SYNOPSIS – PROTOCOL N° UC-0160/1617

A) TRIAL IDENTIFICATION

SPONSOR – PROTOCOL CODE NUMBER: UC-0160/1617

VERSION (NR & DATE): **Version 7.0 (20 April 2020)**

TRIAL TITLE:

Adjuvant radiotherapy in patients with pathological high-risk bladder cancer. A randomised multicentre phase II study

ABBREVIATED TITLE: **BLADDER-ART**

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NUMBER OF PARTICIPATING CENTRES (ESTIMATE): 24	NUMBER OF PATIENTS: 109

B) SPONSOR IDENTIFICATION

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C) TRIAL GENERAL INFORMATION

INDICATION:

Patients with pathological high-risk muscle invasive bladder cancer treated by radical cystectomy and pelvic lymph nodes dissection

METHODOLOGY:

Multicenter randomised phase II study in high-risk bladder cancer patients treated by radical cystectomy with pelvic lymph nodes dissection assessing :

- Experimental Arm: adjuvant pelvic radiotherapy consisting of 28 x 1.8 Gy fractions (total dose of 50.4 Gy), 5 days per week, 1 fraction /day (duration of RT is 38 days).
- Standard Arm: surveillance.

Eligible patients will be randomised, in a 3:1 ratio, to receive either: adjuvant pelvic radiotherapy (Experimental Arm), or surveillance (Standard Arm).

PRIMARY OBJECTIVE:

The primary objective of the trial is to assess the efficacy of adjuvant radiotherapy in patients with high-risk bladder cancer after radical cystectomy and pelvic lymph nodes dissection. Efficacy will be assessed in terms of pelvic recurrence-free survival (PRFS) at 3 years.

SECONDARY OBJECTIVES:

For each treatment arm (adjuvant pelvic radiotherapy [Experimental Arm], or surveillance [Standard Arm]), these objectives will be evaluated independently.

- To evaluate 5-year pelvic recurrence-free survival (PRFS)
- To evaluate disease-free survival (DFS) at 3 and 5 years.
- To evaluate overall survival (OS) at 3 and 5 years.
- To evaluate metastasis-free survival (MFS) at 3 and 5 years.
- To evaluate disease-specific survival (DSS) at 3 and 5 years.
- To evaluate the tolerance and safety of each treatment strategy.
- To evaluate patients' quality of life.

Ancillary studies Objectives:

- Investigation of individual predisposition to develop radiotherapy induced late digestive toxicity using the radiation-induced lymphocyte apoptosis (RILA) assay
- The analyse of genomic and transcriptome correlation between different clusters and oncological outcomes
- Dosimetric banking to evaluate the correlation of Dose-Volume Histogram with:
  - ✓ Gastrointestinal toxicity grade ≥2;
  - ✓ Pelvic recurrence (radiotherapy volumes, mapping of recurrences).

DIAGNOSIS AND INCLUSION CRITERIA:

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

1. Patients with **histologically-confirmed muscle-invasive bladder cancer**, either with pure urothelial carcinomas, or dominant urothelial carcinomas (>50%) combined with other histological variants including: micropapillary, epidermoid, or adenocarcinomas, are eligible.
   Patients with small cell variants, pure adenocarcinomas, or pure epidermoid carcinomas **are not eligible**.
2. Patients with radical cystectomy and pelvic lymph nodes dissection with no **microscopic residual disease** (R0 and R1).
   Note that only R1 patients without urinary diversion (as orthotropic neo-bladder replacement) are eligible for the study, to limit cystectomy bed radiation induced toxicities
3. Patients with tumours of TNM staging: pN0-2, M0 by imagery, and pT3a, pT3b, pT4a, and pT4b, as well as, pTX-pN1-2, pTx-Nx R1 are eligible.
4. Patients having received **neo-adjuvant or adjuvant chemotherapy treatment are eligible**. Randomisation is allowed only if AE due to chemotherapy are ≤ grade 2 at randomisation.
5. Patients ≥18 years old.
6. ECOG performance status ≤2.
7. Absolute neutrophil count (ANC) ≥1500 cells/mm^3
8. Platelets ≥100000 cells/mm^3
9. Haemoglobin ≥8 g/dL (Note: following a blood transfusion or another intervention if required).
10. Adequate hepatic function: AST (SGOT) and ALT (SGPT) ≤2.5 x ULN; or ≤3.5 x ULN in the case of concurrent disease with known etiology and for which a corrective treatment is possible.
11. Adequate renal function: clearance >30 mL/min (MDRD).
12. Patients having provided written informed consent prior to any study-related procedures.
13. Patients affiliated to the social security scheme.
14. Patients willing and able to comply with the scheduled visits, treatment plan, laboratory tests, and other study procedures indicated in the protocol.

