SYNOPSIS

A) TRIAL IDENTIFICATION	
SPONSOR – PROTOCOL CODE NUMBER: UC - 0160/1702	
VERSION (NUMBER & DATE): VERSION 2.0 – SEPTEMBER 9TH, 2020	
TRIAL TITLE: An open label, randomized, phase III study, evaluating the efficacy of a **C**ombination of **A**palutamide with **R**adiotherapy and **LH**RH **A**gonist in high-risk post-prostatectomy biochemically relapsed prostate cancer patients	
ABBREVIATED TITLE: CARLHA-2	
COORDINATING INVESTIGATOR: PR STÉPHANE SUPIOT Institut de Cancérologie de l'Ouest Site René Gauducheau Service de radiothérapie Bd Jacques Monod F - 44 805 SAINT HERBLAIN CEDEX Phone: + 33 (0)2.40.67.99.13 Fax: + 33 (0)2.40.67.97.22 Email : stephane.supiot@ico.unicancer.fr	
NUMBER OF PARTICIPATING CENTRES (ESTIMATE): 20-25	NUMBER OF PATIENTS: 490

B) SPONSOR IDENTIFICATION	
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C) TRIAL GENERAL INFORMATION

INDICATION: High-risk biochemically-relapsed prostate adenocarcinoma following radical prostatectomy.

TRIAL DESCRIPTION/DESIGN: This is a parallel-group randomized open label phase III trial comparing the efficacy Apatulamide combined with concomitant prostate-bed salvage radiotherapy (SRT) and androgen deprivation therapy (ADT) versus concomitant prostate-bed SRT and ADT.

Patients will be randomized in a 1:1 ratio.

PRIMARY OBJECTIVE:

To evaluate the clinical benefit of adding the androgen receptor competitive inhibitor apalutamide in combination with a Luteinizing Hormone Releasing Hormone (LHRH) agonist concomitantly to salvage radiotherapy (SRT) after biochemical progression following radical prostatectomy in patients with high-risk prostate adenocarcinoma. The clinical benefit will be evaluated using the progression-free survival (PFS) rate at 5 years.

SECONDARY OBJECTIVES:

- To evaluate the prostate-cancer specific survival rate
- To evaluate the overall survival rate at 10 years
- To evaluate the biochemical relapse rate
- To evaluate the time to castration resistant prostate cancer
- To evaluate safety
- To assess patients' quality of life

DIAGNOSIS AND INCLUSION CRITERIA:

To be eligible, patient must fulfil all of the following inclusion criteria:

1. Patients must have signed a written informed consent form prior to any trial specific procedures
2. Age ≥ 18 years old and ≤ 80 years old
3. Histologically confirmed diagnosis of prostate adenocarcinoma treated primarily with radical prostatectomy
4. Pathologically proven to be lymph node negative by pelvic lymphadenectomy (N0) or lymph node status pathologically unknown (undissected pelvic lymph nodes [Nx])
5. Tumor stage pT2, pT3 or pT4* (*only in case of bladder neck involvement)
6. Patients should have no clinical and radiological signs (^{18}FCH-PET CT-scan or ^{68}Ga-PSMA-PET CT-scan) of metastatic disease. Patients with a local relapse detected on PET CT-scan can be randomized
7. ECOG performance status ≤ 1
8. PSA ≤ 0.5 ng/mL after radical prostatectomy
9. PSA ≥ 0.2 ng/mL and ≤ 2 ng/mL at the time of randomization with an elevation of PSA over three consecutive. PSA increases over a 2-months intervals minimum.
10. At least 3 months between radical prostatectomy and inclusion
11. High-risk features as defined by at least one of these characteristics: PSA at relapse > 0.5 ng/mL or Gleason score > 7 or tumor stage pT3b or resection margins R0 or PSA doubling time ≤ 6 months
12. Adequate renal function: serum creatinine < 1.5 x upper limit of normal (ULN) or a calculated corrected creatinine clearance ≥ 60 mL/min according to the Cockcroft-Gault formula, creatinemia < 2 ULN
13. Adequate hepatic function: total bilirubin ≤ 1.5 x ULN (unless documented Gilbert's syndrome), AST and ALT ≤ 2.5 x ULN
14. Patients with QTc prolongation < 500 ms*, inclusion should considered after close benefit/risk assessment and cardiologist advice

