GETUG

French Study Group for Genito-Urinary Tract Tumours

Protocol AFU-GETUG 20/0310

EudraCT n°:2010-022037-29

PHASE III RANDOMISED STUDY TO EVALUATE THE BENEFIT OF ADJUVANT HORMONAL TREATMENT WITH LEUPRORELIN ACETATE (ELIGARD® 45MG) FOR 24 MONTHS AFTER RADICAL PROSTATECTOMY IN PATIENTS WITH HIGH RISK OF RECURRENCE.

V3.1 dated 05th May 2011

Version n°3.0 – date – approved by the CPP and the French Health Products Safety Agency

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CLINICAL TRIAL AUTHORISATION FOR PROTOCOL AFU-GETUG 20/0310

Title of trial: **Phase III randomised trial to evaluate the benefit of adjuvant hormonal treatment with leuprorelin acetate (Eligard® 45 mg) for 24 months after radical prostatectomy in patients with high risk of recurrence.**

CLINICAL TRIAL AUTHORISATION	
French Health Products Safety Agency (Afssaps)	**Date of authorisation: 07/01/2011**
	Afssaps ref: A101324-12
COMMITTEE FOR THE PROTECTION OF PERSONS	**Date of opinion: 31/01/2011**
NAME OF CPP: CPP KREMLIN-BICETRE	**CPP ref: 10-036**

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SYNOPSIS – PROTOCOL AFU-GETUG 20/0310

A) IDENTIFICATION OF THE CLINICAL TRIAL

SPONSOR CODE NUMBER: **AFU-GETUG 20/0310**

VERSION AND DATE: V3.1 DATED MAY, 05TH 2011

TITLE OF TRIAL: Phase III randomised trial to evaluate the benefit of adjuvant hormonal treatment with leuprorelin acetate (Eligard® 45 mg) for 24 months after radical prostatectomy in patients with high risk of recurrence.

ABBREVIATED TITLE: AFU-GETUG 20/0310

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ESTIMATED NUMBER OF CENTERS: 40 (some of which are abroad)	NUMBER OF PATIENTS: 700

B) IDENTIFICATION OF THE SPONSOR

NAME OF ORGANISATION: FNCLCC / BECT

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C) GENERAL INFORMATION ABOUT THE TRIAL

INDICATION: PROSTATIC ADENOCARCINOMA WITH HIGH RISK OF RECURRENCE.

METHODOLOGY: Phase III randomised, open, multicentre trial to evaluate the benefit of adjuvant hormonal treatment with leuprorelin acetate (Eligard® 45 mg) for 24 months after radical prostatectomy in patients with high risk of recurrence.

PRINCIPAL OBJECTIVE: Evaluation of effectiveness in terms of survival without metastases to 10 years, of adjuvant hormonal treatment with leuprorelin acetate (Eligard® 45 mg) for 24 months after radical prostatectomy in patients with high risk of recurrence.

SECONDARY OBJECTIVE(S):
- PSA evolution
- Evaluation of testosterone level
- Specific survival
- Overall survival
- Tolerance
- Quality of life (QLQ-C30 questionnaires)

INCLUSION CRITERIA:

1. Patients who have received the information leaflet and signed the consent form
2. ≥ 18 years of age with a life expectancy of at least 10 years
3. Performance Status (ECOG) ≤ 2
4. Radical prostatectomy (RP) with or without extended pelvic lymphadenectomy in the 3 months preceding inclusion
5. Histologically confirmed prostatic adenocarcinoma
6. Patients with postoperative Gleason score > 7, or ≥ 7 with the presence of high-grade Gleason patterns (5) and R0, N0 or Nx , M0
   or Patients pT3b, R0, N0 or Nx , M0 whatever the Gleason score
7. Postoperative PSA < 0.1 ng/mL (dosage perform within 2 months after surgery)
8. Neutrophils ≥ 1500/mm^3, platelets ≥ 100 000/mm^3
9. Bilirubin ≤ upper normal limit (this will not apply to subjects with Gilbert's syndrome, persistent or recurrent hyperbilirubinemia that is predominantly uncongugated in the absence of evidence of hemolysis or hepatic pathology);
   ASAT and ALAT ≤ 1.5 times upper normal limit;
   Creatinine < 140 µmol/l (or clearance > 60mL/min)
10. Patients affiliated to a social security scheme

CRITÈRIA FOR NON-INCLUSION:

1. Previous treatments for prostatic adenocarcinoma (HT or orchyectomy or CT)
2. Presence of metastases:
   - positive bone scintigraphy, including Patients with medullary compression
     and/or
   - abdominal-pelvic CT scan or MRI showing lymph node and/or visceral involvement.
3. History of cancer, with the exception of basal cell carcinoma or any other cancer treated in the 5 years before inclusion and in complete remission.
4. Incompatible concomitant treatment(s)
5. Hypersensitivity to other GnRH agonists and/or any of the excipients of Eligard®
6. Any illness or problem including geographic, psychiatric or psychological which is incompatible with being monitored during the trial
7. Persons deprived of their freedom or under supervision (including guardianship),
8. Patients already included in another therapeutic trial with an experimental drug or having been given an experimental drug within a period of 30 days.

PRINCIPAL EVALUATION CRITERION: The principal criterion is the evaluation of effectiveness in terms of survival without metastases to 10 years, of adjuvant treatment with leuprorelin acetate (Eligard® 45 mg) for 24 months after radical prostatectomy.

In case of biological reccurence, the presence of metastases will be evaluated with an abdominal-pelvic CT scan (or MRI) and bone scintigraphy.

SECONDARY EVALUATION CRITERIA:

- Evaluation of PSA progression
- Evaluation of testosterone level
- Evaluation of specific survival
- Evaluation of overall survival
- Evaluation of tolerance to the treatment
- Evaluation of quality of life (QLQ-C30 questionnaires)

D) DESCRIPTION OF THE EXPERIMENTAL DRUGS

DRUGS:

Drug name (INN)	Proprietary name(1)	Pharmaceutical form	Means of administration	Dosage
Leuprorelin Acetate	Eligard® 45mg	Powder + solvent for injectable solution - 45 mg	Subcutaneous injection	1 injection every 6 months for 24 months

(1) In the case of a generic drug, state only the INN, the choice of brand is left to the clinical investigation center .

TREATMENT PLAN:

The treatment will be randomly allocated between 2 groups of patients who have received the information leaflet and signed the consent form, and for whom the eligibility criteria have been verified:

- Arm A: Observation

- Arm B: Leuprorelin acetate (Eligard ®), 1 subcutaneous injection every 6 months for 24 months (making 4 doses) with the first injection at the time of randomisation

Immediate postoperative radiotherapy is allowed (each center must indicate at the time of the initiation visit whether or not it offers this option to all patients)

In the two arms, patients who present with a biological recurrence, that is PSA > 0.2 ng/mL will not be considered to be in clinical progression. They will receive treatment according to the guidelines (EAU 2010) and should perform the paraclinical exams (Abdominal-pelvic CT scan or MRI and Bone scintigraphy) every year. These patients will be monitored according to the protocol.

In the case of initiation of a new therapy, patients should perform the paraclinical exams before starting the new treatment.

In the case of bone pain, bone scintigraphy should be performed every year even if biological recurrence is not observed.

DURATION OF TREATMENT: 24 months

E) STATISTICAL CONSIDERATIONS

CALCULATION OF THE NUMBER OF SUBJECTS NECESSARY:

The principal evaluation criterion is survival without metastases. The aim is to increase survival by 10%, an increase considered to be clinically significant, being from 60% to 70% which corresponds to a hazard ratio of 0.7. A total of 700 patients (350 in each arm) and 250 events are required to have 80% ability to detect a difference with a bilateral Logrank test with $\alpha = 0.05$ and $\beta = 0.20$.
Based on recruitment by the research centers of patients with this profile for this trial, 175 patients per year, the inclusion of patients should be complete in 4 years.

An interim analyse is planned to test the null hypotheses. The decision rules will be determined by the O' Brien-Fleming sequential boundaries at the time of the analysis. The interim analysis is planned at the 125th event (50% of events) for 6.5 years after the start of the trial.

The final analysis is planned for 12 years after the inclusion of the first patient.

METHOD OF STATISTICAL ANALYSIS:

Categorical variables will be presented by frequencies, percentages and confidence intervals and will be compared between groups by Chi2 tests or Fisher's exact test.
Continuous variables will be presented by means, standard deviations, medians, and range and will be compared between groups by a non-parametric Wilcoxon test.

The survival rates will be estimated by the Kaplan-Meier method and presented with 95% confidence intervals. The logrank test, adjusted on the stratification factors will be used to compare the survival rates between the groups. All survival times will be calculated from the date of randomization.
Multivariate analyses will be performed using the Cox proportional hazards regression model adjusted on the stratification factors and are applied to study the factors of prediction and determine factors pronostic of the survival. The estimated hazard ratios will be presented with their 95 % confidence intervals.
All the statistical tests are two-sided and $p<0.05$ is considered as statistically significant. The Capture/System software (Clinsight) will be used for data management and the statistical analyses with be done with STATA.

F) BIOLOGICAL MATERIALS COLLECTED FOR THE BIOMEDICAL RESEARCH

TYPES OF SAMPLE(S): NA

G) EXPECTED DURATION OF THE TRIAL

PERIOD OF INCLUSION: 4 YEARS

PÉRIOD OF TREATMENT: 24 MONTHS

PÉRIOD OF OBSERVATION: 8 years

EXPECTED LENGTH OF TIME UNTIL ANALYSIS OF THE PRINCIPAL OBJECTIVE: 12 YEARS

OVERALL DURATION OF THE TRIAL (INCLUDING PERIOD OF OBSERVATION): 12 YEARS

H) RESEARCH SUMMARY TABLE

VISITS	Treatment period [1]					Follow-up after treatment							
Visits	**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**
Visit dates	**D0 Inclusion assessment**	**M6**	**M12**	**M18**	**M24**	**M36**	**M48**	**M60**	**M72**	**M84**	**M96**	**M108**	**M120**
Criteria for inclusion/non-inclusion	X												
Consent form signed	X												
Randomisation (R)	X												
CLINICAL EXAMINATION													
Clinical examination: Height, Weight, PS (WHO)	X	X	X	X	X								
Vital signs	X	X	X	X	X								
Concomitant treatments		X	X	X	X								
Toxicity		X	X	X	X	X	X	X	X	X	X	X	X
PARACLINICAL TESTS													
Abdominal-pelvic CT scan (or MRI)	X		X[3]		X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]
Bone scintigraphy	X		X[3]		X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]
BIOLOGICAL ASSESSMENT													
CBC, Platelets	X	X	X	X	X								
Blood electrolyte test (Na,Ca , K, Mg)	X	X	X	X	X								
Hepatic assessment (Bilirubin, ASAT, ALAT, ALP)	X	X	X	X	X								
Renal assessment (Creatinin, Urea)	X	X	X	X	X								
PSA	X	X	X	X	X	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
Testosterone level	X	X	X	X	X								
Lipid assessment: total chollesterol, HDL, LDL, triglycerides	X	X	X	X	X								
Fasting glycemia	X	X	X	X	X								
TREATMENT (Arm B)													
Leuprorelin	X	X	X	X									
TRANSLATIONAL RESEARCH													
QUALITY OF LIFE QUESTIONNAIRE													
QLQC30	X	X	X	X	X		X		X				

1- Visits mandatory for Arm A and B patients. Arm A patient will not receive the treatment.
2- Every 6 months
3- Exams to be perform only for patients with PSA > 0.2 ng/mL and patients who present with bone pain (even if biological reccurence is not observed).

