

# **A Phase II randomized trial of bicalutamide in patients receiving intravesical BCG for non-muscle invasive bladder cancer (BicaBCa).**

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## **Study overview:**

The scientific literature, including our prior research, has demonstrated an important role for androgens and the androgen receptor (AR) pathway in the carcinogenesis and progression of bladder cancer. Based on these clinical and animal results, we propose to combine androgen suppression with bicalutamide, an AR-antagonist, with bacillus Calmette-Guérin (BCG) intravesical therapy for men at risk of recurrences of non-muscle-invasive urothelial carcinoma of the bladder.

## **PROTOCOL SIGNATURES**

**A Phase II randomized trial of bicalutamide in patients receiving intravesical BCG for non-muscle invasive bladder cancer (BicaBCa).**

**BicaBCa Protocol, Version 4.3**

**November 12, 2024**

### **INVESTIGATOR SIGNATORY**

I agree to conduct this clinical study in accordance with the protocol and to abide by all its provision. I am aware of my responsibilities as an investigator under the local, provincial and national regulations, including the CHU de Québec-Université Laval clinical research SOPs and ICH-GCP/Health Canada guidelines. I will appropriately assist and supervise the research personnel involved in the trial. I authorize verification and inspection activities.

**INVESTIGATOR'S NAME**

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**SIGNATURE**

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**DATE**

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### **SPONSOR SIGNATORY**

This protocol observes local, provincial and national regulations, including the CHU de Québec-Université Laval clinical research SOPs and ICH-GCP/Health Canada guidelines. I certify information is exact and complete.

**REPRESENTATIVE SPONSOR'S NAME**

Dr Paul Toren

**SIGNATURE**

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**DATE**

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## List of abbreviations and definitions

ADT: Androgen Deprivation Therapy

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AEs: Adverse events  
AR: Androgen receptor  
5ARI: 5-alpha reductase inhibitors  
BCa: Bladder cancer  
BCG: Bacillus Calmette-Guerin  
BUSS : Bladder Utility Symptom Scale questionnaire  
CHUQc-UL: Centre Hospitalier Universitaire de Québec-Université Laval  
CIS: Carcinoma in situ  
CR: Complete response  
CTA: Clinical trial application  
CTCAE: Common terminology criteria for adverse events  
DVT/PE: Deep vein thrombosis/Pulmonary embolism  
eGFR: estimated glomerular filtration rate  
ENZ: Enzalutamide  
EPC: Early prostate cancer  
EU: European Union  
GnRH: Gonadotropin releasing hormone  
HR: Hazard ratio  
ICF: Informed consent form  
ICH-GCP: International Committee on Harmonization-Good clinical practice  
ICMJE: International committee of medical journal editors  
INR/PTT: International normalized ratio/Partial thromboplastin time /  
IP: Investigational product  
IPSS: International Prostate Symptom Score  
mAb: Monoclonal antibody  
MBT-2: Mouse bladder transitional  
Mcg: Microgram  
Mg: Milligrams  
MIBC: Muscle-invasive bladder cancer  
NCI: National cancer institute  
NMIBC: Non-muscle invasive bladder cancer  
PD-1: Programmed cell death protein  
Poly (I:C): Polyinosinic:polycytidylic acid  
pTa: neoplasms that are confined to the epithelial layer of the bladder  
QLQ-C30: Quality of life questionnaire  
REB: Research ethics board  
SAEs: Serious adverse events  
SOC: Standard of Care  
SOP: Standard operating procedures  
SUSAR: Suspected, unexpected, serious adverse reactions  
TUR: Transurethral resection  
TURBT: Transurethral resection of the bladder tumour  
ul: Microlitre  
US: United States

## Summary of product information

<b>A. SUMMARY OF PRODUCT INFORMATION</b>	
<b>Proprietary Name of Drug Product</b>	pms-Bicalutamide
<b>Non-proprietary or Common Name of Drug Substance</b>	Bicalutamide
<b>Sponsor</b>	No sponsor for this drug. Generic bicalutamide is commercially available and will be purchased for use in the study.
<b>Dosage Form(s)</b>	3 tablets of 50 mg daily for a total dose of 150 mg
<b>Strength(s)</b>	50 mg/tablet
<b>Route of Administration</b>	Oral
<b>Proposed Indication(s)</b>	Bicalutamide for male patients receiving intravesical Bacillus Calmette-Guérin (BCG) for treatment of non-muscle invasive bladder cancer (NMIBC).
<b>B. Product Monograph</b>	
<b>Product Monograph</b>	Refer to the Product Monograph for detailed information regarding preparation, handling and storage of the investigational product (IP).
<b>C. CONTACT INFORMATION</b>	
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## **Protocol Summary**

**Full title:** A Phase II randomized trial of bicalutamide in patients receiving intravesical BCG for non-muscle invasive bladder cancer (NMIBC).

### **Study Objectives:**

- 1) The primary objective of the study is to evaluate whether daily bicalutamide given at time of induction BCG decreases the rate of bladder tumor recurrence in NMIBC patients compared to the standard of care (SOC) induction BCG.
- 2) Secondary objectives include to assess whether use of bicalutamide in combination with BCG will decrease incidence of tumour progression, number of tumour recurrences and number of tumours at first recurrence, as well as improve quality of life, and urinary symptoms compared to standard of care BGC alone/BCG with placebo.

### **Primary outcome:**

The primary outcome will be the time to recurrence of bladder cancer (BCa). Recurrence will be defined as pathologically confirmed urothelial carcinoma obtained by biopsy or surgery. To avoid bias which may occur due to differential wait times between sites, the recurrence will be dated to the cystoscopy after which the surgery was planned or the cystoscopy at which time the biopsy was taken (if biopsy taken without anesthesia).

### **Secondary outcomes:**

Secondary outcomes will be defined as follows:

*Incidence of tumour progression:* the proportion of patients in each arm who experienced tumor progression at the end of follow-up. Progression is defined as a recurrence with an increase in tumour grade to high grade, or an increase in stage, or the new presence of carcinoma in situ (CIS).

*Number of tumour recurrences:* this is defined as the number of recurrences per patient in each group.

*Number of tumours at first recurrence:* this is defined as the number of tumors at the first recurrence will be compared between groups among patients who experienced a tumor recurrence. This information is based on cystoscopic findings at time of the cystoscopy preceding surgical resection or the cystoscopy without anesthesia at which the biopsy indicating recurrence was taken.

*Quality of life:* Quality of life will be evaluated with a quality of life questionnaire (QLQ-C30) as well as a bladder cancer-specific utility scale (BUSS).

*Urinary symptoms:* male urinary symptoms will be evaluated using the overall score on the International Prostate Symptom Score (IPSS) questionnaire.

*Tolerability:* tolerability will be evaluated by treatment adherence, need for dose reduction and compliance (for patients in cohort B).

### **Trial design:**

This is a Phase II, multicenter randomized trial of standard induction BCG versus combination bicalutamide and induction BCG for patients with NMIBC. Cohort A is open label without placebo control and Cohort B is double-blind with a matching placebo control.

### **Treatment population:**

Patients for which induction BCG is recommended by their treating urologist will be invited to take part in this clinical trial.

**Expected accrual rate and trial timeline:**

We estimate that 36 months of patient accrual will be necessary to meet the goal accrual of 80 patients per arm. Patients will be followed for a minimum of 12 months, with the trial complete once the last patient accrued has completed at least 12 and up to 48 months of follow-up.

**Total number of sites and number of Canadian sites:**

There will be several sites involved in the conduct of this clinical trial. All the sites involved in this clinical trial are located in Canada.

## 1. Background and Rationale:

### 1.1 Bladder cancer epidemiology and treatment

BCa is the second most common urological cancer after prostate cancer. NMIBC is the most common form (~75%). Muscle-invasive BCa (MIBC) is found at presentation in ~25% of patients, with 10-20% of NMIBC eventually becoming MIBC[1,2]. Risk groups for NMIBC are based on number of tumours, stage and size[1]. Almost half of patients with MIBC eventually progress to metastatic disease. Although overall BCa mortality is low and associated almost entirely to MIBC, it is the most expensive cancer to treat on a per patient basis due to the need for lifetime monitoring by cystoscopy and the treatment of multiple recurrences by transurethral resection (TUR) and intravesical therapy[3–5].

BCa incidence is 3-4 times higher in men, though women tend to develop more aggressive tumours[6]. Indeed, women are more frequently diagnosed with primary MIBC than men (85% vs 51%), and consequently have a poorer survival[7–9]. Smoking and male sex are the principle risk factors for BCa[1,2]. At similar levels of tobacco consumption, female smokers have a 30-50% higher risk of BCa than male smokers[10]. Several hypotheses have been put forward for this, including lifestyle and occupational exposures, with most evidence pointing towards sex hormones, and notably androgens, as playing an important role in the etiology of BCa[11].