    **In patients with a history or risk factors for QT prolongation, and in patients receiving concomitant medicines that may prolong the QT interval, a cardiologist should assess the benefit / risk balance taking into account the potential risk of torsade de pointes before initiating treatment with apalutamide*
15. Patients must be willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations
16. Patients must be affiliated to the Social Security System

NON-INCLUSION CRITERIA:

Patient must not be enrolled if he/she fulfils any of the following non-inclusion criteria:

1. Histologically proven lymph nodes involvement at initial lymphadenectomy: pN1, pN2, pN3
2. Previous treatment with hormone therapy for prostate cancer
3. Histology other than adenocarcinoma
4. Surgical or chemical castration
5. Other malignancy except adequately treated basal cell carcinoma of the skin or other malignancy from which the patient has been cured for at least 5 years
6. Previous pelvic radiotherapy
7. History of Inflammatory bowel disease or any malabsorption syndrome or conditions that would interfere with enteral absorption
8. Uncontrolled hypertension (defined as systolic blood pressure (BP) ≥ 160 mmHg or diastolic BP ≥ 100 mmHg). Patients with a history of hypertension are allowed provided blood pressure is controlled by anti-hypertensive treatment
9. Clinically significant history of liver disease consistent with Child-Pugh class B or C
10. History of seizure or condition that may pre-dispose to seizure (including, but not limited to prior stroke, transient ischemic attack or loss of consciousness ≤ 1 year prior to randomization; brain arteriovenous malformation or intracranial masses such as schwannomas and meningiomas that are causing edema or mass effect)
11. Medications known to lower the seizure threshold must be discontinued or substituted at least 4 weeks prior to study entry
12. Severe or unstable angina, myocardial infarction, symptomatic congestive heart failure, arterial or venous thromboembolic events (e.g pulmonary embolism, cerebrovascular accident including transient ischemic attacks) or clinically significant ventricular arrhythmias within 6 months prior to randomization
13. Certain risk factors for abnormal heart rhythmas/QT prolongation: torsade de pointes ventricular arrhythmias (e.g, heart failure, hypokalemia, or a family history of a long QT syndrome), a QT or corrected QT (QTc) interval > 500 ms at baseline
14. Medications known to prolong QTc
15. Known hypersensitivity to apalutamide or to any of its components
16. Galactosemia, Glucose-galactose malabsorption or lactase deficiency
17. Inability or willingness to swallow oral medication
18. Individual deprived of liberty or placed under the authority of a tutor
19. Patients already included in another therapeutic trial with an experimental drug or having been given an experimental drug within the 30 days before inclusion

PRIMARY ENDPOINT:

The primary endpoint is the 5-year-progression free survival (PFS) accordingly to PERCIST 1.0 and RECIST 1.1 criteria.

PFS is defined as the time from the date of randomization to the date of first evidence of loco-regional recurrences, or distant metastases, or death from any cause whichever occurs first, or the date of last known follow-up alive without any such events.

Evidence of loco-regional recurrences is evaluated on PET CT (^{18}FCH-PET CT-scan or ^{68}Ga-PSMA PET)

Evidence of distant metastases is evaluated on PET CT (^{18}FCH-PET CT-scan or ^{68}Ga-PSMA PET)

Relapse at a distant metastatic site is defined as the occurrence of PET CT defined bone or soft tissue distant metastasis.

SECONDARY ENDPOINT(S):

Efficacy:

1. Cancer-specific overall survival is defined as the time from the date of randomization to the date of death related to prostate cancer or the date of last known follow-up alive.
2. Overall survival (OS) will be assessed at 10 years. OS is defined as the time from the date of randomization to the date of death from any cause or the date of last known follow-up alive.
3. Biochemical relapse-free survival will be retrospectively defined by the interval between the date of randomization and the date of the first PSA elevation following the 6-months treatment in both arms (PSA ≥ 0.5 ng/mL confirmed by two consecutive PSA increases over a 2-months interval).