CONTENTS

The French national federation of cancer centers - La Fédération Nationale des Centres de Lutte Contre le Cancer – sponsor, declares that trial AFU-GETUG 20/0310 will be conducted in accordance with the Protocol, the French public health code articles 1121-1 onwards, its decrees and orders in force and the Good Clinical Practice guidelines of 24th November 2006.

1. SCIENTIFIC JUSTIFICATION AND GENERAL DESCRIPTION OF THE RESEARCH

1.1 Name and description of the experimental drug(s)

This protocol aims to evaluate the drug Eligard® 45mg (INN: Leuprorelin acetate) indicated for the treatment of advanced stage hormone-dependent prostate cancer.

Leuprorelin acetate is a synthetic nonapeptide, an agonist of naturally occurring gonadotrophin releasing hormone (GnRH) which with prolonged administration inhibits the secretion of hypopyseal gonadotrophins and suppresses the synthesis of testicular steroids in humans.

1.2 Rationale for the trial

Definition

High risk prostate cancers (HRPC) are biologically defined by their high recurrence potential which compromise primary treatment results and expose patients to a higher risk of mortality. From the clinician's point of view, HRPC are tumours with high probabilities of relapse when treated with either radical prostatectomy-RP or external beam radiation-EBR. The risk of recurrence is usually evaluated based on the following items: clinical stage, prostate specific antigen (PSA) levels and pre-operative Gleason score. [1] None of these variables by itself can objectively define a HRPC.[2, 3, 4, 5] An analysis incorporating the three mentioned elements have allowed clinicians to better define the groups of patients with localized prostate cancer: 3 groups have been identified as follows: low, moderate and high risk of recurrence (Table 1: d' Amico's risk groups).

Table 1. Localized prostate cancer risk groups (d'Amico)

Recurrence risk	Low (a)	Intermediate	High (b)
Clinical stage	≤ T2a	T2b	≥ T2c
Gleason score	< 7	7	> 7
PSA (ng/ml)	< 10	10 - 20	> 20
5y PSA failure free survival after RP or EBR	80%	60%	30%

(a) A low risk implies all 3 criteria.
(b) High risk implies verification of at least one criterion.

Prostate cancer is the most frequent cancer in France and the second cause of mortality. In 2005, 62245 new cases and 9202 prostate cancer related deaths were reported, 8900 were reported in 2006. [1] Around one third of these 62 000 patients, i.e. 23 000 patients have been treated with a radical prostatectomy in 2005.
Patients with an intermediate to high risk prostate cancer, candidate to surgery, will have an extended lymphadenectomy and radical prostatectomy.
At IMM, among the last 3000 radical prostatectomies done within the last 7 years, 400 (13%) had post op criteria of high risk of systemic progression, i.e. patients with seminal vesicle involvement (pT3b R0 Nx-0 M0, with post op PSA< 0.1) and/or Gleason score ≥ 8 (pNx-0 M0, with post op PSA< 0.1),
Standard of care for HRPC and locally advanced prostate cancer are radio-hormone therapy or surgery.

Radio-hormone therapy (RT-HT).

[1] *Guérin S, Doyon F, Hill C.: The frequency of cancer in France in 2006, mortality trends since 1950, incidence trends since 1980 and analysis of the discrepancies between these trends. Bull Cancer. 2009 Feb;96(1):51-7.*

- **Biological rationale for the radio-hormone therapy association.**

Androgen deprivation causes rapid cytological modifications in prostate tumours (quiescence, apoptosis).[1] Initial information on the interaction of radio-hormone therapy was obtained in animal experimental models; Zietman et al verified a feasible dose diminution which allowed them to control 50% of tumours in their animal model. [2,3]
A significant and additional (synergy) apoptosis was verified when using the Rx-HT combination, although the effect was only confirmed when hormone therapy preceded radiation and its effect did not persist in time.[4] The determination of a supra-additive effect for the two therapeutic modalities has been also verified through cellular model analysis. The LNCaP cell lines can be grown in a special environment, with or without androgens. Cell lines undergoing radiation show similar survival curves when they are grown with or without androgen deprivation. The effect appears purely additive and relates only to a slower tumour growth.[5] In another study, the combination of androgen deprivation and radiotherapy was shown to permanently decrease cell proliferation capacity even if the rate of testosterone becomes normal at the end of the study.[6]
Therefore, it is likely that the combined treatment outcome observed in clinical studies can be explained by a simple addition of effects, related essentially to slow tumour proliferation, or perhaps an addition of cytotoxic actions. If the outcome is related to a simple additional effect, the advantage of a combined therapy could also be observed with a surgical local treatment.

- **Superiority of combined local and systemic treatment *vs.* local treatment only.**

Several randomized trials have assessed the importance and benefits of adjuvant androgen deprivation (AD) to radiation in HRPC. Four studies provide the number of patients, statistical power and sufficient follow-up to objectively state the concept of RT-HT as a therapeutic standard in HRPC.[7] Of note, definitions of High risk population in these studies are heterogeneous and do not fully apply to D'Amico's criteria. Most of them considered as High Risk , are patients with a >cT2 tumour.The objectives of the timely studies RTOG 85-31[8] and EORTC[9] were to verify the real benefits of associated AD to radiation in terms of systemic treatment of HRPC. Furthermore, the aim of the study RTOG 86-10 [10] was to evaluate tumour reduction achieved with AD prior to radiation therapy, in order to obtain higher local control of the disease. These studies have all reported benefits in terms of local control of the disease, biochemical relapse and time-to-metastatic progression. The EORTC study highlighted an important benefit on overall survival: at 5 years, 62% in radiotherapy- only arm versus 78% for RT-HT (p = 0. 0002). The RTOG 85-31 study showed a significant benefit in overall survival at a follow-up period of 10 years. At 5 years, overall survival for patients treated exclusively by radiotherapy and RT-HT were 71% and 76%, respectively. At 10 years, overall survival for the same groups were 38% and 47%, respectively (p = 0.0043).
However, for the subpopulation of patients with Gleason score 8-10, whatever the size of the tumour, a significant difference in survival was already verified at 5 years (53% versus 67%; p = 0.0061).

Table 2: radiotherapy ± AD in clinical high risk patients

Overall Survival	**5 years**	**10 years**
EORTC[14]	62 % vs 78 % (p = 0.0002)	-
RT 0485 -31[13]	71 % vs 76 % (p = ns)	38 % vs 47 % (p=0.0043)
Subpopulation: Gleason ≥ 8	53 % vs 67 % (p = 0.0006)	Not reported

- **Type of hormone deprivation: LH - RH agonist**

All major reported studies have used LH - RH agonists as AD and therefore these drugs currently represent the benchmark in RT-HT. One large study associated with radiation with the anti-androgen bicalutamide at a dose of 150 mg/day during 5 years. This study has shown a benefit in survival for the combined treatment compared with exclusive radiation.[11] [12] That said, this study presents methodological biases, which might preclude its evidence based application.

- **Androgen deprivation duration: long term *vs.* short term**

Two trials compared directly a long term AD (2 or 3 years) versus a short term AD (4 or 6 months). The RTOG 92-02 study[13] included patients with prostate adenocarcinoma at clinical stages T2c to T4 without positive lymph nodes and initial PSA ≤ 150 ng/mL. All patients received conventional radiation. Even when no benefits in terms of overall survival were observed, a specific survival improvement was verified in the long term AD arm. Furthermore, for patients with a Gleason score 8 to 10, the benefit of the long term AD was higher. In this subgroup, a statistically improved survival was observed (5 years: 81% *vs*. 70.7%; p = 0.044). EORTC [14] compared radiation associated with AD (LH - RH agonists induced) for 6 or 36 months (n = 487). This study included patients with locally advanced disease: T1c-2bN1-2, pN1-2, or T2c-4, 2 N0, M0; and it achieved a median follow-up of 5.2 years. No matter which outcome criteria is deployed (overall survival, disease-free survival), the long term AD holds a significant benefit to patients. Today, there is no study confirming an objective superiority of a 3-year period of AD vs. one of 2 years:
"So, for high risk cancer patients, the addition of long term LH-RH agonists to radiotherapy has significantly improved survival at 5 and at 10 years". This combination is now the standard treatment for high risks cancers."

***Rationale for the surgical treatment*.**

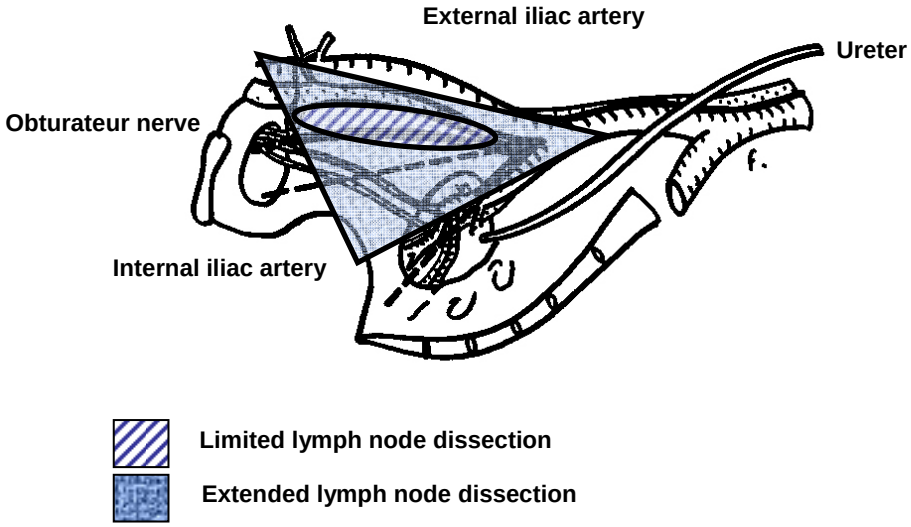
- **Indication of surgery as monotherapy surgery in high risk indication**

The European Association of Urology (EAU) guidelines state that surgery alone is a feasible therapeutic option for patients with good performance status, in selected cases of locally advanced cancers, considered as high risk with the following definitions: PSA < 20 ng/ml, clinical ≤ cT3a, and preoperative biopsy Gleason score ≤ 8.

- **Surgical technique description: surgery and lymph node dissection.**

Technically, the radical prostatectomy (PR) in HRPC implies an extended lymphadenectomy, and a broad dissection of prostate at the apex, the bladder neck, seminal vesicles and neurovascular bundles in order to avoid the risk of positive surgical margin.[15, 16] Cancer control should be certainly accomplished and no functional outcome should be placed before the oncologic result. The surgery is to be performed by an experienced team in order to expose patients to the same potential morbidity of a radical prostatectomy performed for a localized tumour.[17,18]
The extended pelvic lymph node dissection (EPLND) can be performed with an open or a laparoscopic approach, excising the fibrofatty and lymphatic tissues within the anatomical landmarks: superiorly the bifurcation of the common iliac artery where both ureters are identified, and inferiorly the Cooper's ligament. Lymphadenectomy includes laterally the external iliac vein, and medially the bladder. The lower limits involve the obturator fossa, and posteriorly the hypogastric artery and its proximal branches. (Figure 1)

Figure 1. Lymph node dissection anatomical landmarks



- **Overall cancer control with radical prostatectomy**

The radical prostatectomy´s cancer control efficiency and effectiveness for locally advanced prostate cancer is difficult to assess due to the heterogeneity of the reported series and the lack of documentation on the reported adjuvant or salvage treatments. Van der Ouden et al., in a review of 8 series, reported a specific 5-10 years 83 to 92% and 72 to 82 % survival.[19]
More recently, Ward et al presented a series of 5652 prostatectomies done at Mayo Clinic, in which 842 (15%) patients showed a **c**T3 tumour. Sixty-five percent (65%) of patients had received radiotherapy or AD. At 10 years, biochemical recurrence-free survival was 43%, 73% were free of local or systemic disease recurrence, and 10% of patients had died of prostate cancer (average 10.3 years follow-up). Carver et al presented the experience of the MSKCC. One hundred and seventy six patients out of 5182 operated patients had **c**T3 (3%) tumour. At 10 years, biochemical recurrence-free survival was 44% (95%CI 53-35%), the probability of freedom from clinical failure was 76% (95%CI 67-85%) and the probability of death from prostate cancer was 15% (95%CI 8-22%), with an average 6.4 years follow-up[20].

