SYNOPSIS – PROTOCOL N° UC-0160/1716

A) TRIAL IDENTIFICATION	
SPONSOR – PROTOCOL CODE NUMBER: UC-0160/1716 **VERSION : 4.0 – 25 APR 2023 FR**	
STUDY TITLE: Prostate-cancer treatment using stereotactic radiotherapy for oligometastases ablation in hormone-sensitive patients – a GETUG-AFU phase III randomized controlled trial	
ABBREVIATED TITLE: PEACE 6 – ***Oligo*** PRESTO	
COORDINATING INVESTIGATOR: **Prof. Pierre BLANCHARD** Radiation Oncology Gustave Roussy Cancer Center – Villejuif - France CO-COORDINATING INVESTIGATOR: **Dr. Guillaume PLOUSSARD** Urology Department Clinique La Croix du Sud - Quint Fonsegrives - France	
NUMBER OF PARTICIPATING CENTERS (ESTIMATE): 30	**NUMBER OF PATIENTS:** 550

B) SPONSOR IDENTIFICATION	
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C) TRIAL GENERAL INFORMATION
INDICATION: Oligometastatic hormone-sensitive prostate cancer patients.
METHODOLOGY: Open label, double arm, randomized 1:1, multicenter, international phase III study.
PRIMARY OBJECTIVE: To assess the efficacy of ablative radiotherapy (SBRT applied to all oligometastases) administered to all gross tumor sites (metastases +/- prostate), in oligometastatic hormone-sensitive prostate cancer patients.

SECONDARY OBJECTIVE(S):

To evaluate the role of ablative radiotherapy on:

- Overall survival
- Prostate cancer specific survival
- Time to castration resistance
- Time to next symptomatic skeletal event
- Time to next symptomatic skeletal event at the treated metastatic bone sites
- Time to use of intermittent hormonal therapy, as per protocol recommendations
- Duration of intermittent hormonal therapy, in patients allowed to receive intermittent androgen deprivation therapy, as per protocol recommendations
- Time to secondary treatments (local or systemic)
- Acute and late toxicity of stereotactic radiotherapy of oligometastases
- Quality of life
- Cost-effectiveness analysis of the proposed therapeutic strategy

EXPLORATORY OBJECTIVES

- TO IDENTIFY THE ONCOGENIC DRIVERS OF DE OLIGO-METASTATIC PROSTATE CANCER.

DIAGNOSIS AND INCLUSION CRITERIA:

1. Histologically proven adenocarcinoma of the prostate (any T stage, Gleason score or PSA level);
2. Defined as M1 based on the presence of at least one bone metastasis;
3. Diagnostic workup including functional imaging (F or C-Choline-PET/CT or PSMA PET/CT or whole body MRI) – done prior to the start of hormonal therapy;
4. With up to 5 asymptomatic or paucisymptomatic metastatic sites including at least one bone +/- pulmonary lesion +/- nodal mestastases. Are counted as a "separate" metastatic site :
   - each bone lesion, whatever the location (including pelvic localization), except if two lesions show hyperfixation in the same bone and are located < 1cm from each other they can be counted as one lesion
   - each node or nodal area located outside the true pelvis with a small diameter of 1cm or greater or with univoqual abnormal function imaging (PET Scan hyperfixation or hypersignal in whole body MRI); if multiple nodes are in close vicinity (<1cm distance between them and <4cm in total distance including the nodes, amenable to one SBRT treatment) they can be counted as one lesion
   - and patients with lung metastasis can be included
5. Patients with a previous prostatectomy or radiotherapy to the prostate and/or pelvic lymph nodes are eligible provided they have no active disease within the irradiated areas, based on functional imaging findings;
6. Age ≥18 years;
7. ECOG ≤2;
8. Suitable for long term anti androgen therapy;
9. Patient not suitable for docetaxel or abiraterone can be included;
10. Patient that have started long term hormonal therapy are eligible if hormonal therapy has been initiated less than 2 months before randomization;
11. Patients must agree to use adequate contraception methods for the duration of study treatment and for 6 months after completing treatment.
12. Patient must have received the information sheet and signed the consent form;
13. Patients must be willing and able to comply with the protocol for the duration of the study including scheduled visits, treatment plan, laboratory tests and other study procedures;
14. Patient must be affiliated to the social security system.