   If no biochemical relapse is observed, the PSA concentration will be measured every 6 months for 5 years and every year thereafter.

   In order to compare PSA values, PSA assays must always be performed for each patient in the same laboratory.

   Following biochemical relapse, clinical staging (^{18}FCH-PET CT-scan or ^{68}Ga-PSMA PET) will be repeated every 6 months until local or metastatic progression is detected.
4. The time to castration resistance is defined as the time from the date of randomization to the date of appearance of castration resistance defined in the EAU guidelines (Cornford Eur Urol 2017). Castration-resistant prostate cancer (CRPC) is defined as castrate serum testosterone <50 ng/dl or 1.7 nmol/l plus one of the following types of progression:

   - Biochemical progression: Three consecutive rises in PSA 1 wk apart, resulting in two 50% increases over the nadir, and PSA >2 ng/ml

   - Radiologic progression: The appearance of new lesions: either two or more new bone lesions on bone scan or a soft tissue lesion accordingly to PERCIST 1.0 and RECIST 1.1 criteria.

Safety:

Frequency, nature and severity of adverses events will be assessed according to the NCI CTCAE version 5.0 (see Appendix 4)

Acute toxicity related to radiotherapy is defined as occurring during radiotherapy and up to 3 months after completion of radiotherapy.

Late toxicity related to radiotherapy is defined as occurring later than 3 months after end of radiotherapy.

The tolerance will be evaluated up until 10 years.

Patient-reported outcomes:

Quality of life will be assessed at baseline, at end of SRT, at end of treatment visit and at every follow up visit until disease progression by using:

- EORTC QLQ-C30 questionnaire
- EORTC QLQ-PR25 questionnaire
- IIEF-5 questionnaire
- IADL scale for patients ≥ 75 years old

D) INVESTIGATIONAL MEDICINAL PRODUCTS

PRODUCT NAMES AND ADMINISTRATION:
INVESTIGATIONAL MEDICINAL PRODUCT (IMP)

Drug name (INN)	Registered name	Pharmaceutical form	Administration route	Posology
Apalutamide		tablets	Oral	240 mg / day

AUXILIARY MEDICINAL PRODUCT (AMP)
In both arms, the treatment with LHRH agonist (e.g leuprolide, goserelin, triptorelin acetate) will be given for 6 months. Doses of LHRHa may vary due to availability of different brand names and pharmaceutical forms. It will be left to the discretion of the investigator.

THERAPEUTIC REGIMENS:
Patients after radical prostatectomy and biochemical progression will be randomized in a 1 :1 ratio between the two treatment arms:

- ✓ Arm A (Control arm): Salvage Radiotherapy + 6-months of LHRH agonist
- ✓ Arm B (Experimental arm): Salvage Radiotherapy + 6-months of LHRH agonist + 6-months of apalutamide

For patients in both arms:

