


Titre	La radiothérapie stéréotactique dans la gestion de cancer oligométastatique de la prostate résistant à la castration : un essai adaptatif de phase II/III à répartition aléatoire.
Protocole ID	PCS IX
ClinicalTrials.gov ID	NCT02685397
Type(s) de cancer	Prostate
Phase	Phase III
Type étude	Traitement
Institution	CHU DE QUEBEC – UNIVERSITE LAVAL  L'HOTEL-DIEU DE QUEBEC ET CRCEO 11 Côte du Palais, Québec, QC, G1R 2J6
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Statut	Fermé
But étude	This adaptive phase II/III randomized trial is designed to demonstrate that eradication of oligometastases by SBRT is a promising and emerging way to delay disease progression and postpone second line systemic therapies in castration-resistant prostate cancer (CRPC) patients. Only CRPC patients with an oligometastatic recurrence will be eligible to take part in this trial. All participating patients will receive either the standard of care (i.e. LHRH agonist in combination with the new generation of hormonal therapy [Enzalutamide]) or the experimental treatment (i.e. LHRH agonist in combination with the new generation of HT [Enzalutamide] plus the additional SBRT treatment). The patients will undergo different evaluations before treatment, such as imaging to confirm oligometastatic recurrence and blood tests. Patients will be stratified according to the location of metastasis (visceral [with or without bone metastases] vs. bone metastases alone) and PSA doubling time (≤ 3 vs. > 3 months). As per the standard of care, patients will have PSA testing performed every 6-12 weeks and re-imaging at 6, 9, 12, 18 and 24 months or at PSA progression, whichever occurs first.
Critères d'éligibilité	<ul style="list-style-type: none"> • Age 18 or older and willing and able to provide informed consent; • Histologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell features; • Ongoing androgen deprivation therapy with a Gonadotropin-releasing hormone (GnRH) analogue or bilateral orchiectomy (i.e., surgical or medical castration); • Patients who have not had a bilateral orchiectomy must have a plan to maintain effective GnRH analogue therapy for the duration of the trial; • Serum testosterone level ≤ 1.7 nmol/L (50 ng/dL) at the Screening visit; • Patients receiving bisphosphonate therapy/Xgeva must have been on stable doses for at least 4 weeks; • Progressive disease at study entry defined as one or more of the following three criteria that occurred while the patient was on androgen deprivation therapy as defined in eligibility criterion #3: • PSA progression defined by a minimum of two rising PSA levels with an interval of ≥ 1 week between each determination. Patients who received an anti-androgen must have progression after withdrawal (≥ 4 weeks since last flutamide or ≥ 6 weeks since last bicalutamide or nilutamide). The PSA value at the Screening visit should be ≥ 2 $\mu\text{g/L}$ (2 ng/mL); • Soft tissue disease progression defined by RECIST 1.1; • Bone disease progression defined by the Prostate Cancer Clinical Trials Working Group 2 (PCWG2) with two or more new lesions on bone scan; this will require a confirmatory bone scan as per PCWG2. • Metastatic disease documented by bone lesions on bone scan or by measurable soft tissue

- disease by CT/MRI. Patients whose disease spread is limited to regional pelvic lymph nodes, and previously radiated, are not eligible;
- Up to 5 metastatic sites
 - ≤ 4 tumours within any given organ system, excluding brain and liver (e.g. up to 4 bone metastases, or 4 lung metastases)
 - All sites of disease must be amenable to SBRT with no previous radiation to the metastatic site to be treated;
 - In the case of a suspicious lesion in an unusual location such as lung or thoracic lymph nodes (without other abdominal lymph nodes), a biopsy should confirm prostate cancer origin.
 - No prior cytotoxic chemotherapy for prostate cancer;
 - Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 or Karnofsky performance status of $> 70\%$ or higher;
 - Patients and their female partners of childbearing potential must be willing to use two forms of contraception (one of which must include a condom as a barrier method of contraception during sexual activity) throughout the duration of the study starting at screening and continuing for 3 months after the last dose of study drug or per local guidelines where these require additional description of birth control methods. These contraceptive methods must include the following:
 - The use of condoms (barrier method) AND one of the following:
 - the use of oral, injected or implanted hormonal methods of contraception by a female partner
 - placement of an intrauterine device (IUD) or intrauterine system (IUS) by a female partner
 - additional barrier method, such as occlusive cap (diaphragm or cervical/vault cap) with spermicidal foam/gel/film/cream/suppository by a female partner
 - tube ligation in the female partner
 - vasectomy or other procedure resulting in infertility (eg. bilateral orchiectomy) for ≥ 6 months
 - Patients must agree to not donate sperm while taking study drug
 - Estimated life expectancy of ≥ 6 months;
 - Ability to swallow the study drug whole and comply with study.