NON-INCLUSION CRITERIA:

1. Patient with more than 5 metastatic sites;
2. Patient with isolated Rib hyperfixation on functional imaging without a clear correlate on morphological imaging
3. Patient with metastatic sites other than bone, lymph nodes or lung
4. Metastases not amenable to radiotherapy treatment with high/curative doses by multidisciplinary meeting [i.e. SBRT as per protocol or curative doses using moderate hypofractionation (55-60Gy/20) or conventional fractionation (≥74 Gy)] (e.g. gross epidural involvement, involvement of three contiguous vertebral bodies, major soft tissue involvement, and previous radiation treatment);

5. Metastases requiring immediate treatment due to significant pain (use of opioid medication), or at risk of fracture or neurological deficit;
6. Prior radiotherapy or focal ablative treatment (cryotherapy, radiofrequency ablation,…) to metastatic lesions
7. Patients previously treated by Hormonotherapy with castrate testosterone level <50 ng/dL or ≤0.50 ng/mL or 1.73 nmol/L prior use of ADT;
8. Prior invasive (except non-melanoma skin cancer) malignancy unless disease-free for ≥5 years;
9. Contra-indication to MRI (needed for spinal SBRT);
10. Persons deprived of their liberty or under protective custody or guardianship;
11. Patients unwilling or unable to comply with the medical follow-up required by the trial because of geographic, familial, social, or psychological reasons;
12. Participation in another therapeutic trial within 30 days prior to randomization.

PRIMARY ENDPOINT: Castration-resistant prostate cancer free survival, defined as the time from randomization to castration resistance or death from any cause. Castration resistance is defined as either biochemical progression or radiological progression, with serum testosterone being at a castrated level (<50 ng/dL or <1.7 nmol/L). See section 7.1 for complete definition of biochemical and radiological progression.

SECONDARY ENDPOINT(S):

- Overall Survival, defined as the time from randomization to death from any cause;
- Prostate Cancer Specific Survival, defined as the time from randomization to death from prostate cancer;
- Time to castration resistance, defined as the time from randomization to castration resistance, where deaths occurring with no castration resistance (i.e. unrelated to prostate cancer) are censored;
- Time to next symptomatic skeletal event, defined as the time from randomization to symptomatic bone fracture, the use of bone surgery or palliative bone radiotherapy and spinal cord compression;
- Time to next symptomatic skeletal event at the treated metastatic bone sites, defined as above but to a site irradiated as part of the experimental arm;
- Time to use of intermittent androgen deprivation therapy, as per protocol recommendations;
- Duration of intermittent androgen deprivation therapy, in patients allowed receiving intermittent androgen deprivation therapy, as per protocol recommendations;
- Time to use systemic chemotherapy (first line used after relapse);
- Time to use second line hormonal therapy (first line used after relapse);
- Time to use bone directed treatment after disease progression (bisphosphonate or denosumab);
- Time to use an antalgic palliative bone treatment (interventional radiology or radiotherapy);
- Acute and late toxicity of stereotactic radiotherapy of oligometastases;
    - Evaluated using the National Cancer Institute-Common Terminology Criteria for Adverse Events version 5 (NCI-CTCAE v5) at baseline before radiotherapy, week 6, end of treatment, and at every follow-up (every three months for the first three years and every 6 months thereafter, for two years).
    - Bone pain assessment using BPI at all visits.

- Quality of life at baseline at week 6, at M3, at M6, at 1 year, at 2 years, at 3 years, at 4 years, at 5 years, and at castration resistance, evaluated using:
    - A prostate specific tool: the expanded prostate cancer index composite (EPIC-short form).
    - Utility metrics: EQ-5D-3L (with the last questionnaire at time of diagnosis of castration resistance).
- Cost assessments, incremental cost-effectiveness ratio and quality of life adjusted life years (see ancillary cost-effectiveness project in section#12).