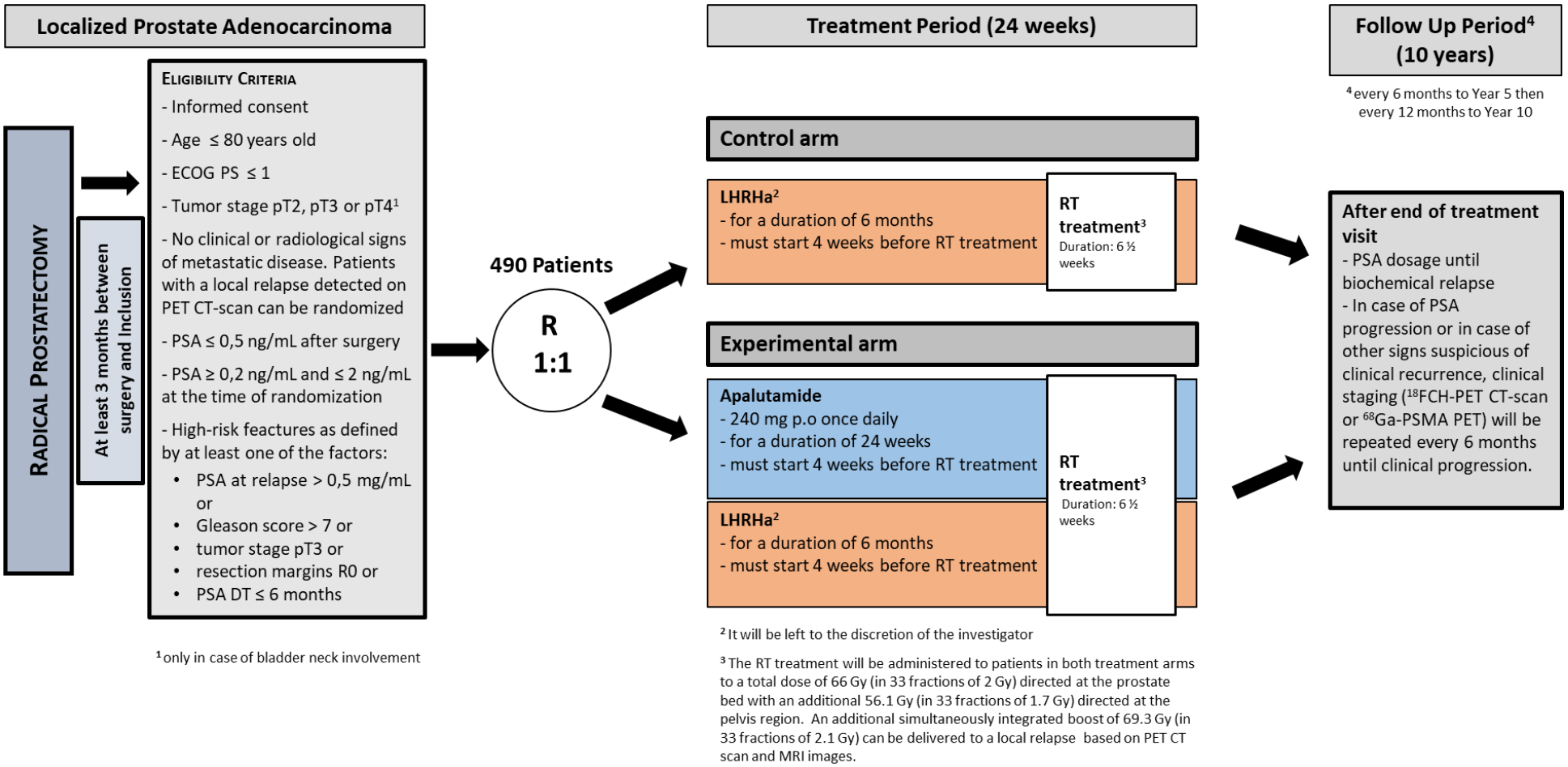
Treatment with LHRHa will start 4 weeks before the first RT fraction (i.e Day 1 of Week 1 of treatment period). The total duration of the LHRHa treatment is 6 months.
Doses of LHRHa may vary due to availability of different brand names and pharmaceutical forms.

SRT will start 4 weeks after the first administration of LHRHa.
The SRT treatment will be administered to a total dose of 66 Gy (in 33 fractions of 2 Gy) directed at the prostate bed with an additional 56.1 Gy (in 33 fractions of 1.7 Gy) directed at the pelvis region. The pelvis will be irradiated in all patients.
An additional simultaneously integrated boost of 69.3 Gy (in 33 fractions of 2.1 Gy) can be delivered to a local relapse based on PET CT and MRI images.

For patients in arm B:

Apalutamide: 240 mg daily, started the same day as the first LHRHa administration for 24 weeks. Treatment with apalutamide should be started within 4 weeks from randomization but at the same time as the first administration of LHRHa (i.e Day 1 of Week 1 of treatment period).