However these results reflect the results of surgery for preop high risk criteria (clinical T3). Indeed, final pathology has found a better prognostic factor of intraprostatic tumour pT2 in 9 to 44 % of cases of HRPC.[21,22]

The advantage of the radical prostatectomy is to give the **final pathological status**. Pathological upgrading and downgrading have been reported in 25 to 45%.[23]
Actuarial 10-year biochemical progression-free survival probabilities were 77% (95% CI 74 to 79) for Gleason sums 2 to 6, 64% (95% CI 56 to 71) for Gleason sum 3 - 4, 50% (95% CI 39 to 60) for Gleason sum
4 -6 and 32% (95% CI 25 to 40) for Gleason sums 8 to 10 disease. The log rank test comparing survival functions across Gleason sums was significant (p ≤0.0001).
Actuarial 10-year biochemical progression-free survival probabilities were 79% (95% CI 76 to 82) for organ confined disease, 62% (95% CI 51 to 72) for disease with extraprostatic extension without cancerous surgical margins, 53% (95% CI 47 to 59) for disease with extraprostatic extension and cancerous surgical margins, 26% (95% CI 18 to 35) for disease with seminal vesicle involvement and 12% (95% CI 3 to 27) for disease with lymph node metastases. The log rank test across pathological stages was significant (p _0.0001).[24]
Therefore, more than 70% of the patients with PT3B (seminal vesicle involvement) and/or patients with Gleason ≥8 are at high risk of relapse at 10 years.

- **Androgen deprivation and surgery**

  - **Neoadjuvant AD**

The association of neoadjuvant AD and surgery did not evidence clear benefits. Randomized studies (HT vs placebo) showed a decrease in the rate of positive margins. None of the published studies has shown improvement on BCR-free, specific or overall survival.[25,26,27, 28, 29]

- **Adjuvant AD**

  - **PN0 patients**

Wirth et al. reported the results of a randomized study with flutamide in 309 patients pT3 - 4 N0. Adjuvant flutamide treatment delayed biochemical progression significantly 75% (HR: 0.51, 95% CI: 0.32-0.81). No improvement in overall survival was verified in this study at a follow-up period of 6.1 years.[30]
Mc Leod at al. reported the results of a randomized, double-blind, placebo-controlled trial study with adjuvant biaclutamide. With a follow up of 6 years, no improvement in overall survival was reported for the pT3[31]
In the SWOG 9921 study, 240 patients pT3b or Gleason > 7 N0 received two years of AD (goserelin + bicalutamide) +/- mitoxantrone and prednisone. In 2007, SWOG 9921 was closed to further accrual after three cases of acute myelogenous leukaemia (AML) were reported in the mitoxantrone treatment arm. However, the study provides interesting results regarding the adjuvant combined androgen blockade. The 5-year overall survival rate was 97.2% (92.2 – 99)[32]
No randomized prospective study has been published so far with LH-RH agonists.

  - **Patients with positive lymph nodes**

The outcomes of patients with positive lymph nodes in final pathology were addressed in the Messing study. Ninety-eight patients treated with radical prostatectomy and featuring positive lymph nodes in final pathology were randomized to an immediate AD or monitoring and AD indication at time of progression. After a median follow-up of 12 years, patients treated with early AD showed a significant improvement in overall survival (hazard ratio 1.84 [95 % CI 1.01-3.35] p = 0. 04).[33]

- **Adjuvant radiotherapy to radical prostatectomy.**

Three prospective randomised trials have assessed the role of immediate post-operative radiotherapy.
The SWOG 8794 trial randomized 425 patient pT3, and the updated results, with a median follow-up of 11.5 years showed that adjuvant radiation significantly improved **metastasis-free survival**, with a 15-year metastasis-free survival of 46 % *vs*. 38 % (p = 0.036) and a 15-year overall survival of 47 % *vs*. 37 % (p = 0.053).[34] **The 10-year metastasis-free survival is estimated at 60%.** However, the inclusion criteria for the study were very large, PSA level at time of inclusion was indifferent (the determination of the PSA was not available as a routine in the preparation of the Protocol) and 8.5 % of patients had neo-adjuvant AD. Therefore, the population of the study is composed by a mixture of patients treated with adjuvant and salvage therapies. One could estimate that more than one third of patients in this series received treatment with salvage intent.
The EORTC 22911 study (1005 patients), compared immediate post-operative radiotherapy (60 Gy) with delayed radiotherapy until local recurrence (70 Gy) in patients classified as pT3pN0 after retropubic radical prostatectomy. Immediate post-operative radiotherapy proved to be well tolerated, with a risk of grade 3-4 urinary toxicity being less than 3.5 %. The study concludes that immediate post-operative radiotherapy, significantly improves five-year clinical or biological survival: 72.2 % vs. 51.8 % (p< 0.0001).[35,36] However, the EORTC study has not yet demonstrated improved metastasis-free and cancer-specific survival in this cohort of patients. The most suitable candidates for immediate radiation therapy might be those with multifocal positive surgical margins and a Gleason score > 7. In this study the inclusion criteria were too large. First of all, a significant number of patients in the control group was eventually treated (cross over). Second, 10% of patients had neoadjuvant AD. Third, 10% of patients treated had a post op PSA level higher than 0.2 ng/mL, the latter was a violation of the inclusion criteria for the mentioned protocol. These three elements all together, as in SWOG 8794 have a mixed population of patients including adjuvant and salvage treatment.

The conclusions of the ARO trial 96-02 (385 patients) echoed those of EORTC since after a median follow-up of 54 months, biochemical progression-free survival was significantly improved in the radiotherapy group: 72% *vs*. 54% (p = 0.0015).[37] When facing a prostatic cancer pT3pN0M0, it is not proved that there is a benefit to irradiate patients without surgical margins. In a pT2pN0M0 cancer with positive surgical margins, revision of the pathological slides should be mandatory and a discussion with the pathologist should focus on the significance of these margins.

Thus, the EAU guidelines updated in 2009, recommend two options for patients classified as pT3 pN0 with a high risk of local failure after radical prostatectomy due to capsular rupture, positive margins and/or invasion of the seminal vesicles, who present with a PSA level of < 0.1 ng/mL one month after surgery:
• either an immediate radiotherapy to the surgical bed upon recovery of urinary function

• or clinical and biological monitoring followed by salvage radiotherapy when the PSA exceeds 0.5 ng/mL.

For the remaining patients, adjuvant radiotherapy to surgery is not considered as a standard option of treatment for pathological high risk cancers;

- **Comparison of the PR-HT *vs*. RX-HT associations.**

A prospective multicenter study comparing surgery-AD association treatment with RT-HT is difficult to perform, because of the important differences between the two local treatments. A Japanese team opened the path in this area and they have reported a prospective multicenter series comparing 46 patients treated with RP-HT *vs*. 49 patients treated with Rx-Hx (40-50 Gy to the whole pelvis and 20 Gy boost to the prostatic area). At a median follow-up of 8.5 years, there was no difference in specific and overall survival between these groups.[38] The results of this study should be analyzed with caution, as the reality of prostate cancer in Asia seems to be different to that of the western countries, and considering the very low number of patients in each cohort.

Rationale for adding AD to radical prostatectomy in patients with a pathological high risk of progression

Among the 20 000 radical prostatectomies performed in France, around 10% (2000) are considered as pathological high risk patients. This population is much better defined after radical prostatectomy than after clinical evaluation only. Despite this fact, In patients with high risk of systemic progression, *i.e*. patients with seminal vesicle involvement (pT3b R0 Nx-0 M0, with post op PSA< 0.1) and Gleason score ≥ 8 (pNx-0 M0, with post op PSA< 0.1), no clear adjuvant strategy is defined after radical prostatectomy although a clear benefit of adding AD to radiotherapy has been known for several years. In a non-randomized comparison, overall survival was superior in men with seminal vesicle involvement treated with radical prostatectomy and immediate hormonal manipulation compared to those with delayed androgen withdrawal.[39] No randomized trials on adjuvant hormonal treatment with LH-RH agonists are available for these patients with a high risk of systemic progression after radical prostatectomy.

Metastase free survival at 10 years in the SWOG 8794 study is estimated at 60%. The aim of the present study is to improve this 10-year disease free survival for this very well defined population of pathological high risk patients, by adding adjuvant long term androgen deprivation to radical prostatectomy. The hypothesis will be to improve disease-free survival rate of 10% (from 60 to 70%). Adding long term adjuvant AD to radiotherapy has led to such an improvement for patients; one can assume that the same approach can be expected by adding long term AD to radical prostatectomy.

2. RESEARCH OBJECTIVES

2.1 Principal objective

The first objective is the evaluation of the effectiveness in terms of survival without metastases of adjuvant hormonal treatment with leuprorelin acetate (Eligard® 45 mg) for 24 months after radical prostatectomy in patients with high risk of recurrence.

2.2 Secondary objectives

- PSA evolution
- Evaluation of testosterone level
- Specific survival
- Overall survival
- Tolerance
- Quality of life (QLQ-C30, Appendix 5)

3. RESEARCH CONCEPT

3.1 Evaluation criteria

3.1.1 Principal criterion

The principal criterion is the evaluation of effectiveness in terms of survival without metastases to 10 years of adjuvant treatment with leoprorelin acetate (Eligard® 45 mg) for 24 months after radical prostatectomy.

3.1.2 Secondary criteria

- Evaluation of PSA progression
- Evaluation of testosterone level
- Evaluation of specific survival
- Evaluation of overall survival
- Evaluation of tolerance to the treatment
- Evaluation of quality of life

3.2 Research methodology

Phase III, randomised, open, multicentre study to evaluate the benefit of adjuvant hormonal treatment with leuprorelin acetate (Eligard® 45 mg) for 24 months after total prostatectomy in patients with high risk of recurrence.

3.3 Randomisation procedure

The treatment of patients who have received the information leaflet and signed the consent form and for whom the eligibility criteria have been verified will be randomized according to a randomization by minimization, between the two arms of treatment with a stratification:

- According to the the lymphe nodes status (PNx or PN0)
- According to the Gleason score (score ≤ 7 or > 7)

After signing the consent form and validating the results of the baseline inclusion examination, eligible patients will be randomised by the trial randomization center.
The investigator must fax the completed and signed randomization form to the management center of the CTD, Biostatistics Department. In return, the data management Center will fax the confirmation of randomization by specifying the treatment arm and patient number.

The contact details of the randomization center are:

Lise ROCA
Department of Biostatistics - Centre Val d'Aurelle-Paul Lamarque
from Monday to Friday between 9 am and 6 pm
Fax : 04 67 61 37 18 Phone : 06 67 61 37 59

3.4 Progression of the research

Every Patient included in the research will participate for a total of 10 years consisting of 2 years of treatment and 8 years of monitoring.

The research schedule is defined in the research summary table (Paragraph H of the synopsis).

3.5 Description of permanent or temporary termination of the research and drop out from the trial

3.5.1 Permanent or temporary termination of the research

The research may be suspended or terminated by the sponsor in consultation with the coordinator or at the request of the Competent Authority and/or the Committee for the Protection of Persons (CPP) for the following reasons:

- unexpected frequency and/or severity of toxicity,
- insufficient recruitment of patients,
- insufficient quality of data collection.