D) THERAPEUTICS REGIMENS

550 included patients will be randomized between 2 treatment arms (with a 1:1 ratio):

- Arm A (Experimental group, 275 pts): SOC + SBRT to oligomestastases,
- Arm B (Control group, 275 pts): SOC alone.

Definition of SOC (prior to randomization):

- Radiotherapy to the prostate in *de novo* metastatic patients
- Radiotherapy to the pelvic lymph nodes in patients with positive pelvic nodes (given as full dose to the positive lymph node and prophylactic dose to the pelvic nodal basin)
- Long term ADT +/- intermittent treatment (cf 6.2.2),
- Additional therapy following tumor board meeting: new generation hormonal therapy (abiraterone, enzalutamide, apalutamide or other approved) or chemotherapy (docetaxel).

With the following radiotherapy modalities :
→ SBRT is delivered using the following regimen: 30Gy (10 Gy x 3 fractions) for axial and appendicular bones and lymph node metastases if present. In case the dose cannot be safely delivered while maintaining a safe dose to the organs at risk, an alternate regimen (35Gy in 5 fractions of 7 Gy) can be used. For lung metastases doses will range from 3x18Gy for peripheral lesions ≤3cm to 5x10-11Gy for lesions central, near chest wall or >3cm, to 5x6-7Gy for ultracentral lesions).

Exception: if a bone lesion is close to the prostate in a *de novo* metastatic patient, then it is acceptable to treat the bone lesion AND the prostate at the same time using conventional fractionation (in which case the bone should receive ≥55Gy/20 fractions or ≥74Gy/37 fractions or similar fractionation)

→ In *de novo* metastatic patients: Prostate and seminal vesicle external beam radiotherapy using either 74-80Gy with conventional fractionation (in fractions of 2Gy) or using a hypofractionated regimen delivering 60 Gy (20 fractions of 3Gy) or stereotactic body radiotherapy (using doses of 35-40 Gy in 5 fractions or 42.1 in 7 fractions), and following institutional guidelines regarding dose constraints.

For the rare case of a patient having undergone radical prostatectomy <6months prior to randomization, this patient would be counted as *de novo* metastatic and could be treated as part of SOC with prostate bed radiotherapy up to 66-70 Gy using a conventional fractionation.

Randomization will be stratified by:

- Number of oligometastases 1-2 vs 3-5,
- Additional systemic treatment to ADT: none vs docetaxel vs new generation hormonal therapy (decided prior to randomization in tumor board),
  De novo metastatic prostate cancer vs recurrence following local therapy (defined as a recurrence occurring >6months after local treatment).

Nota bene:
Once they have reached the primary endpoint (castration resistance), patients randomized in the control arm are allowed to receive SBRT as a subsequent treatment if they are still oligometastatic at that time (5 or fewer metastatic sites).

