening must be discussed with and approved by the sponsor on a case-by-case basis. Patients who are determined to be eligible for rescreening must reconsent and will then be assigned a new screening number.*

7.2. Randomisation

Once all the examinations and procedures described in Section 7.1 have been performed and patient eligibility confirmed, eligible patients will be randomised (1:1) via the IWRS (see Section 3.4) to receive either:

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

7.3. Visits and assessment during treatment period

7.3.1. *Visit 1 - Day 1 (Treatment start)*

Study treatment should be initiated within 24 hours of randomisation.

The following should be performed prior to the administration of IP:

- Assessment of ongoing toxicities including pre-existing symptoms and any concomitant therapies received.
- Assessment of patient quality of life (before initiation of treatment) using the following tools:
  - EORTC-QLQ-C30 (Appendix 10)
  - EORTC QLQ-PR25 (Appendix 11)
  - BPI-SF (Appendix 12).
- ***French Investigational sites only – For patients who provide additional informed consent:*** Collection of blood samples for translational analyses (to be performed prior to treatment initiation - see Section 9.1.1).
- ***Patients who provide additional informed consent:*** Abdominal circumference, body mass index (BMI) and maximum handgrip strength using a hand dynamometer. Handgrip strength should be measured twice.
- Dispensation of treatment for 30 days

7.3.2. *Visit 2 - Day 30 (±3 days)*

The following should be performed:

- Complete clinical examination (major body systems).
- Collection of height and body weight.
- Measurement of vital signs (blood pressure, seated heart rate, body temperature).
- Assessment of ECOG performance status.
- Assessment of ongoing toxicities including pre-existing symptoms and any concomitant therapies received.
- Haematology analysis[1] (see Table 3, page 47).
- Serum chemistry[1] (see Table 3, page 47).
- Measurement of serum PSA and testosterone levels[1].
- ***French Investigational sites only – For patients who provide additional informed consent:*** Collection of blood samples for translational analyses (see Section 9.1.1).
- ***Patients who provide additional informed consent:*** Abdominal circumference, body mass index (BMI) and maximum handgrip strength using a hand dynamometer. Handgrip strength should be measured twice.

[1] *Blood draw may be performed up to 48 hours prior to the visit date*

- Dispensation of treatment for 30 days.

7.3.3. *Visit 3 - Day 60 (±3 days)*

The following should be performed:

- Complete clinical examination (major body systems).
- Collection of height and body weight.
- Measurement of vital signs (blood pressure, seated heart rate, body temperature).
- Assessment of ECOG performance status.
- Electrocardiogram (only in case of abnormal results at screening visit, or if clinically indicated by patient symptoms)
- Assessment of ongoing toxicities including pre-existing symptoms and any concomitant therapies received.
- Haematology analysis[2] (see Table 3, page 47).
- Serum chemistry[2] (see Table 3, page 47).
- Measurement of serum PSA[2] and testosterone levels.
- ***French Investigational sites only – For patients who provide additional informed consent:*** Collection of blood samples for translational analyses (see Section 9.1.1).
- ***Patients who provide additional informed consent:*** Abdominal circumference, body mass index (BMI) and maximum handgrip strength using a hand dynamometer. Handgrip strength should be measured twice.
- Dispensation of treatment for 60 days.

7.3.4. *Visit 4 - Day 120 (±7 days)*

The following should be performed:

- Complete clinical examination (major body systems).
- Collection of height and body weight.
- Measurement of vital signs (blood pressure, seated heart rate, body temperature).
- Assessment of ECOG performance status.
- Electrocardiogram (only in case of abnormal results at screening visit, or if clinically indicated by patient symptoms)
- Assessment of ongoing toxicities including pre-existing symptoms and any concomitant therapies received.
- Haematology analysis[2] (see Table 3, page 47).
- Serum chemistry[2] (see Table 3, page 47).

[2] *Blood draw may be performed up to 48 hours prior to the visit date*

- Measurement of serum PSA[2] and testosterone levels.
- Assessment of patient quality of life using the following tools:
  - EORTC-QLQ-C30 (Appendix 10)
  - EORTC-QLQ-PR25 (Appendix 11)
  - BPI-SF (Appendix 12).
- Assessment of patient geriatric status using the G-CODE assessment tool (Appendix 8).
- ***French Investigational sites only – For patients who provide additional informed consent:*** Collection of blood samples for translational analyses (see Section 9.1.1).
- ***Patients who provide additional informed consent:*** Abdominal circumference, body mass index (BMI) and maximum handgrip strength using a hand dynamometer. Handgrip strength should be measured twice.
- Disease evaluation (see Section 7.3.8).
- Dispensation of treatment for 60 days.

7.3.5. *Visit 5 - Day 180 (±7 days)*

The following should be performed:

- Complete clinical examination (major body systems).
- Collection of height and body weight.
- Measurement of vital signs (blood pressure, seated heart rate, body temperature).
- Assessment of ECOG performance status.
- Electrocardiogram (only in case of abnormal results at screening visit, or if clinically indicated by patient symptoms)
- Assessment of ongoing toxicities including pre-existing symptoms and any concomitant therapies received.
- Haematology analysis[3] (see Table 3, page 47).
- Serum chemistry[3] (see Table 3, page 47).
- Measurement of serum PSA[3] and testosterone levels.
- ***Patients who provide additional informed consent:*** Abdominal circumference, body mass index (BMI) and maximum handgrip strength using a hand dynamometer. Handgrip strength should be measured twice.
- Dispensation of treatment for 60 days.

7.3.6. *Visit 6 - Day 240 (±7 days)*

The following should be performed during, or within 48 hours prior to the visit:

[3] *Blood draw may be performed up to 48 hours prior to the visit date*

- Complete clinical examination (major body systems).
- Collection of height and body weight.
- Measurement of vital signs (blood pressure, seated heart rate, body temperature).
- Assessment of ECOG performance status.
- Electrocardiogram (only in case of abnormal results at screening visit, or if clinically indicated by patient symptoms)
- Assessment of ongoing toxicities including pre-existing symptoms and any concomitant therapies received.
- Haematology analysis[4] (see Table 3, page 47).
- Serum chemistry[4] (see Table 3, page 47).
- Measurement of serum PSA[4] and testosterone levels.
- Assessment of patient quality of life using the following tools:
  - EORTC-QLQ-C30 (Appendix 10)
  - EORTC-QLQ-PR25 (Appendix 11)
  - BPI-SF (Appendix 12).
- Assessment of patient geriatric status using the G-CODE assessment tool (Appendix 8).
- Disease evaluation (see Section 7.3.8).
- ***Patients who provide additional informed consent:*** Abdominal circumference, body mass index (BMI) and maximum handgrip strength using a hand dynamometer. Handgrip strength should be measured twice.
- Dispensation of treatment for 120 days.

7.3.7. *Subsequent Visits*

Additional clinical visits are to be performed every 120 (±14) days during the first 2 years of treatment, and then every 180 (±14) days, until the end of study treatment.

The following should be performed:

- Complete clinical examination (major body systems).
- Collection of height and body weight.
- Measurement of vital signs (blood pressure, seated heart rate, body temperature).
- Assessment of ECOG performance status.
- Electrocardiogram (only in case of abnormal results at screening visit, or if clinically indicated by patient symptoms)

[4] *Blood draw may be performed up to 48 hours prior to the visit date*

- Assessment of ongoing toxicities including pre-existing symptoms and any concomitant therapies received.
- Haematology analysis[4] (see Table 3, page 47).
- Serum chemistry[4] (see Table 3, page 47).
- Measurement of serum PSA[4] and testosterone levels.
- Assessment of patient quality of life using the following tools:
  - EORTC-QLQ-C30 (Appendix 10)
  - EORTC-QLQ-PR25 (Appendix 11)
  - BPI-SF (Appendix 12).
- Assessment of patient geriatric status using the G-CODE assessment tool (Appendix 8).
- Disease evaluation (see Section 7.3.8).
- ***Patients who provide additional informed consent:*** Abdominal circumference, body mass index (BMI) and maximum handgrip strength using a hand dynamometer. Handgrip strength should be measured twice.
- Dispensation of sufficient treatment until the next scheduled study visit.

7.3.8. *Disease evaluation*

Disease evaluation should be performed every 120 (±14) days during the first two years after the initiation of study treatment and then every 180 (±14) days until treatment discontinuation. Additional radiographic disease evaluations should also be performed if clinical symptoms indicate a need for radiographic confirmation of disease progression.

Note: *Changes to the patient's treatment schedule (e.g. treatment interrupted due to toxicity) should not affect the schedule of tumour evaluations: these should continue to be performed every 120 or 180 (± 7) days as planned.*

The following will be performed at each disease evaluation:

- Clinical assessment of palpable or visual lesions.
- Measurement of serum PSA and testosterone levels.
- CT scan or MRI (for measurement of target lesions)
- Bone scan.
- Documentation of response assessment according to PCWG3/RECIST v1.1 (including documentation of size/status of each measurable and non-measurable lesion; see Appendix 3 & Appendix 4).

Note: *The same diagnostic method(s) must be used to evaluate disease status throughout the study.*

According to PCWG3 recommendations, the recommended imaging examinations for disease assessment are as follows: CT Scan or MRI (to assess Visceral lesion/lymph nodes) and Bone scan (to assess bone lesions). If bone scan is not available, PET scan or plain films can be used to confirm the presence or disappearance of bone lesions. Please refer to appendix 3 - The Prostate Cancer Working Group 3 – Recommendations for castration-resistant prostate cancer trials.

Other appropriate radiographic assessment (e.g. 11C-, FCH-, or FDG-labelled PET/CT, ultrasonography), to be performed at the investigator's discretion.

The results of all radiographic assessment (DICOM format) must be provided for central review by the IRC (Section 6.1.1).

7.4. End-of-treatment visit

Patients will continue to receive study treatment and undergo study procedures as outlined above until radiographic disease progression. Study treatment will be continued for subjects who have increasing PSA values in the absence of radiographic or clinical progression. Although serial PSA measurements will be performed in this study, progression or change in PSA values is not considered a reliable measure of disease progression and should not be used as the lone indicator for discontinuation.

In case of clinical progression without radiographic progression, the investigator should also assess whether it is the patient's best interest to stop study treatment and change to another therapy, or in selected cases, to carry on with the study treatment.

Treatment may also be terminated early 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.

If the study treatment is terminated, the ADT should be continued.

Following treatment discontinuation for any reason, the following examinations are to be performed 30 (± 3) days after last dose of study treatment, or before initiating a new antineoplastic therapy, whichever comes first:

- Complete clinical examination (major body systems).
- Collection of height and body weight.
- Measurement of vital signs (blood pressure, seated heart rate, body temperature).
- Assessment of ECOG performance status.
- Electrocardiogram (only in case of abnormal results at screening visit, or if clinically indicated by patient symptoms)
- Assessment of ongoing toxicities including pre-existing symptoms and any concomitant therapies received.
- Haematology analysis (see Table 3, page 47).
- Serum chemistry (see Table 3, page 47).
- Measurement of serum PSA and testosterone levels.
- Assessment of patient quality of life using the following tools:
    - EORTC-QLQ-C30 (Appendix 10)
    - EORTC-QLQ-PR25 (Appendix 11)
    - BPI-SF (Appendix 12)

- Assessment of patient geriatric status using the G-CODE assessment tool (Appendix 8).
- ***For patients who provide additional informed consent:*** Where medically feasible a biopsy should be performed at time of disease progression to collect a treatment-resistant tumour sample.
- ***French Investigational sites only - For patients who provide additional informed consent:*** Collection of blood samples for translational analyses (see Section 9.1.1).
- ***Patients who provide additional informed consent:*** Abdominal circumference, body mass index (BMI) and maximum handgrip strength using a hand dynamometer. Handgrip strength should be measured twice.

Note*: Laboratory examinations that were performed less than 14 days prior to the EoT visit do not need to be repeated, unless clinically indicated (i.e. ongoing toxicity surveillance).*

All AEs that occur prior to the EoT visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. Treatment-related SAEs that occur more than 30 days after the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

7.4.1. *End-of-Treatment Disease Evaluation(s)*

Disease evaluation is to be performed as outlined in Section 7.3.8 within 30 (± 3) days of last dose of study treatment, or before initiating a new antineoplastic therapy, whichever comes first.

Note*: If the last radiographic assessment was performed less than 28 days prior to the last dose of study treatment, it does not need to be repeated.*

For the patients who discontinued treatment for reasons other than disease progression or withdrawal of consent, tumour assessments should be continued and documented according to the protocol schedule until disease progression (Section 7.5.1).

7.5. Follow-up

Long-term follow-up assessments will be performed for all patients every 180 (± 14) days following the EoT visit.

The following information will be collected at each LTFU assessment:

- Patients survival status.
- Subsequent antineoplastic therapies (including regimen administered [drug, dose, frequency, mode], start and stop dates).
- Efficacy data (including response to subsequent antineoplastic therapies, dates of progression and evaluation of serum PSA levels).
- Status of ongoing AEs and/or new treatment-related AEs.

No study specific evaluations will be performed during the LTFU period, other than those described in Section 7.5.1 below. Data collection will be limited to that information which is available in the patient's medical file and evaluations performed as part of patients continued treatment at the site, or obtained via communication with the patients treating physician or via telephone contact with the patient.

Long-term follow-up will continue until death, withdrawal of consent, or 10 years after date of patient randomisation, whichever occurs first.

7.5.1. *Efficacy follow-up*

During the LTFU period, patients who discontinue treatment for reasons other than radiographic disease progression, or withdrawal of consent from the entire study should continue to be assessed by radiographic imaging, PSA and testosterone, ECOG performance status, complete Brief Pain Inventory - Short Form [BPI-SF] and use Opioid therapy according to the protocol schedule, until disease progression or death.

The disease evaluation will be performed according to the methods outlined in Section 7.3.8.

7.6. Provisions in case of treatment or trial interruption

In cases of patient withdrawal of consent or early trial termination, all efforts should be made to perform the EoT visit assessments (see Section 7.4). The patient's future clinical management will be left to the discretion of the treating physician.

8. REPORTING OF ADVERSE EVENTS

8.1. Adverse events

8.1.1. *General definition of adverse event*

An Adverse Event is defined as any untoward medical occurrence, in a patient or clinical trial subject treated by a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of an IMP, is also an AE.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered AEs.

Progression of the disease under study is not considered as AE.

An **Adverse Reaction** is a response to an IMP, which is noxious and unintended.

8.1.2. *Evaluating Adverse Events*

Patients will be monitored for AEs during the trial. Safety assessments may include monitoring of any or all of the following parameters: clinical symptoms, laboratory, pathological, radiological or surgical findings, results of physical examination, or results of other tests and/or procedures.

As far as possible, each AE should be evaluated to determine:

- The severity of the event

- Its relationship to the IMP and/or protocol-specified procedures (related/not related)
- Its duration (start and end dates, or if continuing at final examination)
- Action taken regarding trial treatment and corrective treatment
- The seriousness of the event (see Section **Erreur ! Source du renvoi introuvable.**)

Severity

The intensity (severity) of events will be estimated using the extract of NCI-CTCAE v5.0 (**Erreur ! Source du renvoi introuvable.**). The intensity of adverse events not listed in this classification will be assessed according to the following qualifiers:

- Grade 1 (mild): asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2 (moderate): minimal local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)
- Grade 3: severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care ADL
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to the event

The severity criterion is not to be confused with the seriousness criterion which is the guide for defining the reporting requirements (see Section **Erreur ! Source du renvoi introuvable.**).

Relationship

The investigators must do their best to explain each AE and establish when it exists, the connection to the IMP and/or protocol-specified procedures.

The investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to trial treatment. The following factors should be taken into consideration:

- Temporal relationship of event onset to the initiation of trial treatment
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of trial treatment, or reintroduction of trial treatment (as applicable)
- Known association of the event with trial treatment or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of other related factors that are known to be associated with the occurrence of the event

Follow-up of AE

Adverse events must be followed until they have resolved, stabilized, upon death or withdrawal of consent.

8.1.3. *Adverse Event Reporting*

All AEs that occur from the time the informed consent form is signed until 30 days after the last dose of IMP must be recorded by the investigator in the patients' medical file and reported in the eCRF (see Section **Erreur ! Source du renvoi introuvable.** for the reporting requirements of AEs which meet any serious criteria). The investigator will make every attempt to follow all AEs until resolution and to report their outcome in the eCRF.