For over 40 years, NMIBC has been treated with intravesical installation of BCG[12]. Upon direct exposure to the bladder, BCG results in a non-specific inflammatory response. It is the only treatment which reduces the risk both of tumour recurrence and progression to invasive disease. Nonetheless, 30-40% of patients still relapse or progress.

### 1.2 The androgen receptor axis in bladder cancer

There is significant literature implicating the androgen receptors (AR) in BCa development and progression. Multiple pre-clinical studies support a role of the AR in BCa carcinogenesis and growth[13–17]. In pre-clinical models, AR inhibition decreases the incidence of bladder tumors[15,16,18]. Finally, we and others have observed that the AR is expressed in NMIBC[19–21] (**Figure 1**)

Recent epidemiologic and clinical reports highlight that patients taking medications which suppress the androgen axis have better BCa outcomes and improved responses to BCG therapy[22–25]. For example, 5-alpha reductase inhibitors (5ARI) dutasteride or finasteride decrease testosterone stimulation of the AR. Shiota *et al.* reported that in a cohort of 228 men receiving intravesical therapy, the suppression of androgens via dutasteride or GnRH agonists was associated with a hazard ratio (HR) for BCa recurrence of 0.36[23]; similar results were also reported by Izumi *et al.*[22]. In a large cancer screening study, finasteride use was associated with a decreased incidence of BCa[25]. Moreover, a recent Finnish population-based study found a 25% decreased risk of BCa mortality among 5ARI users, but not in a control group who took alpha-blockers for urinary symptoms[24]. While the incidence of men with BCa receiving androgen deprivation (eg GnRH agonists) or androgen receptor antagonists remains substantially lower, studies including these patients

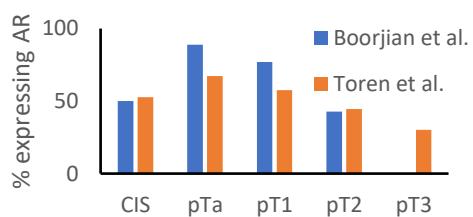


Figure 1: Expression of androgen receptor (AR) according to bladder tumor stage from two series using whole tissue sections to perform AR immunohistochemistry. Non-muscle invasive bladder cancer is represented by stages CIS, pTa and pT1 disease. CIS= carcinoma in situ.

have demonstrated similar results to date[26]. Together, these clinical data support the idea that medications which suppress the AR axis may alter BCa biology to favor better oncologic outcomes[19].

### **1.3 The use of AR inhibitors with BCa immunotherapy**

Our recent studies in mice also implicate sex steroids as important in the immune response to both BCG and anti-PD-1-based immunotherapies. We found that the use of enzalutamide (an AR antagonist) in combination with anti-Programmed cell Death protein 1 (PD-1) monoclonal antibody (mAb) and BCG+Poly(I:C) treatment (a combination more effective than BCG alone[27]) synergized to improve response in the MBT-2 BCa model. MBT-2 tumour cells were originally obtained from a carcinogen-induced tumour in C3H female mice but can be transplanted in both male and female mice. Treatment of male mice with anti-PD-1 mAb reduced MBT-2 tumour growth and resulted in the survival of typically 1 out of 6 mice (17% of complete response (CR)). Enzatulamide (ENZ) alone had no significant inhibitory effect on tumour growth or survival. However, the combination of anti-PD-1 mAb and ENZ induced a delay in tumour growth in all mice and significantly increased the survival to about 4 out of 6 mice which were cured (67% of CR) by the combination of treatments. This percentage of CR resembles that observed in female mice treated with anti-PD1 mAb alone. These sex differences we observed with anti-PD-1 mAb in MBT-2 tumors mirrors prior results with melanoma[28]. Further, we also observed similar synergistic results with the combination of ENZ and BCG against murine MBT-2 bladder tumors. These results suggest that combining an AR antagonist with immunotherapy in male BCa patients could potentiate the antitumour immune response and increase response rates.

With the MBT-2 cell line representative not an AR-driven cell line, our prior results suggest that the alteration of sex steroids induced by AR antagonism in our experiments may in part explain our results. Pre-clinical model suggest higher estrogen levels may protect against BCa[29]. In patients, hormone replacement therapy in women reverses systemic inflammatory immunologic changes associated with menopause[30–32]. These immunologic menopausal changes as well as age-associated declines in sex steroids in men suggest that low sex steroid levels may contribute to lower BCG responses in the elderly[33–35]. Together, these data suggest that the increases in sex steroids induced by AR antagonism may favor improved immunologic-derived prevention of the development of BCa recurrences.

Thus, our pre-clinical data as well as retrospective clinical and epidemiologic studies suggest that combining AR antagonism with BCG may synergize to decrease the recurrence rate of BCa.

### **1.4 Bicalutamide**

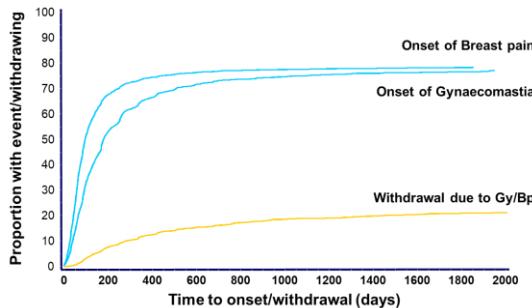
Bicalutamide is an AR antagonist which is off-patent and in addition to blocking the AR results in disruptions in tissue testosterone/estrogen ratios[36,37]. It is an advantageous choice for AR antagonism given its anti-proliferative effects on BCa cells, good tolerability[38], and the low cost as an off-patent medication.

Of the first generation of now off-patent AR antagonists including flutamide, nilutamide and bicalutamide, bicalutamide was the best tolerated and is the only one still in broad use globally. Bicalutamide has been evaluated at 50 mg and 150 mg daily doses for prostate cancer. In patients with localised prostate cancer, bicalutamide 150 mg monotherapy is not recommended in Canada and the US following an overall increase in mortality after 5.4 years of follow-up in one of the early prostate cancer (EPC) randomized trials. The EPC trials randomized thousands of men with localised prostate cancer to

bicalutamide 150 mg vs placebo[38]. Across the EPC trials with longer term follow-up of a median of over 7 years, a reduction in disease progression with no change in mortality was seen with bicalutamide 150 mg was present among patients with locally advanced prostate cancer. However, a trend toward worse overall survival (HR 1.18; 95% CI 0.91, 1.54; p=0.22) was seen in Trial 25 among patients with localized prostate cancer randomized to bicalutamide versus watchful waiting[46]. Though watchful waiting was less commonly employed in the other two EPC trials, a similar trend for decreased overall survival was seen in patients with localized prostate cancer in Trial 24 (HR 1.15; 95% CI 0.93, 1.42; p=0.19). Notably, treatment was recommended to be continue for 5 years among patients treated with local therapy, with no maximum duration among patients on watchful waiting. Further, it is important to consider that 28% of patients received additional therapy with bicalutamide, principally androgen deprivation therapy (ADT), with both the presence of prostate cancer and ADT linked to increased cardiovascular risk[46,47]. Therefore, bicalutamide 150 mg monotherapy is approved for use in locally advanced prostate cancer in the EU and other countries[39,40]. Further, bicalutamide 150 mg in combination with ADT until recently was a treatment option for non-metastatic castrate-resistant prostate cancer[41,42]. Bicalutamide has most recently been evaluated at the 150 mg dose in a Quebec City trial as salvage therapy for non-metastatic prostate cancer[41], but has largely been displaced in prostate cancer care by newer more potent AR antagonists[43–45].

	Patients (%)	
	Bicalutamide 150 mg/day plus standard care (n=1790)	Placebo plus standard care (n=1795)
Gynaecomastia	1216 (67.9)	150 (8.4)
Breast pain	1186 (66.3)	107 (6.0)
Back pain	186 (10.4)	239 (13.3)
Constipation	173 (9.7)	133 (7.4)
Urinary tract infection	173 (9.7)	139 (7.7)
Vasodilation (hot flushes)	172 (9.6)	84 (4.7)
Arthralgia	157 (8.8)	183 (10.2)
Impotence	150 (8.4)	107 (6.0)
Urinary incontinence	148 (8.3)	115 (6.4)
Pain	132 (7.4)	166 (9.2)
Rash	130 (7.3)	96 (5.3)
Hernia	114 (6.4)	146 (8.1)
Hypercholesterolaemia	106 (5.9)	77 (4.3)
Accidental injury	104 (5.8)	127 (7.1)
Weight gain	104 (5.8)	53 (3.0)
Hematuria	96 (5.4)	134 (7.5)
Somnolence	95 (5.3)	57 (3.2)

Table 1 Adverse events occurring in  $\geq 5\%$  of patients in either treatment group showing a  $>1\%$  difference incidence between arms of the Early Prostate Cancer Trial 24. Terms are group using Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART).