3.5.2 Premature drop out from the trial

Reasons for premature drop out from the trial may be as follows:

- Withdrawal of consent,
- Lost to follow-up,
- Other: to be specified precisely

Persons participating in the research may withdraw their consent and ask to leave the trial at any time and for any reason, without having to justify themselves, and without losing their right to be treated by their doctor.

The data concerning patients who have withdrawn their consent will not be used.

4. SELECTION OF PERSONS TO PARTICIPATE IN THE RESEARCH

If they satisfy the criteria for inclusion in the research, patients will be included/randomised in the research.

4.1 Inclusion criteria

1. Patients who have received the information leaflet and signed the consent form
2. ≥ 18 years of age with a life expectancy of at least 10 years
3. Performance Status (ECOG) ≤ 2
4. Radical prostatectomy (RP) with or without extended pelvic lymphadenectomy in the 3 months preceding inclusion
5. Histologically confirmed prostatic adenocarcinoma
6. Patients with postoperative Gleason score > 7, or ≥ 7 with the presence of high-grade Gleason patterns (5) and R0, N0 or Nx , M0
   or Patients pT3b, R0, N0 or Nx , M0 whatever the Gleason score
7. Postoperative PSA < 0.1 ng/mL (dosage perform within 2 months after surgery)
8. Neutrophils ≥ 1500/mm3, platelets ≥ 100 000/mm3
9. Bilirubin ≤ upper normal limit (this will not apply to subjects with Gilbert's syndrome, persistent or recurrent hyperbilirubinemia that is predominantly uncongugated in the absence of evidence of hemolysis or hepatic pathology);
   ASAT and ALAT ≤ 1.5 times upper normal limit;
   Creatinine < 140 µmol/l (or clearance > 60mL/min
10. Patients affiliated to a social security scheme

4.2 Criteria for non-inclusion

1. Previous treatment for prostatic adenocarcinoma (HT or orchyectomy or CT)
2. Presence of metastases:
   - positive bone scintigraphy, including Patients with medullary compression
     and/or
   - abdominal-pelvic CT scan or MRI showing lymph node and/or visceral involvement.
3. History of cancer, with the exception of basal cell carcinoma or any other cancer treated in the 5 years before inclusion and in complete remission.
4. Incompatible concomitant treatment(s)
5. Hypersensitivity to other GnRH agonists and/or any of the excipients of Eligard®
8. Any illness or problem including geographic, psychiatric or psychological which is incompatible with

being monitored during the trial
9. Persons deprived of their freedom or under supervision (including guardianship),
10. Patients already included in another therapeutic trial with an experimental drug or who have been given an experimental drug within a period of 30 days.

5. TREATMENT ADMINISTERED

5.1 Description of the treatments

Patients must have read and initialled the information leaflet and signed the consent form before the eligibility criteria will be validated. The treatment of eligible patients will be randomised in 2 parallel groups to receive treatment in arm A or arm B:

- Arm A: Observation

- Arm B: Leuprorelin acetate (Eligard ®),1 subcutaneous injection every 6 months for 24 months (making 4 doses) with the first injection at the time of randomisation

Immediate postoperative radiotherapy is allowed (each center must indicate at the time of the initiation visit whether or not it offers this option to all patients).

In the two arms, patients who present with a biological recurrence, that is PSA > 0.2 ng/mL will not be considered to be in clinical progression. They will receive treatment according to the guidelines (EAU 2010) and should perform the paraclinical exams (Abdominal-pelvic CT scan or MRI and Bone scintigraphy) every year . These patients will be monitored according to the protocol.
In the case of initiation of a new therapy, patients should perform the paraclinical exams before starting the new treatment.

All new treatments, including radiotherapy, must be reported in the CRF in the concomitant treatment section.

5.2 Treatment administration

Leuprorelin acetate (Eligard ®) must be administered in the form of 1 subcutaneous injection every 6 months for 24 months (making 4 doses) with the first injection at the time of randomisation.

5.3 Dosage adaptation

Not applicable.

5.4 Termination of treatment

The investigator may terminate the treatment prematurely for any reason which best serves the person's interests, including in the case of an intercurrent disease or undesirable event.
In the event of premature termination of the treatment, at any time and for any reason whatsoever, the investigator must document the reasons as fully as possible.
The patients will continue to be monitored in accordance with the protocol and monitoring data will be collected until the end of the research.

5.5 Packaging, labelling and storage conditions

Eligard® 45 mg (leuprorelin acetate) provided by the sponsor will be labelled in accordance with the Good Manufacturing Practices (GMP) guidelines as revised on 11th December 2006.
The primary and secondary packaging as well as the labelling for the clinical trial will be carried out in accordance with the Good Clinical Practice (GCP).

Eligard® 45 mg will be administered in the form of 1 subcutaneous injection every 6 months for 24 months, making 4 doses, the first one being at the time of randomisation.

Eligard® 45 mg comes in the form of 2 pre-filled sterile syringes. After the packaging has been opened, the contents must be mixed immediately, just before administration. The leuporelin contained in syringe B must be mixed only with the solvent in syringe A and must not be mixed with any other drug.

Eligard® 45 mg must be kept **refrigerated (between 2 and 8°C)** in its original packaging. Experimental drugs must be kept in a locked storage area with limited access and in accordance with the manufacturer's recommendations (to be specified cf. Summary of Product Characteristics *Appendix 2)*.

5.6 Distribution, accounting and destruction

Distribution of the experimental drugs, provided by the sponsor, to the different health establishment pharmacies will be carried out in accordance with the Good Distribution Practises guidelines.

The pharmacist of the investigational site will acknowledge receipt of all deliveries by returning a duly completed acknowledgement of receipt to the distributor.

The pharmacist of the investigational site will establish a system of accounting for all drugs delivered, used and unused.

The clinical research associate mandated by the sponsor will verify the accounts of drugs provided and will ensure that an accounting form has been validated and signed by the pharmacist before any request for destruction.

The sponsor is responsible for the destruction of experimental drugs which are not used. The destruction of experimental drugs may be carried out by the investigational sites 's pharmacies in accordance with current legislative and regulatory provisions and with prior approval of the sponsor; a destruction certificate will be provided to the sponsor.

5.7 Radiotherapy cases

Radiotherapy is possible:

- immediately after surgery
  or
- in the event of biological recurrence (according to the EAU 2010 guidelines). In that case, the radiotherapy must be reported in the CRF in the concomitant treatment section.

At the time of the initiation visit of the trial, each center must define its strategy. This information will be reported in the CRF.
The site of radiation (prostatic bed and/or pelvis and/or lymph node areas), the start date and the end date of the radiotherapy will be collected in the CRF.

5.8 Concomitant treatments

To date, no pharmacokinetic drug interaction study has been carried out with Eligard®. No description exists of possible interaction between leuprorelin acetate and other drugs.

All concomitant treatments, including radiotherapy, must be documented in the CRF in the relevant place.

6. PARAMETERS FOR THE EVALUATION OF EFFECTIVENESS AND SAFETY

6.1 Parameters for the evaluation of effectiveness

The principal criterion is the evaluation of effectiveness in terms of survival without metastases to 10 years of adjuvant treatment with leuprorelin acetate (Eligard® 45 mg) for 24 months after radical prostatectomy.

The presence of metastases will be evaluated every year by an abdominal-pelvic CT scan (or MRI) and scintigraphy.

6.2 Parameters for the evaluation of safety

The evaluation of safety will be done by assessment of the general condition (PS, BP, temperature, etc) and clinical condition of the patients and at consultations by gathering information on events occurring and by regular scheduled blood tests. Toxicity will be evaluated using the NCI-CTC-AE version 4.0 toxicity scale (Appendix 4).

In the event of an emergency, the patient or his family or his general practicioner must contact the investigator to inform him of the occurrence of an event and consider possible termination and/or treatments to be implemented.

7. ASSESSMENTS FOR INCLUSION AND MONITORING

The clinical and biological examinations for the inclusion assessment and the randomisation must be carried out in the 30 days following the postoperative PSA assay.

The paraclinical tests for the inclusion assessment could be the tests performed before the surgery, if they have been carried out in the 3 months before randomisation.

The postoperative PSA must be carried out within 2 months following the surgery.

The schedule for evaluation of patients is defined in the flow-chart (Paragraph H of the synopsis).

7.1 Inclusion assessment

Patients eligible for the trial and who have received the information leaflet and signed the consent form will have to undergo an initial assessment before the randomisation.

- **Clinical examination (in the 30 days** following the postoperative PSA assay**)**
  Clinical examination with determination of weight and height
  ECOG performance index (Appendix 1)
  Vital signs (blood pressure)

- **Biological examinations (in the 30 days** following the postoperative PSA assay**)**
  Haematology: CBC, platelets
  Blood electrolyte test
  Fasting glycemia
  Lipid assessment: total cholesterol, HDL, LDL and triglycerides
  Hepatic assessment (bilirubin, ALAT, ASAT, ALP)
  Renal assessment (creatinine, urea)
  Serum PSA (a new PSA assay is not mandatory, the postoperative PSA value can be take as the reference)
  Testosterone level

- **Paraclinical tests (in the 3 months preceding randomisation)**
  Abdominal-pelvic CT scan (or MRI)
  Bone scintigraphy

- **Quality of life questionnaire** (QLQ-C30, Appendix 5)

The questionnaires must be given to the patients who will complete them at the consultation (before or after). The completed questionnaires will be entrusted to the research center team.

7.2 Monitoring assessment

During the first 2 years, (ie during the treatment phase for patients randomised in Arm B) , the patients will be seen in consultation every 6 months. Depending on tolerance, additional consultations will be possible. At each consultation, the patients will be given the following assessment:

- **Clinical examination (every 6 months)**
  Clinical examination with determination of weight
  ECOG performance index (Appendix 1)
  Vital signs (blood pressure)
  Toxicity
  Concomitant medications

- **Biological examinations (every 6 months)**
  Haematology: CBC, platelets
  Blood electrolyte test
  Fasting glycemia
  Lipid assessment: total cholesterol, HDL, LDL and triglycerides
  Hepatic assessment (bilirubin, ALAT, ASAT, ALP)
  Renal assessment (creatinine, urea)
  PSA
  Testosterone level

- **Paraclinical tests only in case of biological recurrence (PSA>0.2 ng/mL), every year.**
  Abdominal-pelvic CT scan (or MRI),
  Bone scintigraphy,

All tests which reveal treatment-related toxicity must be repeated periodically until the toxicity is reversed or until it is deemed irreversible.

- **Quality of life questionnaire:**(QLQ-C30, Appendix 5)

  The questionnaires must be given to the patients who will complete them at the consultation (before or after). The completed questionnaires will be entrusted to the research center team.

In the two arms, patients who present with a biological recurrence, that is PSA > 0.2 ng/mL will not be considered to be in clinical progression. They will receive treatment according to the guidelines (EAU 2010) and should perform the paraclinical exams (Abdominal-pelvic CT scan or MRI and Bone scintigraphy) every year . These patients will be monitored according to the protocol.

In the case of initiation of a new therapy, patients should perform the paraclinical exams before starting the new treatment.
All new treatments must be reported in the CRF in the concomitant treatment section.
New treatments include:

- **radiotherapy**
- **hormonal treatments (bilateral orchiectomy, LHRH agonists, LHRH antagonists, anti-androgens, oestrogens, ketoconazole)**
- **chemotherapy**

In the case of bone pain, bone scintigraphy should be performed every year even if biological recurrence is not observed.

7.3 Follow-up after treatment

Patients will be reviewed **every year for 8 years**. Possible long-term toxic effects and duration of response as well as survival will be evaluated by CT scan (or MRI) and bone scintigraphy.

However, PSA assays will be six-monthly. The assays may be carried out in a ancillary laboratory and as far as possible always in the same laboratory.