8.2. Serious adverse events

8.2.1. *General definition of serious adverse event*

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

- Results in death
- Is life-threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is medically relevant in the context of the pathology and the clinical trial

These characteristics/consequences are to be considered at the time of the event. For example, regarding a life-threatening event, this 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 was more severe.

The terms **disability and incapacity** correspond to any clinically relevant physical or psychological handicap, transient or permanent, which impact the patient's physical condition/activity and/or the quality of life.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious, such as important medical events that might not be immediately life-threatening or result in death or hospitalisation, but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed in the definition above (for example: treatment in an emergency room; blood dyscrasias or convulsions that do not result in hospitalisation, etc.)..

Abnormal laboratory results should be reported as SAE if they possibly put at risk the patient or they require medical intervention to prevent an outcome corresponding to one considered severe according to the criteria.

The following events leading to a hospitalisation or prolongation of hospitalisation **are not considered as SAEs:**

- **Hospitalisation already scheduled before the start of the trial**
- **Hospitalisation required as part of the protocol-specified procedures (e.g. for biopsy, chemotherapy, etc.)**
- **Hospitalisation for social or administrative reason without any associated adverse event**

The following events are considered as SAEs **if they are associated to a seriousness criterion** but should not be managed according to the section **Erreur ! Source du renvoi introuvable.**. These events do not require immediate reporting and should be reported **only in the eCRF:**

- **Hospitalisation occurring in the context of tumour relapse or progression of disease under trial,**
- **Relapse or progression of disease under trial,**
- **Events related to relapse or to progression of disease under trial.**
- **Surgery for disease under trial.**

A **Serious Adverse Reaction** is an adverse reaction which results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect.

A **Suspected Unexpected Serious Adverse Reaction (SUSAR)** is defined as any serious adverse reaction, the nature, severity or outcome of which is not consistent with the applicable drug information (e.g. IB for an unapproved investigational product or package insert/SmPC for an approved product).

The reference documents for the assessment of expectedness in this trial will be the Darolutamide IB.

The assessment of expected/unexpected character of the event is the responsibility of the Unicancer.

The sponsor shall notify the Member States concerned through the EU portal of all unexpected events which affect the benefit-risk balance of the clinical trial, but are not suspected unexpected serious adverse reactions.

8.2.2. *Measures to be taken in case of a serious adverse event*

The investigator shall ensure that adequate medical care is provided to the patient. The investigator must **immediately and no later than 24 hours**, following knowledge of the event, notify the Unicancer pharmacovigilance unit of any SAE defined here above, whether or not related to the research, which occurs during the 'trial reporting period'.

This reporting period:

- Starts at the date of the signature of the informed consent form.
- Covers the entire period during which the patient is receiving Darolutamide/placebo (hereafter "trial treatment)) or is subject to specific procedures related to the trial.
- Covers a period of 30 days after the last administration of the trial treatment (Darolutamide/placebo).

Any later SAE, i.e. occurring after the end of the reporting period, which is considered to be related to the trial treatment (Darolutamide/Placebo), or to the research (protocol required diagnostic procedures and examinations carried out during the research)must be reported without any limitation in terms of deadline.

Notification procedure

The "notification of a SAE" form, located in the Investigator Master File, must be completed as precisely as possible, dated and signed by the physician-investigator and sent by fax to:

R&D UNICANCER

Pharmacovigilance unit, France

Fax: +33 (0)1 44 23 55 70 or fax-pv@unicancer.fr

For any other communication:

Email: pv-rd@unicancer.fr / Phone: +33 (0)1 44 23 04 16

The investigator **shall send additional information to the Unicancer pharmacovigilance unit** using a SAE notification form (by ticking the Follow-up check-box to specify that it is a follow-up and not an initial report) as soon as he is aware of the additional information for the event. The investigator must also submit the last follow-up at the resolution or stabilization of the SAE.

The investigator is responsible for appropriate medical follow-up of patients until the resolution or stabilization of the event or until the death of the patient. This can sometimes mean that the follow-up continues after the patient has left the trial.

The investigator must keep the documents concerning the suspected SAE in order to supplement the information previously submitted if necessary.

Requests for clarification and additional information may be sent to the investigator by the Unicancer pharmacovigilance unit to document and treat the case.

The physician-investigator should also attach to the "notification of a SAE" form, whenever possible:

- A copy of the hospitalisation report or extended hospitalisation report

- A copy of all results of additional investigations carried out, including also relevant negative results, and enclosing the normal laboratory values
- A copy of the autopsy report if necessary
- Any other document deemed to be useful and pertinent

All these documents must be anonymised.

8.2.3. *Reporting instructions for specific events*

8.2.3.1. Overdose

Use of study treatment in dose in excess of that specified in the protocol is considered to be an overdose.

In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

The investigator will use clinical judgment to treat any AE-related to overdose (refer to IB).

In case of study treatment overdose without any associated clinical symptoms or abnormal laboratory results, the event of overdose is to be reported as a SAE using the terminology "**accidental or intentional "darolutamide/placebo" overdose without adverse event**".

If an AE is associated with an overdose of study treatment, the AE is to be reported as a SAE using the terminology "**EVENT resulting from "darolutamide/placebo" overdose**", even if no other serious criteria are met (Section 8.2.1).

All reports of overdose whether associated or not with an AE are to be reported to Unicancer immediately following knowledge of the event.

8.2.3.2. Medication Error

Medication error is defined as an unintended failure in the drug treatment process that leads to, or has the potential to lead to, patient harm .

In the event of study treatment error, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

The investigator will use clinical judgment to treat any AE-related to trial treatment error (refer to IB).

In case of study treatment error without any associated clinical symptoms or abnormal laboratory results, the event of study treatment error is to be reported as a SAE using the terminology "**accidental or intentional "darolutamide/placebo" error without adverse event**".

If anAE is associated with a study treatment error, the AE is to be reported as a SAE using the terminology "**EVENT resulting from "darolutamide/placebo" error**", even if no other serious criteria are met (Section 8.2.1).

All reports of study treatment error whether associated or not with an AE are to be reported to Unicancer immediately following knowledge of the event.

8.2.3.3. Misuse of a medicinal product

Misuse of a medical product is defined as any situations where a medicinal product is intentionally and inappropriately used not in accordance with the terms of this protocol.

In the event of study treatment misuse, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

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The investigator will use clinical judgment to treat any AE-related to trial treatment error (refer to IB).

In case of study treatment misuse without any associated clinical symptoms or abnormal laboratory results, the event of study treatment misuse is to be reported as a SAE using the terminology "**accidental or intentional "darolutamide/placebo" misuse without adverse event**".

If anAE is associated with a study treatment misuse, the AE is to be reported as a SAE using the terminology "**EVENT resulting from "darolutamide/placebo" misuse**", even if no other serious criteria are met (Section 8.2.1)

All reports of study treatment misuse whether associated or not with an AE are to be reported to Unicancer immediately following knowledge of the event.

8.2.3.4. Abuse of a medicinal product

Abuse of medical product is defined as the persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects.

In the event of study treatment abuse, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

In case of study treatment abuse without any associated clinical symptoms or abnormal laboratory results, the event of study treatment abuse is to be reported as a SAE using the terminology "**accidental or intentional "darolutamide/placebo" abuse without adverse event**".

If an AE is associated with study treatment abuse, the EAE is to be reported as a SAE using the terminology "**EVENT resulting from "darolutamide/placebo" abuse**", even if no other serious criteria are met (Section 8.2.1)

All reports of study treatment abuse whether associated or not with an AE are to be reported to Unicancer immediately following knowledge of the event.

8.2.3.5. New primary cancers

New cancer, whether or not related to the research, must be considered as medically relevant and reported to the Unicancer pharmacovigilance unit whatever their time of onset and without any limitation in terms of deadline using the same procedure defined in Section 8.2.2.

8.2.4. *Pregnancy*

Pregnancy is not considered as a SAE.

Any pregnancy that occurs in a female partner of a male trial patient during the treatment period or within 30 days after the last study treatment **"darolutamide/placebo"** administration must be reported to Unicancer via the Pregnancy Notification Form in accordance with the SAE reporting procedures (*Section 8.2.2)*. In order for Unicancer to collect any pregnancy surveillance information from the female partner, the female partner will be asked to sign an informed consent form for disclosure of this information.

***Note**: While pregnancy is not considered as a SAE, any anomaly detected in the foetus or child, any elective termination of a pregnancy for medical reasons, or spontaneous abortion will be reported as an SAE, using the same procedure as an SAE (Section 8.2.2).*

8.3. Development safety update report

The main objective of a development safety update report (DSUR) is to present a comprehensive, thoughtful annual review and evaluation of pertinent safety information collected during the reporting period related to a drug under investigation.

A single safety report on all IMP used in this clinical trial will be prepared.

9. BIOLOGICAL ANCILLARY/TRANSLATIONAL STUDIES

9.1. Biological ancillary study

9.1.1. *Sample collection*

Blood samples and tumour tissue will be collected across all trials in the PEACE 6 programme 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?

De novo metastatic 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. 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:

Archived biopsy material from the primary tumour obtained at time of diagnosis will be collected from consenting patients at study entry and will be used to identify biomarkers of sensitivity and resistance. A FFPE tissue block (or unstained slides) known to contain cancer sufficient to make 10 unstained 10 µm slides and 12 unstained 3 µm slides should be provided from each consenting patient.

Where feasible, a biopsy will also be performed at time of disease progression to collect a treatment-resistant tumour sample.

Blood samples (France only)

Blood samples will be collected from consenting patients prospectively in order to study tumour clonal evolution. 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 various time points during treatment and at disease progression, as illustrated in Table 4.

Table 4. Schedule of blood sample collection

Time point	Blood draw volume	Tube Type	Processing
Day 1[1]	1x 10 ml	EDTA tube	Whole blood
	2x 10 ml	EDTA tube	Whole blood for CTCs
	2x 10 ml	EDTA tube	Plasma
Day 30 (±3 days)	1x 5 ml	EDTA tube	Plasma
Day 60 (±3 days)	2x 10 ml	EDTA tube	Whole blood for CTCs
Day 120 (±7 days)	1x 5 ml	EDTA tube	Plasma
At disease progression	2x 10 ml	EDTA tube	Whole blood for CTCs
	1x 10 ml	EDTA tube	Plasma

CTC: Circulating tumour cells; EDTA: Ethylenediaminetetraacetic acid; SST: Serum-separating tube
[1] Prior to IP treatment initiation

Blood samples (whole blood, plasma) will be collected in EDTA tubes and processed within 6 hours of collection according to standard procedures. The procedures for blood sampling and processing are described in greater detail in a separate Laboratory Manual. Processed samples will be stored on site at -80°C.

Storage

All samples will be stored on site until such a time as the Sponsor request transfer to the Unicancer Biological Resource Centre, under the responsibility of Ms. Séverine Tablone-Eglinger, located at the following address:

Centre des Ressources Biologiques - Centre Léon Berard,

Bâtiment CHENEY B Rez de Chaussée,

28 rue Laënnec, 69373 Lyon cedex 08, France

9.1.2. *Analyses*

Exome analysis

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

Both host and somatic tumour DNA will be then used for whole-exome sequencing in order to investigate (a) the genomic landscape (single nucleotide variation, copy number variation) 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 3µm FFPE tumour tissue. 12 slides will be necessary to assess 10 markers 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 in two cohorts from the PEACE-6 programme (see Section 1.2).

Whole blood samples will be processed by the PCCR laboratory (*Plateforme cellules circulantes rares*) at Gustave Roussy to obtain CTCs and control white blood cells. Circulating tumour cells will be enriched from 20 mL blood by hematopoietic blood-cell depletion with the RosetteSep reagent, stained by four colour immunofluorescence (Hoechst 33342/CD45/pan-neuroendocrine markers/pan-cytokeratins), and isolated as single-cells using a BD FACSARIA III cell sorter (BD Biosciences). Standard operational procedures already implemented at Gustave Roussy based on previous results will be used (Massard, 2016b; Pailler, 2016; Lindsay, 2016). We estimate that on average ten single-CTCs will be isolated for each 20 mL blood sample. Control single white blood cells will be collected for each patient.

Whole genome amplification (WGA) will be performed by the LM-PCR method using the Ampli1 kit (Menarini Silicon Biosystems). Control of WGA quality will be performed by PCR as published (Polzer, 2014). Copy number alterations will be analysed on CTC and control white blood cell WGA samples by the LowPassGenome technique using the Ampli1 LowPass kit (Menarini Silicon Biosystems). LowPass whole genome sequencing will be performed by the Gustave Roussy Genomic Platform. Germline DNA will be analysed for each patient. The bioinformatic analysis will be performed in collaboration with the Gustave Roussy Bioinformatic Platform. All the techniques and bioinformatic methodology for single CTC analysis are already established (Pailler, 2019; Faugeroux, 2020; Faugeroux, 2020b).

9.2. Translational study on sarcopenia

9.2.1. *Background*

Sarcopenia is a progressive and generalized skeletal muscle disorder that is associated with increased likelihood of adverse outcomes including falls, fractures, physical disability and mortality.

A previous meta-analysis demonstrated that low skeletal muscular index (SMI) at cancer diagnosis was associated with worse survival in patients with solid tumors. Other studies showed an association with shorter time of tumor control and increased toxicity from chemotherapy. In several studies, SMI was an independent prognostic factor for overall survival (OS). Sarcopenia can be therefore considered a robust prognostic factor of negative outcome and its diagnosis would allow introducing adapted dietary rules and monitoring of these frail patients.

For sarcopenia measurement, the imaging tool of choice for patients with cancer is Computed Tomography (CT). There is no reference method for the segmentation of the muscle area even if the manual method seems to be the most widespread. In oncology, patients undergo several CT examinations for baseline and follow-up assessment and could allow determining the patient's baseline condition in terms of sarcopenia and its evolution over time. However, despite its potential clinical impact, this measurement is not used in current practice because manual segmentation is time- consuming and is not always reproducible. One solution could be Deep Learning (DL)-based segmentation algorithms, which would improve data processing speed and reproducibility (when deterministic) and offer an alternative to measure the sarcopenic profile of patients in a way compatible with the daily workflow of radiologists.

9.2.2. *Hypothesis*

Sarcopenia will influence prognosis, treatment response and adverse events in patients included in the PEACE-6 vulnerable trial.

9.2.3. *Methods*

Patients

This ancillary study will be proposed to centres on a voluntary basis. All patients in the centre will be proposed this ancillary study, to avoid recruitment bias. Patients will be prospectively included.

Clinical data

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, which should be measured sitting down, on a chair with no arm rest. The following instructions should be given to the patient before measurement: “I want to measure your hand grip strength. You can bend your underarm to an angle of 90 degrees. Your arm is not allowed to touch the trunk. Your shoulders should be relaxed. When I say “squeeze”, you have to squeeze as hard as you can until I say stop. You might not feel any displacement of the handles, the strength of your grip is displayed on the meter. The measurement will be repeated two times. After each measurement the muscles are allowed to relax for a while. If you experience pain orany discomfort, we will not continue the measurement.”.
  The highest value of the two measurements will be recorded.

Radiological measurement of sarcopenia

Skeletal muscle index was measured on baseline CT on two contiguous axial slices at the level of L3, based on prior publications showing the L3 level was optimal for visualizing the psoas, paraspinal, and abdominal wall musculature and was correlated statistically with whole-body muscle.

A deep-learning based algorithm was developed by the In vivo imaging laboratory (team 2, PARCC, INSERM U970) and more specifically by V Roblot et al. The technical and clinical performance of the tool has been validated (publication accepted European Radiology, appendix). Briefly, a Deep Convolutional Neural Network (DCNN) was developed using 'DeepLabv3' with ResNet101. The DeepLabv3 uses Atrous Convolutions with different dilation rates to capture information on multiple scales, without significant loss in image size. A pixel-wise weighted loss was applied to the boundaries to increase accuracy. The algorithm is deterministic therefore has the advantage to always come up with the same result given the same inputs. The code is available on https://github.com/ygiret/radio-advisor.

The DL algorithm yields a segmentation of abdominal muscles allowing calculation of the skeletal muscle area as the average of the areas of the segmentation of the two slices per patient. The SMI will be calculated as following: SMI = lumbar muscle area/body surface (cm2/m2) where body surface corresponds to the patients' squared height.