**Figure 2: Onset and incidence of breast pain and gynecomastia among patients in the EPC 24 trial.**

re-analysis demonstrated that the side effects accumulated over time, reaching a plateau after approximately 200-250 days of treatment (**Figure 2**). In the EPC 24 trial, 17.8% of patients randomized to bicalutamide withdrew due to breast pain and/or gynecomastia. All adverse events with a reported incidence of  $\geq 5\%$  in either treatment group showing a  $>1\%$  difference incidence between arm are shown in Table 1[48].

Based on this literature, we select a dose of bicalutamide 150 mg monotherapy to maximise AR blockade as well as to achieve disruption of the testosterone/estrogen balance in male patients with NMIBC. An oral route fits with prior studies and common practice of urologists who are the exclusive providers who treat NMIBC. A duration of 3 months of treatment is selected to decrease the incidence of side effects which accumulate over time, while providing sufficient suppression of the potential AR axis in tumors which could develop.

## 1.5 NMIBC patient population

With AR antagonism with bicalutamide potentially acting both as a suppressor of the AR axis in bladder tumors and as a treatment which may synergize with BCa immunotherapies, we will evaluate its efficacy in male patient recommended to receive intravesical BCG for NMIBC. Our focus on male patients follows both the pre-clinical studies, but also the experience of use of bicalutamide, which is not commonly prescribed to female patients. With prostate cancer the principal indication for bicalutamide use, there remains limited data on AR antagonists in female patients, where this class of medication can also have teratogenic effects if given to females of child-bearing age.

NMIBC has a high propensity to recur, which is the reason intravesical BCG therapy is given as adjuvant treatment. Due to the urinary toxicity which may result from intravesical BCG treatment, it is recommended that BCG be given only to a subgroup of patients with NMIBC at higher risk to develop more aggressive and infiltrative BCa. Given the substantial risk of recurrence of NMIBC, patients are followed with interval cystoscopy inspections of the bladder. In addition to the initial “induction” of 6 treatments of BCG, further maintenance treatments of 3 weekly treatments are recommended for 1-3 years later.

Among all patients receiving BCG for NMIBC, the risk of recurrence over time remains high. In our large institutional cohort of 613 patients with a median follow up of 37 months, over 63% of patients experience at least one recurrence despite BCG treatment. More than half of all recurrences occurred in the first two years following BCG treatment. Moreover, BCG treatment remains largely unchanged since it was discovered as an effective treatment for BCa almost 50 years ago. Therefore,

In terms of side effects, the largest trials of bicalutamide monotherapy at the 150 mg dose were the EPC programme of trials. Since newer AR antagonists are currently only prescribed in males with concomitant ADT, the results from monotherapy in these EPC trials do not have any significant more recent comparator to newer AR antagonists. Across these trials, the most common adverse effects of bicalutamide 150 mg were breast pain and gynecomastia. Although the exact mechanism remains difficult to define, it is the disruption in the balance of estrogens and androgens which are thought to cause breast pain and gynecomastia in patients treated with AR antagonists. In the EPC 24 trial, a

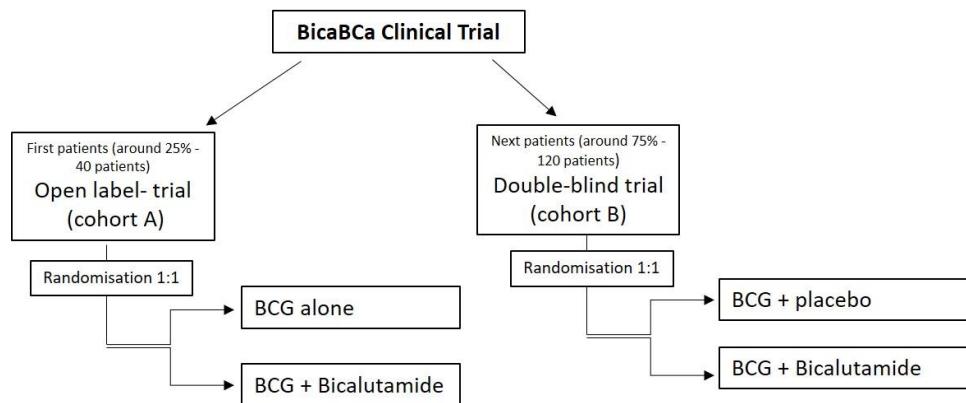
effects accumulated over time, reaching a plateau after

17.8% of patients randomized to bicalutamide withdrew due to breast pain and/or gynecomastia. All adverse events with a reported incidence of  $\geq 5\%$  in either treatment group showing a  $>1\%$  difference incidence between arm are shown in Table 1[48].

there remains a need to identify novel approaches to improve the recurrence-free survival of patients diagnosed with NMIBC.

## 2. Study Overview

This is a Phase II, multicenter, randomized trial of standard induction BCG with or without placebo versus combination bicalutamide with induction BCG for patients with NMIBC composed of two cohorts. The study started with an open-label cohort (cohort A), which includes approximately 25% patients (40 patients) without use of placebo, where patients were randomized to SOC BCG alone or in SOC BCG plus bicalutamide. At each site once implemented recruitment in cohort A will stop and the study will continue with follow-up of patients in cohort A and start of recruitment in cohort B as a double-blind, placebo-controlled study (approximately 75%, 120 patients). This is summarized in **Figure 3**.



*Figure 3: Overview of the clinical trial with the two cohorts (cohort A: open-label trial followed by the cohort B double-blind trial).*

The primary objective is to assess whether use of bicalutamide use at time of induction BCG will decrease the rate of tumor recurrence for patients treated with induction. Subjects will be enrolled upon referral for induction BCG treatment, which occurs in clinical follow-up discussion of their transurethral resection of bladder tumor (TURBT) pathology results. This typically occurs 3-4 weeks post-operatively.

According to established practice guidelines[1,49], induction BCG treatment is the SOC for patients who have pathologic stage T1 disease who do not desire or who are not candidates for radical cystectomy or have recurrent pTa high grade disease. Induction treatment consists of 6-weekly intravesical installations of 50 mcg BCG. For all patients treated with induction BCG, maintenance treatments with 3-weekly instillations at 3 and 6 monthly intervals according to clinical guidelines is subsequently given when there are no intravesical recurrences[49]. Treatment with BCG reduces the risk of recurrence to about 30% at 1 year and 40% at 2 years[50].

The investigator or his/her representative will explain the nature of the study to the potential subject and answer all questions regarding this study. The patient may take the consent home to discuss with family and friends. Then, prior to any study-related screening procedures being performed on the subject, the informed consent form (ICF) will be reviewed, signed and dated by the subject, the person who administered the ICF and any other signatories according to local requirements.

At baseline (visit 1) and during follow-up at 3 (visit 4) and 12 months (visit 6), the patient will complete the QLQ-C30, BUSS and IPSS questionnaires.

Cohort A: open-label	Cohort B: doubled-blind + placebo
<p>Patients randomized will undergo a physical exam that will be performed by one of the study investigators at screening (visit 1) and at 3-month follow-up (visit4). Further, an electrocardiogram will be performed at screening (visit 1) to exclude undetected cardiac problems and bloodwork will be obtained prior to the first BCG treatment (visit1) and at three months (visit 4), including complete blood count creatinine, Ca2+ and Mg2+ measurement and liver enzyme function tests, aminotransferases ALT (if abnormal aspartate aminotransferase (AST) will be performed) and bilirubin for patients treated. Patients in the control arm will follow standard clinical care.</p> <p>Patients will be monitored for adverse reactions or side effects from bicalutamide at scheduled follow-up visits. The investigator and medically qualified designee(s) are responsible for detecting, documenting and recording events that met the definition of an adverse event (AE) or serious adverse event (SAE). All AEs (related and unrelated to bicalutamide) will be collected as scheduled in Table 2.</p> <p>Patients will also be given a card with pertinent study information and contact numbers to give to their healthcare providers or in case of an emergency while in the study. Further, subjects with partners of child-bearing potential will be contacted and reminded about maintaining birth control until at least 130 days after bicalutamide discontinuance. We recommend to the patient to not do sperm donation until 130 days after bicalutamide discontinuance.</p>	<p>Patients will undergo a complete physical exam that will be performed by one of the study investigators at screening (visit 1), and at 3-month follow-up (visit 4). Further, an electrocardiogram will be performed at screening (visit 1) to exclude undetected cardiac problems. Bloodwork will also be obtained prior to the first BCG treatment (visit 1) and at three months (visit 4), including complete blood count creatinine, Ca2+ and Mg2+ measurement and liver enzyme function tests, aminotransferases ALT (if abnormal aspartate aminotransferase (AST) will be performed), and bilirubin.</p> <p>Patients will be monitored for adverse reactions or side effects at scheduled visits. The 6-month follow-up visit (visit 5) will be a safety follow-up visit since 3 months will have passed since the last medication was taken. Adverse Events (AEs) and an update on concomitant medications will be collected one last time. The investigator and medically qualified designee(s) are responsible for detecting, documenting and recording events that met the definition of an AE or serious adverse event (SAE). All AEs will be collected as scheduled in Table 2.</p> <p>Patients will also be given a cohort B card with pertinent study information and contact numbers to give to their healthcare providers or in case of an emergency while in the study. Further, subjects with partners of child-bearing potential will be contacted and reminded about maintaining birth control until at least 130 days after bicalutamide/placebo discontinuance. We recommend to the patient to not do sperm donation until 130 days after bicalutamide/placebo discontinuance.</p> <p>Study participants may be asked to provide blood, urine and stool for biobanking, using a distinct consent form at each local site.</p>

