SYNOPSIS – PROTOCOL N° UC-0160-1715

A) STUDY IDENTIFICATION	
SPONSOR – PROTOCOL CODE NUMBER: UC-0160-1715 VERSION (NUMBER AND DATE): **Version 4.1 – 19 Apr 2021**	
STUDY TITLE: Phase II study of maintenance anti-PD-L1 treatment with atezolizumab after chemo-radiotherapy for muscle-infiltrating bladder cancer patients not eligible for radical cystectomy: Bladder Sparing	
ABBREVIATED TITLE: **BLADDER SPARING**	
COORDINATING INVESTIGATOR: **Prof Christophe HENNEQUIN** Département d'Oncologie Radiothérapie Hôpital Saint-Louis, Paris CO-COORDINATING INVESTIGATORS: **Prof Olivier CHAPET** Département d'Oncologie Radiothérapie Centre Hospitalier Lyon Sud, Pierre Benite **Prof Morgan ROUPRET** Service d'Urologie CHU Pitié-Salpétrière, Paris	
NUMBER OF PARTICIPATING CENTRES (ESTIMATE): 10-15	NUMBER OF PATIENTS: 77

B) SPONSOR IDENTIFICATION	
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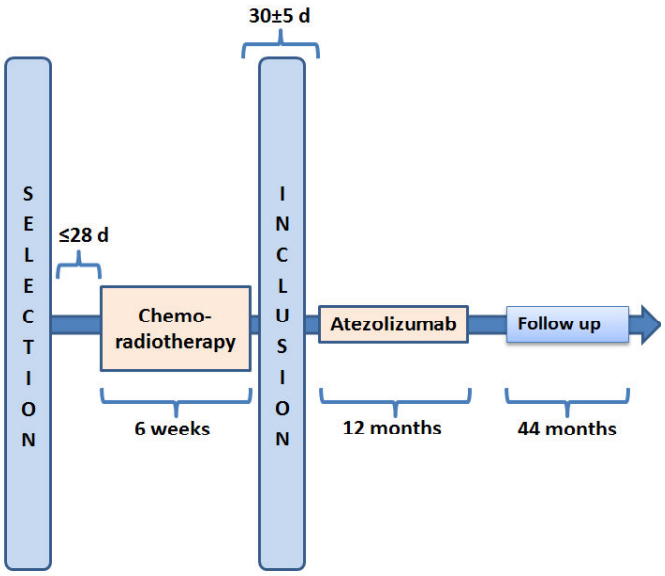
C) STUDY GENERAL INFORMATION

INDICATION:

Patients older than ≥18 years, with muscle-invasive bladder cancer unfit for radical cystectomy because of age, comorbidities, and/or patient's refusal.

METHODOLOGY:

This study is designed as a multicentre, single-arm phase II study.



PRIMARY OBJECTIVE:

The primary objective of this study is to evaluate the efficacy of a maintenance therapy with atezolizumab, an anti-PD-L1, after adjuvant chemo-radiotherapy for the treatment of patients with muscle-invasive bladder cancer not eligible for radical cystectomy, in terms of disease-free survival (DFS) assessed at 2 years.

SECONDARY OBJECTIVES:

- To evaluate local control at 2 and 5 years.
- To evaluate disease-free survival (DFS) at 5 years.
- To evaluate overall survival (OS) at 2 and 5 years.
- To evaluate the tolerance and safety of the treatment strategy.
- To evaluate patients' quality of life

SELECTION PHASE

INCLUSION CRITERIA

1. Muscle-invasive bladder cancer (MIBC) pT2-T3 histologically confirmed:
   - Urothelial and squamous cell histological types are allowed.
   - De novo MIBC or after a history of non-muscle-invasive bladder cancer.
2. Complete transurethral resection of bladder tumour (TURBT), either:
   - ✓ within 6 weeks of selection if no chemotherapy was administered,
     or
   - ✓ before starting chemotherapy.
3. Patients for which chemo-radiotherapy is planned
4. No major pelvic involvement: pelvic nodes ≤15 mm on CT scan.
5. No distant metastasis.
6. Patient unfit for radical cystectomy because of age, comorbidities, or patient's refusal.
7. Patients ≥18 years old
8. ECOG performance status ≤2.
9. Life expectancy ≥12 months.
10. Haematological and biological parameters:
    - White blood cell count ≥4000/mm^3
    - Platelet count ≥100000 cells/mm^3
    - Haemoglobin level ≥9 g/dL or corrected after transfusion
    - Adequate renal function: clearance >50 mL/min (Cockcroft).
    - 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. Patients of childbearing potential who agree to use a medically acceptable method of contraception during the study and for 120 days after the last study treatment. Women must have a negative urine or serum pregnancy test before receiving the study treatment and within 14 days prior to selection.
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:

Patients are not eligible if they comply with any of the following criteria:

1. Patient with bladder carcinoma in situ (CIS).
2. Prior pelvic irradiation.
3. MIBC histology other than urothelial or squamous cell carcinomas (e.g., adenocarcinomas, micropapillary, sarcomas, or small cell histological types).
4. History of neoplastic disease, during the 3 years before selection, except completely resected cutaneous basal-cell carcinomas, carcinoma in-situ or localised prostate cancer without biochemical recurrence following definitive treatment.
5. Prior treatment with CD137 agonists or immune checkpoint inhibitors, including anti-cytotoxic T lymphocyte-associated antigen 4 (anti-CTLA-4), anti-programmed death-1 receptor (anti-PD-1), and anti-programmed death-ligand 1 (anti-PD-L1) therapeutic antibodies.
6. Contraindications for pelvic radiotherapy (e.g., inflammatory bowel disease).
7. History of immunodeficiency, including HIV infection, or systemic steroid therapy for any other disease.
8. A history of active autoimmune disease, except autoimmune-related hypothyroidism and type I diabetes mellitus (see appendix 5).
9. History of severe allergic anaphylactic reactions to chimeric, human or humanised antibodies, or fusion proteins.
10. Known hypersensitivity to Chinese hamster ovary (CHO) cell products or any component of the atezolizumab formulation.
11. Prior allogeneic stem cell or solid organ transplant.
12. Patients with the following severe acute co-morbidity are not eligible:

- Unstable angina or congestive heart failure that required hospitalisation in the 6 months before selection.
- Transmural myocardial infarction in the 6 months prior to selection.
- Acute bacterial or fungal infection requiring intravenous antibiotics at selection.
- Chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalisation or precluding study therapy at the time of selection.
- Severe hepatic disease: Child-Pugh Class B or C.

13. Patients with any other disease or illness which requires hospitalisation or is incompatible with the study treatment are not eligible.
14. 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.
15. Patients enrolled in another therapeutic study within 30 days of selection.
16. Pregnant or breast feeding women.
17. Person deprived of their liberty or under protective custody or guardianship.

INCLUSION PHASE

INCLUSION CRITERIA

1. Patients who have received standard (chemo)-radiotherapy ≥60Gy or equivalent on the bladder according to the local practice.
2. The first administration of atezolizumab must be performed within 30 (+/-5) days after the last session of RT.

3. ECOG performance status ≤2.
4. Haematological and biological parameters:

- White blood cell count ≥3000/mm^3
- Platelet count ≥100000 cells/mm^3
- Haemoglobin level ≥9 g/dL or corrected after transfusion
- Adequate renal function: clearance >50 mL/min (Cockroft)
- 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.

5. Patients of childbearing potential who agree to use a medically acceptable method of contraception during the study and for 120 days after the last study treatment. Women must have a negative urine or serum pregnancy test before receiving the study treatment and within 14 days prior to inclusion.
6. Patients having provided written informed consent prior to any study-related procedures.
7. 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:

In addition to the same non-inclusion criteria of selection phase that have to be respected, patients who have previously experienced a severe cutaneous reaction during previous treatment with an immune-stimulating anti-cancer agent.

PRIMARY ENDPOINT:

Disease-free survival (DFS) will be assessed at 2 years. DFS is defined as the delay between date of inclusion and tumour relapse (local, regional, or distant) or death from any cause, whichever occurs first.