Patients will be classified as sarcopenic according to Martin et al's definition:

SMI < 43 cm2/m2for men with a BMI < 25 kg/m2

SMI < 53 cm2/m2 for men with a BMI ≥ 25 kg/m2

SMI < 41 cm2/m2for women regardless of BMI.

CT images from patients participating in this translational study will be transferred to Pr Laure Fournier's team for analysis at the end of the inclusion period for retrospective analysis. Results of sarcopenia evaluation will not be communicated to the investigators in real-time to not bias the study as initially conceived.

9.2.4. *Statistical analysis*

A descriptive analysis will first be performed to describe proportion of sarcopenic vs non-sarcopenic patients in the population, results of questionnaires, clinical and radiological evaluations.

The prognostic value of sarcopenia in patients will be evaluated by comparing Kaplan–Meier overall survival (OS) curves with the log rank test. Second, a Wilcoxon-Mann-Whitney test will be used to compare the distribution of overall survival between sarcopenic and non-sarcopenic patients.

The predictive value of sarcopenia will be evaluated by comparing rate of response (proportion of complete and partial responses) in sarcopenic and non-sarcopenic patients. A waterfall plot will be generated to compare the two populations. Similarly, to overall survival, Kaplan-Meier progression-free survival curves will be compared with the log rank test, and the distribution using a Wilcoxon-Mann- Whitney test.

Finally, the rate of adverse events (global and severe i.e. grades 3-5) will be compared in sarcopenic vs non-sarcopenic patients.

Sarcopenia evaluated by CT will be correlated to questionnaire and clinical evaluation. Prognostic and predictive values of the questionnaires and clinical tests will be evaluated in the same way as sarcopenia calculated by CT, and compared to CT results.

10. DESCRIPTION OF STATISTICAL METHODS

The statistician will produce an initial statistical analysis plan before the inclusion of the first patient (version n°1). This document will be validated by the Steering Committee. The SAP may be revised during the course of the trial in case of substantial modification of the protocol or following recommendations of the Independent Data Monitoring Committee (IDMC). Any revision of the SAP will be validated by the Steering Committee.

10.1. Statistical hypothesis and sample size determination

The primary evaluation criterion/endpoint for this study is radiographic progression-free survival (Section 3.2.1).

Assuming a median rPFS of 12 months for the control group[5], 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.

Based on the randomization rates observed since the inclusion of the first patient and the projected rates according to the opening of investigator sites (see below), patient inclusion-randomisation is expected to be complete in 60 months.

	Number of randomized patients during the period	Cumulative number (cumulative percentage) of randomized patients at the end of the period
March 2022-Feb 2023	18 pts (1.5 pts/months)	18 (6%)
March 2023-Feb 2024	50 pts (4.167 pts/months)	68 (22.67%)
March 2024-Feb 2025	53 pts (4.4 pts/months)	121 (40.33%)
Mars 2025-Feb 2027*	179 pts (7.5 pts per month)*	300 (100%)*

*Grounded on projections

An additional 15 months following termination of accrual (i.e. a total of 75 months since the randomization of the first patient) is expected to obtain the required 197 events, assuming that events will follow an exponential distribution with a constant hazard rate.

The final analysis is scheduled 10 years after the last patient inclusion-randomisation.

[5] *Based on data from the control arm of the LATITUDE trial (Fizazi, 2017), and taking into account that (i) patients with oligo-metastatic disease (low risk patients) will not be enrolled, and (ii) some patients are expected to die from other causes before they reach a progression endpoint, making the median rPFS probably shorter than that seen in the LATITUDE trial*

10.2. Trial populations to be analysed

- Intent-to-treat (ITT) population: all randomised participants
- Safety population: participants who took at least one dose of trial treatment/intervention

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.

Safety analyses will be performed on the safety population. Patients will be analysed according to the treatment received, regardless of the arm to which they were randomised.

10.3. Statistical analysis plan

10.3.1. *Demographic and other baseline characteristics*

Descriptive statistics will be used to summarize demographics, medical history and baseline characteristics by treatment group. The number of patients in each of the analysed study populations will be described. Unless otherwise specified, all continuous endpoints will be summarized using descriptive statistics, which will include the number of subjects with a valid measurement (n), mean, standard deviation (SD), median, minimum, and maximum. All categorical endpoints will be summarized using frequencies and percentages.

10.3.2. *Primary efficacy endpoint analysis*

The primary endpoint is radiographic PFS, defined as the time from randomisation to radiographic progression or death by any cause, whichever occurs first. Radiographic PFS will be right-censored according to the rules shown in Table 5.

Table 5. Censoring rule for primary analysis of radiographic progression-free survival

Censoring situation	Date of censoring
No baseline assessment	Date of randomisation
No post-baseline assessment and no death prior to first scheduled assessment	Date of randomisation
No radiographic progression or death on study	Date of last tumour assessment
Withdrawn from the study without documented radiographic progression	Date of last tumour assessment

The primary analysis for the rPFS endpoint will be done considering the first radiographic progression observed under study (even if this first radiographic progression is observed under a subsequent line of therapy). As a sensitivity analysis, in case of initiation of a subsequent line of therapy before observing a radiographic progression, the data will be censored at the time of initiation of the salvage treatment.

The final analysis of the primary endpoint will be event-driven, to be performed when at least 197 patients have experienced radiographic progression or death.

Inference for the primary endpoint will be assessed using a two-sided stratified log-rank statistic as the primary analysis. The analysis on stratification factor at randomisation: LATITUDE risk criteria (high risk versus low risk) and ECOG performance status score (0 or 1 vs 2).

A patient is considered as high risk according to the LATITUDE criteria if he has at least two of the three following high-risk factors associated with poor prognosis: a Gleason score of 8 or more (on a scale of 2 to 10, with higher scores indicating more aggressive disease), at least three bone lesions, and the presence of measurable visceral metastasis. He is otherwise considered as low risk (Fizazi, 2017).

In case the stratification factor does not have sufficient number of patients (less than 3%) and the inferential analyses would be negatively impacted, the stratification factor will not be included as a stratification factor in this analysis.

The proportional hazard assumption will be assessed graphically by plotting log (-log[estimated survival distribution function]) against log(survival time). The resulting graphs should have approximately parallel lines when the assumption holds. If the proportional hazards assumption is reasonably met, then a stratified Cox proportional hazard model will be used to estimate the treatment effect using Hazards Ratio (HR) and its two-sided 95% confidence interval (95%CI). If the proportional hazards assumption is violated, then the inference remains statistically valid for testing equality in survival distributions. In addition, rPFS will be descriptively summarized using Kaplan-Meier methodology, including medians and two–sided Rothman's 95%CI (Kaplan, 1958; Rothman, 1978).

Stratification factors will include:

- LATITUDE risk criteria (high risk versus low risk, Fizazi, 2017)
- ECOG performance status score (0 or 1 vs. 2).

If final analysis of the primary endpoint meets the pre-specified hypothesis (see Section 10.1), an additional sensitivity analysis of rPFS will be performed using the results of a centralised disease evaluation by an independent review committee (IRC).

All the other secondary time to event endpoints (namely, CRPC-free survival, clinical progression-free survival, time to worsening in prostate cancer-related urinary symptoms, time to next symptomatic skeletal event, prostate cancer specific survival and overall survival, time to first subsequent SACT and time to second subsequent SACT) will be analysed using the same methods as the primary endpoint (stratified two-sided log-rank test, stratified Cox proportional hazards models). Secondary endpoints will be analysed according to the investigators' assessment of response. Censoring rules for these endpoints will be detailed in the SAP.

The median follow-up will be estimated using the inverse Kaplan-Meier method (Schemper, 1996).

10.3.3. *Safety analysis*

Safety analysis will be summarized on the Safety Population (i.e. all patients who receive any part of investigational treatment).

Extent of exposure to study drug will be summarized by treatment group, using descriptive statistics. Duration of study treatment will be calculated in days and presented in months as the date of the last dose of any study treatment – date of the first dose of any study treatment + 1. Dose modification will be summarized. Patients who discontinue study drug or are removed from the study prematurely will also be reported. Reasons for study drug therapy discontinuation, and time of withdrawal from the study will be described.

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.

To adjust for unequal lengths of study treatment duration among subjects, and potentially between treatment groups, an additional summary based on event rate per 100-subject years of treatment duration will also be summarized, if necessary. The event rate per 100-subject years of treatment duration is calculated as the total number of treatment emergent events divided by the total treatment duration per 100-subject years.

Serious AE and deaths will be provided in a listing. All adverse events resulting in discontinuation, dose modification, dose interruption, and/or treatment delay of study drug will also be listed and tabulated by preferred term.

10.3.4. *Quality of life analysis*

The expectation is that changes in patient quality of life will not differ significantly between the two treatment groups. Changes in patient quality of life over time will be investigated with particular attention paid to the following characteristics: Physical function, cognitive function, and fatigue (EORTC-QLQ-C30), pain (BPI-SF) and urinary symptoms (EORTC-QLQ PR25).

Detailed hypotheses will be developed in the statistical analysis plan (SAP).

10.3.5. *Geriatric status*

Patient autonomy will be evaluated using ADL and 4-IADL evaluations. Change over time in ability to perform ADL and IADL will be investigated.

For exploratory purposes, Time to definitive deterioration in ADL will be compared. Time to definitive deterioration of ADL will be defined as the interval between randomisation and the first decline in the ADL score ≥2 points compared to the ADL at inclusion with no further improvement in score ≥2 points. Progression or death will considered as an event.

In a complementary analysis, competing risks approach will be used to decompose Time to definitive deterioration of ADL considering death and progression as a competing event.

Change over time in other geriatric parameters will be investigated.

10.3.6. *Missing data*

For time-to-event endpoints, missing values will be handled thanks to censoring. For all other endpoints, valid percent (excluding missing values) will be reported in the descriptive tables; number of missing data will be reported for each parameter.

10.3.7. *Analysis Specifications*

In general, all hypotheses testing will be performed at a 2-tailed significance level of $\alpha = 0.05$. All interval estimations will be reported using 95% confidence intervals.

The following endpoints are considered as key secondary endpoints:

- Castration-resistant prostate cancer-free survival,
- Clinical progression-free survival,
- Overall survival,

Key secondary efficacy endpoints will be tested using the Hochberg test procedure to control the familywise type I error rate; i.e., testing will begin with p value $P_{(m)}$ with corresponding hypothesis $H_{(m)}$, where $P_{(m)}$ is the largest ordered p values amongst 'm' secondary endpoints (i.e., "the least significant p-value") and $H_{(m)}$ is the corresponding hypothesis. If $P_{(m)} \leq \alpha$, then all null hypotheses are rejected. If not, then $P_{(j)}$, the (j)th largest p-value, is compared with $\alpha/(m-j+1)$. If smaller, then all

hypotheses from $H_{(j)}$ to $H_{(1)}$ are rejected. The testing procedure continues in this manner until no significant result is found. This procedure controls the overall level of significance at the 2-tailed, 0.05 level.

All other endpoints will be considered as exploratory endpoints and will also be analysed. No adjustment for multiple testing will be made. Each endpoint will be tested at a 2-tailed 0.05 level of significance.

10.4. Statistical rules for trial early trial termination / Interim analysis

An 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 (Lan, 1983) with O'Brien-Fleming type spending function (O'Brian, 1979) will be followed to conclude at each sequential analysis.

The interim analysis boundary values are determined using the software EASTR.

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: +/-2.437)
- Final analysis (197 events, i.e. 100% expected events): p-value to reject $H_0 \leq 0.045$ (equivalent to the stopping boundaries Z-Scale: +/-2.0)

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

These values are given as an indication and will be recalculated according to the actual number of events at the time of the intermediate and final analysis.

11. OVERSIGHT COMMITTEES

11.1. Independent data monitoring committee

An IDMC, with expertise and experience in the pathology, and without direct involvement in the conduct of the trial, will be set up specifically to guarantee:

- Effective protection of patients.
- Insure the ethical conduct of the trial.
- Benefit/risk ratio of the trial.
- Ensure the independent review of the scientific results during and at the end of the trial.

The IDMC will be composed of at least 3 expert members (2 clinicians and 1 statistician). IDMC members must have no financial interest in the outcome of the trial and be independent from the Investigators, Funding bodies, Sponsor, Steering committee and any other institutions involved in the trial.

The IDMC committee shall meet in any of the following cases:

- In the event of an alert issued by the pharmacovigilance department,
- In case of concerns from the Steering Committee for the analysis or interpretation of the efficacy results according to the hypotheses defined in the protocol,
- In the event event of an unsatisfactory enrolment rate,

- To review the results of predefined interim analyses

Once formed and during the first meeting, the committee shall define the schedule of meetings until the end of the trial. This schedule can be modified depending on safety signals.

The IDMC will perform a blinded review of accumulated data regarding overall safety and efficacy of the study treatment including the results of scheduled analyses, collected safety reports prepared by the Sponsor as well as published data and information provided by the IP license holder concerning concurrent studies. Data presented to IDMC are strictly confidential.

The IDMC will provide recommendations regarding continued recruitment or termination of enrolment in each cohort, or if new cohorts/indications should be considered as well as any modifications of protocol design which might be necessary.

The IDMC may recommend the early termination of the trial if one of the following conditions is met:

- The interim analyses are in favour of stopping the trial for futility or for efficacy.
- An unacceptable level of toxicity is reported.
- All available data from the trial or any other source of information are sufficiently convincing to influence the therapeutic practices of the majority of clinicians.

The IDMC has only a consultative role; it will inform the Sponsor and Steering Committee who will decide whether the IDMC recommendation will be followed.

The roles and responsibilities of the IDMC are further detailed in the IDMC Charter.

11.2. Steering Executive Committee

A Steering Committee has been implemented for this trial. The Steering Committee will meet on a annual basis. Additional meetings may be set, as required.

The Steering Committee is composed of:

- The trial Coordinating Investigator
- The trial Biostatistician
- The Coordinating Investigator of the PEACE 6 programme
- Project Manager (or delegate)
- Other participants as required depending the meeting agenda

The Steering Committee will review the accumulated data regarding overall safety and efficacy of the study treatment, including the results of programmed analyses, collated safety reports prepared by the Sponsor, as well as published data and information provided by the IP license holder concerning concurrent studies. The Steering Committee will also review, or may request, recommendations made by the IDMC. The Steering Committee, based on this information, will assist the Sponsor in resolving issues and/or questions encountered during the conduct of the trial and will make recommendations regarding modifications to the protocol.

Recommendations made by the steering committee will be implemented as soon as possible following Sponsor approval. Any recommendations which would result in substantial modifications to the conduct of the study or amendment of the protocol design must obtain approval from the applicable Health Authorities and local ethics committees prior to implementation in each participating country.

The roles and responsibilities of the Steering Committee are further detailed in the Steering Committee Charter.

12. QUALITY ASSURANCE

12.1. Data collection

Data necessary for patient randomisation and treatment allocation/management will be entered into the trial IWRS, hosted by EURAXI (10 Rue Gutenberg, 37300 Joué-lès-Tours, France).

All data necessary for the research must be entered into the trial eCRFs in a timely manner. eCRFs will be completed by the principal investigator and other staff members duly designated. The data entered must be accurate and complete.

The trial database will be hosted by AZ Network (40 Rue Ampère, 61000 Alençon – France) under the responsibility of the Unicancer Data Department.

Database management with be performed by the Unicancer Data Center (Institut du Cancer Montpellier (ICM) – Val d'Aurelle, Unité de Biométrie – CTD INCa, 208 rue des Apothicaires - Parc Euromédecine, 34298 Montpellier Cedex 5 – France) under the responsibility of Mrs Sophie Gourgou.

The database will be accessed via an eCRF developed using the CSOnline module of Ennov Clinical® software. In case of technical problem with the eCRF, the investigator may refer to the specific operating procedure of the eCRF or directly contact:

from Monday to Friday 9 am-5 pm

email: support.ecrf@icm.unicancer.fr

Fax: +33 (0)4 67 61 37 18

Tel: +33 (0)4 67 61 45 48/24 52

The access code (login) and passwords to access the eCRF (via the website - https://ecrf.icm.unicancer.fr/CSOnline) will be generated automatically by CSOnline and sent directly to the users registered email account.

A password non-disclosure certificate will be signed by the principal investigator of each site engaging his/her responsibility regarding the confidentiality of the access codes for all users of the eCRF at their site.