	Biological samples will be collected at different time points.
--	--

Regular follow up cystoscopies will occur according to guideline-based care as in **Figure 4**[49]. Recurrence will be defined according to pathologic confirmation of a recurrent tumor either by biopsy or surgical resection.

The results of this study will be the first prospective study to demonstrate prospectively the efficacy of androgen antagonism in male BCa patients. The results are anticipated to be used to develop further studies to develop novel, sex-specific strategies to decrease tumor recurrences in patients with NMIBC.

### 3. Study Design

#### 3.1 Intervention:

Following screening, eligible patients consented to participate will be randomized to::

- **cohort A:** SOC BCG only or 90 days of oral bicalutamide 150 mg daily in combination with SOC BCG
- **cohort B:** 90 days of oral bicalutamide 150 mg daily in combination with SOC BCG or 90 days of oral placebo daily in combination with SOC BCG.

#### 3.2 Study Objectives:

- 1) The primary objective of the study is to evaluate whether daily bicalutamide given at time of induction BCG decreases the rate of bladder tumor recurrence in NMIBC patients compared to the SOC induction BCG.
- 2) Secondary objectives include assessing whether the use of bicalutamide in combination with BCG may decrease the incidence of tumour progression, decrease number of tumour recurrences and number of tumours at first recurrence, and improve quality of life or urinary symptoms compared to standard of care BGC alone/BCG with placebo.

#### 3.3 Primary outcome

The primary outcome will be to the time to recurrence of BCa for all patients included in the study (cohorts A and B). Recurrence will be defined as pathologically confirmed urothelial carcinoma obtained by biopsy or surgery. To avoid bias which may occur due to differential wait times between sites, the recurrence will be dated to the cystoscopy after which the surgery was planned or the cystoscopy at which time the biopsy was taken (if biopsy taken without anesthesia).

For patients for whom the pathologically confirmed recurrence occurs prior to 12 months, it is not necessary to complete the 12-month evaluation, but the discontinuation visit may include the same components planned for the 12 month evaluation. As with all patients in the study, it is strongly recommended that consent for future contact or medical chart review pertinent to the study be maintained.

### **3.4 Secondary outcomes**

Secondary outcomes will be defined as follows:

*Incidence of tumour progression:* the proportion of patients in each arm who experienced tumor progression at the end of follow-up. Progression is defined as a recurrence with an increase in tumor grade to high grade, or an increase in stage, or the new presence of CIS.

*Number of tumour recurrences:* this is defined as the number of recurrences per patient in each group.

*Number of tumours at first recurrence:* this is defined as the number of tumors at the first recurrence will be compared between groups among patients who experienced a tumor recurrence. This information is based on cystoscopic findings at time of the cystoscopy preceding surgical resection or the cystoscopy without anesthesia at which the biopsy indicating recurrence was taken.

*Quality of life:* quality of life will be evaluated with the QLQ-C30 questionnaire as well as using the bladder cancer specific BUSS questionnaire.

*Urinary symptoms:* male urinary symptoms will be evaluated using the overall score on the IPSS questionnaire.

*Tolerability:* tolerability will be evaluated by treatment adherence, need for dose reduction and compliance (only for patients in cohort B) as detailed in the statistical analysis plan.

### **3.5 Randomization**

Cohort A: open-label	Cohort B: doubled-blind + placebo
<p>Randomization will assign patients 1:1 to SOC 6 cycles of induction BCG or bicalutamide 150 mg for 90 days with SOC induction BCG.</p> <p>Block randomization will be performed using REDCap and be stratified by site. Among patients randomized to bicalutamide with SOC BCG, they will be dispensed the allocated medication by the site pharmacy. The medication will be dispensed with instruction to begin one week prior to the BCG treatments which are scheduled according to standard practice.</p>	<p>Randomization will assign patients 1:1 to 150mg of placebo or 150 mg of bicalutamide for 90 days to start before SOC induction BCG.</p> <p>The study statistician will generate the randomization lists stratified by site, with a separate list for each site's pharmacy. The site pharmacy will be responsible for blinding the clinical study, and they will dispense the medication with instruction to begin one week prior to the BCG treatments which are scheduled according to standard practice.</p>

### **3.6 Blinding only for cohort B**

All patients, study site staff (including investigators), and sponsor staff and its representatives will be blinded to treatment assignment. The pharmaceutical staff at each site will be the only ones to know the assignment of patients in each group.

The blinded control for bicalutamide will be placebo tablets manufactured to be identical in appearance to the bicalutamide tablets.

The procedure for breaking the blind in an emergency is provided in Section 6.2.

### 3.7 Duration of Study

We estimate that 36 months will be necessary to meet the goal accrual of 80 patients per arm. Patients will be followed for a minimum of 12 months, with the trial complete once the last patient accrued has completed at least 12 and up to 48 months of follow-up.

### 3.8 Study Design flowchart

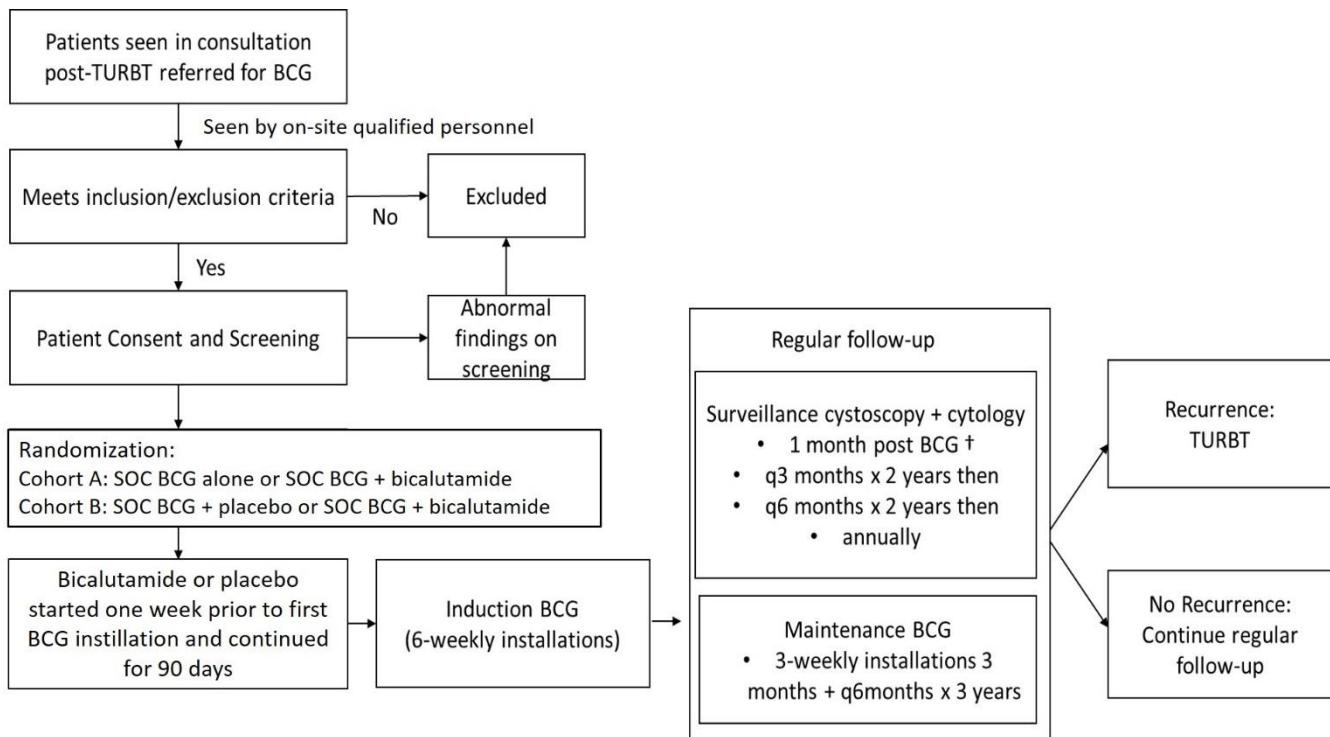


Figure 4: Overview of the trial. TURBT: transurethral resection of bladder tumor; SOC: standard-of-care; BCG – Bacille Calmette Guérin.