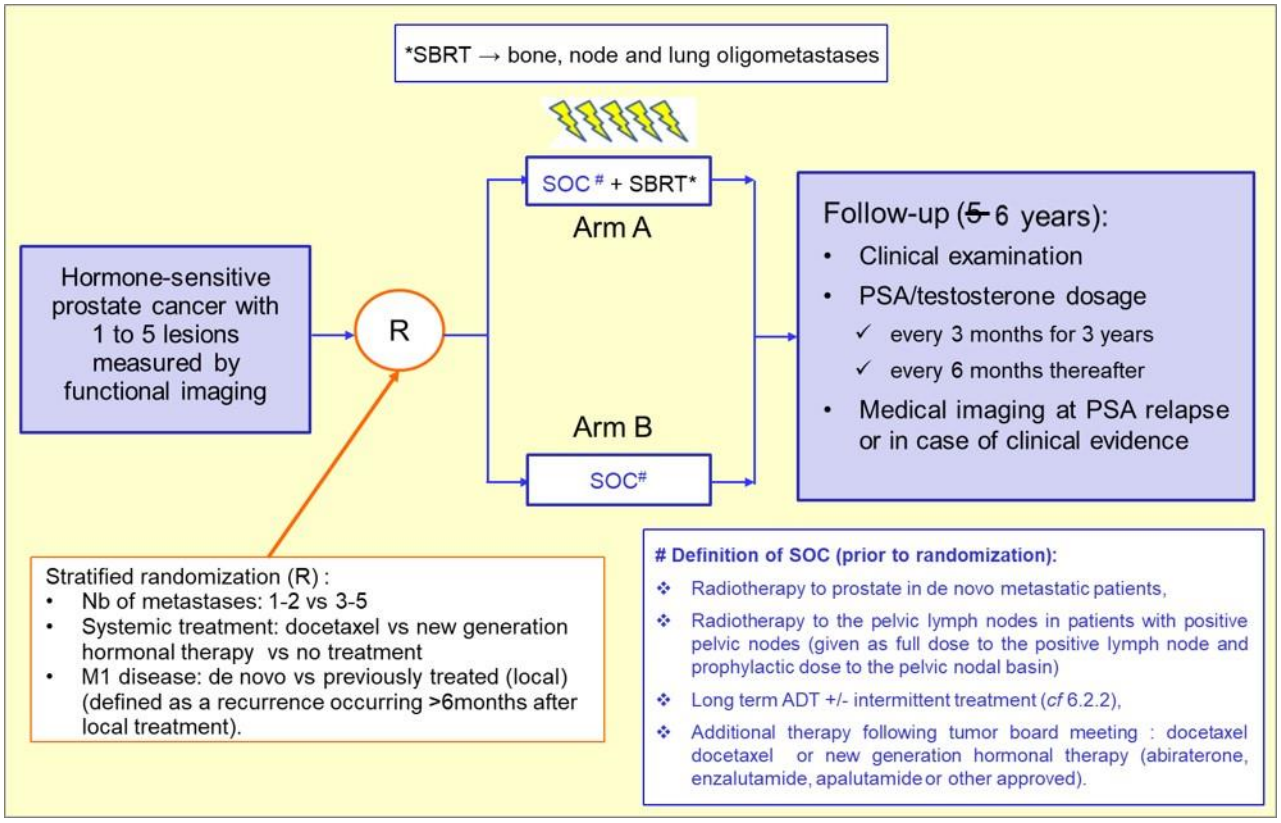

Figure 1: Study Schema

E) STATISTICAL ANALYSIS PLAN

REQUIRED NUMBER OF PATIENTS TO BE SCREENED / INCLUDED:

With **550 patients (275 in each arm) and 248 events**, a 5% level two-sided test of equal exponential survival (max length of follow-up=69.6 months, no dropout) will have a 80% power to detect a survival difference of between standard and experimental arms (median castration resistance free survival 36 months vs. 51.4 months), with the hypothesis of a constant hazard ratio HR = 0.7. This calculation takes into the presence of an intermediate analysis and an increasing inclusion rate over time (3 patients per months from M0 to M6 after the inclusion of the first patient, then 5 patients per month from M7 to M12, then 8 patients per month from M13 to M18 and then 13 patients per months until the end of the accrual period).

INTERIM ANALYSIS:

An intermediate analysis will be done after observing 50% of the number of expected events (i.e. 124 events).

Stopping rules using the spending function approach of Lan and DeMets with O'Brian-Fleming type spending function will be followed to conclude at each sequential analysis. The interim analysis boundary values are determined using the software EAST®.

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

Efficacy interim analysis (124 events, i.e. 50% expected events): p-value to reject H0≤0.003 (equivalent to the stopping boundaries Z-Scale: ±2.963).

Final analysis (248 events, i.e. 100% expected events): p-value to reject H0≤ 0.049 (equivalent to the stopping boundaries Z-Scale: ± 1.969).

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

Safety data will also be presented to the IDMC members, as well as data regarding the compliance to the treatments planned at randomisation, which are stratification factors.

IDMC:

The objective of the IDMC is to detect any unexpected adverse events associated with SRBT. An IDMC will be organized 18 months after the inclusion of the first patient in the study. Further IDMC meetings may be organized during the study, if required.
During the IDMC period, the registrations will not be stopped.