Trial data will be entered into the eCRF by the principal investigator, or by designated staff members of each site, and will be controlled and validated according to the standard procedures (including those built-in to the software and the sponsor's quality assurance procedures). All access to the eCRF and changes made to the data are recorded by the software (audit trail). At the end of the trial and once all the eCRF data are validated, the investigator will login to the eCRF to sign all the pages to validate the data entered for each patient.

The sponsor will create and send an electronic copy (PDF file) of each patient's CRF to the corresponding investigator. This pdf file must be printed and signed by the investigator, and then archived at the investigator's site.

12.2. Access to data

The sponsor has direct access to all investigator sites, original records, source data/document and reports to allow quality control and auditing by the sponsor or on behalf of the sponsor.

Investigators will make available to the authorized persons the documents and the patients' individual data that are essential to monitor the trial on an ongoing basis, to perform quality control and audit of this research in accordance with national regulatory requirements.

12.3. Trial monitoring

To ensure the authenticity and credibility of data in accordance with the current ICH-GCP guidelines, the sponsor has establishes a quality assurance system that consists of:

- The management and the monitoring of the trial according to Unicancer procedures. The monitoring strategy is built according to a systematic, prioritized, risk-based approach, and is documented in the monitoring plan.
- The quality control of data at the investigational sites by the monitor(s), which involves:
  - ✓ Verifying that the protocol, as well as the current guidelines ICH-GCP, the national regulatory requirements, are adhered to.
  - ✓ Verifying the informed consent and the eligibility of each patient participating in the trial.
  - ✓ Verifying that the eCRF data is consistent and in agreement with the source documents.
  - ✓ Verifying the notification of each SAE.
  - ✓ Verifying the drug traceability (dispatching, storage, and accountability).
  - ✓ Verifying *(if applicable)* that patients are not already participating in another clinical study making them ineligible for this protocol. The monitor will also verify that patients have not participated in another study within the delay indicated in the non-inclusion criterion N°14.
- The quality control of data by a centralized monitoring process. Centralized monitoring is a remote evaluation of data, performed in a timely manner, supported by appropriately qualified and trained persons (e.g., data managers, biostatisticians). Review, that may include statistical analyses, of accumulating data from centralized monitoring can be used to:
  - ✓ Identify missing data, inconsistent data, data outliers, unexpected lack of variability, and protocol deviations.
  - ✓ Examine data trends such as the range, consistency, and variability of data within and across sites.
  - ✓ Evaluate for systematic or significant errors in data collection and reporting at a site or across sites; or potential data manipulation or data integrity problems.
  - ✓ Analyse site characteristics and performance metrics.
  - ✓ Select sites and/or processes for targeted on-site monitoring.
- The audit of participating investigational sites when deemed necessary

The monitors/CRAs in charge of trial monitoring will be mandated by the sponsor. They must have direct access to all patient data required to perform their duty in accordance with the national regulatory requirements. The monitors/CRAs are bound by professional secrecy under the national regulatory requirements. Written reports must be issued to ensure the traceability of monitoring visits.

To ensure optimal research quality control the investigator will ensure that the monitor/CRA has direct access to all trial patient files.

12.4. Audits and inspections

As part of Unicancer's audit programme, the sponsor may audit some investigational sites. The site and the investigator agree that audits be carried out by Sponsor or any person duly authorized during the trial and for at least 25 years after closure of the trial.

The investigational site and the investigator agree to devote the time necessary for the audit procedures, allow the control of the trial documentation, and provide additional information requested by the sponsor.

A Competent Authority may also request a trial inspection (during the trial or after its completion). If a Competent Authority requests an inspection, the investigator must inform the sponsor immediately of this request. The investigator must allow the inspectors direct access to the trial documents and source documents.

The investigational site and the investigator agrees to devote the time necessary for inspections procedures, allow the control of the trial documentation, and provide additional information requested by the inspectors of the concerned Competent Authority.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. General requirements

The clinical trial will be conducted in accordance with:

- The principles of ethics as stated in the last version of the Declaration of Helsinki (Appendix 1).
- The Good Clinical Practices defined by the current ICH–GCP
- Regulation (EU) no 536/2014 of the European Parliament and of the Council on clinical trials on medicinal products for human use.
- Regulation (EU) 2016/679 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation).
- The specific laws and regulations of each participating country.

13.2. Patient identification

All patients will receive a unique patient identification number when signing the informed consent form by the patient and before any trial procedure is performed. This number will be used to identify the patient throughout the trial and must be used on all trial documentation related to this patient. The patient identification number must remain constant throughout the trial.

13.3. Patient information and consent

The patient information sheet and informed consent form (PIS/ICF) must be written in accordance with the current ICH-GCP and applicable local regulations.

The French version of the PIS/ICF will be considered as the template that will be translated and adapted to the appropriate national and local regulations. The changes made and the reason for the changes must be provided to Unicancer. The adapted documents must be validated by Unicancer before being implemented in the specific country.

Prior to the participation of a patient in the trial, this patient will be informed both verbally and in writing about the objectives of the trial, its methods, anticipated benefits and potential risks and the discomfort to which they may be exposed. All items must be explained by the investigator in a language and in terms that are easy to understand by the patient. The patients must be given enough time to consider their participation and decide whether they wish to participate or not in the trial. Patients will also be informed that their participation is voluntary and that they have the right to withdraw from the trial at any time without giving the reasons and without this impacting their subsequent medical care.

The patient information sheet and the informed consent form must be associated within the same document to ensure that all information regarding the trial is provided to the patient. Patients will confirm their consent in writing prior to starting the trial and before undergoing any trial-related procedure. Two original informed consent forms must be personally dated and signed by the patient and investigator. An original copy will be filed in the Investigator Site File (ISF). The other original patient information sheet and the signed informed consent form will be given to the patient.

In the event that the patient decides to withdraw from the trial, the patient is not obliged to give reason(s) for withdrawing. However, the investigator should make a reasonable effort to obtain the reason(s) while fully respecting the patient's rights.

In conformance with the data protection regulation, the patient may use their right to access to, rectify or oppose the use of their personal data in the research. In these situations, the investigator shall inform the sponsor without delay in order to take the appropriate steps.

If any changes in the written patient information or informed consent form occur during the trial, the investigator will ensures that all patients impacted by the changes and still participating in the trial receive the updated patient information in a timely manner and are asked for written consent for the changes made.

At their request, patients will be informed of the overall results of the research at the end of the study, by making a request to the investigators. In addition, patients will be able to consult a lay summary, intended for the general public, of the scientific results of this research. Information on this clinical trial and its results is available on the websites of the European Medicines Agency (https://euclinicaltrials.eu/home), and the U.S. National Library of Medicine (www.clinicaltrials.gov).

13.4. Reporting of Serious Breaches of the Protocol or ICH-GCP

A serious breach is defined as any deviation of the approved protocol version, GCP or the clinical trial regulation that is likely to affect the safety, rights of trial participants and/or data reliability and robustness to a significant degree in a clinical trial.

Unicancer is responsible for the notification via the Clinical Trials Information System (CTIS) without undue delay and at the latest within 7 calendar days of becoming aware of a serious breach. Unicancer will report serious breaches according to the last version of the "Guideline for the notification of serious breaches of Regulation (EU) No 536/2014 or the clinical trial protocol".

The principal investigator should have a process in place to ensure that the site staff are able to identify the occurrence of a serious breach and that a serious breach is promptly reported to Unicancer, to meet the legal obligations. Furthermore, suspected serious breaches should be promptly reported to Unicancer by investigators (Notification form in the ISF) in order for Unicancer to perform further investigation and assess if the breach qualifies as serious.

13.5. Insurance compensation

Unicancer, the sponsor of the trial certifies that it has taken out a civil liability insurance policy covering its civil liability for this clinical trial under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance of the sponsor does not exempt the investigator and its team from maintaining their own liability insurance policy.

13.6. Sponsor responsibilities

The main sponsor responsibilities are to:

- Write the protocol and amendments, as well as trial-related documents
- Ensure that the trial is adequately financed to cover the anticipated expenses
- Take out a liability insurance policy covering the clinical trial
- To register the clinical trial with the European Union Clinical Trials Register
- Record the clinical trial in a publicly accessible research database
- Obtain clinical trial authorisation from the competent authorities and the ethics committees of the participating countries for the initial protocol and any subsequent amendments thereof
- Provide trial-related information to the investigators, pharmacists, and executive management of each investigational centre
- Provide training to investigators, pharmacists, and on site study teams regarding the clinical trial and study drugs
- Report any suspicion of a SUSAR to the competent authorities and notification of this information to the trial investigators
- Record any suspicion of a SUSAR in the European pharmacovigilance database (Eudravigilance)

- Simultaneously inform the competent authorities and Ethics Committees of any new event/unexpected event, serious breach (when applicable), or urgent safety measures according to local or European requirements
- Guarantee ongoing evaluation of the safety of patients included in this clinical trial
- Submit DSUR via CTIS according to European regulations
- Notify the competent authorities and Ethics Committees of the beginning and the end of the trial according to local or European regulations
- Write and distribute a final clinical study report according to local or European regulations
- Write and publish a summary of the clinical trial results
- Write and publish a lay summary of the clinical trial results
- Ensure essential trial documents are conserved for a minimum of 25 years after the end of the trial

13.7. Investigator responsibilities

The principal investigator of each investigational site participating in the trial commits to conduct the trial as specified in this protocol and in accordance with the current Declaration of Helsinki (see Appendix 1) as well as the current ICH-GCP (Appendix 2).

It is the responsibility of the principal investigator to:

- Provide to the sponsor with their curriculum vitae (CV) and those of their collaborators, and evidence that the site will be able to conduct the trial. The CV must be current (no older than 1 year), dated and signed.
- Identify the members of their team who participate in the trial and define each team member's role and responsibilities.
- Start recruiting patients only after receiving approval from the sponsor.
- Be available for monitoring visits, audits, and investigator meetings (if applicable).

It is the responsibility of each principal investigator and each investigator team member to:

- Ensure the confidentiality of all data recorded during the trial.
- Collect the informed consent, written, dated, and signed personally by each individual research participant before any specific selection procedure for the trial.
- Regularly complete the eCRF for each patient included in the trial and allow CRA(s), mandated by the sponsor, direct access to the source documents in order to validate the data collected in the eCRF.
- Declare to the sponsor as soon as being aware of, any serious adverse event occurring during the trial according to provisions of this protocol.

- Accept regular visits by the CRA(s) and possibly those of auditors mandated by the sponsor or the inspectors of the respective regulatory authorities.
- Date, correct, and sign the corrections made in the eCRF and the requests of the data correction forms for each patient included in the trial.
- Inform the sponsor of any serious breaches of the Regulation (EU) No 536/2014 or the clinical trial protocol.

13.8. Federation of the Patient Committees for Clinical Research in Cancerology

This committee reviews trial documents provided to patients in oncology clinical studies, and makes suggestions for improving these, in terms of the quality of information given to patients.

The “Ligue Nationale Contre le Cancer” and the French National Cancer Institute (*Institut National Du Cancer*, INCa) coordinate the French patient committees’ federation.

Patient associations/committees also review the lay summary distributed to trial participants and general public upon completion of the research.

13.9. Human biological samples collection

Biological studies are necessary to increase the knowledge of diseases, which may allow the development of new and more effective treatments. These studies use human biological samples (blood and tumour samples) than are collected from patients either while they receive medical care (examination, surgery) or specifically for the research purpose.

These biological samples will be prepared, stored, shipped, and used for the purpose of research.

These biological samples are subject to written consent from the patient. This consent is revocable at any time during the trial. Similarly, at any time during the research, the patient has the possibility to request the destruction of their samples.

Concerning genetic research patients must consent to participation in these studies after being informed of the proposed research, irrespective of the type of sample collected (already existing or specifically collected).

Furthermore, it must be noted that the results of biological studies may be published only if all data relative to the patients are made anonymous.

13.9.1. *Storage and use of disease assessment samples (blood, biopsy, tumour specimen, etc.)*

At study entry, archived FFPE biopsy material obtained as part of the standard medical care (e.g. confirmation of diagnosis) or prior surgical intervention will be collected and shipped to the Unicancer Biological Resources Centre at the Centre des Resources Biologiques - Centre Leon Berard (CRB-CLB) 28 rue Laënnec – 69373 Lyon - Cedex 08, Bâtiment CHENEY B Rez de Chaussée – France (see Section 9.1).

Any biological specimens not used for genomic profiling will be stored centrally in the Unicancer Biobank located at the Unicancer Biological Resources Centre.

The patient will be informed via a patient information sheet that, in the absence of opposition of his part, these biological samples will be prepared, stored and used for this research.

The preparation, storage and use of the biological samples does not modify or imply any change with respect to the diagnosis, cares and treatments that will be administrated to the patient.

13.9.2. *Collecting additional biological samples for research purpose*

An objective of this research is to study the tumour clonal evolution during treatment. To perform this research, additional blood sample(s) will be collected on Day 1 (prior to IP treatment initiation) and during the treatment period at various time points as described in Section 9.1. Where medically feasible, an additional tumour biopsy sample may also be collected at the time of disease progression.

These biological samples will be prepared, stored and used for the purpose of the research.

Collection of these additional samples is subject to a specific additional written consent from the patient. This specific consent for the ancillary/translational research is revocable at any time. In addition, the patient has the right to request the destruction of their samples at any moment.

14. DATA PROCESSING AND CONSERVATION OF DOCUMENTS AND DATA OF THE RESEARCH

14.1. Data processing

14.1.1. *Under the responsibility of the sponsor*

The trial data will be transferred to the trial statistician for analysis. The trial data remain the property of Unicancer, the research sponsor.

The software ENNOV will be used for data entry, management, and archiving of data. The statistical analysis will be performed using the Statistical Analysis System (SAS) version 9.4, or higher (SAS Inc, Cary, NC) and R (https://www.R-project.org/) software packages.

14.1.2. *In the investigational site, when computerised medical records are used*

If computerized patient records are used in a participating site to process or store trial data, the site must:

- Verify and document that the computer system used to process the data conforms with the requirements concerning data completeness, accuracy, and reliability with respect to expected performances (quality validation).
- Define and follow the standardized procedures related to these systems.
- Ensure that these systems allow modifications of collected data, that each modification is automatically authenticated, and that the data cannot be removed (i.e. any change or modification of the data must be traceable).
- Set up and maintain a security control to prevent unauthorized access to the data.
- Establish and regularly update the list of persons authorized to have access and modify the data.
- Carry out appropriate backups of the data.
- Ensure confidentiality, whenever it is applicable (e.g. during data input).
- Ensure that the individual computerized patient data are processed according to local regulations.

If data are transformed while being processed, it should always be possible to compare them with the original observations/records.

The computerized system used to identify trial patients must not be ambiguous and must allow the identification of all data collected for each patient while maintaining confidentiality in accordance with the national legal requirements.

14.2. Retention of documents by investigator sites

The investigator must maintain source documents for each trial patient.

All information in case report forms must be traceable and consistent with source documents, which are generally maintained in the patient's file. The source documents should contain all demographic and medical information, laboratory data, radiology, electrocardiograms, etc., including the original copy of the signed patient information sheet and informed consent form.

The investigator must retain essential documents as described below. The investigator agrees to adhere to the document retention procedures by signing the protocol. Essential documents include:

- Approvals from the responsible ethics committee for the trial protocol and all amendments.
- Authorizations from respective regulatory authorities for the trial protocol and all amendments.
- All source documents and laboratory records.
- CRF copies.
- Patients' informed consent forms.
- Investigator master file and pharmacy file.
- Any other pertinent trial document.

All trial documents must be kept in a locked and secured place and be considered as confidential.

Data will be archived under the responsibility of the principal investigator of each participating site according to the national regulatory requirements. The trial documents, including a list of the patients' identifications must be archived for a minimum period of 25 years after the end of the trial. Unicancer will inform the investigational sites when the trial-related records are no longer required.

The investigational site may destroy the data only after written authorization from the sponsor.

15. DATA OWNERSHIP AND CONFIDENTIALITY

By signing the protocol, the investigator agrees to keep all information provided by Unicancer strictly confidential and to ensure similar confidentiality from their staff. This obligation does not cover information provided to the patients and information already publically available.

Trial documents provided by Unicancer (protocols, investigators' brochures, eCRFs, and other material) will be stored appropriately to ensure their confidentiality. The information provided by Unicancer to the physician-investigator may not be disclosed to others without direct written authorization from Unicancer.