### 3.9 Inclusion Criteria

Subjects are eligible to be included in the study only if all of the following criteria apply:

- 1) Males, age 18 or greater and able to provide informed consent for the trial.
- 2) Patients with histologically confirmed non-muscle invasive urothelial carcinoma.
- 3) Patients have been recommended for a course of intravesical BCG induction treatment by their urologist.
- 4) Patients who received gemcitabine, epirubicin or mitomycin C instillations immediately post-operatively will be eligible for enrollment.
- 5) Patients with partners of child-bearing potential must agree to 2 acceptable forms of birth control and be continued for at 130 days after study drug is discontinued.

### **3.10 Exclusion Criteria**

Subjects meeting any of the following exclusion criteria are not eligible for this study:

- 1) Patients who have received induction BCG therapy within the last 5 years will be ineligible for enrolment.
- 2) Patients with a history of myocardial infarction or hospital admission for heart failure within the previous 12 months or who have unstable cardiovascular status will be ineligible for enrolment.
- 3) Patients who have uncontrolled hypertension (for our purposes, defined as those having a systolic blood pressure > 160 documented on 2 occasions despite appropriate medical therapy) will similarly be ineligible.
- 4) Patients with a history of liver disease whose hepatic enzymes, alkaline phosphatase or bilirubin are greater than twice the upper limit of normal will be ineligible.
- 5) Patients with clinical hypogonadism, those on androgen replacement therapy, or those with prostate cancer or other diseases treated with systemic hormonal therapy will be ineligible for study enrolment. Patients receiving 5ARIs will not be excluded.
- 6) Patients who have cancer treatment ongoing or planned in the near future which can be anticipated to decrease their 2-year survival or BCa treatment plan will be ineligible.
- 7) Patients taking an investigational drug within 2 weeks of enrolment into this study will be ineligible.
- 8) Patients receiving or planning to receive coumadin therapy will be ineligible.

### **3.11 Screen failure**

A screen failure is defined as a potential subject who signed the ICF but did not meet one or more criteria required for participation in the study and was not enrolled.

Patients who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Patients who are enrolled but subsequently found not to meet all the eligibility criteria must not be randomized or initiated on treatment and must be withdrawn from the study.

When a patient does not meet all the eligibility criteria but is randomized in error, or incorrectly started on treatment, the investigator should inform the Principal Investigator immediately and a discussion should occur regarding whether to continue or discontinue the patient from treatment. In the event of a patient started on treatment in error, treatment with study intervention should be stopped and general supportive measures initiated, taking into consideration the half-life of approximately one week for bicalutamide. The Principal Investigator must ensure all decisions are appropriately documented.

For screen failures, the demographic data, date of signing the ICF, inclusion and exclusion criteria, AEs up to the time of screen failure and reason for screen failure will be collected in the electronic data source.

### **3.12 Rescreening**

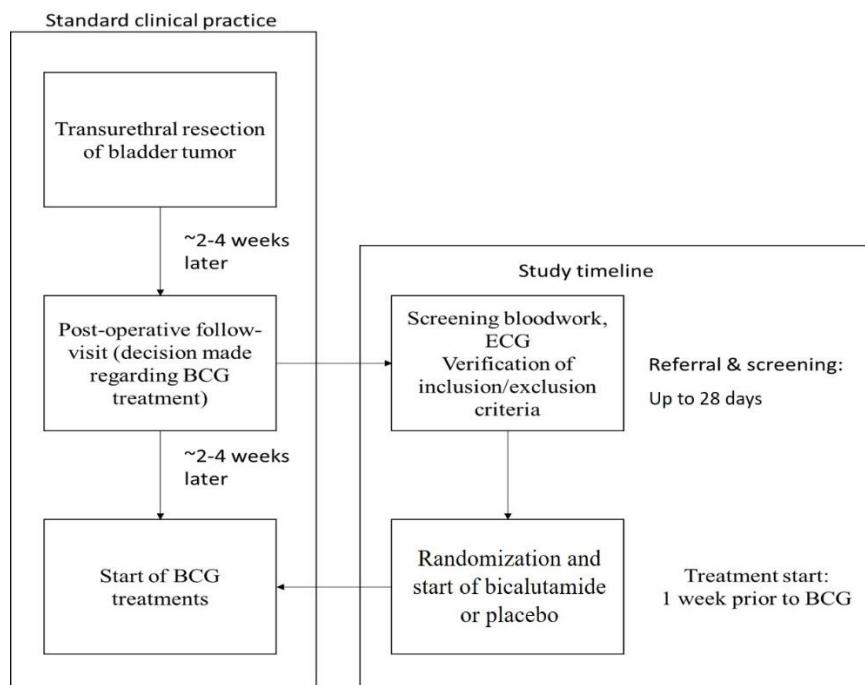
Results of screening assessments that do not meet the parameters required by eligibility criteria (e.g., clinical laboratory tests, vital signs, physical examination, ECG, etc.) may be repeated once within the 28-day screening period without the need to register the subject as a screen failure. If more than 28 days

elapses from the date of signing the ICF, the subject must be documented as a screen failure. In order to re-screen, a new ICF must be signed, and the subject entered into screening with a new subject identification number. Rescreening is only allowed once for an individual subject.

### 3.13 Study medication dosing

Patients will be randomized to treatment with bicalutamide 150 mg or SOC (cohort A) and with bicalutamide 150mg or placebo (cohort B). Bicalutamide 150mg will be dispensed as three 50mg tablets, while placebo will be given as three identical tablets. These are to be taken oral daily at the same time. Dose reduction to bicalutamide 50mg (or 1 placebo tablet since blinding will continue) due to side effects or compliance concerns may be performed at any time at the discretion of the investigator. The timing and reason for this reduction is to be documented on the appropriate case report form (CRF).

Treatment initiation of bicalutamide or placebo is to be started one week before the start of BCG treatments which are planned. If this is not possible due to logistical challenges, the bicalutamide may be started up to the second induction BCG treatment. Treatment is continued for 90 days. **Figure 5** summarizes the expected screening, randomization and start of treatment phase.



*Figure 5: Summary of expected screening, randomization and start of treatment phase*

### 3.14 Allocation concealment (only for cohort B)

Patients and physicians will be blinded to treatment allocation, with randomization codes kept by the pharmacy at each site. Treatment unblinding will only occur once follow-up of all patients is completed and the study is closed. Patients and physicians will not automatically be contacted, but this information will be made available upon reasonable request. During the study, unblinding may only occur with the permission of the medical monitor where the knowledge of the treatment allocation is deemed to be critical for patient care.

### **3.15 Previous and concomitant medications**

Medications taken within 28 days prior to the screening visit (visit 1) and up to the first dose of study medication will be documented on the appropriate CRF as a prior medication.

Any concomitant medication(s), including herbal preparations, all vitamins, over the counter and prescription medications taken from the time of screening until 90 days following the end of the dosing of bicalutamide or placebo will be documented on the appropriate CRF.

Patients must be instructed not to take any medications or herbal preparations without first consulting with the investigator.

Prohibited concomitant medications include any investigational anti-cancer therapy. This does not include different strains of BCG which are approved for evaluation by Health Canada. Further, concomitant coumadin use within 7 days of randomization or during the 90-day treatment is prohibited. In the event coumadin is taken after the start of the study, the investigator should monitor closely International normalized ratio/Partial thromboplastin time (INR/PTT) levels since these can be increased with concomitant use of bicalutamide and coumadin.

### **3.16 Safety Follow-up**

The 6-month follow-up visit (visit 5) will be a safety follow-up visit since 3 months will have passed since the last medication was taken. AEs and a last update on concomitant medications will be collected one last time.

### **3.17 Follow-up during the study**

Patient assessments will follow SOC, with assessments detailed in Table 2. All randomized patients will be followed up by medical record review for disease recurrence and survival once a year until disease progression, withdrawal of consent or the end of the study. Assessment of urinary symptoms will be performed using the IPSS. Quality of life will be evaluated using the QLQ-C30 and BUSS questionnaires.