Critères d'exclusion

- Severe concurrent disease, infection, or co-morbidity that, in the judgment of the Investigator, would make the patient inappropriate for enrollment;
- Known or suspected brain metastasis or active leptomeningeal disease;
- History of another malignancy within the previous 5 years other than curatively treated non-melanoma skin cancer;
- Absolute neutrophil count $< 1,500/\mu\text{L}$, platelet count $< 100,000/\mu\text{L}$, or hemoglobin $< 5.6 \text{ mmol/L}$ (9 g/dL) at the Screening visit (NOTE: patients may not have received any growth factors within 7 days or blood transfusions within 28 days of the hematologic laboratory values obtained at the Screening visit);
- Total bilirubin, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.5 times the upper limit of normal at the Screening visit;
- Creatinine $> 177 \mu\text{mol/L}$ (2 mg/dL) at the Screening visit;
- Albumin $< 30 \text{ g/L}$ (3.0 g/dL) at the Screening visit;
- History of seizure or any condition that may predispose to seizure (e.g., prior cortical stroke or significant brain trauma). Also, history of loss of consciousness or transient ischemic attack within 12 months of enrollment (Day 1 visit);
- Clinically significant cardiovascular disease including:
 - Myocardial infarction within 6 months;
 - Uncontrolled angina within 3 months;
 - Congestive heart failure New York Heart Association (NYHA) class 3 or 4, or patients with history of congestive heart failure NYHA class 3 or 4 in the past, unless a screening echocardiogram or multi-gated acquisition scan performed within three months results in a left ventricular ejection fraction that is $\geq 45\%$;
 - History of clinically significant ventricular arrhythmias (e.g., ventricular tachycardia, ventricular fibrillation, torsades de pointes);
 - History of Mobitz II second degree or third degree heart block without a permanent pacemaker in place;
- Hypotension as indicated by systolic blood pressure < 86 millimeters of mercury (mmHg) at the Screening visit;
- Bradycardia as indicated by a heart rate of < 50 beats per minute on the Screening ECG;
- Uncontrolled hypertension as indicated by systolic blood pressure $> 170 \text{ mmHg}$ or diastolic blood pressure $> 105 \text{ mmHg}$ at the Screening visit.
- Gastrointestinal disorder affecting absorption (e.g., gastrectomy, active peptic ulcer disease within last 3 months);
- Major surgery within 4 weeks of enrollment (Day 1 Visit);
- Use of opiate analgesics for pain from prostate cancer within 4 weeks of enrollment (Day 1 visit);
- Radiation therapy for treatment of the primary tumour within 3 weeks of enrollment (Day 1 visit);
- Radiation or radionuclide therapy for treatment of metastasis;
- Primary disease not treated
- More than 5 metastases
- Hormone naïve prostate cancer patients
- Treatment with flutamide within 4 weeks of enrollment (Day 1 visit);
- Treatment with bicalutamide or nilutamide within 6 weeks of enrollment (Day 1 visit);
- Treatment with 5- α reductase inhibitors (finasteride, dutasteride), estrogens, cyproterone within 4 weeks of enrollment (Day 1 visit)
- Treatment with systemic biologic therapy for prostate cancer (other than approved bone targeted agents and GnRH-analogue therapy) or other agents with anti-tumour activity within 4

weeks of enrollment (Day 1 visit);

- History of prostate cancer progression on ketoconazole;
- Prior use, or participation in a clinical trial, of an investigational agent that blocks androgen synthesis (e.g., abiraterone acetate, TAK-700, TAK-683, TAK-448) or targets the androgen receptor (e.g., BMS 641988);
- Participation in a previous clinical trial of enzalutamide;
- Use of an investigational agent within 4 weeks of enrollment (Day 1 visit);
- Use of herbal products that may have hormonal anti-prostate cancer activity and/or are known to decrease PSA levels (e.g., saw palmetto) or systemic corticosteroids greater than the equivalent of 10 mg of prednisone per day within four weeks of enrollment (Day 1 visit);
- Any condition or reason that, in the opinion of the Investigator, interferes with the ability of the patient to participate in the trial, which places the patient at undue risk, or complicates the interpretation of safety data.