SECONDARY ENDPOINTS:

- Local control rate will be evaluated by cystoscopy at 2 and 5 years. The presence of non-muscle-invasive or muscle-invasive bladder cancers will be considered as a local failure. To be defined as locally controlled, the bladder must be completely free of tumour.
- Disease-free survival (DFS) will be assessed at 5 years. DFS is defined as the delay between date of inclusion and tumour relapse (local, regional, or distant) or death from any cause, whichever occurs first.
- Overall Survival (OS) which will be assessed at 2 and 5 years. OS is defined as the delay between the date of inclusion and the date of death, from any cause.
- The tolerance and safety will be evaluated by toxicity (acute [<6 months after the start of atezolizumab] and late [≥6 months after the start of atezolizumab]), assessed using the NCI CTCAE v5.0 (see Appendix 2). The tolerance will be evaluated up until 5 years at 2 years and 5 years.

- Quality of life (QoL) will be assessed by the:
  - ✓ EORTC QLQ-C30 (see Appendix 3)
  - ✓ The EORTC 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 [1].
  - ✓ EORTC QLQ-BLM30
  - ✓ EORTC QLQ-ELD14 - Oncogeriatric evaluations (for patients' ≥70 years old)
  - ✓ G8 oncodage (at baseline for patients' ≥70 years old)

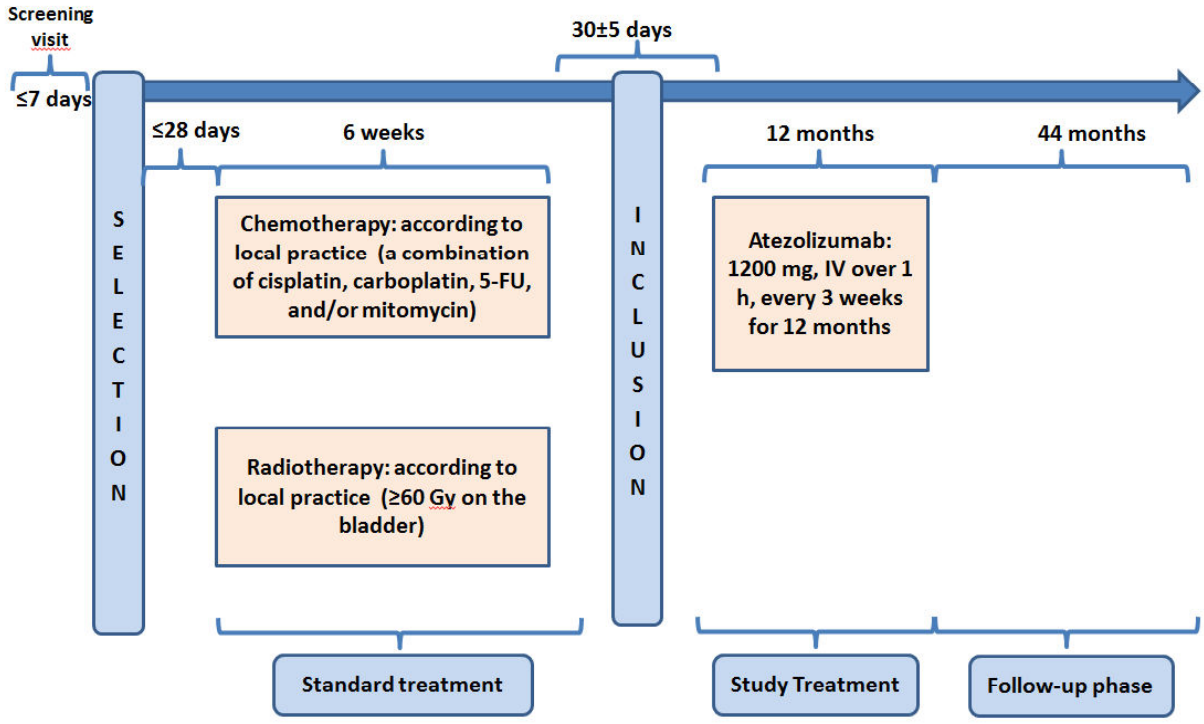
D) INVESTIGATIONAL MEDICINAL PRODUCTS

PRODUCT NAMES AND ADMINISTRATION:

Drug name (INN)	Registered name(1)	Pharmaceutical form	Administration	Posology
Atezolizumab	TECENTRIQ™	1200 mg/20 mL (60 mg/mL)	Intravenous	1200 mg

(1) When any generic drug can be is used indicate only the INN name. The choice of the registered name or brand name is left to the decision of the investigation center.