Recurrences will be defined according to pathologic confirmation of a recurrent tumor either by biopsy or surgical resection. The decision to performed biopsies or surgical resections will be according to standard clinical practice and the judgement of the investigator.

## **4. Investigational product (IP)**

Refer to the pharmacy manual for detailed information regarding these sections.

<b>Name</b>	<b>pms-Bicalutamide</b>
<b>Dosage Form</b>	Tablet
<b>Physical Description</b>	Each white, round, coated tablet, debossed with "BIC" over "50" on one side and plain on the other side, contains 50 mg of bicalutamide
<b>Unit Dose Strength</b>	50 mg

<b>Route of Administration</b>	Oral
<b>Administration Instruction</b>	The daily dose of bicalutamide is 150 mg/day given in 3 tablets (50 mg each) by mouth. Patients should self-administer bicalutamide by mouth once daily, with or without food. The tablets should be swallowed whole without chewing, dissolving, or cutting them. Patients should not make up missed or vomited doses; dosing should resume on the next calendar day unless otherwise instructed.
<b>Sourcing</b>	The study drug will be purchased commercially for participating sites (details are provided in the Pharmacy manual).

#### 4.1 Ordering, packaging and labelling

Bicalutamide used in this study will be ordered by qualified staff at each participating site in accordance with Sponsor's designee Standard Operating Procedures (SOPs), Good Manufacturing Practice (GMP) guidelines, ICH GCP guidelines and applicable local laws/regulations.

In the unlikely event of a prolonged commercial unavailability of pms-bicalutamide 50 mg/50 mg due to inadequate stocks available and in consultation with the medical monitor, alternative generic versions of bicalutamide may be substituted until pms-bicalutamide is again available. In the event of this substitution, there will be no alteration of the bicalutamide packaging, which will continue to be performed as per pms-bicalutamide.

Provision of placebo will be supplied by the Sponsor in bottle of 300 tablets. Placebo is composed by two main ingredients: Prosolv Easytab and OPADRY.

The bottles used to dispense placebo and bicalutamide should be the same. Each IP or placebo bottle will be appropriately labeled by qualified staff at each participating site conforming to regulatory guidelines, Good Manufacturing Practice and local laws and regulations which identifies the contents as investigational drug.

#### 4.2 Handling, Storage and Accountability

Refer to the Product Monograph for detailed information regarding preparation, handling and storage of the IP.

The investigator, head of study site or designee will prepare and retain records of the IP's receipt, the inventory at the study site, the use by each subject, and disposal of unused study drugs. These records should include dates, quantities, batch/serial numbers, expiration dates, and the unique code numbers assigned to the IP and subjects.

At the conclusion or termination of this study, the investigator, head of study site or designee agrees to conduct a final drug supply inventory and to record the results of this inventory on the Drug Accountability Record. It must be possible to reconcile delivery records with those of used and/or destructed medication.

### **4.3 Treatment Compliance**

Compliance with bicalutamide or placebo will be assessed once at the follow-up cystoscopy at 3 months (visit 4) but questions about medication taking will be asked at visit 3. The compliance will be done through assessment of pill count and patient interview by the qualified personnel. Deviations from the prescribed dose regimen will be recorded on the appropriate CRF.

Study subjects should be counseled on the need to meet 100% compliance with study drug unless study drug is withheld for a toxicity. Investigator or designate should ensure that study subjects meet this goal throughout the study period.

## **5. Study procedures**

### **5.1 Laboratory Assessments**

Refer to schedule of assessments for timing and frequency of laboratory assessments. Liver function tests alanine aminotransferase (ALT) (if abnormal aspartate aminotransferase (AST) will be performed) and total bilirubin (Tbili) will be assessed. Creatinine, complete blood count and Ca<sup>2+</sup> and Mg<sup>2+</sup> will be obtained. All samples for laboratory analysis must be collected, prepared, labeled, and shipped according to laboratory requirements.

The investigator or sub-investigator must review the laboratory report and document this review.

Clinical significance of out-of-range laboratory findings is to be determined and documented by the investigator or sub-investigator who is a qualified physician.

### **5.2 Vital Signs**

Vital sign measurements will include blood pressure (BP), heart rate (HR), temperature, respiratory rate. All measurements should be obtained from the subject in the sitting position. Height and weight will be measured at screening only (visit 1).

### **5.3 Complete physical Examination**

Complete physical examinations will be per standard care at the study site and may include dermatologic, cardiac, respiratory, lymphatic, gastrointestinal, musculoskeletal, and neurologic systems, and other systems if clinically indicated by symptoms.

### **5.4 Targeted physical exam**

For visits that do not require a full physical exam, the investigator or qualified designee will perform a targeted physical exam as clinically indicated prior to trial treatment administration.

### **5.5 Electrocardiogram**

Obtain per local practice and read locally to confirm eligibility.

## **6. Safety and Adverse Event Management**

### **6.1 Management of potential adverse effects**

Management of all potential adverse effects will be done as per standard clinical practice. A potential side effect of bicalutamide is hot flushes. Patient counselling for management of potential side effects such as hot flushes from bicalutamide includes wearing layers of clothing to address changes in temperature, use of cooling pads, lukewarm showers, damp towels and avoidance of potential triggers. Pharmacological management at the discretion of the clinician may include gabapentin, venlafaxine or medroxyprogesterone acetate or cyproterone acetate as per standard clinical practice.

### **6.2 Emergency Procedure for Unblinding (only for cohort B)**

Unblinding of patient allocation should only be done when deemed essential to address an unexpected medical emergency. In order to remove the blind, the local site investigator should contact the Medical Monitor for the study. Only the Medical Monitor for the study can approve unblinding of a subject, with this performed during the operating hours of the CHU de Québec Pharmacy. In case of a delay and depending on the clinical context, the medical emergency should act as the treatment was bicalutamide and a suspension of study administration may be indicated. In all cases, the local site investigator is to document and communicate reasons for unblinding to the study coordinator.

Patients whose treatment assignment has been unblinded will permanently discontinue randomized study drug treatment but continue follow-up.

### **6.3 Discontinuation**

An individual patient will not receive any further treatment in any of the following circumstances:

- Withdrawal of consent. The patient is free at any time to discontinue treatment of bicalutamide or placebo, without prejudice to further treatment.
- An adverse event that in the opinion of the investigator or the CHUQc-UL, contraindicates further dosing.
- Non-compliance with the study protocol that, in the opinion of the investigator or the CHUQc-UL, warrants withdrawal from the study.
- Progression of disease such that radical cystectomy or radiotherapy to the bladder is planned.

### **6.4 Procedures for discontinuation**

A patient who decides to discontinue the randomized medication will always be asked about the reason(s) for discontinuation and the presence of any AEs. If possible, they will be seen and assessed by an investigator. The investigator should be notified of any ongoing AE that may delay treatment or necessitate permanent discontinuation of treatment.

Patients who are permanently discontinued from further receipt of bicalutamide or placebo, regardless of the reason, will be identified as having permanently discontinued treatment. If a patient

discontinues from study treatment, followed up by medical record review for disease recurrence and survival will continue once a year until disease progression, withdrawal of consent or the end of the study. These patients are not eligible for re-treatment with bicalutamide or placebo at any time.

The discontinuation of bicalutamide or placebo does not alter the dosing or treatment regimen of BCG which continues according to standard practice and the recommendation of the treating physician.

## **6.5 Study accrual management following discontinuation**

Regardless of the timing of and the reason for study treatment discontinuation, all randomized patients will be followed up by medical record review for disease recurrence and survival once a year until disease progression, withdrawal of consent or the end of the study.

Patients withdrawn from the study will be included in the total patient population planned, with no replacements.

## **6.6 Data monitoring committee**

A Data Monitoring Committee of the CHUQc-UL will provide oversight of study progress and safety by review of accrual and events at regularly scheduled meetings. The frequency of review is determined by the size, risk, and complexity of the trial according to the CHUQc-UL research ethics committee. They will monitor AE rates, including all SAEs at their annual meeting to confirm toxicity grade, expectedness, relatedness, sequelae, follow up required, and risk to current or future subjects. Events that are serious, unexpected, and related will require expedited review within 10 calendar days to the study team. The committee chair will determine whether further action is required, and when patient safety is of concern, an interim meeting may be called.

An annual progress report will be submitted to respective research ethics committee for review. The review will include for each cohort and treatment arm: the number of subjects enrolled, withdrawals, significant toxicities as described in the protocol, SAEs both expected and unexpected, and responses observed. The Principal Investigator maintains a database of all adverse events with toxicity grade and information regarding treatment required complications or sequelae. The Principal Investigator will submit a copy of the AE spreadsheet along with the progress report to the institutional ethics committee.