The physician-investigator commits to not publish, spread or use in any manner, directly or indirectly, the scientific and technical information and results related to the trial.

16. PUBLICATION RULES

All information resulting from this trial is considered to be confidential, at least until appropriate analysis and checking has been completed by the sponsor, the principal investigator and the statistician of the trial.

Any publication, abstract or oral presentations including results of the trial must be submitted to the sponsor (Unicancer) for approval.

Additionally, all communications, manuscripts or oral presentations must include a section mentioning Unicancer as well as any institution, physician-investigators, collaborative research group, scientific society that has contributed to the trial, including organizations that have provided financial support.

The first author and writer of the main publication will be the principal investigator. The principal investigator may however designate another person to (co-) write the publication.

As for the main publication, authors are listed in the following order:

- The trial coordinator (first or last author).
- The other investigators will appear in the list of co-authors in decreasing order, according to the number of recruited patients regardless of their affiliation to a cooperative group.
- A person representing each cooperating group, if a representative is not listed in the sites with the highest recruitment rates.
- The statistician (the statistician's position is among the first three authors or the last author of the publication).
- A Unicancer representative.

Similarly, publication of the sub-studies (e.g. biological/ancillary studies) will include persons who have carried out the sub-studies as well as the names of all individuals who have contributed to these sub-studies and a sponsor representative.

It is desirable to include the contributors from weakly recruiting sites who have not been mentioned in the first article in the later publications.

Any conflict regarding publication authorship will initially be submitted to the trial IDMC and then to Unicancer's Strategic Research Committee (*Comité Stratégique Recherche* [CSR]) for resolution in case of major disagreement.

Unicancer will arbitrate and rule any dispute that may arise.

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18. APPENDICES

Appendix 1. World Medical Association - Declaration of Helsinki

The current Declaration of Helsinki can be found on the World Medical Association web page via the link provided below:

https://www.wma.net/

Appendix 2. ICH Harmonised Tripartite Guideline for Good Clinical Practice (ICH-GCP)

The current ICH-GCP can be found on the European Medicine Agency web page via the link provided below:

https://www.ema.europa.eu/

Appendix 3. The Prostate Cancer Working Group 3 – Recommendations for castration-resistant prostate cancer trials

Scher HI, Morris MJ, Stadler WM, *et al*. Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3. *J Clin Oncol*. 2016;34(12):1402-1418

1. Baseline disease assessment:

Imaging of the chest, abdomen, and pelvis using a contrast-enhanced computed tomography (CT) scan with ≤ 5-mm axial slices is advised for all patients. For those intolerant of contrast, a cross-sectional magnetic resonance imaging (MRI) scan of the abdomen and pelvis, with a non-contrast CT scan of the chest, may be considered.

Visceral lesions/lymph nodes

PCWG3 advises following Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST 1.1; Eisenhauer, 2009) for extra-skeletal disease but ***recommends that up to five lesions be recorded per site of metastatic spread*** (eg, lung, liver, lymph nodes as separate sites) to address disease heterogeneity and to track patterns of metastatic progression (see Appendix 4).

Bone lesions

The number and sites of all bone lesions present at baseline should be recorded separately.

Note: *Use of the Prostate Cancer Clinical Trials Consortium (PCCTC) a bone scan data capture tool for clinical trials is recommended for the evaluation of bone lesions during the trial (see Appendix 13 for a version adapted to this study)*

The use of ^{99m}Tc-methylene diphosphonate radionuclide bone scintigraphy is considered as the standard for bone imaging. If not available, PET scan or plain films can be used to confirm the presence or disappearance of bone lesions.

Prostate-serum antigen level

Baseline PSA levels should be recorded

2. Disease outcomes:

Radiographic progression

Radiographic progression is defined as either:

a) A nodal or visceral progression according to RECIST v1.1 (Appendix 4):

- **Target lesions:** At least a 20% increase in the sum of diameters of target lesions, taking as reference the lowest value (nadir) obtained during the trial (this includes the baseline sum if that is the lowest on trial). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

  Lymph nodes must have grown by at least 5mm in the short axis from baseline or nadir and be ≥1.0 cm in the short axis to be considered to have progressed.

  Warning*: when a progression is recorded with respect to the nadir but there is a response with respect to baseline, progression must be considered.*

- **Non-target lesions:** Unequivocal progression of existing non-target lesions.
- **New lesions:** The appearance of one or more new lesions is also considered progression).

b) The appearance of two or more new bone lesions on a bone scan.

Note: *Results should be confirmed by a second scan at least 6 weeks later. In this case the date of progression will be considered as the date of the initial post-treatment scan, when the first two new lesions were documented.*

The appearance of a single new bone lesion will not be considered as radiographic progression. The patient may receive local stereotactic body radiation therapy (SBRT) to the new bone lesion but no alteration should be made to the study treatment before confirmation of radiographic progression.

The date of radiographic progression will be the date of progression as per the above definition.

Castration resistance

Castration resistance is defined as serum testosterone being at a castrated level ≤ 50 ng/dL (equivalent to 0.50 ng/mL or 1.73 nmol/L), plus either:

a) Biochemical progression: Two consecutive increases in PSA of at least >1 ng/mL over the nadir, measured at least 1 week apart, (see Figure 3 below).

The date of biochemical progression will be the date where the PSA testing confirms that the progression criteria have been met.

OR

b) Radiographic progression: as per the above definition

The date of castration resistance will be the first date among the date of biochemical progression and the date of radiographic progression.

The appearance of a single new bone lesion in the absence of biological progression will not be considered as castration resistance. Resistance to castration will be characterized by the appearance of a second bone lesion (or a visceral lesion) and / or biological progression. In this case, the date of detection of the second lesion will be the date of resistance as per the above definition.

Note*: Symptomatic progression should be subject to further investigation before diagnosing CRPC. It is not sufficient alone to diagnose castration resistance.*

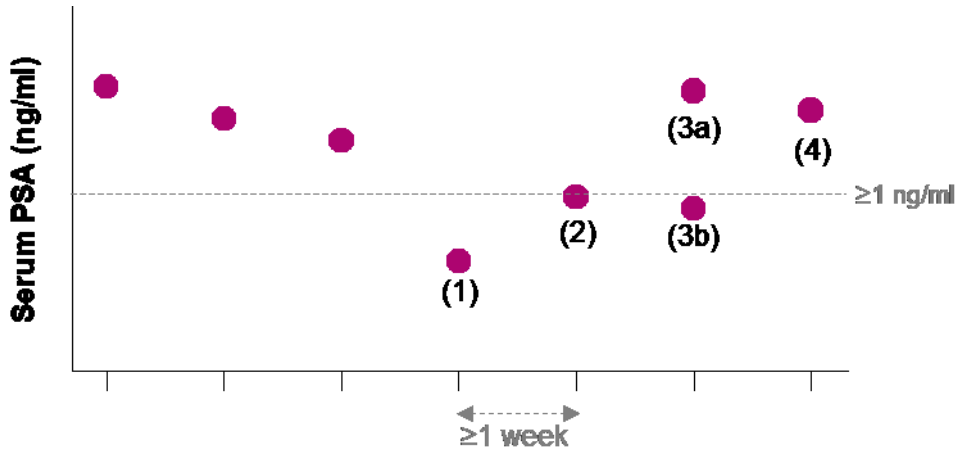

Figure 3. Example of variation in PSA levels used to define castration-resistant prostate cancer.

The reference value, or "nadir" (1) is the lowest reported PSA measurement before increases are documented, with subsequent values obtained a minimum of 1 week apart. The criteria for castration-resistance are met when there is an increase in PSA above the nadir of at least 1 ng/mL (2) confirmed by a second measurement (3a) taken at least 1 week later. The date of CRPC is the date of the confirmatory measurement (3a).

If the PSA level at the second measurement is less than 1 ng/mL above the nadir (3b), then castration-resistance has not been met. However if a later measurement (4) confirms the increase seen at measurement (2) the patient is considered as having CRPC (The date of CRPC will be the date of measurement (4) in this case).

[*Reproduced from Scher HI, Halabi S, Tannock I, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol. 2008;26(7):1148-1159. updated with PCWG3 recommendations*]

Appendix 4. Summary of Response Evaluation Criteria in Solid Tumours (RECIST) v1.1

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, *et al*. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009; 45(2):228-247.

Full article available at: http://ctep.cancer.gov/

3. Measurability of Tumour at Baseline:

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

a) Measurable

Tumour lesions: Must be accurately measured in a 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 calliper measurement by clinical exam;
- 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.

b) 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.

Note: Bone lesions, cystic lesions, and lesions previously treated with local therapy require special considerations regarding lesion measurability (see below):

c) 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.

4. Target lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ)[6] representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. Pathological nodes which are defined as

[6] ***Note :*** *PCWG3 guidelines recommend that up to five lesions be recorded per site of metastatic spread (eg, lung, liver, lymph nodes as separate sites) to address disease heterogeneity and to track patterns of metastatic progression*

measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan.

The baseline sum diameters will be used as reference to further characterise any objective tumour regression in the measurable dimension of the disease.

5. Non-target lesions

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' during the trial.

6. Response criteria:

a) 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

  ***Warning**: lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on trial.This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. In order to qualify for CR, each node must achieve a short axis <10 mm*.

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

- **Progressive Disease (PD):** At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on trial (this includes the baseline sum if that is the smallest on trial). 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).

  ***Warning**: when a progression is recorded with respect to the Nadir but there is a response with respect to baseline, progression must be considered.*

- **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 trial.

b) Non-target lesions

- **Complete Response (CR):** Disappearance of all non-target lesions and normalisation of tumour 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 tumour marker level above the normal limits.

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

7. Overall response:

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	=	**Not-evaluable**
PD	No change	Yes or No	=	**PD**
No change	PD	Yes or No	=	**PD**
No change	No change	Yes	=	**PD**

Special considerations regarding baseline lesion measurability

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.

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 noncystic 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. Trial protocols should detail the conditions under which such lesions would be considered measurable.

Appendix 5. Eastern Cooperative Oncology Group Performance Status Scale

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, *et al*. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982 Dec;5(6):649-655.

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

Comparing the ECOG Performance Status to the Karnofsky* Performance Status

The ECOG and Karnofsky* Performance Status scales are two widely used methods to assess the functional status of a patient. Both scales have been in the public domain for many years as ways to classify a patient according to their functional impairment, compare the effectiveness of therapies, and assess the prognosis of a patient.

The table below displays a comparison of the two systems.

ECOG PERFORMANCE STATUS	KARNOFSKY* PERFORMANCE STATUS
0 Fully active, able to carry on all pre-disease performance without restriction	100 Normal, no complaints; no evidence of disease 90 Able to carry on normal activity; minor signs or symptoms of disease
1 Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work	80 Normal activity with effort, some signs or symptoms of disease 70 Cares for self but unable to carry on normal activity or to do active work
2 Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours	60 Requires occasional assistance but is able to care for most of personal needs 50 Requires considerable assistance and frequent medical care
3 Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours	40 Disabled; requires special care and assistance 30 Severely disabled; hospitalization is indicated although death not imminent
4 Completely disabled; cannot carry on any selfcare; totally confined to bed or chair	20 Very ill; hospitalization and active supportive care necessary 10 Moribund
5 Dead	0 Dead

*Karnofsky D, Burchenal J, The clinical evaluation of chemotherapeutic agents in cancer. In: MacLeod C, ed. Evaluation of Chemotherapeutic Agents. New York, NY: Columbia University Press; 1949:191–205.

Appendix 6. Common Terminology Criteria for Adverse Events

In the present trial, adverse events will be recorded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0, *(Published November 27th, 2017)*

A copy of the toxicity evaluation scale can be obtained from the NCI website: http://ctep.cancer.gov/

NATIONAL CANCER INSTITUTE

Cancer Therapy Evaluation Program

The intensity of adverse events not listed in the CTCAE v5.0 classification will be assessed according to the following qualifiers:

- **Grade 1**: **Mild**; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2**: **Moderate**, minimal local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).
- **Grade 3**: **Severe** or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
- **Grade 4**: **Life-threatening** consequences; urgent intervention indicated.
- **Grade 5**: **Death** related to the event.

Appendix 7. G8 Screening tool

Soubeyran, P., Bellera, C.A., Gregoire, F., Blanc, J., Ceccaldi, J., Blanc-Bisson, C. *et al*. Validation of a screening test for elderly patients in oncology. *J Clin Oncol*. 2008;26: 20568 (Meeting Abstracts)

The G8 screening questionnaire is a short, nurse-administered survey that takes 5-10 minutes to perform. It consists of eight questions to establish:

- Appetite, weight loss, BMI
- Mobility
- Mood and cognition
- Number of medications
- Patient-related health
- Age categories

A patient's result is considered abnormal if the score ≤ 14

	Items	**Possible answers (score)**
A	Has food intake declined over the past 3 months due to loss of appetite, digestive problems, or chewing or swallowing difficulties?	0: severe decrease in food intake
		1: moderate decrease in food intake
		2: no decrease in food intake
B	Weight loss during the last 3 months	0: weight loss > 3 Kg
		1: does not know
		2: weight loss between 1 and 3 kg
		3: no weight loss
C	Mobility	0: bed or chair bound
		1: able to get out of bed/chair but does not go out
		2: goes out
E	Neurophychological problems	0: severe dementia or depression
		1: mild dementia or depression
		2: no psychological problems
F	Body mass index (BMI weight in kg)/height in m	0: BMI < 18.5
		1: BMI = 18.5 to BMI < 21
		2: BMI = 21 to BMI < 23
		3: BMI ≥ 23
H	Takes more than 3 prescription drugs per day	0: yes
		1: no
P	In comparison with other people of the same age, how do they consider their health status	0: not as good
		0.5: does not know
		1: as good
		2: better
	Age	0: > 85 years old
		1: 80-85 years old
		2: < 80 years old
	Total Score	**0-17**

Appendix 8. Geriatric Core Dataset (G-Code)

Paillaud E, Soubeyran P, Caillet P, Cudennec T, Brain E, *et al*. G-CODE collaborators. Multidisciplinary development of the Geriatric Core Dataset for clinical research in older patients with cancer: A French initiative with international survey. *Eur J Cancer*. 2018;103:61-68.

The Geriatric Core Dataset (G-Code) assessment consists of eight evaluations to be administered by hospital staff to the patient.

1. Social environment

1. Do you live alone? ☐ **YES** ☐ **NO**

Note: *For people living in nursing homes, the answer is "no".*

2. Do you have any person able to provide you care and support? ☐ **YES** ☐ **NO**

Note: *Answering "yes" to this question means that the patient has a primary caregiver, support at home, or a strong circle of family / friends / neighbour capable of meeting the patient's needs at the time of the evaluation.*

2. Functional status

a) Assessment of daily living

To be assessed using the Katz index of independence in activities of daily living (Katz, 1970) excluding the question of urinary continence.

Activity	Description	Points	Score
Bathing	Bathes self completely or needs help bathing only a single part of the body such as the back, genital area or disabled extremity.	1	|___| points
	Needs help with bathing more than one part of the body, getting in or out of the tub or shower.	½	
	Requires total bathing	0	
Dressing	Gets clothes from closets and drawers and puts on clothes and outer garments complete with fasteners (May require help tying shoes).	1	|___| points
	Needs some assistance dressing or undressing self	½	
	Totally dependent on others to dress or undress	0	
Toileting	Goes to toilet, gets on and off, arranges clothes, cleans genital area without help.	1	|___| points
	Needs help transferring to the toilet, cleaning self	½	
	Cannot go to the toilet by themselves, or uses bedpan or commode.	0	
Transferring	Moves in and out of bed or chair unassisted. Mechanical transfer aids are acceptable.	1	|___| points
	Needs help to stand up or walk	½	
	Cannot move unaided, bedridden or in a wheelchair	0	
Feeding	Gets food from plate into mouth without help. Preparation of food may be done by another person.	1	|___| points
	Requires help to cut meet or peel fruit	½	
	Totally dependent on others to feed them	0	

TOTAL SCORE = |___| / 5

b) 4-Instrumental activities of daily living

To be assessed using a modified Lawton – Brody instrumental activities of daily living scale (4-IADL; Lawton, 1969).