In the two arms, patients who present with a biological recurrence, that is PSA > 0.2 ng/mL will not be considered to be in clinical progression. They will receive treatment according to the guidelines (EAU 2010) and should perform the paraclinical exams (Abdominal-pelvic CT scan or MRI and Bone scintigraphy) every year . These patients will be monitored according to the protocol.

In the case of initiation of a new therapy, patients should perform the paraclinical exams before starting the new treatment.
All new treatments, including radiotherapy, must be reported in the CRF in the concomitant treatment section.

In the case of bone pain, bone scintigraphy should be performed every year even if biological recurrence is not observed.

The questionnaires will be completed at every visit for the first two years and at the last visit in case of drop out before the first 2 years of follow up.

8. SAFETY EVALUATION

8.1 Adverse event

An adverse event (AE) is defined as any harmful reaction in a patient or participant in a clinical trial being treated with an experimental drug, which is not necessarily related to the experimental drug or the research.
(*Possibly to be detailed according to the protocols*)
All adverse events will be recorded in the case report form from the date of signature of consent of the patient until 28 days after the last administration of the product (90 days in the case of radiotherapy).

! Patients are under treatment 6 months + 28 days after the last administration of Eligard®

8.2 Serious adverse event: General definitions

Eeffects or events related or not to the experimental drug are considered to be serious adverse events (SAE) if they:

- Resulting in death,
- Are life threatening,
- Resulting in hospitalisation or extension of existing hospitalisation,
- Causing permanent disability or serious temporary incapacity,
- Leading to congenital anomaly, foetal malformation or abortion

The terms *disability* and *incapacity* correspond to any temporary or permanent physical or psychological handicap which is clinically significant and has an effect on physical activity and/or the patient's quality of life.

The following are not considered to be serious adverse events (SAE):

- Hospitalisation < 24 hours,
- Hospitalisation already scheduled before the start of the trial and/or which is part of the protocol (biopsy, chemotherapy, etc)
- *Possibly to be detailed according to the protocols*

Adverse effect of an experimental drug: any harmful and unwanted reaction to an experimental drug whatever the dose administered.

Definition of an expected serious adverse event (E- SAE): An expected SAE is a known event linked to the experimental drug which is already mentioned in the most recent version of the investigator's brochure or in the Summary of Product Characteristics for drugs which already have a marketing authorisation (MA).

Definition of an unexpected serious adverse event (U-SAE): An unexpected SAE or Suspected Unexpected Serious Adverse Reaction (SUSAR) is an **unknown** event linked to the experimental drug which is not mentioned in or is different in its nature, intensity and progression from the investigator's brochure or the Summary of Product Characteristics for drugs which already have a marketing authorisation (MA).

Severity criterion: The criterion for severity (intensity) must not be confused with the seriousness criterion which is the guide for defining the reporting requirements.

The severity of events will be estimated according to the extract from the CTC-AE version 4.0 classification (Appendix 5). The severity of adverse events not listed in this classification will be assessed according to the following qualifiers:

Mild (grade 1): does not affect the patient's normal daily activity
Moderate (grade 2): disrupts the patient's normal daily activity
Severe (grade 3): prevents the patient from carrying out his normal daily activity
Very severe (grade 4): requires resuscitation / is life-threatening
Death (grade 5)

8.3 Action to be taken in the event of a serious adverse event

The investigator must immediately inform the pharmacovigilance department at BECT (PV-BECT) of any Serious Adverse Event, whether or not related to the research, which occurs during the study or in the 28 days following the last administration of the experimental drug.

Any delayed Serious Adverse Events (occurring after a period of 30 days) which are considered to be reasonably related to the experimental treatment(s) or to the research (other treatments used, diagnostic procedures and examinations carried out during the research) must be reported without any limitation in terms of deadline.

Notification must be carried out as soon as the investigator is aware of the event, by fax to the pharmocovigilance department at BECT (PV-BECT) by sending the form entitled "**notification of a serious adverse event**", located in the investigator file, completed as precisely as possible, dated and signed by the investigator:

Bureau d'Etudes Cliniques et Thérapeutiques
Unité de Pharmacovigilance
Tel.: 00 33 (0)1 44 23 04 16 – Fax: 00 33 (0)1 44 23 55 70
Email: pv-bect@fnclcc.fr

The investigator will note, among other things, for each event:
- Its description as clearly as possible according to the medical terminology,
- The severity,
- The start and end dates of the event,
- The measures taken and whether or not there was a requirement for corrective treatment,
- Whether the treatment of the trial was stopped,
- Its outcome. In the case of a non-fatal event, the outcome must be followed up to recovery or return to the previous state or stabilisation of possible sequelae,
- The causal relationship between this event and the study treatment or any constraint linked to the research (treatment-free period, additional examinations requested as part of the research etc),
- The causal relationship between the pathology treated, another pathology or another treatment.

Please note that for patients receiving radiotherapy after radical prostatectomy according to the site standard treatment, radiotherapy should be reprorted in the form as investigational medicinal product with the following information:

- **Date of the first radiotherapy session**
- **Date of the last radiotherapy session**
- **Dose (Gy)**
- **The radiation sites (prostatic bed and/or pelvis and/or lymph node areas)**

If patients receiving other additionnal treatments to Eligard® at the biological reccurrence, treatments should be reported in the form as investigational medicinal product. The start date and the end date of treatment and the type of treatment should be specified.

The investigator should also attach to the serious adverse event report, whenever possible:

- A copy of the hospital report or extended hospitalisation report,
- A copy of the autopsy report if necessary,
- A copy of all results of additional examinations carried out, including relevant negative results, and enclosing the normal laboratory values
- Any other document which he believes to be useful and pertinent.

All these documents must be anonymised.

Additional information can be requested (by fax, mail, telephone or visit) by the monitor and/or the pharmacovigilance department of BECT using a Data Clarification Form (DCF)

In the event of an unexpected SAE which is reasonably related to one of the treatments of the study, additional information will be requested by the pharmacovigilance department from the investigator via a specific procedure in English.
Any event which is expected but is different by its severity, outcome or frequency will be considered as unexpected by the pharmacovigilance department.

The most up to date Summaries of Product Characteristics, located in the investigator's file, will be used for each product.

8.4 Modalities and duration of follow-up of persons after the occurrence of a serious adverse event

The investigator is responsible for appropriate medical follow-up of patients until the resolution or stabilisation 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 shall send additional information to the Pharmacovigilance department of the BECT using an SAE declaration form (by ticking the Follow-up n° X box to specify that it is a follow-up and not an initial report) as soon as he is aware of the event. He shall also submit the last follow-up at the resolution or stabilisation of the SAE.

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

The investigator must respond to requests for additional information from the Pharmacovigilance department of the BECT in order to document the initial observation.

9. BIOLOGICAL STUDY

No biological study has been planned.

10. STATISTICS

Main criterion
The Primary Endpoint is the comparison of the metastase-free survival between the two arms to 10 years.

The metastases relapse will be defined as the appearance of one or more lesions.

The MFS is defined as the interval between the date of randomization and the date of metastatic relapse
Patients alive at last follow-up without distant recurrence were censored at the time of last visit; patients dead without distant recurrence were censored at the date of death.

Secondary criteria
Comparison of overall survival, specific survival, tolerance, PSA progression, evaluation of testosterone level and evaluation of the quality of life using EORTC QLQ-C30 (version 3)
The OS is defined as the interval between the date of randomization and the date of death from any cause.

10.1 Number of subjects required

The principal evaluation criterion is survival without metastases. According to the literature, survival to 10 years after radical prostatectomy in those at high risk is 60%.
The aim is to increase survival by 10%, an increase considered to be clinically significant, being from 60% to 70% which corresponds to a hazard ratio of 0.7.
A total of 700 patients (350 in each arm) and 250 events are required to have 80% ability to detect a difference with a bilateral Logrank test with $\alpha = 0.05$ and $\beta = 0.20$.
Based on recruitment by the research centers of patients with this profile for this trial, 175 patients per year, the inclusion of patients should be complete in 4 years.
The final analysis is planned for 12 years after the inclusion of the first patient.

Intermediate analysis:

An interim analyse is planned to test the null hypotheses. The decision rules will be determined by the O' Brien-Fleming sequential boundaries at the time of the analysis. The interim analysis is planned at the 125th event (50% of events) for 6.5 years after the start of the trial.

10.2 Statistical analysis

The analysis will take place when the median follow-up of patients is at least 10 years after the inclusion of the last patient.

Intermediate analyses will be carried out when 125 events have been observed.

Categorical variables will be presented by frequencies, percentages and confidence intervals and will be compared between groups by Chi2 tests or Fisher's exact test.
Continuous variables will be presented by means, standard deviations, medians, and range and will be compared between groups by a non-parametric Wilcoxon test.

The survival rates will be estimated by the Kaplan-Meier method and presented with 95% confidence intervals. The logrank test, adjusted on the stratification factors will be used to compare the survival rates between the groups. All survival times will be calculated from the date of randomization.
Multivariate analyses will be performed using the Cox proportional hazards regression model adjusted on the stratification factors and are applied to study the factors of prediction and determine factors pronostic of the survival. The estimated hazard ratios will be presented with their 95 % confidence intervals.
All the statistical tests are two-sided and $p<0.05$ is considered as statistically significant. The statistical analyses with be done with STATA.

10.3 Statistical rules for terminating the research

NA

10.4 Methods for dealing with missing or invalid data

NA

10.5 Definition of population

Intent-to-treat population
All randomized patients will be included in the intent-to-treat population (ITT), whether or not any study medication was administered, and regardless of the eligibility status. As far as statistical inferences are concerned, patients are analyzed in the treatment group and in the stratum to which they were assigned by the randomization.

Eligible population
Eligible patients are patients with no major violations of the inclusion and exclusion criteria. The final decision on patients' eligibility rests with the IDMC that will eventually give a decision on the eligibility of all patients.

Patients lost to follow-up
Patients lost to follow-up will be censored at the date of last contact. A patient lost to follow-up is a patient who never came back to the hospital and for whom repeated attempts to contact have failed. Patients free of disease and not lost to follow-up at the cut-off date for the analysis will be censored at that cut-off date if data exists that documents patient status beyond the cut-off date, or censored at the date of the last visit otherwise.

The criteria considered to be major violations are:
- prohibited concomitant treatment
- the introduction of a new treatment without a biological recurrence

Quality of life
The analysis will consist in the comparison of the different scores of "Global health status/Qol" (primary objective) and dysphagia, asthenia, pain and physical functions (secondary objectives).

10.6 Management of changes to the analysis plan for the initial strategy

Any changes to the initial statistical analysis plan (SAP) must be detailed, reasoned and commented on in an updated version of the SAP. These changes may involve additional exploratory analyses not initially planned.

11. QUALITY CONTROL AND ASSURANCE

11.1 Monitoring committees

11.1.1 Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) could be set up in order to guarantee the protection of patients, to ensure that the trial is conducted in an ethical manner, to evaluate the benefit/risk ratio of the trial and to ensure the independent review of the scientific results during or at the end of the trial.

IMPORTANT: Indication of the reasons which do or do not justify the establishment of an independent monitoring committee will be specified.

If possible, the interim analysis will be presented to the IDMC.

11.1.2 Conditions of premature trial termination

The IDMC may propose the premature termination of the trial if one of the following conditions is fulfilled:

- the results of the interim analysis clearly show ($p<0.003$) that the study treatment is indicated or contra-indicated,
- the overall data available from the trial or other sources is sufficiently convincing to influence the therapeutic practises of the majority of doctors.

The committee has an advisory role supporting the Sponsor, who has the final decision regarding the implementation of recommendations proposed by the committee.

The IDMC may be called upon at any time regarding the data.

11.1.3 Executive Steering Committee

The research will be followed on a quarterly basis by the Executive Steering Committee of the GETUG tumour group.

