NCT # 02605863

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Study Title:
The Effect of Androgen Deprivation Therapy with Enzalutamide on Bladder Cancer Chemoprevention

Trial Category:
Phase 2

Type of Support Requested:
Drug and Funding

Study Overview:

Previous studies conducted by our group have demonstrated that androgen-mediated signals and the androgen receptor (AR) promote bladder carcinogenesis. Based on the results from our animal experiments, we are proposing a single arm, open label Phase 2 study to evaluate the effect of androgen deprivation therapy (ADT) through administration of Enzalutamide on preventing bladder cancer (BC) recurrence in patients with non-muscle invasive bladder cancer (NMIBC).

Scientific Rationale for Study:

Bladder cancer, primarily urothelial carcinoma, is the fifth most commonly diagnosed non-cutaneous malignancy in the United States, with more than 70,000 new cases diagnosed per year. Over 70% of these cases are non-muscle invasive BCs (NMIBC)[1]. Although recurrence rates depend on a variety of factors—including tumor grade, stage, size, multiplicity, and associated genetic mutations—the data from multiple trials has consistently shown that in aggregate, approximately 45% of patients with NMIBC will have a recurrence of their disease within 2 years of their initial transurethral resection of bladder tumor (TURBT), and approximately 35% will have a recurrence within the first year alone[2-7]. More than 14,000 Americans ultimately die from BC each year, and there has been little reduction in BC mortality over the past 20 years. Interestingly, BC is the fourth most common cancer among men in the United States, but only the tenth most common cancer among women. Epidemiological studies have shown that males have approximately three times the risk of developing bladder cancer as females. The etiology of this sex difference in the incidence of bladder cancer remains unknown, and it cannot be explained entirely by different rates of carcinogen exposure[8].

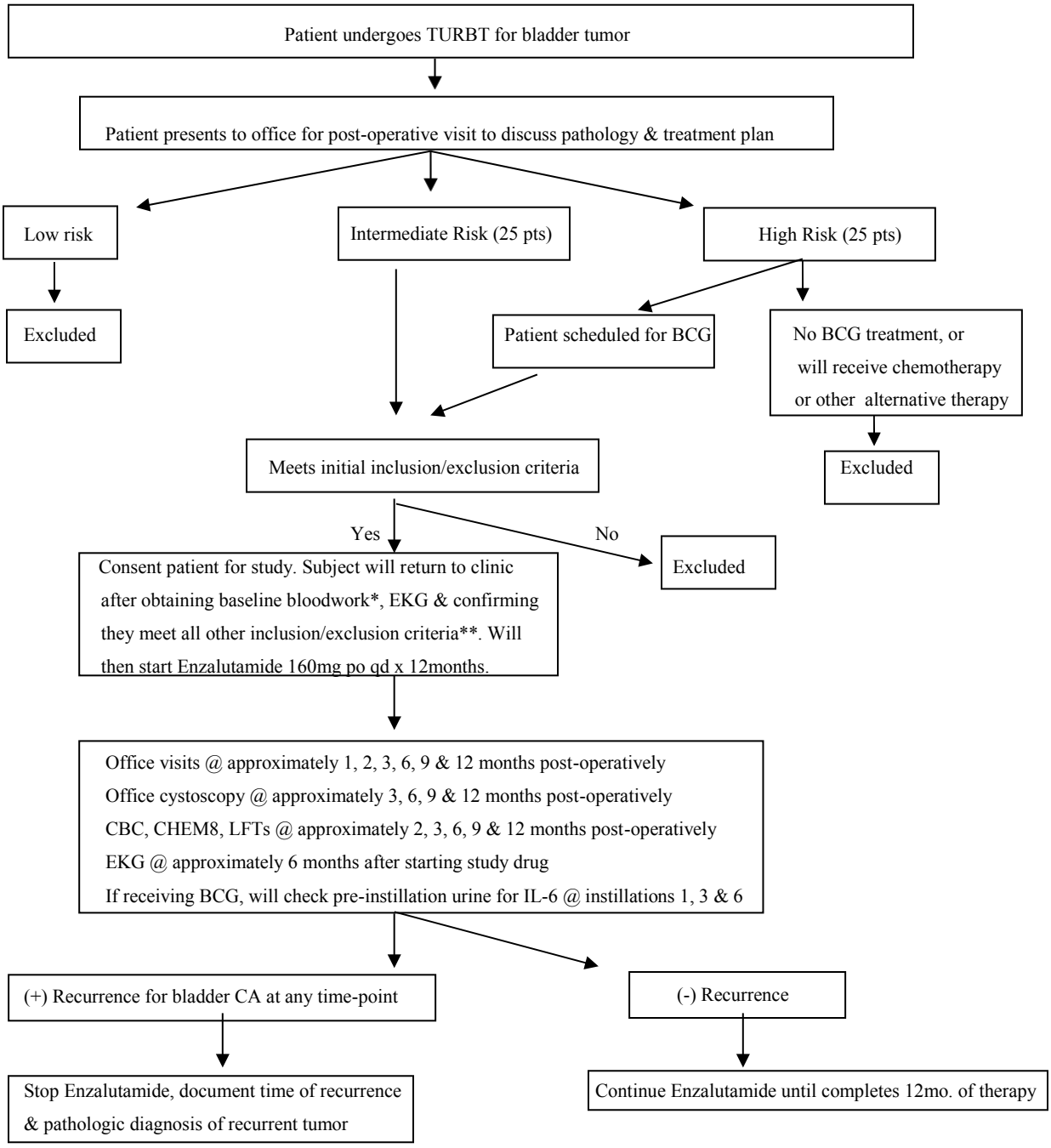
Several recent studies have suggested the involvement of androgens in bladder carcinogenesis. Using AR knockout (ARKO) mice, preliminary studies from our own institution found that the AR might play a critical role in the development of chemical carcinogen-induced bladder cancer. In addition, we discovered that at least two bladder cancer cell lines express a functional AR, and that androgens promoted tumor cell growth in these cell lines while anti-androgens antagonized this effect[9,10]. Multiple studies from various institutions have ultimately demonstrated AR expression in approximately half of all human bladder cancer tissues examined, with preliminary results indicating the AR as a potential therapeutic target[11-18].