STATISTICAL ANALYSIS:

The primary analysis of castration resistance free survival will be estimated using the Kaplan-Meier method with Rothman's 95% confidence Intervals. A log-rank test stratified on the stratification factors will provide the statistical significance of the randomized treatment effect. Additionally, a Cox model adjusted on the stratification factors will provide an estimate of the randomized treatment effect (hazard ratio).
All other time-to-event endpoints will be analyzed similarly using a stratified log-rank test and a adjusted Cox model.

Safety analysis will be summarized using the Safety Population. Incidence of AEs will be summarized by system organ class and preferred term, and will be presented by treatment groups and overall. AEs will be summarized by grade, according to the worst grade experienced. In the summary of AE, an AE occurring more than once will be counted only once, using the worst grade experienced. Adverse events occurring within six months from randomization will be considered as acute adverse

event while those occurring after six months will be considered as late adverse events.
Quality of life data will be analyzed using generalized estimating equations to estimate the change of quality of life sub-domains over time.
F) SAMPLES COLLECTED FOR OPTIONAL TRANSLATIONAL RESEARCH
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** • Blood samples will be collected prospectively during the study from patients who provide their additional consent. At baseline, at 3 months, at 6 months and at disease progression, 2x10 ml of blood will be collected in EDTA tube from each patient.

G) TRIAL DURATIONS
INCLUSION PERIOD: 4,5 YEARS
TREATMENT PERIOD: 1-3 WEEKS
FOLLOW-UP: 6 YEARS
DURATION UNTIL PRIMARY ENDPOINT EVALUATION: APPROXIMATELY 13 MONTHS AFTER INCLUSION OF LAST PATIENT
OVERALL TRIAL DURATION (INCLUDING FOLLOW-UP): 10.5 YEARS

H) TRIAL FLOW-CHART

	Baseline		Treatment[1]	Follow up[3]								
			Week 6	M3	M6	M9	Y1 (M12)	Y2 (M15/M18/ M21/M24)	Y3 (M27/M30/ M33/M36)	Y4 (M42/M48)	Y5 (M60)	Y6 (M72)
Inclusion / non-inclusion criteria	X											
Signed informed consent	X											
PHYSICAL EXAMINATION												
BMI, PS (WHO)	X[2]		X	X	X	X	X	X	X	X	X	X
PSA, testosterone levels	X[3#]		X	X	X	X	X	X	X	X	X	X
Medical/Treatment history	X											
Toxicity/ AE assessment	X[2]		X	X	X	X	X	X	X	X	X	X
Pain assessment (BPI questionnaire)	X[2]		X	X	X	X	X	X	X	X	X	X
PARACLINICAL EXAMINATION												
Spinal MRI (if spinal bone metastases)	X[5]			X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]
F or C-Choline or PSMA PET/CT or whole body MRI	X[3]			X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]
TAP CT*	X[3]			X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]
Histological confirmation	X[7]											
TRANSLATIONAL RESEARCH												
Tumour samples	**X**											
Blood samples	**X**			X	X							
QUALITY OF LIFE												
EPIC-short form and EQ-5D-3L questionnaires	X[2]		X	X	X		X	X[6]	X[6]	X[6]	X[6]	X[6]
ECONOMIC STUDY												
Ressources consumed for cost calculation				X	X		X	X[6]	X[6]	X[6]	X[6]	X[6]

RANDOMIZATION

1. SBRT will start within 4 weeks after randomization
2. Within 2 weeks before randomization
3. Before hormonal therapy (less than 2 months before randomization)
4. If required during follow-up from M3 to Y6, medical imaging technique will only be used in case of biological relapse or if clinically indicated, otherwise left at the discretion of the treating physician. It is mandatory to use the same imaging modality for disease recurrence as for baseline.
5. Mandatory for patient with spinal metastases. Spinal MRI is used for SBRT planning (contouring/dosimetry) and can be done after randomization (but prior to SBRT delivery).

6. Only at M24, M36, M48, M60 AND M72 at castration resistance
7. At any time before randomization (no new biopsy is required in case of recurrence post treatment)

testosterone assessment at baseline is mandatory only for oligo-recurrent prostate cancer previously treated by Hormonotherapy
* the thorax/abdomen/pelvic CT-scan is mandatory only if the functional imagery is the whole body MRI.