11.2 Quality assurance

11.2.1 Data collection

All data required by this research must be recorded as soon as possible in the trial Case Report Form (CRF). The investigator or a person designated by the investigator must complete the CRF.
Entry of data in the case report form must be done using a ballpoint pen and must be legible.
Pencils and correction fluid must not be used.
If corrections prove to be necessary, they must be done by the investigator or an authorised member of his team in the following manner: the erroneous data must be crossed out, while remaining legible, and the correct data must be written next to it. Corrections must be certified by date and initials. For corrections concerning adverse events or the principal variable of effectiveness, the reason for the correction must be provided.

During the trial, correction requests can be issued by the data-management centre Val d'Aurelle. These must be completed in the same way by persons authorised to complete the CRF.

The Capture/System software (Clinsight) will be used for data management.
.

11.2.2 Monitoring of the research

In order to guarantee the authenticity and credibility of the data in accordance with the GCP guidelines of 24th November 2006, the sponsor will establish a system of quality assurance which includes:

- management and monitoring of the trial according to the procedures of the BECT of the FNCLCC,
- quality control of the site investigator's data by the monitor whose role is:
  - to verify compliance with the protocol, GCP and the current laws and regulations,
  - to verify the consent and eligibility of each of the patients participating in the research,
  - to verify the concordance and consistency of the data in the case report form compared to the source documents,
  - to verify notification of each serious adverse event,
  - to follow the traceability of the study drugs (dispensation, storage and accounting of drugs),
  - to ensure, if necessary, that persons wishing to take part in the research are not already participating in research which would render impossible their inclusion in the proposed research. The monitor also ensures that patients have not participated in research for which an exclusion period is currently required.
- possible audit of clinical investigation sites,
- centralised review of certain protocol criteria(if applicable),

The monitors in charge with the quality control of this biomedical research are duly mandated to this effect by the sponsor and must have access to personal data of the participants in the research strictly as necessary for this control. The monitors are subject to professional secrecy under the conditions defined in articles 226-13 and 226-14 of the penal code. The traceability of monitoring visits is ensured by written monitoring reports.

So that the monitors can best ensure the quality control of the research, the investigators are committed to letting them have direct access to the medical file of each patient.
This also applies to representatives of the health authorities.

11.2.3 Audits

As part of the audit programme, the Sponsor may audit certain Investigational Sites. The site and the Investigator accept that audits could be carried out by the sponsor or any person duly mandated for at least ten years from the end of the Study.

More generally, the Sites and the Investigator are committed to giving all the time necessary to the procedures of audit or inspection, control and additional information produced by the Sponsor or requested by the Competent Authority or any official organisation.

12. ETHICAL AND REGULATORY CONSIDERATIONS

The clinical trial must be conducted in accordance with:

- European Directive (2001/20/CE) on the conduct of clinical trials,
- Huriet Law (n° 88-1138) of 20th December 1988 relating to the protection of persons participating in biomedical research as amended by the Public Health law (n° 2004-806) of 9th August 2004,
- Law n° 78-17 of 6th January 1978 relating to data processing, files and personal freedom and privacy as amended by law n° 2004-801 of 6th August 2004 relating to the protection of individuals with regard to the processing of personal data,
- Bioethics law n° 2004-800 of 6th August 2004.
- Guidelines for Good Clinical Practice of 24th November 2006

12.1 Clinical trial authorisation

The protocol was submitted to the Ethics Committee (CPP) of "Ile de France VII" which issued a favourable opinion.

The protocol was submitted to the French Health Products Safety Agency (Competent Authority) which gave its authorisation.

12.2 Participant Information and Consent

Prior to conducting biomedical research on a person, voluntary, informed and written consent must be obtained from that person after they have been thoroughly informed by the investigator.

The information sheet and informed consent form must constitute a single document in order to ensure that all the information is given to the research participant.

The consent form must be dated and signed personally by the research participant and the investigator. The original will be filed in the investigator file and a copy will be given to the research participant.

In the case of trials where the objective is to carry out genomic or proteomic analyses, the information sheet must specify the type of research which will be carried out and the patient must have the opportunity to agree to or refuse the preservation of biological samples for the purpose of scientific research.

In the case of trials carried out on minors, an information sheet adapted to their comprehension capacity must be writed. The authorisation must come, in principle, from the two holders of parental authority.

12.3 Sponsor responsibilities

The sponsor of the clinical trial, the French Federation of Comprehensive Cancer Centers (FNCLCC), takes the initiative for this biomedical research; it undertakes the management of the trial and verifies that the funding is provided.

The main responsibilities of the sponsor are:

- the purchase of a civil liability insurance policy,
- obtaining the EudraCT n° and registering the trial in the European database (European Drug Regulatory Authorities Clinical Trials),
- obtaining the clinical trial authorisation for the initial project and possible amendments from the Ethics Committee (CPP) and the French Health Products Safety Agency; opinion from the CPP and decision from the French Health Products Safety Agency.
- notification to the competent authority of any Suspected Unexpected Serious Adverse Event and the transmission of this information to the Ethics Committee (CPP) and the trial investigators,
- annual transmission of the safety report to the competent authority and the Ethics Committee (CPP),
- providing the information of the trial to the establishment directors, pharmacists and investigators,
- notification to the competent authority of the start and end of the trial,
- drafting of the final report of the trial and transmission of the summary to the French Health Products Safety Agency,
- providing information on the results of the trial to the competent authority, the Ethics Committee (CPP) and the research participants,
- archiving of the essential documents of the trial in the sponsor's file for at least 15 years after the end of the research.

12.4 Investigator responsibilities

The principal investigator of each concerned establishment is committed to conducting the clinical trial in accordance with the protocol and the current regulations and in particular in accordance with the decision of 24th November 2006 regarding the Good Clinical Practise.

It is the responsibility of the principal investigator:

- to provide the sponsor with his curriculum vitae as well as those of the co-investigators,
- to identify the members of his team who are participating in the trial and to define their responsibilities,
- to begin the recruitment of patients after authorisation from the sponsor,
- to make himself available for visits and investigator meetings.

It is the responsibility of every investigator:

- to respect the confidentiality of the trial,
- to obtain the informed consent personally signed and dated by each research participant before any selection procedure specific to the trial,
- to regularly complete the case report forms (CRF) for each of the patients included in the trial and to allow the monitor (CRA) mandated by the Sponsor to have direct access to the source documents so that they can validate the data in the CRF,
- to inform the Sponsor, as promptly as possible, of any serious adverse event occurring during the research,
- to accept regular visits from the monitor and possibly the auditors appointed by the sponsor or inspectors from the supervisory authorities.
- to date, correct and sign corrections to the case report forms (CRF) and data clarification forms (DCF).

12.5 Collection of human biological samples

NA

12.6 French federation of patient associations for clinical research in oncology (Fédération des Comités de Patients pour la Recherche Clinique en Cancérologie = FCPRCC)

The French federation of patient associations for clinical research in cancer (FCPRCC) was created at the initiative of the French Federation of Comprehensive Cancer Centers (Fédération Nationale des Centres de

Lutte contre le Cancer , FNCLCC) and the French National League Against Cancer (Ligue Nationale Contre le Cnacer, LNCC), with the aim of reviewing the protocols of clinical trials in oncology. The federation of patient associations is coordinated by BECT and includes the patient associations of the league as well as those of other health establishments. It aims to review the protocols and propose improvements, in particular regarding the quality of the information sheet, the provision of a treatment and observation plan, and the suggestion of measures aiming to improve patient comfort.

13. TREATMENT OF DATA AND STORAGE OF DOCUMENTS AND DATA RELATING TO THE RESEARCH

13.1 Treatment of data

13.1.1 By the sponsor

Treatment of the trial data is delegated by the FNCLCC to *the biostatistics unit of Val d'Aurelle* under the responsibility of Dr Jean-Pierre Bleuse; the data remains the property of the FNCLCC, sponsor of the research.

The data processing software is the Capture/System software (Clinsight).

In accordance with the revision to the Data Protection Act of 6th August 2004 and its implementing order, the FNCLCC is committed to following reference methodology MR001 of the French National Commission for Data Protection.

13.1.2 By the centers, in the case of computerised medical records

If the necessary data for biomedical research in the centers is subject to computerised processing or managed by computerised systems, each Center:

a) must ensure and document the fact that the computerised systems used in the research conform to the established requirements for integrity, accuracy, reliability of data and compliance with expected performances (that is validation);

b) must implement and ensure the monitoring of standard operating procedures relating to the use of the systems;

c) must ensure that the design of the systems allows for modification of the data in such a way that the modifications are documented and no data collected is deleted (that is keep a track of data audit and modifications);

d) must implement and ensure the monitoring of a security system which prevents any unauthorised access to the data;

e) must maintain the list of persons authorised to modify the data;

f) make appropriate backup copies of data;

g) preserve the blinding, if applicable (for example when gathering and processing data);

h) ensure that the processing of personal data carried out as part of the research is done under the conditions defined by law n° 78-17 of 6th January 1978 relating to data processing, files and liberty as amended by law n° 2004-801 of 6th August 2004 and the regulatory texts made thereunder.

If the data is altered during processing, it must always be possible to compare the original data and observations and the data after the alteration.

The system used to identify persons taking part in the research should not present any ambiguity and must allow identification of all the data collected for each person, while maintaining the confidentiality of personal information and in compliance with law n° 78-17, amended.

13.2 Storage of documents

All documentation related to the trial (protocol, consent forms, case report forms, correction requests, investigator file etc), as well as the original documents (laboratory results, radiology results, consultation reports, clinical examination reports, etc) is considered to be confidential and must be kept in a safe place.
For each center and under the decree of 8th November 2006, the Principal Investigator must keep the data as well as a list identifying the patients for at least 15 years after the end of the study. After this time, the center may only destroy this documentation after having obtained written agreement from the sponsor.

14. CONFIDENTIALITY AND OWNERSHIP OF THE DATA

All information provided or obtained and the data and results generated as part of the trial, belong by right to the FNCLCC, who can freely dispose of them. The trial must not be the subject of any written or oral communication without the agreement of the sponsor.

The investigator undertakes, for himself and for all persons who may follow the progress of the trial, to guarantee the confidentiality of all information provided by the FNCLCC until the publication of the results of the trial. This obligation of confidentiality does not apply to information that the investigator will have to communicate to patients as part of their participation in the trial, or to information already published.
The investigator undertakes not to publish, disclose or use, in any way whatsoever, directly or indirectly, the scientific or technical information relating to the trial.

Nevertheless, in accordance with article R 5121-13 of the Public Health Code, the center and investigator may give information relating to the trial:

- to the Minister for Health,
- to public health medical inspectors,
- to public health pharmacist inspectors,
- to the Director General and the inspectors from the French Health Products Safety Agency (AFSSAPS).

15. RULES RELATING TO PUBLICATION

All information resulting from this trial is considered to be confidential, at least until the appropriate analysis and control have been carried out by the sponsor, the coordinating investigator and the trial statistician.

All publications, abstracts or presentations including the results of the trial must be submitted to the sponsor (FNCLCC) for approval.

In addition, all communications, manuscripts or presentations must include a section which mentions without fail the FNCLCC, the French National League Against Cancer (LNCC), all the institutions, investigators, cooperative groups and learned societies who have contributed to the trial, as well as the organisations who have financially supported the research.

For the main publication, French or English, the authors are:

- the study coordinator (first author or last author) ;
- the investigators who recruited the most patients (listed by level of recruitment) whichever cooperating group they belong to ;
- a representative from each cooperating group not mentioned among the investigation centers with the most recruits ;
- the study statistician

- a representative of the sponsor

It is desirable to include in future publications the people from the weaker recruitment centers who have not been mentioned in the main publication.

