SYNOPSIS – PROTOCOL AFU-GETUG 20/0310

A) IDENTIFICATION OF THE CLINICAL TRIAL

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

VERSION AND DATE: VERSION 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).