An SAE is defined as any AE regardless of dose, causality or expectedness, that:

- Results in death.
- Is life-threatening.
- Require hospitalization or prolongation of existing hospitalization.
- Results in significant or persistent disability/incapacity.
- Is a congenital anomaly or birth defect.
- Is any other medically important event, as assessed by an investigator.

## **6.7 Adverse event grading**

The grading scales found in the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate, and

severe events into CTCAE grades should be used. A copy of the CTCAE version 5.0 is available at <http://ctep.cancer.gov>.

Variables to be collected for each adverse event includes the type, CTCAE grade (if applicable), date of occurrence, whether serious, investigator attributed causality, administration of related treatment and outcome. For SAEs, the date it was considered serious, as well as related information on hospital admission, or death as applicable will also be recorded.

## **6.8 Serious adverse event reporting**

All SAEs must be reported to the trial leads (Co- and sponsor) within 24 hours of site staff becoming aware of the SAE.

SAEs that are related AND expected or unrelated AND unexpected will be reported at the quarterly meeting. SAE reports are expected to include sufficient detail so that the committee can determine the severity, toxicity grade, expectedness, treatment required, and a follow up report documenting resolution or if there are sequelae. Serious adverse events that require detailed reports are expected, related, non-hematologic toxicities of grades 3, 4 or 5.

The following are not considered SAEs and are not to be reported as such:

- Events occurring prior the study drug administration.
- Elective admission for procedures which were planned at the time of consent.

Any SAEs that is serious, related, AND unexpected (Suspected, Unexpected, Serious Adverse Reactions: SUSAR) must be reported to Health Canada and local research ethics for assessment within the specified timeframe. Specifically, for SUSARs which is neither fatal nor life threatening, this will be done by within 15 days after becoming aware of the information. If the SUSAR is fatal or life-threatening, this will be done with 7 days of becoming aware of the information. Within 8 days after having informed Health Canada, a complete report of a fatal or life-threatening SUSAR will be submitted that includes an assessment of the importance and implication of any findings made.

In cohort B, single patient unblinding may be required for SUSARs to certain regulatory authorities. Access to this information will be strictly limited and will not require unblinding at the study site.

## **6.9 Safety analysis**

All AEs and SAEs are reported at each visit started from the beginning of the treatment (bicalutamide or placebo) until the safety follow-up visit (visit 5) three months after the last treatment.

Assessment of safety will be performed in conjunction with each meeting of the Data Monitoring Committee. A list of all SAE events and percentages between treatment arms will be provided. Similarly, lists of all AEs with percentages of events per arm will be updated for each meeting. Upon request, the Data Monitoring Committee may obtain the randomization lists, for cohort B, from the statistician to assess for differences in events between treatment arms. They will have access to data from the initial open-label phase (cohort A) for comparison as well. All patients are expected to have greater than 4 months of follow-up from the end of treatment at the end of study and thus no extended safety follow-up is planned. Given the extensive prior use of bicalutamide 150 mg monotherapy in a similar patient

populations and continued use in advanced prostate cancer patients in various jurisdictions[38,41,51], no pre-specified safety stopping endpoint is considered warranted beyond that specified in Section 6.5.

## 7. Statistical analysis

### 7.1 Power calculation

Our institutional chart review found a one-year recurrence rate of 25% for men following induction BCG therapy, which plateaued at 58% at 5-years of follow-up, consistent with the literature[52–55]. Based on two year recurrence rates of 50%, our sample size calculations indicate that with 71 patients per arm we will have 81% power to detect a HR of 0.50 in the time to recurrence ( $\alpha=0.05$ , two-side log-rank test), with follow-up completed at 4 years. To accommodate any other withdrawals or lost to follow-up, we plan for a total of 80 patients per arm.

### 7.2 Data set analysis groups

The primary objective is to assess whether bicalutamide reduces the recurrence rate of patients initiating BCG. To include contribution of patients from the initial open label phase of the study (cohort A), and since this outcome is not expected to be altered by the lack of a placebo, all randomized patients (open-label or placebo-controlled phases, cohorts A and B) will be included together for this analysis. Thus, the primary objective will be evaluated by comparing the BCG SOC plus bicalutamide arm to BCG SOC alone/BCG with placebo. The ensemble of cohorts A and B is therefore considered the “primary analysis group”.

The secondary outcomes characterizing the recurrence (tumour progression and number of tumours) will be similarly analyzed using this primary analysis group (cohorts A and B together).

Since some assessment of the secondary outcomes (quality of life, urinary symptoms and tolerability) may be different during the placebo-controlled phase of the study, these secondary outcomes will be analyzed separately between the open-label (cohort A) and placebo-controlled (cohort B) phases of the study. In the open-labelled phase of the study (cohort A), all patients randomized to BCG SOC arm will be compared to open-label bicalutamide arm, to form the “open-label analysis group”; and in the placebo-controlled phase (cohort B), all patients randomized to double-blind BCG placebo arm will be compared to BCG plus bicalutamide arm to form the “placebo-controlled analysis group”.

### 7.3 Interim analysis

An interim futility analysis will be conducted when 80 patients accrued have >6 months of follow-up. Statistical analysis will be performed by the CHUQc-UL statistical platform as detailed in the Statistical Analysis Plan. At the interim analysis, there will be an assessment of the primary analysis group which includes testing of the primary outcome, descriptive statistics of the secondary outcome events and SAEs which occur by treatment arm.

To protect allocation concealment, unblinding of individual data from cohort B will not be performed by the study statistician (who is aware of treatment assignment), with only aggregate data for both open-label (cohort A) and placebo-controlled (cohort B) phases presented regarding oncologic futility. Data on safety will be evaluated separately by the DMC but will not be part of the interim

analysis.

Assessment of futility at the interim analysis will be non-binding, with results available to the data monitoring committee and the sponsor. Based on uniform accrual at the time of the interim analysis, with 27 events we will use a lower boundary of -2.157 for the futility analysis (to be met for both possibilities of treatment assignment). Futility boundaries may be adjusted based on the exact number of recurrence-free survival events at the time of analysis using a beta-spending function approach provided in the PASS software. Given that this is the first study of bicalutamide in bladder cancer, no interim efficacy analysis is planned.

#### **7.4 Final statistical analysis:**

The final statistical analysis will be performed with the last patient accrued has 12 months of follow-up as detailed in the Statistical Analysis Plan. Statistical significance for the final analysis will be defined as  $p<0.05$  using a one-side test. Analyses will be performed in an intention to treat manner.

For the primary outcome, tumor recurrence will be defined as pathologically confirmed urothelial carcinoma obtained by biopsy or surgery. To avoid bias which may occur due to differential wait times between sites for surgery, the recurrence will be dated to the cystoscopy after which the surgery was planned or the cystoscopy at which time the biopsy was taken (if biopsy taken without anesthesia). If the surgical procedure under general or spinal anesthesia yields no pathologically confirmed cancer but a recurrence was identified as the reason for the surgery, the recurrence date will be similarly backdated to the preceding cystoscopy. Censoring of data for the primary outcome will be dated to the last cystoscopy date. Censoring may occur due to patient withdrawal from the study, death or lost to follow-up.

Time to recurrence will be compared using Kaplan-Meier and Cox regression models adjusted for the effect of covariates (eg. stage and grade). For the evaluation of recurrence-free survival, this will be restricted to patients who met all eligibility criteria and had at least one cystoscopy follow-up after induction BCG. Regression analyses will also assess the effect of covariates (e.g. tumour stage and grade) on the risk of recurrence. Descriptive statistics including means and variance for continuous data and frequencies for categorical data will be performed.

For secondary outcomes, patient reported QLQ-C30, BUSS and IPSS scores will be summarized descriptively at each subsequent time point as a change from baseline, with means and 99% confidence intervals to account for multiplicity across subscales and timepoints for the open label (cohort A) and placebo-controlled (cohort B) analysis groups. Differences in the proportion of patients experiencing progression occurring at any time during follow-up between treatment arms will be compared using a Fisher's exact test. The differences in mean number of recurrences will be compared between treatment arms using a Wilcoxon signed rank test. Assuming the recurrences follow a Poisson distribution, we will compare the total number of recurrences per patient between treatment arms using a Poisson logistic regression analysis, adjusting for the same two factors (grade, stage) as for the primary analysis.

### **8. Trial conduct and administration**

#### **8.1 Trial administration**

This trial will be conducted under the regulation of competent authorities with regards to clinical trials in Canada. As such, this trial will be run under a clinical trial application (CTA) from Health Canada as well as an authorization from the CHUQc-UL research ethics board (REB). In accordance with the

ICH-GCP guidelines and as per local requirement, this trial will be run according to the CHUQc-UL clinical research SOPs and the protocol.