In case of dispute, the order of authors will be arbitrated by the Strategic Orientation Committee (Comite d'Orientation Startégique, COS).

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17. APPENDICES

- Appendix 1: ECOG Classification
- Appendix 2: Summary of Product Characteristics
- Appendix 3: NCI – CTC AE scale Version 4.0
- Appendix 4: Quality of life questionnaire: QLQ-C30
- Appendix 5: Patient information sheet and consent form

Appendix 1 – Evaluation of general status using the ECOG scale

Reference: Common Toxicity Criteria v2.0 revised (CTC), published 30th April 1999

GENERAL STATUS ECOG-ZUBROD/WHO	SCORE
Activity normal, without restriction.	0
Restriction in strenuous physical activity but patient ambulatory and able to carry out light work	1
Ambulatory and capable of all self care but unable to carry out work activities for more than 50% of the time	2
Capacity for self care much more limited. Spends more than 50% of the time in bed or in a chair.	3
Completely bedridden. Cannot carry out any self care. The patient is totally confined to a bed or chair.	4

Appendix 2 – Summary of Product Characteristics

SPC « to be specified » are attached separately in the investigator file.

It is also possible to refer to the latest versions on the websites of the French Health Products Safety Agency, EMEA or VIDAL:

http://agmed.sante.gouv.fr/
http://www.emea.eu.int/
http://www.vidalpro.net/

Appendix 3 – Toxicity criteria (CTCAE)

Refer to the CTCAE toxicity evaluation scale which is attached separately in the investigator's file or which can be downloaded from the NCI website

Cancer Therapy Evaluation Program

http://ctep.cancer.gov/

Common Terminology Criteria for Adverse Events v4.0 (CTCAE)

(Publish Date May 28, 2009)

Appendix 4 – Quality of life questionnaire: QLQ-C30

EORTC QLQ-C30 (version 3) *réservé à l'informatique* |__|__|__|

Nous nous intéressons à vous et à votre santé. Répondez vous-même à toutes les questions en entourant le chiffre qui correspond le mieux à votre situation. Il n'y a pas de "bonne" ou de "mauvaise" réponse. Ces informations sont strictement confidentielles.

Merci de préciser:

Vos initiales: |__|__|__|__|__|__|
(3 premières lettres du nom / 2 premières lettres du prénom)

Votre date de naissance (jour/mois/année): |__|__| |__|__| |__|__|__|__|

La date d'aujourd'hui (jour/mois/année): |__|__| |__|__| |__|__|__|__|

		Pas du tout	Un peu	Assez	Beaucoup	
1.	Avez-vous des difficultés à faire certains efforts physiques pénibles comme porter un sac à provision chargé ou une valise? |__|	1	2	3	4	*ne pas écrire ici*
2.	Avez-vous des difficultés à faire une longue promenade?	1	2	3	4	|__|
3.	Avez-vous des difficultés à faire un petit tour dehors?	1	2	3	4	|__|
4.	Etes-vous obligé de rester au lit ou dans un fauteuil pendant la journée?	1	2	3	4	|__|
5.	Avez-vous besoin d'aide pour manger, vous habiller, faire votre toilette ou aller aux W.C.?	1	2	3	4	|__|

Au cours de la semaine passée :		**Pas du tout**	**Un peu**	**Assez**	**Beaucoup**	
6.	Avez-vous été gêné pour faire votre travail ou vos activités de tous les jours?	1	2	3	4	|__| *ne pas écrire ici*
7.	Avez-vous été gêné dans vos activités de loisirs?	1	2	3	4	|__|
8.	Avez-vous eu le souffle court?	1	2	3	4	|__|
9.	Avez-vous eu mal?	1	2	3	4	|__|
10.	Avez-vous eu besoin de repos?	1	2	3	4	|__|
	Avez-vous eu des difficultés pour dormir?	1	2	3	4	|__|
12.	Vous êtes-vous senti faible?	1	2	3	4	|__|
13.	Avez-vous manqué d'appétit?	1	2	3	4	|__|
14.	Avez-vous eu des nausées (mal au coeur)?	1	2	3	4	|__|
15.	Avez-vous vomi?	1	2	3	4	|__|

Passez à la page suivante S.V.P.

Au cours de la semaine passée:		**Pas du tout**	**Un peu**	**Assez**	**Beaucoup**	*ne pas écrire ici*
16.	Avez-vous été constipé ?	1	2	3	4	⌊__⌋
17.	Avez-vous eu de la diarrhée ?	1	2	3	4	⌊__⌋
18.	Etiez-vous fatigué ?	1	2	3	4	⌊__⌋
19.	Des douleurs ont-elles perturbé vos activités quotidiennes ?	1	2	3	4	⌊__⌋
20.	Avez-vous eu des difficultés à vous concentrer sur certaines choses par exemple pour lire le journal ou regarder la télévision ?	1	2	3	4	⌊__⌋
21.	Vous êtes-vous senti tendu ?	1	2	3	4	⌊__⌋
22.	Vous êtes-vous fait du souci ?	1	2	3	4	⌊__⌋
23.	Vous êtes-vous senti(e) irritable?	1	2	3	4	⌊__⌋
24.	Vous êtes-vous senti déprimé ?	1	2	3	4	⌊__⌋
25.	Avez-vous eu des difficultés pour vous souvenir de certaines choses?	1	2	3	4	⌊__⌋
26.	Votre état physique ou votre traitement médical vous ont-ils gêné dans votre vie familiale?	1	2	3	4	⌊__⌋
27.	Votre état physique ou votre traitement médical vous ont-ils gêné dans vos activités sociales (par exemple sortir avec des amis, aller au cinéma...)?	1	2	3	4	⌊__⌋
28.	Votre état physique ou votre traitement médical vous ont-ils causé des problèmes financiers?	1	2	3	4	⌊__⌋

Pour les questions suivantes, veuillez répondre en entourant le chiffre entre 1 et 7 qui s'applique le mieux à votre situation

29. Comment évalueriez-vous votre état de santé au cours de la semaine passée?

1 2 3 4 5 6 7 ⌊__⌋

Très mauvais *Excellent*

30. Comment évalueriez-vous l'ensemble de votre qualité de vie au cours de la semaine passée?

1 2 3 4 5 6 7 ⌊__⌋

Très mauvais *Excellent*

Appendix 5 – Patient information sheet and consent form

Note d'information(1) et formulaire de recueil de consentement destinés aux patients participant à la recherche biomédicale AFU-GETUG 20/0310- N°EudraCT : 2010-022037-29

(1) ***Toutes les pages de ce document doivent être paraphées par le patient et l'investigateur. Un exemplaire de ce document, dont le formulaire de recueil de consentement cosigné, doit être remis au patient.***

Titre du protocole :

ETUDE DE PHASE III RANDOMISEE EVALUANT LE BENEFICE D'UN TRAITEMENT HORMONAL ADJUVANT PAR LEUPRORELINE ACETATE (ELIGARD® 45 MG) PENDANT 24 MOIS APRES PROSTATECTOMIE TOTALE CHEZ DES PATIENTS A HAUT RISQUE DE RECIDIVE.

Note d'information destinée aux patients.

Monsieur,

Votre médecin vous a expliqué que vous êtes atteint d'un cancer de la prostate pour lequel une ablation de la prostate (prostatectomie totale) a été récemment réalisée. Il vous propose maintenant de participer à l'étude de recherche biomédicale AFU-GETUG 20/0310 dans le cadre de la prise en charge de votre maladie.

1- Quel est l'objectif de cette étude?

L'étude à laquelle nous vous proposons de participer a pour objectif d'évaluer l'efficacité d'un traitement hormonal adjuvant(1), l'acétate de leuproréline (Eligard ® 45mg), chez les patients à haut risque de rechute après prostatectomie totale, c'est-à-dire chez les patients qui ont un risque de voir leur maladie réapparaitre (on parle alors de rechute ou de récidive) malgré le traitement chirurgical.

Vous êtes dans une telle situation de risque de récidive de la maladie dans la mesure où l'analyse de votre prostate a mis en évidence une atteinte par la maladie des vésicules séminales et/ou un score de Gleason (qui évalue le degré de différenciation de la tumeur) supérieur ou égal à 8.

L'acétate de leuproréline est une molécule qui va empêcher la sécrétion d'hormones impliquées dans le développement du cancer de la prostate. Nous cherchons à savoir si l'administration de ce traitement après prostatectomie totale chez les patients qui présentent des risques de rechute permet ou non de retarder ou d'empêcher cette rechute.

2- Combien de personnes vont participer à cette étude ?

Cette étude se déroulera en France et sans doute dans d'autres pays européens pendant 12 ans. Il est prévu d'inclure 700 patients.

3- Comment va se dérouler cette étude ?

Si vous acceptez de participer à cette étude, le traitement qui vous recevrez vous sera attribué par tirage au sort. Il y aura deux groupes de patients :

- le premier groupe ne recevra pas la leuproréline acétate et sera surveillé
- le second recevra le traitement par leuproréline acétate et sera surveillé

Le traitement sera administré à raison d'une injection sous-cutanée tous les 6 mois pendant 24 mois, soit 4 administrations au total dont la première le jour de l'attribution du traitement, lors de la visite d'inclusion. Les 3 autres injections seront faites au cours des visites de suivi qui sont prévues dans le calendrier de cette étude, soit par le médecin qui vous suit, soit par une infirmière de l'équipe. Il n'y a pas besoin de vous hospitaliser pour l'administration de ce traitement.

Tous les patients seront suivis de la même façon, quel que soit le groupe de traitement.

Si vous rechutez au cours du traitement ou pendant le suivi, quel que soit votre groupe de traitement, votre médecin vous proposera une prise en charge qui sera la plus adaptée à votre cas.

Le détail des examens prévus dans le cadre du protocole est présenté dans le calendrier prévisionnel présenté en page 6.

En résumé, un bilan biologique (prise de sang) ainsi qu'un scanner (ou une IRM) et une scintigraphie osseuse seront réalisés au début de l'étude. Un bilan biologique sera ensuite effectué tous les 6 mois pendant 2 ans puis tous les ans. Si le PSA devait s'élever au cours du suivi au-delà de 0,2 ng/ml, les examens radiologiques seraient réalisés également tous les ans.

Si vous avez des douleurs osseuses, une scintigraphie sera pratiquée tous les ans, même si le PSA n'a pas significativement augmenté.

4- Quelle est la durée de votre participation à cette étude ?

Pendant la période de traitement, vous verrez votre médecin tous les 6 mois pendant 24 mois. Après le traitement, vous serez suivi tous les ans pendant 10 ans.

5- Quels sont les risques possibles ?

La leuproréline acétate peut entrainer les effets indésirables suivants : des bouffées de chaleur, des nausées, des diarrhées, une fatigue ou encore une irritation locale et transitoire (c'est-à-dire temporaire) au point d'injection ou encore des ecchymoses (des bleus).

Un peu plus rarement, la leuproréline acétate peut provoquer des rhinopharyngites, une sudation nocturne, une arthralgie (c'est-à-dire des douleurs articulaires), des douleurs au niveau des membres, des douleurs musculaires, une modification/perturbation de la composition sanguine, une augmentation du temps de coagulation, un malaise, un prurit (des démangeaisons) au site d'injection, une sensibilité mammaire, une hypertrophie mammaire, une stérilité, des douleurs testiculaires, une atrophie (c'est-à-dire une diminution de volume ou de taille) des testicules et des perturbations mictionnelles[2] (diminution de la fréquence, dysurie[3], nycturie[4] ou oligurie[5]).

6- Quels sont les bénéfices attendus de cette étude

Actuellement, le traitement de référence après prostatectomie radicale est la surveillance. Il se peut que le traitement hormonal par leuproréline acétate permette de retarder ou d'empêcher la rechute.