THERAPEUTIC REGIMENS:



The standard treatment comprises:

- Chemotherapy: depending on the physiological status of the patients a number of chemotherapy protocols will be proposed according to local standard practice. Chemotherapy will include one or more of the following: cisplatin, carboplatin, 5-fluorouracil (5-FU), and mitomycin C.
- Radiotherapy: Bladder irradiation: ≥ 60Gy or equivalent according to local practice.

The study treatment comprises:

- Anti-PD-L1 immunotherapy: atezolizumab (1200 mg) administered IV over 1 h every 3 weeks for 12 months (18 injections). Beginning 30 days (±5 days) after chemo-radiotherapy.

TREATMENT DURATION:

- Immunotherapy: every 3 weeks for 12 months

E) STATISTICAL ANALYSIS PLAN

REQUIRED NUMBER OF PATIENTS TO BE ENROLLED: 77 patients

The sample calculation is based on a Fleming single stage phase II design.

Null hypothesis: DFS rate at 2-years with chemo-radiotherapy is expected to be 50% [12]. This hypothesis takes into account intercurrent deaths occurring before 2 years.
We hypothesise that maintenance treatment with atezolizumab will increase the DFS by at least 15% resulting in a DFS of ≥65% at 2 years.

A sample of 67 patients is required to assess the DFS at 2 years, controlling for a type I error: α=0.05 and type II error: β=0.20.

The study will conclude in favour of the benefit of maintenance treatment with anti-PD-L1 if a minimum of 41 patients are alive without relapse at 2 years among the 67 patients.

Thus to allow for 15% of enrolled patients who will not be treated with atezolizumab, the study will enrol an additional 10 patients. Overall, 77 patients will be enrolled in the study.

STATISTICAL ANALYSIS:

- The eligible population will be described in terms of compliance with eligibility criteria, socio-demographics, clinical and laboratory characteristics, as well as characteristics of the treatments received.
- Median follow-up time will be estimated using the reverse Kaplan-Meier method.
- DFS at 24 months (Primary endpoint analysis):
  DFS is defined as the delay between the date of inclusion, and tumour progression (local, regional, or distant) or death of any cause, whichever occurs first. DFS will be analysed for all patients at 2 year as a main endpoint: alive without disease or not. After two year, DFS will still be recorded and analysed as a time-to-event secondary endpoint; patients will be censored at the date of last contact.

- Local control rate at 2 and 5 years.
  Duration of local control will be calculated from the date of inclusion until the date of positive cystoscopy. In case of regional or distant relapse occurring before local relapse, data will be censored at the time of relapse. The date will also be censored at death or in case of a second primary tumour.
- Overall survival (OS) at 2 and 5 years.
  OS is defined as the delay between the date of inclusion and the date of death, of any cause. Patients will be censored at the date of last contact for patients alive at the time of database lock.
- Acute and late toxicities (NCI CTCAE v5.0):
  - ✓ Adverse events (by toxicity grade),
  - ✓ Serious adverse events,
  - ✓ Adverse events related to study interventions,
  - ✓ Counts, frequencies, and 95% confidence intervals will be reported.
- The EORTC QLQ-C30 will be scored according to the EORTC QLC-C30 scoring manual. Scales with more than 50% of the constituent items completed, a pro-rated score will be computed, consistent with the scoring manual and validation paper. For subscales with less than 50% of the items completed, the subscales will be considered as missing. Summary statistics of absolute and normalised scores of the QLQ-C30 scales and their changes from baseline will be calculated at each assessment time point for each study arm. The mean (and 95% confidence interval) and median (and inter-quartile ranges) of the absolute scores and changes from baseline will be reported.
- EORTC QLQ-BLM30.
- EORTC QLQ-ELD14 and oncodage G8 (at baseline for patients' ≥70 years old)).
  The data will be analysed to evaluate the impact of the treatment on the QoL of elderly patients (≥70 years old). The ELD14 module consists of 14 items, each with four response levels.
- Additional quantitative variables will be described using means and standard deviations if the normality assumption is satisfied, if not, other descriptive statistics (median, range, quartiles) will be used.
- Additional qualitative variables will be described using frequency and percentage.