STUDY SCHEMA

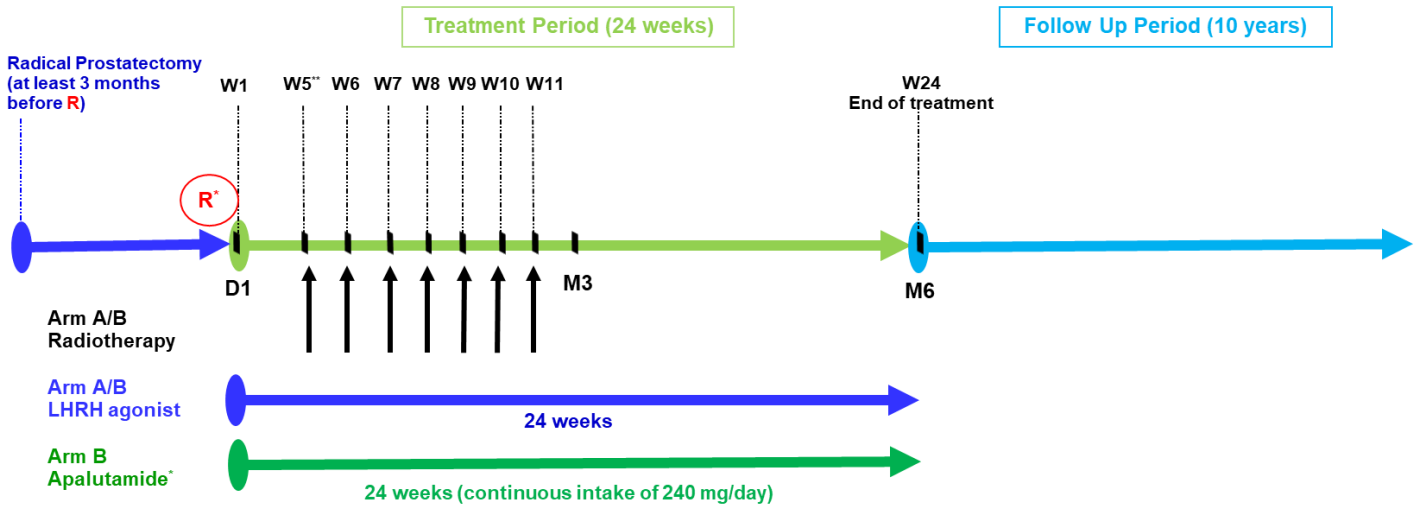


[1] only in case of bladder neck involvement

[2] It will be left to the discretion of the investigator

[3] The RT treatment will be administered to patients in both treatment arms to a total dose of 66 Gy (in 33 fractions of 2 Gy) directed at the prostate bed with an additional 56.1 Gy (in 33 fractions of 1.7 Gy) directed at the pelvis region. An additional simultaneously integrated boost of 69.3 Gy (in 33 fractions of 2.1 Gy) can be delivered to a local relapse based on PET CT scan and MRI images.

Schema of treatment



R*: randomization 1:1 / Treatment with Apalutamide may be started within 4 weeks from randomization but must start 4 weeks before radiotherapy treatment

D1: Day 1 of Week 1= first administration of LHRH agonist / Starting 4 weeks before radiotherapy treatment

W5** (Week 5) = Radiotherapy starting 5 weeks after 1st LHRH administration

E) STATISTICAL ANALYSIS PLAN

REQUIRED NUMBER OF PATIENTS TO BE SCREENED/INCLUDED:

In the GETUG 16 data[42], biochemical relapse-free survival at 5 years was close to 80% in the RT + ADT arm. In adjuvant radiotherapy studies *(Bolla et al. Lancet 2012; Thompson et al. JURO 2010)* clinical progression (local or metastatic or start of the LHRH agonist treatment) usually occurs 2 years after biochemical relapse. Moreover, retrospective data show that relapses at 7 years occur locally (6%) or distantly (23%) in all salvage radiotherapy patients *(Goenka et al. Int J Radiat Oncol Biol Phys 2012)*. Indeed, in higher-risk GETUG 16 patients (PSA at relapse > 0.5 ng/ml or pT3b or R0 or PSA DT ≤ 6 months), biochemical relapse-free survival was 67.7% at 7 years.