CATEGORY / Description	Score (0 or 1)
A. ABILITY TO USE TELEPHONE	
1. Operates telephone on own initiative. Looks up and dials numbers, etc. **(1 POINT)**	
2. Dials a few well known numbers **(1 POINT)**	|___|
3. Answers telephone but does not dial **(1 POINT)**	
4. Does not use telephone at all **(0 POINTS)**	
F. MODE OF TRANSPORTATION	
1. Travels independently on public transportation or drives own car **(1 POINT)**	
2. Arranges own travel via taxi, but does not otherwise use public transportation **(1 POINT)**	
3. Travels on public transportation when accompanied by another **(1 POINT)**	|___|
4. Travel limited to taxi or automobile with assistance of another **(0 POINTS)**	
5. Does not travel at all **(0 POINTS)**	
G. RESPONSIBILITY FOR OWN MEDICATIONS	
1. Is responsible for taking medications in correct dosages at correct time **(1 POINT)**	
2. Takes responsibility if medication is prepared in advance in separate dosage **(0 POINTS)**	|___|
3. In not capable of dispensing own medication **(0 POINTS)**	
H. ABILITY TO HANDLE FINANCES	
1. Manages financial matters independently (budgets, writes checks, pays rent, goes to bank), collects and keeps track of income **(1 POINT)**	
2. Manages day-to-day purchases, needs help with banking, major purchases, etc. **(1 POINT)**	|___|
3. Incapable of handling money **(0 POINTS)**	
TOTAL SCORE = |___| / 4	

3. Mobility: Timed up and go test

Description

The timed up and go (TUG) test (Podsiadlo, 1991) is a measure of function with correlates to balance and fall risk.

Equipment

Stopwatch, Standard chair, Measured distance of 3 meters

Patient instructions

“My commands for this test are going to be ‘ready, set, go’. When I say go, I want you to stand up from the chair. You may use the arms of the chair to sand up or sit down. Once you are up, you may take any path you like, but I want you to move as QUICKLY as you feel safe and comfortable until you pass this piece of tape (or end of marked course) with both feet. Turn around and walk back to the chair. I will stop the clock when your back touches the back of the chair. You will complete one practice run and two that are counted.”

Therapist instructions

Start timing on the word “GO” and stop timing when the patient is seated again correctly in the chair with their back resting on the back of the chaire. The patient wears their regular footwear, may use any gait aid that they normally use during ambulation, but may not be assisted by another person. There is no time limit. They may stop and rest (but not sit down) if they need to.

Interpretation

Allow one point for accomplishment of each of the following steps (0 if not completed in the time allowed):

- Stand up from the chair |___|
- Walk the marked distance (3m) |___|
- Turn around |___|
- Return and sit down in the chair |___|

Time required: |___| seconds

- ≤ 10 seconds = normal
- 10 - 20 seconds = good mobility, can go out alone, mobile without gait aid
- 20 - 30 seconds = problems, cannot go outside alone, requires gait aid

  **Note: A score of ≥ 14 seconds has been shown to indicate high risk of falls*

4. Nutritional status

Determine if the patient has experienced weight loss during the last 6 months and calculate the patient’s body mass index (BMI). If one of the test is abnormal, the nutritional status is considered impaired.

Unintentional weight loss in the last six months? ☐ **YES** ☐ **NO**

BMI = weight (kg) / height^2 (m) |___|

5. Cognitive status - Mini-Cog™

Instructions for administration and scoring

Step 1: Three word registration

Look directly at the person and say, “Please listen carefully. I am going to say 3 words that I want you to repeat back to me now and try to remember. The words are [select a list of words from the versions below]. Please say them for me now”. If the person is unable to repeat the words after three attempts, move to Step 2 (clock drawing).

The following and other word lists have been used in one or more clinical studies. For repeated administrations, use of an alternative word list is recommended.

Version 1	Version 2	Version 3	Version 4	Version 5	Version 6
Banana	Leader	Village	River	Captain	Daughter
Sunrise	Season	Kitchen	Nation	Garden	Heaven
Chair	Table	Baby	Finger	Picture	Mountain

Step 2: Clock drawing

Say, “Next I want you to draw a clock for me. First, put in all of the numbers where they go”. When that is completed, say, “Now, set the hands to 10 past 11”.

Use the pre-printed circle provided for this exercise. Repeat instructions as needed as this is not a memory test. Move to step 3 if the clock is not complete within three minutes.

Step 3: Three word recall

Ask the person to recall the three words you stated in Step 1. Say “What were the three words I asked you to remember?” Record the word list version number and the person’s answers below.

Word list version: _____ Patients answers _____ _____ _____

Scoring

Word recall: _____ (0-3 points)	1 point for each word spontaneously recalled without cueing
Clock draw: _____ (0 or 2 points)	Normal clock = 2 points. A normal clock has all numbers placed in the correct sequence and approximately correct position (e;g. 12, 3, 6, 9 are in anchor positions) with no missing or duplicate numbers. Hands are pointing to the 11 and 2 (11:10). Hand length is not scored. Inability or refusal to draw a clock (abnormal) = 0 points
Total score: _____ (0-5 points)	Total score = Word recall score + Clock draw score. A cut point of <3 in the Mini-Cog has been validated for dementia screening, but many individuals with clinically meaningful cognitive impairement will score higher. When greater sensitivity is desired, a cut point of <4 is recommended s it may indicate a need for further evaluation of cognitive status.

6. Depressive mood: Mini-Geriatric Depression Scale

The patient's depressive mood will be assessed using the Mini-GDS (Cheng, 2005; Clément, 1997).

Mini-GDS			Score
1. Are you basically satisfied with your life?	YES = 0	**NO = 1**	|___|
2. Do you feel that your life is empty?	**YES = 1**	NO = 0	|___|
3. Do you feel happy most of the time?	YES = 0	**NO = 1**	|___|
4. Are you afraid that something bad is going to happen to you?	**YES = 1**	NO = 0	|___|
		Total	|___| / **4**

Interpretation

0 = not depressed.

1 = uncertain.

2 to 4 = depressed

7. Comorbidities: Updated Charlson Comorbidity Index

Comorbidities will be assessed using the Charlson comorbidity index updated according to Quan *et al*. (Quan, 2011).

Check the item when the patient presents the comorbid condition, and add each point to obtain the total score. Cancer or hematological malignancy should also be scored.

Clinical condition		
☐	Metastatic solid tumour	6 points
☐	AIDS / HIV	4 points
☐	Moderate / severe liver disease	4 points
☐	Any malignancy, including leukemia and lymphoma	2 points
☐	Mild liver disease	2 points
☐	Hemiplegia or paraplegia	2 points
☐	Congestive heart failure	2 points
☐	Dementia	2 points
☐	Chronic pulmonary disease	1 point
☐	Rheumatologic disease	1 point
☐	Renal disease	1 point
☐	Diabetes with chronic complications	1 point

Score |___|___| / **24**

Appendix 9. Cumulative Illness Score Rating-Geriatrics (CISR-G)

Miller MD, Paradis CF, Houck PR, Mazumdar S, Stack JA, *et al*. Rating chronic medical illness burden in geropsychiatric practice and research: application of the Cumulative Illness Rating Scale. *Psychiatry Res*. 1992; 41: 237-248.

Online calculator available: https://www.mdcalc.com/cumulative-illness-rating-scale-geriatric-cirs-g

SCORING SHEET

Instructions: Please refer to the CIRS-G manual. Write brief descriptions of the medical problem(s) that justified the endorsed score on the line following each item.

Rating strategy

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

Score calculation

Category	Description	Score
Heart	.....	_____
Vascular	.....	_____
Haematopoietic	.....	_____
Respiratory	.....	_____
Eyes, Ears, Nose Throat & Larynx	.....	_____
Upper GI	.....	_____
Lower GI	.....	_____
Liver	.....	_____
Renal	.....	_____
Genitourinary	.....	_____
Musculoskeletal/Integument	.....	_____
Neurological	.....	_____
Endocrine/metabolic & Breast	.....	_____
Psychiatric illness	.....	_____
Total number of categories endorsed		_____
Total score		_____
Severity index (total score/total number of categories endorsed)		_____
Number of categories at level 3 severity		_____
Number of categories at level 4 severity		_____

A MANUAL OF GUIDELINES FOR SCORING THE CUMULATIVE ILLNESS RATING SCALE FOR GERIATRICS (CIRS-G)

MAY 1991

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PHILOSOPHY AND DEVELOPMENT OF THE SCALE

Compiling and quantifying medical problems in the elderly population would allow meaningful comparison of medical burden and treatment outcomes in elderly patients with variable and complex medical problems. The Cumulative Illness Rating Scale (CIR), developed by Lin, Lin and Gurel, published in JAGS in 1968 [1] appealed to the writers intuitively as a user friendly but comprehensive review of medical problems by organ system, based on a 0 thru 4 rating, yielding a cumulative score. This scale was revised to reflect common problems of the elderly with an emphasis on morbidity using specific examples and was renamed the Cumulative Illness Rating Scale for Geriatrics (CIRS-G).

Some "arbitrary" decisions were made for categorizing certain conditions that could overlap more than one category and thus be counted twice, e.g., dementia is categorized in psychiatry although it overlaps with neurology, vertigo in the Ear, Nose and Throat category although it could also be in neurology, and CNS vascular lesions are confined to neurology although they technically overlap with "vascular." See individual sections of the manual for further details.

EDUCATION OF RATER

Nurses, physician assistants, nurse practitioners or physicians are required to have the necessary background for completing this scale. Due to the judgement required, some physician consultation may be necessary to clarify complex medical problems or their severity.

THE MINIMUM DATABASE REQUIRED

It is expected that every patient have a complete history and physical with a designated problem list, height, weight, and baseline labs including a complete blood count and differential, chem profile to include electrolytes, liver and kidney function, serum B12, thyroid function, cholesterol level, and an EKG. For rating psychiatric conditions the rater is expected to be familiar with the Folstein Mini-Mental Status Exam (Folstein, Folstein, & McHugh, 1975 [2]) and the Diagnostic and Statistical Manual III-R (DSM III-R) [3].

Other information of more specialized nature will increase the accuracy of the rating in a given patient and should be used when available. Scoring "live" patients (rather than retrospective chart reviews) is recommended to be able to clarify points that could differentiate two score levels more accurately.

RATING STRATEGY

Scoring contingencies for every possible medical problem is obviously too cumbersome and quickly exhausts efforts to maintain simplicity and ease of use. The CIRS-G scale seeks to outline intuitive severity levels within each category to serve as a guide for the rater to interpolate the particular problem set of a given patient. We acknowledge that judgement is ultimately required for a "best fit" and that rigorous specificity may be traded off for the intuitive "face validity" and ease of use of this scale.

SCORING

Scoring was modified in the CIRS-G to yield five numbers: the total number of categories endorsed, the total score, the ratio of total score/number of endorsed categories (yielding a severity index per category), and the number of categories at level 3 and 4 for a given patient. This rating strategy allows the reader to see at a glance whether a given patient's total score reflects a few serious problems or multiple problems of mild to moderate severity as well as potential severe problems that merit a 3 or 4 rating. A single page scoring sheet also provides a rating for each organ system as well as space for a brief written description of the particular problem that merited the score (See sample scoring sheet).

Space provided on the scoring sheet is intended for a brief description of the problem that merited the endorsed score to facilitate more detailed retrospective analysis.

RATING ACTIVE VS CHRONIC PROBLEMS

Repeating this scale on the same patient at two different points of time may show a decline in total score if there were acute problems at time 1 that had resolved at time 2, however, this scale is clearly weighted toward chronic problems (including "status post" diagnoses) and is therefore cumulative such that the CIRS-G score will generally increase over time in a given patient.

RATING SUGGESTIONS (GENERAL)

We have found it easier to rate the severity of medical problems within a category by defining "mild" and "extremely severe" first, i.e., 1 and 4 and subsequently "moderate" and "severe," (2 and 3). The bulk of judgement, in our experience, rests in differentiating 2 and 3.

Note the following descriptors for a given level of severity:

0 - No Problem,

1 - Current mild problem or past significant problem

2 - Moderate disability or morbidity/ requires "first line" therapy

3 - Severe/constant significant disability/ "uncontrollable" chronic problems

4 - Extremely Severe/immediate treatment required/end organ failure/severe impairment in function

Level 1 - Current mild problem or past significant problem.

Any current medical problem that causes mild discomfort or disability, or has occasional exacerbations that have an overall minor impact on morbidity should be rated a "1," for example, a hiatal hernia with occasional heartburn treated with prn antacids. Medical problems that are not currently active but were significant problems in the past should also be listed as a "1," for example, passage of a kidney stone. Past childhood illnesses, minor surgery, uncomplicated healed fractures, minor injuries, teeth extractions, or events so remote without sequelae (e.g., one febrile seizure in childhood) need not be listed at all. However, if any of the above leave a suspicion of potential future complications the rater should err on the side of inclusion, and briefly describe his/her concerns in the space provided.

Level 2 - Moderate disability or morbidity/requires "first line" therapy.

Level 2 should be endorsed for medical conditions that require daily medication of "first line" nature, for example, patients requiring daily nonsteroidal anti-inflammatory drugs for arthritis or daily digoxin to control congestive heart failure.

Level 3 - Severe/constant significant disability/"uncontrollable" chronic problems.

Level 3 should be endorsed for chronic conditions that are not compensated for with first line therapy, for example, requiring steroids for rheumatologic conditions or lung disease. "Constant significant disability" describes patients whose underlying pathology is not fully compensated by medical regimens, for example, patients with exertional angina would endorse a level "3" because their underlying pathology is not fully compensated by medical regimens but many less strenuous activities are possible (i.e., level "4" is not indicated).

Level 4 - Extremely Severe.

Immediate treatment required/end organ failure/severe impairment in function. This level describes the late stages of disease or disability within a category. Generally, this level reflects the failure to arrest the disease process with resulting disability, pain, or restricted activities of daily living (ADL's). Alternatively, any acute condition that requires immediate treatment e.g., bladder outlet obstruction would also qualify as a "4." Severely limited ambulation or ADL's or sensory impairment would also endorse a "4," in the appropriate category for example, blindness, deafness or being wheelchair bound.

RATING MALIGNANCIES

Consistent scoring of severity ratings for various malignancies is a difficult problem. Each malignancy has its own rating system and prognostic indicators, the complexity of which would quickly exceed the scope of the intended simplicity and ease of use of this scale.

The following general guidelines are intended to provide a reasonably accurate delineation of medical burden for cancer without excessive complexity.

Level 1: Cancer diagnosed in the remote past without evidence of recurrence or sequelae in the past 10 years.

Level 2: Cancer diagnosed in the past without evidence of recurrence or sequelae in the past five years.

Level 3: Required chemotherapy, radiation, hormonal therapy or surgical procedure for cancer in the past five years.

Level 4: Recurrent malignancy of life threatening potential/failed containment of the primary malignancy/palliative treatment stage.

These ratings are to be made in the appropriate organ category for a given malignancy.

ORGAN SPECIFIC CATEGORIES

The following organ specific categories will attempt to provide guidelines for consistent rating of comparable severity. Common conditions will be stressed with the focus on the "judgement strategy" that can then be applied to other problems not listed.

Heart

0). No problem.

1). Remote MI (> five years ago)/occasional angina treated with prn meds.

2). CHF compensated with meds/daily anti-angina meds/left ventricular hypertrophy/atrial fibrillation/bundle branch block/daily antiarrhythmic drugs.

3). Previous MI within five years/abnormal stress test/status post percutaneous coronary angioplasty or coronary artery bypass graft surgery.

4). Marked activity restriction secondary to cardiac status (i.e., unstable angina or intractable congestive heart failure).

The bulk of heart disease is encompassed by atherosclerotic heart disease, arrythmias, congestive heart failure and valvular disease. Within each of these categories the 1-4 rating of severity must be judged.

Atherosclerotic Heart Disease

Mild through extremely severe stages of atherosclerotic heart disease are reflected in the above levels as outlined.

Congestive Heart Failure

Requiring daily medications for CHF merits at least a "2," intractable CHF a "4" and an intermediate condition a "3."

Arrhythmias

EKG findings of atrial fibrillation, right or left bundle branch block, or the necessity of daily antiarrhythmic drugs merits "2" at least, a bifasicular block a "3." In patients who require a pacemaker, placement for an incidental finding of periods of bradycardia during a holter monitor would score a "2," whereas placement of a pacemaker for cariogenic syncope would merit a "3."

Valvular Disease

Detectable murmurs that indicate valvular pathology without activity restriction would merit a "1," more severely compromising valvular disease would require a progressively higher rating.