NON-INCLUSION CRITERIA:

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

1. Patients with **R1** resection **and** with **orthotropic neo-bladder reconstruction as urinary diversion** are not eligible.
2. Patients with clinical or radiological evidence of metastases or N3 staged bladder cancer are not eligible.
3. Prior invasive solid tumours or haematological malignancies unless disease free for a minimum of 3 years prior to randomisation, except:
   - ✓ skin basal cell carcinoma,
   - ✓ *in situ* epithelioma of the cervix,
   - ✓ or prostate cancer: incidentally discovered during cystoprostatetectomy and pelvic lymph node dissection and with a good prognosis (T stage <pT3b and/or Gleason <8 and pN- and/or post-operative PSA <0.1 ng/mL),
4. Prior pelvic radiotherapy.
5. Patients with active inflammatory bowel disease.
6. Patients who required surgical treatment for bowel obstruction before bladder cancer diagnosis or after cystectomy.
7. Prior chemotherapy for other malignant diseases within the previous 5 years, except for neoadjuvant pre-cystectomy chemotherapy or adjuvant chemotherapy which are permitted.
8. Patients with the following severe acute co-morbidity are not eligible:
   - ✓ Unstable angina or congestive heart failure that required hospitalization in the 6 months before randomisation.
   - ✓ Transmural myocardial infarction in the 6 months prior to randomisation.
   - ✓ Acute bacterial or fungal infection requiring intravenous antibiotics at randomisation.
   - ✓ Chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of randomisation.
   - ✓ Severe hepatic disease: Child-Pugh Class B or C hepatic disease.
   - ✓ Known acquired immune deficiency syndrome (AIDS); the study treatment could impact blood count.
9. Patients with any other disease or illness which requires hospitalization or is incompatible with the study treatment are not eligible.
10. Patients unable to comply with study obligations for geographic, social, or physical reasons, or who are unable to understand the purpose and procedures of the study.
11. Patients enrolled in another therapeutic study within 30 days prior of randomisation.
12. Person deprived of their liberty or under protective custody or guardianship.

PRIMARY ENDPOINT:

The primary endpoint is the pelvic recurrence-free survival (PRFS) which will be assessed at 3 years. The PRFS is defined as the delay between randomisation and pelvic recurrence or death, whichever occurs first.

SECONDARY ENDPOINTS:

- PRFS will also be assessed at 5 years (see the definition for the primary endpoint).
- Disease-free survival (DFS) will be assessed at 3 and 5 years. DFS is defined as the delay between randomisation and tumour progression (local, regional, or distant) or death of any cause, whichever occurs first.
- Overall Survival (OS) will be assessed at 3 and 5 years. OS is defined as the delay between randomisation and death, of any cause.
- Metastasis-free survival (MFS) will be assessed at 3 and 5 years. MFS is defined as the delay between randomisation, and metastasis (clinical or radiological) or death of any cause whichever occurs first.
- Disease-specific survival (DSS) will be assessed at 3 and 5 years. DSS is defined as the delay between randomisation and death due to bladder cancer.
- The tolerance and safety will be evaluated by toxicity: acute (<6 months after RT) and late (≥6 months after RT), assessed using the NCI CTCAE Version N°4.0. The tolerance will be evaluated until 5 years.
- Quality of life will be assessed by the:
  - ✓ EORTC QLQ-C30
    The QLQ-C30 is composed of five functional scales, three symptom scales, a global health status/QoL scale, and six single items. All of the scales and single-item measures range in score from 0 to 100. A high score represents a higher response level. Scores will be analysed following the EORTC QLQ-C30 Scoring Manual.
  - ✓ The Bladder Cancer Index (BCI)
    The BCI was developed for local treatment of bladder cancer. The index consists of 3 principal domains and 6 overall subdomains. The index ranges in score from 0 to 100. A high score represents a higher response level.