Based on these data, we can estimate that progression-free survival will reach 80 % at 5 years in the control arm (Arm A), in a higher-risk population (PSA 0.2-2 ng/ml post-prostatectomy + at least one high-risk criterion). It is expected that the 5-year clinical progression-free survival will be 90 % in the experimental arm (Arm B).

Wishing to be 95% (α<5%) certain that any difference is not due to chance and aiming at being able to detect such difference with 90% power (β =10%), we need to randomize 490 patients over a 42 month-period to be able to analyze 213 evaluable patients in each treatment arm (84 events of PFS), 426 in total + 64 patients (15%) we anticipate to be lost to follow-up (426 x 1.15 = 490).

STATISTICAL ANALYSIS:

All patients are analysed in the treatment arm assigned by randomization.

The primary objective of the phase III study is to evaluate the progression-free survival (PFS) at 5 years. PFS will be determined on the intention to treat (ITT) population and analyzed using Kaplan-Meier method. The log-rank test will be performed to compare progression-free survival between the two treatment arms, a bilateral test will be realized with a significance threshold of 5%. Median duration of progression-free survival will be presented for both treatment arms.

PFS calculated from the date of randomization until the date of first evidence of loco-regional recurrences or distant metastases or death from any cause whichever occurs first or the date of last known follow-up visit alive without any such events.

The primary endpoint analysis ("final analysis") is planned to take place when 84 events of PFS have been observed.

Secondary objectives:

All secondary efficacy endpoints will be reported in the intent-to-treat population.

(1) Cancer-specific overall survival at 10 years calculated from the date of randomization to the date of death related to prostate cancer or the date of last known follow-up alive, estimated by specific cumulative incidence function.

(2) Overal survival at 10 years calculated from the date of randomization to the date of death from any cause or the date of last known follow-up alive, estimated by the Kaplan-Meier method.

(3) Biochemical relapse-free survival calculated from the interval between the date of randomization and the date of the first PSA elevation following the 6-months treatment in both arms (PSA ≥ 0.5 ng/mL confirmed by two consecutive PSA increases over a 2-months interval).

(4) The time to castration resistance calculated from the date of randomization to the date of appearance of castration resistance defined in the EAU guidelines *(Cornford Eur Urol 2017).* Castration-resistant prostate cancer (CRPC) is defined as castrate serum testosterone <50 ng/dl or 1.7 nmol/l plus one of the following types of progression:

- Biochemical progression: Three consecutive rises in PSA 1 wk apart, resulting in two 50% increases over the nadir, and PSA >2 ng/ml
- Radiologic progression: The appearance of new lesions: either two or more new bone lesions on bone scan or a soft tissue lesion using the Response Evaluation Criteria in Solid Tumours

(5) Safety analysis will be performed using the safety population (any patients who has received at least one dose of apalutamide or at least one administration of LHRH agonist or at least one fraction of RT) will be analyzed for safety). Verbatim descriptions of adverse events will be mapped to MeDRA terms. Descriptive statistics will characterize the tolerance profile in each treatment arm using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTC-AE) version 5.0 toxicity scale (Appendix 1). Safety endpoints will be summarized descriptively for vital signs, adverse events, clinical laboratory parameters, and ECG. Serious adverse events and deaths, and patients discontinued from study treatment are listed.

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

(6) Quality of life will be measured using the EORTC QLQ-C30 questionnaire, EORTC QLQ-PR25 questionnaire, the IIEF-5 score and the IADL scale for patients ≥ 75 years old.

F) SAMPLES COLLECTED FOR TRANSLATIONAL RESEARCH

All patients enrolled in the study will be offered to participate in an optional biobanking for translational research wich aims to determine novel prognostic factors predictive of the response to radiotherapy with LHRH agonists and apalutamide.

SAMPLE TYPES: FFPE prostatectomy tissue block

SAMPLE QUANTITIES: In addition, 1 x 10 ml blood sample (Streck® tube) will be collected before start of treatment period and 30 days after start of treatment.