Pericardial Pathology

A pericardial effusion or pericarditis would merit at least a "3."

Vascular

0). No problem.

1). Hypertension compensated with salt restriction and weight loss/serum cholesterol > 200 mg/dl.

2). Daily antihypertensive meds/one symptom of atherosclerotic disease (angina, claudication, bruit, amaurosis fugax, absent pedal pulses)/aortic aneurysm < 4 cm.

3). Two or more symptoms of atherosclerosis [see above].

4). Previous surgery for vascular problem/aortic aneurysm > 4 cm.

Hypertension

Defined as a persistently elevated diastolic pressure > 90 mm Hg. When managed drug free - "1," requiring single daily antihypertensive - "2," requiring two or more drugs for control or with evidence of left ventricular hypertrophy - "3."

Peripheral Atherosclerotic Disease

Evidence of at least one physical symptom or imaging evidence (e.g., angiogram) merits a "2," two or more symptoms a "3" and if bypass graft surgery was required or is currently indicated a "4" is merited.

Intracranial vascular event

For consistency, CNS vascular events are listed under neurology.

Aortic Aneurysm

If < 4 cm a "3," if > 4cm a "4."

Hematopoietic (blood, blood vessels and cells, marrow, spleen, lymphatics)

0). No problem.

1). Hemoglobin: females > 10 < 12, males > 12 < 14/anemia of chronic disease.

2). Hemoglobin: females > 8 < 10, males > 10 < 12/anemia secondary to iron, vitamin B12, or folate deficiency or chronic renal failure/total white blood cell count > 2000 but < 4000.

3). Hemoglobin: females < 8, males < 10/total WBC < 2000.

4). Any leukemia, any lymphoma.

Malignancy

Any hematological malignancy would merit a "4."

Anemia

Sex specific hemoglobin cut-offs are provided above. An identifiable etiology other than chronic disease merits a "2"or higher if the anemia is more severe.

Leucopenia

Total WBC cut-offs are provided.

Respiratory (lungs, bronchi, trachea below the larynx)

0). No problem.

1). Recurrent episodes of acute bronchitis/currently treated asthma with prn inhalers/cigarette smoker > 10 but < 20 pack years.

2). X-ray evidence of COPD/requires daily theophylline or inhalers/treated for pneumonia two or more times in the past five years/smoked 20-40 pack years.

3). Limited ambulation secondary to limited respiratory capacity/requires oral steroids for lung disease/smoked > 40 pack years.

4). Requires supplemental Oxygen/at least one episode of respiratory failure requiring assisted ventilation/any lung cancer.

Smoking Status

Smoking is a significant respiratory and cardiovascular risk and is rated according to lifetime pack years (the number of packs smoked per day X the number of years smoked in their lifetime). Ex-smokers, e.g., those with 25 pack-years but who have been smoke-free for the most recent 20 years would merit a lower rating than a 25 pack-year patient who is currently smoking (in this case a "1" instead of a "2").

Chronic Bronchitis, Asthma, and Emphysema

These conditions are rated "1" if only prn inhalers are required, "2" if daily theophylline or inhalers are required, "3" if steroids are required and "4" if supplemental oxygen is required.

More objective evidence, e.g. blood gases would help to sharpen the appropriate level.

Pneumonia

An acute pneumonia treated as an outpatient would merit a "3," and if hospitalization was required a "4". Two or more episodes of pneumonia in the past five years would merit a "2".

Eyes, Ears, Nose & Throat and Larynx

0). No problem.

1). Corrected vision 20/40;/chronic sinusitis/mild hearing loss.

2). Corrected vision 20/60 or reads newsprint with difficulty/requires hearing aid/chronic sinonasal complaints requiring medication/requires medication for vertigo.

3). Partially blind (requires an escort to venture out)/unable to read newsprint/conversational hearing still impaired with hearing aid.

4). Functional blindness/functional deafness/laryngectomy/requires surgical intervention for vertigo.

Impaired vision

To simplify the potential complexity of this category, the developers decided to score according to severity of the sensory disability and avoid rating each type of pathology. Therefore, whether cataracts, glaucoma, macular degeneration or other pathology is underlying the impaired vision, it is rated as follows: if they complain of decreased vision despite corrective lenses but have no restriction in activities and can read newsprint rate it a "1", if they have difficulty reading newsprint or driving due to vision - "2," if they cannot read newsprint or require assistance from a sighted person - "3," and if the are "functionally blind" i.e., unable to read, recognize a familiar face from across the room or negotiate a novel environment alone, a "4" is merited.

Note: The term "functional" refers to ability to function and does not imply psychogenic origin.

Hearing Impairment

Similarly, hearing is rated by degree of sensory impairment as outlined above.

Vertigo, Lightheadedness and Dizziness

These complaints are very frequent in the elderly and would merit a "2" if medications are required for control and a "4" if surgical intervention is required.

Other conditions

Of the myriad of other EENT conditions, rating should be based on an estimate of the level of disability or impairment e.g., laryngectomy merits a "4" as it severely limits communication. etc.

Upper GI (esophagus, stomach, duodenum)

0). No problem.

1). Hiatal hernia/heartburn complaints treated with prn meds.

2). Needs daily H2 blocker or antacid/documented gastric or duodenal ulcer within five years.

3). Active ulcer/guiac positive stools/any swallowing disorder or dysphagia.

4). Gastric cancer/history of perforated ulcer/melena or hematochezia from UGI source.

Ulcers

Symptoms of heartburn, and the diagnoses of hiatal hernia, gastritis and gastric or duodenal ulcer can be seen on a continuum of severity, i.e., mild symptoms requiring prn antacids merit a "1," daily antiacid regimens - "2," an active ulcer or in combination with guiac positive stools - "3," and a history of perforated ulcer or heavy bleeding from an UGI source a"4."

Cancer

Any UGI malignancy generally merits a "4." (see "Rating Malignancies").

Lower GI (intestines, hernias)

0). No problem.

1). Constipation managed with prn meds/active hemorrhoids/status post hernia repair.

2). Requires daily bulk laxatives or stool softeners/diverticulosis/untreated hernia.

3). Bowel impaction in the past year/daily use of stimulant laxatives or enemas.

4). Hematochezia from lower GI source, currently impacted, diverticulitis flare up/status post bowel obstruction/bowel carcinoma.

Constipation

Constipation is rated by severity most easily by what type and how frequent laxatives are required or by a history of impaction as above.

Bleeding and Cancer

Any active bleeding generally merits a "4" as does the diagnosis of cancer (see "Rating Malignancies").

Diverticular Disease

A diagnosis of diverticulosis or a history of diverticulitis in the past merits a "2," an active flare-up of diverticulitis merits a "4" and an intermediate condition a "3."

Liver (including biliary and pancreatic trees)

0). No problem.

1). History of hepatitis > five years ago/cholecystectomy.

2). Mildly elevated LFT's (up to 150% of normal)/hepatitis within five years/cholelithiasis/ daily or heavy alcohol use within five years.

3). Elevated bilirubin (total > 2)/marked elevation of LFT's (> 150% of normal)/requires supplemental pancreatic enzymes for digestion.

4). Biliary obstruction/any biliary tree carcinoma/cholecystitis/pancreatitis/active hepatitis. As the hepato-biliary system is difficult to assess through the physical exam, therefore, lab results must be used.

Gall bladder Disease

A remote cholecystectomy merits a "1," cholelithiasis or gall stones visualized with imaging techniques merits a "2," and acute cholecystitis a "4."

Hepatitis

A history of hepatitis within five years that is inactive at present merits a "2," active hepatitis a "4."

Pancreatic Disease

Pancreatic insufficiency requiring supplemental enzymes or chronic pancreatitis merits a "3," acute pancreatitis merits a "4."

Carcinoma

Any hepato-biliary tree carcinoma generally merits a "4" (see "Rating Malignancies").

Renal (kidneys only)

0). No problem.

1). s/p kidney stone passage within the past 10 years or asymptomatic kidney stone/ pyelonephritis within five years.

2). Serum creatinine > 1.5 but < 3.0 without diuretic or antihypertensive medication.

3). Serum creatinine > 3.0 or serum creatinine > 1.5 in conjunction with diuretic, antihypertensive, or bicarbonate therapy/current pyelonephritis.

4). Requires dialysis/renal carcinoma.

Renal function must also rely on laboratory tests reflected in the above cut-off values.

Some patients are asymptomatic with an elevated creatinine and thus differentiating a "2" from a "3" will depend on whether adjunctive medications are required. Either peritoneal or hemodialysis would merit a "4" as would any end stage renal state or renal carcinoma. Specific glomerular disease or nephrotic syndromes would merit a "2" or "3" depending on the treatment required.

Genitourinary (ureters, bladder, urethra, prostate, genitals, uterus, ovaries)

0). No problem.

1). Stress incontinence/hysterectomy/BPH without urinary symptoms.

2). Abnormal pap smear/frequent UTI's (three or more in past year)/urinary incontinence (non stress) in females/BPH with hesitancy or frequency/current UTI/any urinary diversion procedure/status post TURP.

3). Prostatic cancer in situ (i.e., found incidently during TURP)/vaginal bleeding/cervical carcinoma in situ/hematuria/status post urosepsis in past year.

4). Acute urinary retention/any GU carcinoma except as above.

This category is long on description as sex-specific pathology must be considered separately.

Urinary incontinence

This problem is more common in elderly women and merits a "2" if it occurs only occasionally or in response to a cough, etc. (stress incontinence). Daily incontinence requiring adult diapers or regular nighttime incontinence would merit a "3."

Vaginal bleeding and abnormal PAP smears

Vaginal bleeding of significant persistent nature merits a "3," a previous hysterectomy for bleeding or fibroid nonmalignant tumors merits a "1" (as the bleeding has been cured). One abnormal PAP smear can result from chronic vaginitis and is usually repeated, a definite abnormal smear merits a "2," cervical carcinoma in situ merits a "3," and any GU carcinoma merits a "4."

Urinary Infections

Recurrent UTI's (three or more in the past year) merits a "1" in women and at least a "3" in men. A current UTI merits a "2," a history of urosepsis in the past year a "3" and current urosepsis a "4."

Prostate problems

An enlarged prostate on physical exam merits a "1," with urinary hesitancy or frequency or status post Trans Urethral Prostatectomy (TURP) merits a "2," an incidental finding of carcinoma in situ found during a TURP merits a "3," and prostate carcinoma or bladder outlet obstruction generally merits a "4" (see "Rating Malignancies").

Urinary Diversion Procedure

Patients with ileal loops, indwelling catheters or nephrostomies would merit at least a "2."

Musculoskeletal/Integument (muscles, bone and skin)

0). No problem.

1). Uses prn meds for arthritis or has mildly limited ADL's from joint pathology/excised non-melanotic skin cancers/skin infections requiring antibiotics within a year.

2). Daily antiarthritic meds or use of assistive devices or moderate limitation in ADL's/daily meds for chronic skin conditions/melanoma without metastasis.

3). Severely impaired ADL's secondary to arthritis/requires steroids for arthritic condition/vertebral compression fractures from osteoporosis

4). Wheelchair bound/severe joint deformity or severely impaired usage/osteomyelitis/any bone or muscle carcinoma/metastatic melanoma.

Skin cancers

Malignant melanoma must be differentiated from other localized skin cancers that merit a "1." A melanoma diagnosis merits a "2," with metastasis, a "4."

Arthritis

Arthritis is most simply rated according to resulting disability or level of treatment required as outline above.

Osteoporosis, Osteomyelitis, and Cancer

Osteoporosis with compression fractures a "3." Osteomyelitis requires intensive inpatient treatment generally and merits a "4." Any muscle or joint cancer generally merits a "4" (see "Rating Malignancies").

Neurological (brain, spinal cord and nerves)

0). No problem.

1). Frequent headaches requiring prn meds without interference with daily activities/a history of TIA phenomena (at least one).

2). Requires daily meds for chronic headaches or headaches that regularly interfere with daily activities/S/P CVA without significant residual/neurodegenerative disease (Parkinson's, MS, ALS, etc) - mild severity.

3). S/P CVA with mild residual dysfunction/any CNS neurosurgical procedure/ neurodegenerative disease - moderate severity.

4). S/P CVA with residual functional hemiparesis or aphasia/neurodegenerative disease-severe.

Headaches

Frequent Headaches requiring prn medication merits a "1," requiring daily anti-headache prophylaxis or intermittent severe headaches (e.g., migraines that require bed rest) merits a "2."

TIA's and Strokes

One transient ischemic attack (TIA) merits a "2." Cerebrovascular accidents (CVA) are rated as above according to the level of residual deficit or disability, for example, a patient who had hemiparesis and speech slurring but regained articulate speech and walks with only a slight remaining gait disturbance would be scored a "3,"

Vertigo, Dizziness and Lightheadedness

For consistency these are grouped under Ear, Nose and Throat although this category overlaps with neurology.

Neurodegenerative Disease

Parkinson's Disease, Multiple Sclerosis, and Amyotrophic Lateral Sclerosis (ALS) are three examples of a wide variety of degenerative neurological diseases. These illness are rated according to the severity of impairment at the time of rating, beginning at the "2" level. An example of a "3" would be a parkinsonian patient who shows residual bradykinesia and shuffling gait despite anti-parkinsonian medication, an example of a "4" would be patient unable to care for their own basic needs (bathing, toileting etc.) because of the severe progression of their illness.

Dementia (see "Psychiatric Conditions")

Although dementia can be considered a neurological as well as a psychiatric condition, for simplicity it should be grouped under "psychiatric conditions" as it's effect on functioning is primarily in this realm. For arbitrary clarity, Alzheimer's disease should be listed only under psych. If the dementia stems from multi-infarct dementia or other neurological condition with concomitant neurological signs or symptoms, both "neurologic" and "psychiatric" categories should be endorsed at the appropriate level for severity.

Endocrine/Metabolic and Breast (includes diffuse infections and poisonings)

0). No problem.

1). Diabetes mellitus compensated with diet/obesity: BMI > 30*/requires thyroid hormone replacement.

2). Diabetes mellitus requiring insulin or oral agents/fibrocystic breast disease.

3). Any electrolyte disturbance requiring hospital treatment/morbid obesity BMI > 45*.

4). Brittle or poorly controlled diabetes mellitus or diabetic coma in the past year/requires adrenal hormone replacement/adrenal, thyroid or breast carcinoma.

Diabetes Mellitus

Recognized diabetes mellitus controlled with diet merits a "1," when insulin or oral agents are required, a "2" is merited; brittle or poorly controlled diabetes or a history of diabetic ketoacidosis or nonketotic hyperosmolar coma in the past year merits a "4," and an intermediate level of severity e.g., fairly well controlled blood sugars in the 300 mg/dl range with some retinopathy or peripheral neuropathy would merit a "3."

Hormone replacement /Electrolyte disturbance

Thyroid replacement in the elderly is common and should be rated a "1" if otherwise uncomplicated. Potassium supplementation for patients taking diuretics is routine and would not merit a rating unless the serum potassium level was severely low. Abnormalities of other electrolytes can be serious conditions, for simplicity, we have designated those conditions that require hospital treatment to merit at least a "3." Adrenal hormone replacement merits a "3."

Other endocrine conditions require judgement of relative severity according to the level of morbidity caused by the condition.

Obesity

Obesity is considered a risk for a variety of conditions and is rated with guidelines of relative severity using the Body Mass Index (BMI) [4] as the current standard for measuring weight for a given height. Note the sex specific charts or nomograms provided in the index of this manual.

Breast Pathology

For lack of a better place, breast problems were included with endocrine/metabolic even though the breast is technically and exocrine gland. Listing it near the end of this manual is not meant to imply any relative unimportance. Fibrocystic breast disease merits a "2," breast cancer generally merits a "4" (see "Rating Malignancies").

Psychiatric illness

0). No psychiatric problem or history thereof.

1). Minor psychiatric condition or history thereof. Specifically: previous outpatient mental health treatment during a crisis/outpatient treatment for depression > 10 years ago/current usage of minor tranquilizers for episodic anxiety (occasional usage)/mild early dementia (MMS > 25 < 28).

2). A history of Major Depression (by DSM III-R criteria) within the past 10 years (treated or untreated)/mild dementia (MMS 20-25)/any previous psychiatric hospitalization/any psychotic episode substance abuse history > 10 years ago.