F) SAMPLES COLLECTED FOR BANKING

SAMPLE TYPES:

- Tumour samples: sample used for diagnosis and from any positive TURBT performed.
- Blood samples:
  - before chemo-radiotherapy (at selection visit),
  - before initiating atezolizumab (at D1 visit)
  - During treatment at M3, M6, and M12 study treatment visits,
  - After end of atezolizumab at 3 months, 6 months and 12 month post treatment.

SAMPLE QUANTITIES:

- Tumour samples: 2 slides containing tumour
- Blood samples: 2 x 10 mL (EDTA tubes)

G) STUDY DURATIONS

INCLUSION PERIOD: 48 months
TREATMENT PERIOD: 15 months
FOLLOW-UP: 44 months after treatment period
STUDY DURATION UNTIL PRIMARY ENDPOINT EVALUATION: 48 months
OVERALL STUDY DURATION (INCLUDING FOLLOW-UP): 107 months

H) STUDY FLOW-CHART

STUDY VISIT	Selection visit	Standard treatment (chemo-radiotherapy)	Inclusion visit	Study Treatment visits (D1, W3, W6, W9…)	Study treatment visits (M3, M6, M9 and M12)	Discontinuation / End of treatment visit	Follow-up visits (M20, 32, 44, and 56)
TIMELINES	Within 7 days of selection	Within 28 days of screening visit	14±3 days before starting atezolizumab	At first administration, then every 3 weeks (± 2 days)	Every 3 months (± 2 weeks)	< 30 days after last visit	At 20, 32, 44, and 56 months after starting immunotherapy (± 4 weeks)
Verification of eligibility criteria	X		X				
Signing of informed consent form	X$^{\pi}$		X				
Treatment		X		X	X		
PHYSICAL EXAMINATION							
Weight, height, ECOG PS, and vital signs	X		X	X	X		X
Demographic data and medical history	X						
Concomitant treatments	X		X	X	X	X	X
Safety, toxicity	X		X	X	X	X	X
PARACLINICAL EXAMINATION							
Tumour evaluation (cystoscopy)*	X			Xφ	X	X	X
Thoracic abdominal CT scan	X				X§	X§	X§
Bone scan	X						
Transurethral resection of bladder tumour (TURBT)	X$^{\#}$		X$^{\#}$	X$^{\#}$	X$^{\#}$	X$^{\#}$	X$^{\#}$
LABORATORY TESTS							
CBC, platelets	X		X	X	X	X	X
Hepatic function	X		X	X	X	X	X
Renal function	X		X	X	X	X	X
TSH, free T3, free T4	X		X	X	X	X	X
Pregnancy test (if applicable)	X		X	X	X	X	X
QUALITY of LIFE							
QLQ-C30	X		X		X$^{\beta}$	X$^{\beta}$	X$^{\beta}$
QLQ-BLM30	X		X		X$^{\beta}$	X$^{\beta}$	X$^{\beta}$
G8 oncodage questionnaire**	X						
QLQ-ELD14 questionnaire**	X		X		X$^{\beta}$	X$^{\beta}$	X$^{\beta}$
BIOBANKING							
Tumour biobanking	X$^{\alpha}$		X$^{\alpha}$		X$^{\alpha}$		X$^{\alpha}$
Blood sample	X$^{\mu}$			X$^{\mu}$	X$^{\theta}$		X$^{\Psi}$

(π) the informed consent form can be sign up to 30 days before the selection visit (*)Tumour evaluation by cystoscopy until disease relapse; (φ) Only at D1; (§) Only at M6, 12, 20, 32, 44, and 56; (#) TURBT will be performed if required; (**) Only for patients ≥70 years old; (β) Only at M3, 12, and 20; (α) Tumour samples must be collected from all positive TURBT and blood samples before chemo-radiotherapy(μ) and before initiating atezolizumab at D1, (θ) only at M3, 6 and 12. (Ψ) only at 3, 6 and 12 months after end of treatment.