The uro-oncology research unit of the CHU de Québec will be responsible for coordination of the trial. Data will be kept in the CRF as per standard of practice in the CHUQc-UL, and the study coordinators will be responsible for source data traceability, under the supervision of the clinical Principal Investigator.

## **8.2 Data collection**

Data will be stored on a REDCap server developed for the purpose and hosted on the secure network servers of the CHUQc-UL. Data will be entered online by participating sites at regular intervals. The following variables will be recorded for each patient:

- 1) Demographics,
- 2) Clinical laboratory,
- 3) Prior and Concomitant medications,
- 4) Medical history/BCa history,
- 5) Prior bladder cancer treatments,
- 6) Cystoscopy and urine cytology results from scheduled cystoscopy visits,
- 7) Surgical pathology results,
- 8) Medication dosing and compliance,
- 9) AEs, reported toxicities and management,
- 10) Date of visits including last follow-up.

## **8.3 Monitoring**

All participating sites in the trial will permit trial-related monitoring and audits to be performed by the clinical trial lead team according to good clinical practice. This will include direct access to source data and regulatory documents related to the trial conduct.

## **8.4 Clinical records**

Patient confidentiality throughout the trial will remain a high priority. Data will be kept on secure REDCaP servers on the CHUQc-UL network. Data will be anonymized for statistical analysis, with only the clinical investigators and study coordinators having access to clinical data.

Study documentation for the trial will be stored according to institutional norms for 15 years prior to destruction.

## **8.5 Discontinuation of the study**

The study may be stopped if, in the judgment of the sponsor, study patients are placed at undue risk because of clinically significant findings that meet any of the following criteria:

- Are considered significant.

- Are assessed as causally related to study drug.
- Are not considered to be consistent with continuation of the study.

In addition, the study may be stopped based on the findings of the Data Monitoring Committee. Regardless of the reason for termination, all data available for the patients at the time of discontinuation must be documented.

## **8.6 Financial benefit for participants**

Participants in this trial will not be entitled to any financial benefits. Costs incurred by the participants with regard to the non- standard of care (SOC) part of their participation will be covered as per local guidelines (ex: parking fees).

## **8.7 Publication policy**

The trial results will be submitted for publication in a relevant medical journal and authorship will be determined by the principal investigators. The international committee of medical journal editors (ICMJE) criteria will be used to assign authorship. Draft of any publication, including manuscript, abstracts, slides and posters will be circulated to the relevant parties involved in the trial prior to final submission.

## **8.8 Trial Registration**

The trial will be registered on clinicaltrials.gov once the protocol is approved by the CHUQc-UL Research Ethics committee.

	Screening	Bicalutamide dispensing Visit	Treatment and disease assessment																		End of treatment/Discontinuation <sup>6</sup>	Long term Follow-up					
BCG Treatment (months)			Induction BCG						Month 3				Month 6				Month 9				Month 12						
Week	Up to 28 days	up to 1 week before BCG	1	2	3	4	5	6	12	13	14	15	25	26	27	28	38	39	40	41	51	52	53	54	Progression	24-36-48 months	
Visits	V1	V2							V3 $\pm 1$ week				V4 $\pm 1$ week				V5 $\pm 1$ week				V6 $\pm 1$ week				V7	V8-V9-V10	
Informed consent	X																										
Study procedure																											
Verify exclusion/inclusion criteria	X																										
Medical History/Disease History/Demographics	X																										
Prior and Concomitant Medication Review	X								X			X					X										
Physical examination (full)	X											X					X										
Targeted physical exam (based on symptoms)																		X				X			X		
Vital signs (blood pressure, heart rate, temperature, respiratory rate, height and weight) <sup>4</sup>	X								X			X				X					X			X			
ECG	X <sup>2</sup>																										
Bicalutamide Dispensing		X																									
Compliance with bicalutamide									X <sup>7</sup>			X															
Medical chart review for disease progression and survival																										X <sup>5</sup>	
Laboratory assessments																											
Clinical Lab	X											X															
Urine analysis													As per usual clinical practice														
Monitoring																											
AEs, SAEs													At every visit														
BCG (induction and maintenance) treatment administration																											
BCG treatments (standard clinical practice)					X	X	X	X	X	X		X	X	X		X	X	X				X	X	X			
Questionnaires																											
IPSS questionnaire	X												X										X				
BUSS questionnaire <sup>8</sup>	X												X										X				
QLQ-C30 questionnaire	X												X										X				
Disease assessment																											
Cystoscopy (as per usual practice) <sup>3</sup>													X				X				X			X			
Urine cytology														As per usual clinical practice													
Imaging of upper urinary tracts															As per usual clinical practice												
Biobanking (optional)																											
Biobanking Informed Consent	X																										
Blood and urinary sample collection	X												X			X				X							
Food Frequency Questionnaire													X			X				X							
Fecal kit distribution	X												X			X				X							
Fecal sample recovery			X										X			X				X							

**Table 2 – Schedule assessments for open-label (cohort A) patients**

*ECG: electrocardiogram; AE: adverse event; SAE: serious adverse event; IPSS: International Prostate Symptom Score; QLQ-C30: Core Quality of Life*

1. *Clinical lab to be collected during the screening period as SOC. If these clinical laboratory tests were performed within 30 days of study drug administration, they do not need to be performed again.*
2. *If ECG was performed within 30 days of study drug administration, they do not need to be performed again.*
3. *Cystoscopy can be made until 1 week before the scheduled visit in order to have the results at time of the visit.*
4. *Height and weight will be measured at screening only.*
5. *The long term follow-up will be done on medical chart.*
6. *Visit to be performed if a patient is discontinued from study, during bicalutamide treatment period.*
7. *At visit 3 the patient will be questioned about the medication compliance, with pill counts performed at V4.*
8. *Optional for patients already recruited.*

	Screening	Bicalutamide or placebo dispensing Visit	Treatment and disease assessment																				End of treatment /Discontinuation <sup>6</sup>	Long term Follow-up		
BCG Treatment (months)			Induction BCG						Month 3				Month 6				Month 9				Month 12				Every 12 months ( $\pm 1$ month)	
Week	Up to 28 days	Up to week before BCG	1	2	3	4	5	6	12	13	14	15	25	26	27	28	38	39	40	41	51	52	53	54	Progression	24-36-48 months
Visits	V1	V2							V3 $\pm 1$ week				V4 $\pm 1$ week				V5 $\pm 1$ week				V6 $\pm 1$ week				V7	V8-V9-V10
Informed consent	X																									
Study procedure																										
Verify exclusion/inclusion criteria	X																									
Medical History/Disease History/Demographics	X																									
Prior and Concomitant Medication Review	X								X				X				X									
Physical examination (full)	X												X													
Targeted physical exam (based on symptoms)									X								X					X			X	
Vital signs (blood pressure, heart rate, temperature, respiratory rate, height and weight) <sup>1</sup>	X								X				X				X					X			X	
ECG	X <sup>2</sup>																									
Bicalutamide or placebo Dispensing		X																								
Compliance with bicalutamide or placebo									X <sup>3</sup>				X													
Medical chart review for disease progression and survival																										X <sup>4</sup>
Laboratory assessments																										
Clinical Lab	X <sup>5</sup>												X													
Urine analysis																										
Monitoring																										
AEs, SAEs																										
At every visit																										
BCG (induction and maintenance) treatment administration									X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
BCG treatments (standard clinical practice)									X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Questionnaires																										
IPSS questionnaire	X																									X
BUSS questionnaire	X																									X
QLQ-C30 questionnaire	X																									X
Disease assessment																										
Cystoscopy (as per usual practice) <sup>6</sup>																	X				X			X		
Urine cytology																										
Imaging of upper urinary tracts																										
Biobanking «optional»																										
Biobanking Informed Consent	X																									
Blood and urinary sample collection	X												X			X					X					X
Food Frequency Questionnaire													X			X					X					
Fecal kit distribution	X												X			X					X					
Fecal sample recovery			X										X			X					X					

**Table 3 – Schedule assessments for open-label (cohort B) patients**

ECG: electrocardiogram; AE: adverse event; SAE: serious adverse event; IPSS: International Prostate Symptom Score; QLQ-C30: Core Quality of Life.

1. *Clinical tests to be collected during the screening period as standard of care. If these clinical laboratory tests were performed within 30 days of study drug administration, they do not need to be performed again.*
2. *If ECG was performed within 30 days of study drug administration, they do not need to be performed again.*
3. *Cystoscopy can be made until 1 week before the scheduled visit in order to have the results at time of the visit.*
4. *Height and weight will be measured at screening only.*
5. *The long term follow-up will be done on medical chart.*
6. *Visit to be performed if a patient is discontinued from study, during bicalutamide treatment period.*
7. *At visit 3 the patient will be questioned about the medication compliance, with pill counts performed at V4.*

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