3). Currently meets DSM III-R criteria for major depression or two or more episodes of major depression in the past 10 years/moderate dementia (MMS 15-20)/current usage of daily antianxiety medication/currently meets DSM III-R criteria for substance abuse or dependence/requires daily antipsychotic medication.

4). Current mental illness requiring psychiatric hospitalization, institutionalization, or intensive outpatient management, e.g., patients with severe or suicidal depression, acute psychosis or

psychotic decompensation, severe agitation from dementia, severe substance abuse etc./Severe dementia (MMS < 15).

Rating psychiatric illness in keeping with the stated principles of this scale may seem like a daunting task particularly for raters with little mental health experience. Psychiatric consultation may be required for clarification. Thorough mental health histories and mental status exams are rarely obtained in the course of medical/surgical evaluations, therefore, retrospective rating from charts may show an inadequate database to properly rate all but the most obvious mental health impairments. Nevertheless, the following organizing threads are intended to guide the rater to reasonable assessments. It is assumed the rater has a working familiarity with DSM III-R3 and the Mini-Mental Status Exam (Folstein et al., 1975)[2].

For the elderly, dementia and depression are the most common psychiatric diagnoses and are a focus of the rating categories according to severity and time period since the last episode. Common sense dictates that those patients with more severe illness or more frequent episodes or who require more intensive intervention merit a higher severity rating.

The outlined criteria follow patterns of increasing severity for five major categories of illness: dementia, depression, anxiety, psychosis, and substance abuse. These representative categories were chosen as generally representative of the larger group of significant mental illnesses.

Rating strategies for a myriad of other disorders would overwhelm the scope of this scale.

As in the medical categories, other psychiatric disorders must be judged by the rater as meeting a similar level of impairment as the listed examples.

Patients with Personality disorders are defined broadly as having chronic difficulties maintaining satisfying interpersonal relationships. These disorders may produce severe impairments in some patients and should be rated accordingly; e.g., suicidal potential requires inquiry into the lethality and intent of any previous suicide attempts and may merit a "3" or "4." Psychiatric consultation is recommended for the inexperienced rater. Delirium (see DSM III-R definition) is assumed to have an underlying organic etiology and should be scored both according to the level of psychiatric impairment and in the appropriate medical category, e.g., delirium secondary to hyponatremia requiring hospitalization would merit a "4" for "Psych" and at least a "3" for "Metabolic" (depending on severity).

Psychosomatic disorders are often difficult to differentiate from "pure" medical disorders and judgement is ultimately required to endorse a psychiatric rating if it best fits the clinical picture.

References

(1) Linn BS, Linn MW, Gurel L. Cumulative illness rating scale. J Amer Ger Soc 1968;16:622-626.

(2) Folstein MF, Folstein SE, McHugh PR. Mini-mental state: A practical method for grading the cognitive state of patients for the clinician. J Psych Res 1975;12:189-198.

(3) American Psychiatric Association: Diagnostic and statistical manual of mental disorders, 3rd Edition - Revised. Washington, D.C., 1987.

(4) Bray, GA, et al. Evalaution of the obese patient. I. An algorithm. JAMA 1976;235:1487.

Scoring Sheet

Appendix 10. EORTC-QLQ-C30

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ____
Your birthdate (Day, Month, Year): ____
Today's date (Day, Month, Year): 31 ____

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 11. EORTC-QLQ-PR25

EORTC QLQ - PR25

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at all	A little	Quite a bit	Very much
31. Have you had to urinate frequently **during the day**?	1	2	3	4
32. Have you had to urinate frequently **at night**?	1	2	3	4
33. When you felt the urge to pass urine, did you have to hurry to get to the toilet?	1	2	3	4
34. Was it difficult for you to get enough sleep, because you needed to get up frequently at night to urinate?	1	2	3	4
35. Have you had difficulty going out of the house because you needed to be close to a toilet?	1	2	3	4
36. Have you had any unintentional release (leakage) of urine?	1	2	3	4
37. Did you have pain when you urinated?	1	2	3	4
38. Answer this question only if you wear an incontinence aid: Has wearing an incontinence aid been a problem for you?	1	2	3	4
39. Have your daily activities been limited by your urinary problems?	1	2	3	4
40. Have your daily activities been limited by your bowel problems?	1	2	3	4
41. Have you had any unintentional release (leakage) of stools?	1	2	3	4
42. Have you had blood in your stools?	1	2	3	4
43. Did you have a bloated feeling in your abdomen?	1	2	3	4
44. Did you have hot flushes?	1	2	3	4
45. Have you had sore or enlarged nipples or breasts?	1	2	3	4
46. Have you had swelling in your legs or ankles?	1	2	3	4

Please go to the next page

During the last 4 weeks:	Not at all	A little	Quite a bit	Very much
47. Has weight loss been a problem for you?	1	2	3	4
48. Has weight gain been a problem for you?	1	2	3	4
49. Have you felt less masculine as a result of your illness or treatment?	1	2	3	4
50. To what extent were you interested in sex?	1	2	3	4
51. To what extent were you sexually active (with or without intercourse)?	1	2	3	4

PLEASE ANSWER THE NEXT FOUR QUESTIONS ONLY IF YOU HAVE BEEN SEXUALLY ACTIVE OVER THE LAST 4 WEEKS:

52. To what extent was sex enjoyable for you?	1	2	3	4
53. Did you have difficulty getting or maintaining an erection?	1	2	3	4
54. Did you have ejaculation problems (eg dry ejaculation)?	1	2	3	4
55. Have you felt uncomfortable about being sexually intimate?	1	2	3	4

Appendix 12. Brief Pain Inventory - Short Form

1903

Date: (month) / (day) / (year)

Subject's Initials : _____

Study Subject #:

PLEASE USE BLACK INK PEN

Study Name: _____

Protocol #: _____

PI: _____

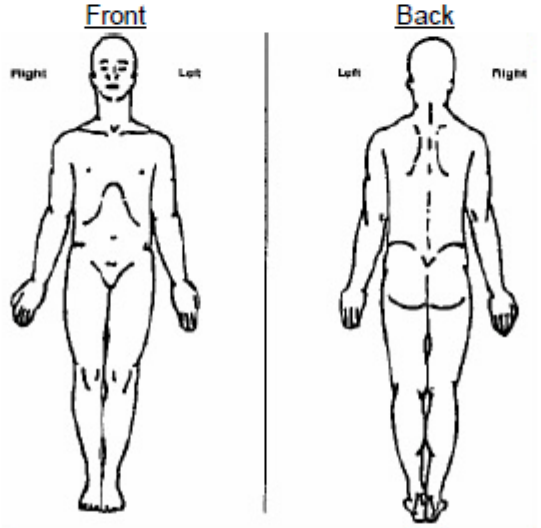
Revision: 07/01/05

Brief Pain Inventory (Short Form)

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

☐ Yes ☐ No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by marking the box beside the number that best describes your pain at its worst in the last 24 hours.

☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

No Pain — Pain As Bad As You Can Imagine

4. Please rate your pain by marking the box beside the number that best describes your pain at its least in the last 24 hours.

☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

No Pain — Pain As Bad As You Can Imagine

5. Please rate your pain by marking the box beside the number that best describes your pain on the average.

☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

No Pain — Pain As Bad As You Can Imagine

6. Please rate your pain by marking the box beside the number that tells how much pain you have right now.

☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

No Pain — Pain As Bad As You Can Imagine

Page 1 of 2

1903

Date: (month) / (day) / (year)

Subject's Initials : _____

Study Subject #:

Study Name: _____

Protocol #: _____

PI: _____

Revision: 07/01/05

PLEASE USE BLACK INK PEN

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please mark the box below the percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
☐ No Relief	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐ Complete Relief

9. Mark the box beside the number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

B. Mood

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

C. Walking ability

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

D. Normal Work (includes both work outside the home and housework)

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

E. Relations with other people

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

F. Sleep

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

G. Enjoyment of life

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

Page 2 of 2

Appendix 13. The Prostate Cancer Clinical Trials Consortium (PCCTC) bone scan data capture tool for clinical trials

PCCTC Bone Scan Assessment Tool
Baseline scan

Date (*dd/mmm/yyyy*): |__|__||__|__|__||__|__|__|__|

Patient identifier: |_____|

Is tracer uptake related to metastatic disease?

◯ **Yes** ◯ **No**

Note: If "No", do not fill out the form below

If yes, indicate the total number of lesions related to metastatic disease
(please select one)

◯ **1** ◯ **2-4** ◯ **5.9** ◯ **10-20** ◯ **>20**

Comments:		Investigator's signature	

Version 1.0

PCCTC Bone Scan Assessment Tool
Day 120 scan

Date (*dd/mmm/yyyy*): |__|__|/|__|__|__|/|__|__|__|__|

Patient identifier: |_____|

Is tracer uptake related to metastatic disease?

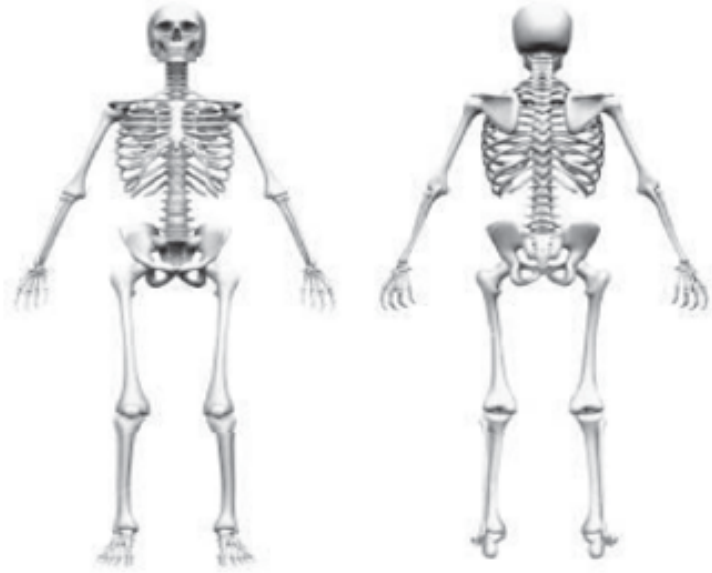
◯ **Yes** ◯ **No**

Note: If "No", do not fill out the form below

Draw site(s) of NEW lesion(s) on skeleton

Check region(s) of NEW disease:

- ☐ **Skull**
- ☐ **Thorax**
- ☐ **Spine**
- ☐ **Pelvis**
- ☐ **Extremities**



If yes, indicate the total number of NEW lesions compared to Baseline Scan
(please select one)

◯ **0** ◯ **1** ◯ **2** ◯ **3** ◯ **4** ◯ **5** ◯ **>5**

Note: Presence of new lesions at this time does not confirm progression

Clinical impression
(please select one)

◯ **Improved** ◯ **Stable** ◯ **Progression**

Comments:		Investigator's signature	

Version 1.0

PCCTC Bone Scan Assessment Tool

Day |__|__|__| scan

** To be compared to D120 scan **

Date (*dd/mmm/yyyy*): |__|__||__|__|__||__|__|__|__|

Patient identifier: |_____|

Is tracer uptake related to metastatic disease?

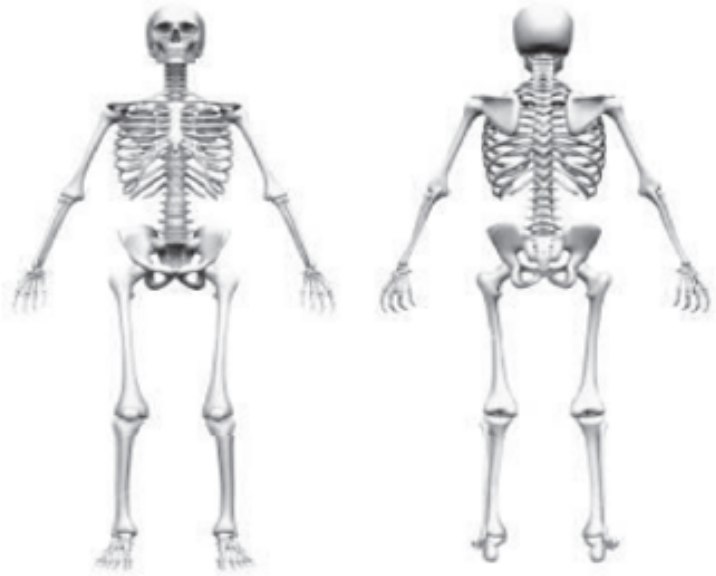
◯ **Yes** ◯ **No**

Note: If "No", do not fill out the form below

Draw site(s) of NEW lesion(s) on skeleton

Check region(s) of NEW disease:

- ☐ **Skull**
- ☐ **Thorax**
- ☐ **Spine**
- ☐ **Pelvis**
- ☐ **Extremities**



If yes, indicate the total number of NEW lesions compared to D120 Scan

(please select one)

◯ **0** ◯ **1** ◯ **2** ◯ **3** ◯ **4** ◯ **5** ◯ **>5**

Clinical impression

(please select one)

◯ **Improved** ◯ **Stable** ◯ **Progression**

Version 1.0

Page 1 of 2

PCCTC Bone Scan Assessment Tool

Day |__|__|__| scan

** To be compared to D120 scan **

Date (*dd/mmm/yyyy*): |__|__||__|__|__||__|__|__|__|

Patient identifier: |_____|

1. Are there 2 or more new lesions compared to the D120 scan?

◯ **Yes** ◯ **No**

If "Yes", proceed to question 2
If "No", the patient does not have radiographic progression by bone scan

2. Is this the first scan performed after the D120 scan?

◯ **Yes** ◯ **No**

If "Yes", proceed to question 3A
If "No", proceed to question 3B

3A. Were there 2 or more new lesions at the D120 SCAN compared to the BASELINE SCAN?	**3B. Does this scan confirm the presence of 2 or more new lesions since the D120 SCAN?**
◯ **Yes** ◯ **No**	◯ **Yes** ◯ **No**

If "Yes", patient has met conditions for radiographic progression by bone scan
If "No", the patient does not have radiographic progression by bone scan

Comments:		Investigator's signature	

Version 1.0 Page 2 of 2

Appendix 14. Diagnostic and Laboratory Evaluation for DILI

This appendix is based on the recommended work-up by Council for International Organizations of Medical Sciences (CIOMS), published in their Consensus in 2020, to be followed to identify a potential case of DILI.

It is not intended to be a comprehensive guide for the management of elevated LFTs. During the study, the investigator is responsible for determining the nature of the alteration in LFTs at any point during the study. If the investigator suspects DILI, the Sponsor Medical Representative must be informed as soon as possible.

DILI is a diagnosis of exclusion. In case of liver enzyme alterations, please consider the following comprehensive work-up and document the results appropriately including:

- A detailed, “liver-focused” medical history, including liver metastasis/liver cancer, alcohol-related liver disease, non-alcoholic steatohepatitis, liver cirrhosis, viral hepatitis, ischemic/congestive hepatic injury, vaccination, biliary obstruction, hematochromatosis, pancreatitis, recent systemic infection/sepsis, COVID-19 infection, auto-immune disease, alcohol abuse or drug abuse, and any other clinically relevant information.

- A complete list of concomitant medications, prior chemotherapy or hormonal therapy, antineoplastic drugs, herbal substances, nutritional supplements, complementary and alternative medicines, or exposure to any hepatotoxic agents.

- Imaging: abdominal imaging (e.g., Ultrasound, CT, and MRI)

- Serological tests:
  - Hepatitis A testing: IgM, Anti-HAV
  - Hepatitis B testing: Anti-HBc IgG, IgM, HBsAg, HBV DNA
  - Hepatitis C testing: Anti HCV, HCV RNA (PCR)
  - Hepatitis E testing: anti-HEV (IgG, IgM); HEV RNA
  - Alcoholic hepatitis: carbohydrate-deficient transferrin
  - Anti-Cytomegalovirus (CMV) IgM antibodies
  - Anti-Epstein Barr Virus (EBV) IgM antibodies
  - Herpes Simplex IgG, IgM
  - Auto-antibody and Immunoglobulin testing: ANA, ASMA, ANCA, p-ANCA, AMA
  - Quantitative IgG, IgM, and IgA
  - Metabolic disease: Alpha-1-antitripsin, ceruloplasmin, iron, ferritin, GGT, LDH, transferrin, transferrin saturation

- Other tests:
  - PT-INR
  - Serum Albumin
  - CK Values
  - Amylase, lipase