G) TRIAL DURATIONS

INCLUSION PERIOD: 42 MONTHS
TRIAL TREATMENT PERIOD: 6 MONTHS
FOLLOW-UP: 10 YEARS AFTER END OF TREATMENT VISIT
DURATION UNTIL PRIMARY ENDPOINT EVALUATION: 5 YEARS
OVERALL TRIAL DURATION (INCLUDING FOLLOW-UP): 14 YEARS

TRIAL FLOWCHART

STUDY VISITS N°	Baseline	RANDOMISATION	Treatment Period									End of Treatment Visit	Follow-up Period (10 years)	
	V0		V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	Every 6 months (+/- 2 weeks)	Every 12 months (+/- 1 month)
	Day -28 to Day -1		D1 of Week 1	D1 of Week 5	D1 of Week 6	D1 of Week 7	D1 of Week 8	D1 of Week 9	D1 of Week 10	Last day of RT	Week 24 (+/- 3 days)	Week 28 (+/- 3 days)	Year 1 to Year 5	Up to Year 10
INFORMED CONSENT	X													
ELIGIBILITY CRITERIA	X													
RADIOTHERAPY (RT) (ARM A / ARM B)				X	X	X	X	X	X	X				
LH-RH AGONIST (ARM A / ARM B)			Number of administrations may vary due to availability of different brand names and pharmaceutical forms											
APALUTAMIDE (ARM B)			Continuous intake of 4 tablets per day											
DISPENSING OF APALUTAMIDE			X							X				
DEMOGRAPHICS	X													
MEDICAL HISTORY	X													
PRIOR TREATMENT HISTORY	X													
PHYSICAL EXAMINATION	X		X	X	X	X	X	X	X	X	X	X	X	X
DRE	X		X[a]	X[a]						X[a]	X[a]	X[a]	X[a]	X[a]
ADVERSES EVENTS	X		X	X	X	X	X	X	X	X	X	X	ONLY RELATED TO RT AND/OR APALUTAMIDE	
CONCOMITANT MEDICATIONS	X		X	X	X	X	X	X	X	X	X	X		
BIOLOGICAL TESTS	X		X[b]	X[b]						X[b]	X[b]	X[b]	X	X
PSA/TESTOSTERONE	X		X[c]	X[c]						X[c]	X[c]	X[c]	X[c]	X[c]
ECG (12-LEAD)	X		X[d]	X[d]						X[d]	X[d]	X[d]		
OSTEODENSITOMETRY	X											X		
PET-SCAN	X[e]										X[f]	X[f]	X[f]	X[f]

STUDY VISITS N°	Baseline	RANDOMISATION	Treatment Period									End of Treatment Visit	Follow-up Period (10 years)	
	V0		V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	Every 6 months (+/- 2 weeks)	Every 12 months (+/- 1 month)
	Day -28 to Day -1		D1 of Week 1	D1 of Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Last day of RT	Week 24 (+/- 3days)	Week 28 (+/- 3days)	Year 1 to Year 5	Up to Year 10
QUALITY OF LIFE QUESTIONNARIES	X									X		X	X	X
VITAL STATUS													X	X
FURTHER ANTI-CANCER TREATMENT													X	X
ANCILLARY STUDIES														
BLOOD SAMPLE (CTC)			X[g]	X										
FFPE PROSTATECTOMY TISSUE BLOCK	X													

[a] Only in case of suspected progression
[b] TSH test (Arm B only)
[c] Only until biochemical relapse. The assessment of V1 must be done before ADT and the one of V2 before the first RT fraction.
[d] Arm B only
[e] Do not need to be done again if performed within 3 months prior the baseline visit
[f] Following biochemical relapse, clinical staging (^{18}FCH-PET CT-scan or ^{68}Ga-PSMA PET) will be repeated every 6 months until local or metastatic progression is detected
[g] Blood sample at V1 before 1st administration of treatment. If CTC enumeration is positive then collect an additional blood sample (10 mL) at V2 before 1st RT fraction