D) THERAPEUTIC INTERVENTIONS

The study therapy consists of adjuvant radiotherapy: 28 x 1.8 Gy fractions (total dose of 50.4 Gy), 5 days per week (duration of RT is 38 days).

Radical cystectomy with pelvic lymph-node dissection, with or without neoadjuvant or adjuvant chemotherapy is the standard patient care. The radical cystectomy with pelvic lymph-node dissection must be performed according to the EAU guidelines. No concomitant chemoradiotherapy is permitted in this study.

Patients will be randomised within 16 weeks of radical cystectomy. Patients with postoperative (adjuvant) chemotherapy (2-4 cycles of standard chemotherapy) will be randomised after chemotherapy. A delay of at least 4 to 8 weeks from the end of the last chemotherapy cycle and radiotherapy must be respected. Patients with severe chemotherapy-related toxicity (grade ≥3) not resolved within 16 weeks of the cystectomy must not to be randomised. All patients randomised in the Experimental Arm must begin radiotherapy within 16 weeks of cystectomy.

- Experimental Arm: adjuvant pelvic radiotherapy consisting of 28 x 1.8 Gy fractions (total dose of 50.4 Gy), 5 days per week (duration of RT is 38 days).
- Standard Arm: surveillance.

TREATMENT DURATION:

The duration of adjuvant radiotherapy is 38 days. Patients will be followed up for 5 years after randomisation.

E) STATISTICAL ANALYSIS PLAN

REQUIRED NUMBER OF PATIENTS TO BE SCREENED / INCLUDED:

Hypotheses are the following:

- ✓ Null hypothesis: 3-year pelvic recurrence-free survival (PRFS) rate of 80%.
  - PRFS rate is about 80-90% for pT3-4 and/or pN1-2 and R0 patients and 40-70% for R1 patients.
  - More recently, in a cystectomy series including extended pelvic lymph node dissection and chemotherapy, 20% of loco-regional recurrence for all stages appears as a realistic rate and could support our hypothesis.
  - It is however expected that R1 patients will account for a small proportion of inclusions (4% to 15%). Thus, we expect an overall 80% PRFS rate.
- ✓ Alternative hypothesis: 3-year PRFS rate of 90%,
- ✓ 2-year accrual period,
- ✓ 3-year follow-up time per patient,
- ✓ 2-sided 5% error rate,
- ✓ 80% power.

A total of 74 eligible and assessable patients are required. The anticipated 95% confidence interval for the PRFS at 3 years is (71%; 87%).

- **Standard arm**

Assuming a 3:1 randomisation ratio, 25 eligible and assessable patients are needed in the standard arm.

- **Overall sample size**

- ✓ 74 + 25 = 99 eligible and assessable patients
- ✓ Assuming that approximately 10% of patients cannot be assessed for the primary endpoint, 109 patients will need to be recruited.

STATISTICAL ANALYSIS:

- No comparison between arms will be performed.
- Eligible population and eligible and assessable populations will be described in terms of compliance with eligibility criteria, socio-demographic, clinical and laboratory characteristics, as well characteristics of the treatments received.
- Median follow-up time will be estimated using the reverse Kaplan-Meier.
- Primary outcome analysis: Pelvic recurrence-free survival (PRFS) will be estimated in the eligible and assessable population using the Kaplan-Meier method. Median survival time will be reported with 95% confidence interval.

F) SAMPLES COLLECTED FOR ANCILLARY STUDIES

SAMPLE TYPES:

- Peripheral blood samples that will be used for radiation-induced lymphocyte apoptosis (RILA) assay and proteomic analysis, only for the patients in experimental arm.
- Tumour sample that will be used to analyse the genomic and transcriptome correlations between different clusters and oncological outcomes

SAMPLE QUANTITIES:

- Blood sampling for RILA assay proteomic analysis: only in the Experimental Arm prior to radiotherapy (one 4 mL sample in a heparin tube and two 6 mL samples in EDTA tubes).
- Biobanking of tumour samples: At least one formalin-fixed paraffin-embedded sample from the cystectomy and pelvic lymph nodes dissection.

G) TRIAL DURATIONS
INCLUSION PERIOD: 5.5 years
TREATMENT PERIOD: 38 days
FOLLOW-UP: 5 years
DURATION UNTIL PRIMARY ENDPOINT EVALUATION: 10.5 years
OVERALL STUDY DURATION (INCLUDING FOLLOW-UP): 10.5 years