7- Aspects réglementaires

Pour participer à cette étude, vous devez être bénéficiaire d'un régime de sécurité sociale en tant qu'assuré ou ayant-droit. Vous ne serez inclus dans l'étude que si vous signez et paraphez le consentement qui vous sera remis. Vous ne pourrez pas participer en même temps à une autre recherche biomédicale. Après votre participation à l'étude AFU-GETUG 20/0310, vous pourrez participer à une autre étude que dans un délai de 30 jours.

Si vous acceptez de participer à cette étude, vous pourrez vous retirer à tout moment sans justification, sans conséquence sur la suite de votre traitement ni sur la qualité des soins qui vous seront fournis et sans conséquence sur la relation avec votre médecin. Vous serez suivi par la même équipe médicale. Si vous en faites la demande écrite, les données recueillies jusqu'à votre retrait de participation ne seront pas utilisées.

Le promoteur de cet essai qui en assure la gestion et la responsabilité est la Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) située au 101, rue de Tolbiac, 75654 Paris Cedex 13 – France. Elle en assure également la prise en charge globale.

La FNCLCC a pris toutes les dispositions prévues par la loi sur les Recherches Biomédicales (anciennement Loi Huriet- décret d'application 2006-477 du 26 avril 2006 modifiant le titre II du livre

1 du Code de la Santé Publique) relative à la protection des personnes se prêtant à des recherches biomédicales.

La FNCLCC devant assumer l'indemnisation des éventuelles conséquences dommageables de la recherche biomédicale pour la personne qui s'y prête, a souscrit une assurance de recherches biomédicales, conformément à la législation en vigueur (n° de contrat 906812010008 Protocole AFU-GETUG 20/0310), auprès de la Société Gerling France (111-113 rue de Longchamp, 75016 Paris – Tél. 01 44 05 56 00)

Lorsque la responsabilité du promoteur n'est pas engagée, les participants peuvent être indemnisés auprès de l'ONIAM, (Office National d'Indemnisation des Accidents Médicaux, 36, Avenue du Général de Gaulle, 93175 BAGNOLET Cedex, N° Vert : 0800 779 887).

Ce protocole a été autorisé par 2 instances ayant pour mission de vérifier la pertinence scientifique et éthique de l'essai, les conditions requises pour votre protection et le respect de vos droits.

Ces instances sont les suivantes :

1) L'Autorité Compétente (l'Agence Française se Sécurité Sanitaire des Produits de Santé, l'AFSSAPS) qui a autorisé cet essai le 07/01/2011 sous le n° A101324-12.

2) Le Comité de Protection des Personnes CPP Ile de France VII, qui a rendu un avis délibératif favorable le 31/01/2011.

Votre dossier médical reste confidentiel et ne peut être consulté que sous la responsabilité du médecin s'occupant de votre traitement ainsi que par les autorités de santé et par des personnes dûment mandatées par le promoteur de l'essai et soumises au secret professionnel.

Dans le cadre de la recherche biomédicale à laquelle il vous est proposé de participer, un traitement automatisé et anonyme de vos données personnelles sera fait.

Vos données médicales sont transmises au Promoteur de la recherche. Ces données sont identifiées par un numéro de code et/ou vos initiales. Ces données peuvent également, dans des conditions assurant leur confidentialité, être transmises aux autorités de santé françaises.

Conformément à la loi relative à l'informatique et aux libertés (loi n° 78-17 du 6 janvier 1978 modifiée par la loi n° 2004-801 du 6 août 2004) vous disposez d'un droit d'accès, de rectification et d'opposition relative au traitement de vos données personnelles. Ces droits s'exercent auprès du médecin en charge de la recherche qui seul connaît votre identité. Vous pouvez également accéder directement ou par l'intermédiaire d'un médecin de votre choix à l'ensemble de vos données médicales en application des dispositions de l'article L 1111-7 du Code de la Santé Publique. Les informations concernant votre identité seront tenues confidentielles par votre médecin.

Par ailleurs, toutes informations nouvelles survenant au cours de l'étude et susceptibles de modifier le consentement vous seront transmises. De même, vous serez informé, à votre demande auprès du médecin qui vous a pris en charge dans le cadre de cette étude, des résultats globaux de l'essai.

Enfin, vous pouvez avoir accès à des informations sur l'essai en consultant le site Internet de la Fédération (http://www.fnclcc.fr/)

8- A qui devez-vous vous adresser en cas de question ou de problème?

En cas de problèmes, d'événements indésirables en cours d'essai ou de questions, vous pouvez-vous adresser aux personnes suivantes :

Vos contacts dans l'étude *(titre, nom, prénom, adresse et téléphone) :*
.....
.....
Coordonnées du médecin référent du patient
.....
.....

9- Quel est le calendrier des examens et du traitement ?

VISITES	Période de traitement [1]					Suivi après traitement							
Visites	V0	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
Dates des visites	J0 Bilan inclusion	M6	M12	M18	M24	M36	M48	M60	M72	M84	M96	M108	M120
Critères d'inclusion / non inclusion	X												
Consentement éclairé signé	X												
Randomisation (R)	X												
EXAMEN CLINIQUE													
Taille, Poids, PS (OMS)	X	X	X	X	X								
Signes vitaux	X	X	X	X	X								
Examen clinique		X	X	X	X								
Toxicité		X	X	X	X	X	X	X	X	X	X	X	X
EXAMENS PARACLINIQUES													
Scanner abdomino-pelvien (ou IRM)	X		X[3]		X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]
Scintigraphie osseuse	X		X[3]		X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]
BILAN BIOLOGIQUE													
NFS, Plaquettes	X	X	X	X	X								
Ionogramme sanguin	X	X	X	X	X								
Bilan hépatique	X	X	X	X	X								
Bilan rénal	X	X	X	X	X								
PSA	X	X	X	X	X	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
Testostéronémie	X	X	X	X	X	X	X	X					
Bilan lipidique: cholesterol total, HDL, LDL, triglycerides	X	X	X	X	X								
Glycémie à jeun	X	X	X	X	X								
TRAITEMENT (Bras B)													
Leuproréline	X	X	X	X									
RECHERCHE TRANSLATIONNELLE													
QUESTIONNAIRE QUALITE DE VIE													
QLQC30	X	X	X	X	X		X		X				

1- Visites à réaliser pour les patients des 2 bras. Les patients du bras A ne recevront pas le traitement.
2- Examens à faire tous les 6 mois.
3- Examens à faire seulement pour les patients avec un PSA > 0.2 ng/mL ou qui ont des douleurs osseuses (même si le PSA n'a pas significativement augmenté).

LEXIQUE

(1) Traitement adjuvant : Cet adjectif qualifie un traitement anticancéreux complémentaire d'un traitement principal.

(2) Mictionnel(le) : Adjectif relatif à l'action d'uriner (la miction).

(3) Dysurie : La dysurie est la difficulté à uriner.

(4) Nycturie : La nycturie est le fait d'uriner la nuit.

(5) Oligurie : L'oligurie est la diminution du volume des urines.

FORMULAIRE DU RECUEIL DE CONSENTEMENT DE PARTICIPATION DU PATIENT A L'ETUDE AFU-GETUG 20/0310, N°EudraCT : 2010-022037-29

Titre de l'essai : **Etude de phase III randomisée évaluant le bénéfice d'un traitement hormonal adjuvant par leuproréline acétate (Eligard® 45 mg) pendant 24 mois après prostatectomie totale chez des patients à haut risque de récidive.**

Promoteur de l'étude : Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC), 101 rue de Tolbiac, 75654 PARIS cedex 13

Investigateur coordonnateur : Dr. François Rozet, Service d'Urologie, Institut Montsouris, 42 Bd Jourdan, 75014 PARIS, France

Je soussigné(e) : Nom :.....Prénom :.....

Adresse :.....

Ai pris connaissance de la note d'information m'expliquant le protocole de recherche mentionné ci-dessus.

- J'ai reçu et j'ai bien compris les informations qui m'ont été remises par le Dr ..... qui m'a expliqué l'objectif et le déroulement de cette recherche biomédicale.
- J'ai pu poser toutes les questions que je voulais, j'ai reçu des réponses adaptées et j'ai pu disposer d'un temps de réflexion suffisant entre l'information et ma décision de participer à cet essai.
- J'ai bien noté que je serai libre à tout moment d'arrêter ma participation, j'en informerai par écrit le Dr .....
- J'ai bien noté le droit d'accès prévu par la loi "Informatique et Libertés" du 6 janvier 1978, modifiée par les lois n°94-548 du 1er juillet 1994, n°2002-303 du 4 mars 2002 et n°2004-801 du 6 août 2004. Le droit d'accès est prévu article 39 et le droit de rectification article 40 et s'exerce à tout moment auprès du médecin en charge de la recherche, qui seul connaît mon identité.
- J'ai été informé et j'accepte que certaines données nominatives me concernant et issues de la recherche feront, pour cette étude, l'objet d'un traitement informatisé par le promoteur ou pour son compte conformément à la loi n° 2004-801 du 6 août 2004 relative à la protection des personnes physiques à l'égard des traitements de données à caractère personnel et modifiant la loi n° 78-17 du 6 janvier 1978 relative à l'informatique, aux fichiers et aux libertés.
- J'ai été informé de mon droit de m'opposer au traitement automatisé des données nominatives me concernant.
- J'ai bien noté que le promoteur a pris toutes les dispositions prévues par la loi sur les Recherches Biomédicales (anciennement Loi Huriet- décret d'application 2006-477 du 26 avril 2006 modifiant le titre II du livre 1 du Code de la Santé Publique) relative à la protection des personnes se prêtant à des recherches biomédicales.
- J'ai bien noté que le droit d'accès et de rectification, que m'ouvrent les textes susvisés, pourra s'exercer à tout moment auprès du Dr..... et

que les données me concernant pourront m'être communiquées par l'intermédiaire d'un médecin de mon choix.

- Je certifie sur l'honneur être affilié à un régime de Sécurité Sociale ou bénéficiaire d'un tel régime.
- Je m'engage à ne participer à aucun autre protocole pendant cette étude.
- J'ai bien noté que cette étude a reçu l'autorisation de l'AFSSAPS et du CPP Ile de France VII.
- J'ai compris que les données de cette étude resteront strictement confidentielles. Je n'autorise leur consultation que par les personnes qui collaborent à la recherche, désignées par le promoteur.
- J'ai bien noté que j'ai le droit, à ma demande, d'être informé des résultats globaux de cette recherche selon les modalités qui ont été précisées dans la note d'information.
- J'ai lu et reçu un exemplaire signé de ce document et j'accepte de participer au présent protocole.

Compte-tenu des informations qui m'ont été transmises : ***cocher les cases appropriées en fonction de votre volonté (OUI/NON)***	**OUI**	**NON**
J'accepte librement et volontairement de participer à la recherche biomédicale [a] [b] de l'essai AFU-GETUG 20/0310 N° EudraCT: 2010-022037-29	☐	☐

[a] loi sur les Recherches Biomédicales (anciennement Loi Huriet- décret d'application 2006-477 du 26 avril 2006 modifiant le titre II du livre 1 du Code de la Santé Publique).
[b] loi n° 2004-801 du 6/08/2004 relative à la protection des personnes physiques à l'égard des traitements de données à caractère personnel et modifiant la loi n°78-17 du 6/01/1978 relative à l'informatique, aux fichiers et aux libertés.

Mon consentement ne décharge pas les organisateurs de la recherche de leurs responsabilités. Je conserve tous mes droits garantis par la loi.

Partie à remplir par le participant à la recherche	***Partie à remplir par le médecin investigateur***
Nom et prénom	Nom et prénom
Signature :	Signature :
Date :	Date :

[1] un exemplaire cosigné doit être remis à la personne qui participe à la recherche