There is further evidence that anti-androgens may increase the anti-tumor effects of BCG therapy for NMIBC. Instillations of BCG have been shown in numerous phase 3 randomized studies to be the most effective means to prevent recurrences of high risk NMIBC. It is also the only therapy (when combined with TURBT) that has been repeatedly shown to prevent progression of high risk NMIBC to

muscle invasion[19]. It is believed that BCG must bind to urothelial tumor cells, usually through α5β1 integrin, and that binding and subsequent internalization induces cytokine release, including that of interleukins (IL-6 and IL-8) and tumor necrosis factor alpha (TNFα)[20]. If there is depletion of cells of the innate immune system, BCG loses its effect in animal models, indicating that its key activity is via this immunologically mediated mechanism. AR activity, however, has been shown to inhibit expression of α5β1 integrin in human BC cells in vitro, thereby preventing this cascade of events from occurring. AR signaling has also been shown to directly inhibit the expression of IL-6 by human BC cells exposed in vitro to BCG—an effect that could be blocked by anti-androgens. Moreover, activation of the AR in cells of the innate immune system has been shown to inhibit these cells' activity directly as well[11].

Taken together, these observations form the basis of our hypothesis that androgens and the AR play a key role in bladder carcinogenesis, and may be an important mediator of the response to BCG. Through this Phase 2 study we therefore hope to demonstrate that anti-androgens can be used to retard bladder carcinogenesis, and may even be an effective adjunct to BCG therapy. By administering Enzalutamide (MDV 3100) and using historical control data, we hope to achieve a 15% reduction in the overall risk of recurrence of NMIBC within the first year following TURBT.

Figure 1: Study Design Flowchart:



* Includes Testosterone, Dihydrotestosterone, Estrogen, & Vitamin D levels

** Includes testing TURBT specimens for AR+/- status

Target: 50 subjects total (25 intermediate-risk and 25 high-risk + BCG)

Maximum AR(-) subjects in either cohort = 8 subjects (1/3 of each cohort)

Study Design/Description:

The proposed study is a single arm, open label, Phase 2 study to evaluate the effect of androgen deprivation therapy (ADT) via Enzalutamide on preventing bladder cancer (BC) recurrence in patients with non-muscle invasive bladder cancer (NMIBC). Subjects will be enrolled in the study at the time of their return to the office to discuss the results of their TURBT, which usually occurs 7-10 days post-operatively. Subjects will ultimately be categorized based on their risk of bladder cancer recurrence per the European Association of Urology guidelines, and only subjects with intermediate or high risk disease will be enrolled. These patients have a 24-38% and 55-67% risk of recurrence at 1 year, respectively[21].

The standard of care for patients with high risk disease is to offer treatment with a course of intravesical BCG, which is known to reduce the risk of recurrence at 1 year by approximately one half, thereby giving subjects in this cohort a 27-32% expected recurrence rate at 1 year[22]. Patients with high risk disease who do not undergo treatment with BCG will ultimately be excluded. Hence, we expect both our intermediate risk group and our high risk+BCG group to have an approximately 30% risk of recurrence at 1 year.

There will be a pre-screening process to identify potential subjects via the Urology Clinic schedules and eRecord. Once a potential subject is identified and the urologist is notified, the study team member will approach the potential subject to introduce the study. The exam room door will be closed to ensure privacy. The subject may take the consent form home to discuss with family and friends. The study team member may telephone the potential subject to check interest in participation and answer any questions they may have. If a subject is interested, a screening visit will be scheduled.

After subjects consent to be enrolled in the study, baseline blood-work and an EKG will be obtained. This blood draw will check levels of testosterone, dihydro-testosterone, estradiol, and Vitamin D. Pre-study blood-work will also include a complete blood count (CBC), basic metabolic panel (BMP/CHEM8) and liver function test (LFT) if any of these labs were not drawn within 1 month prior to the subject's TURBT. Surgical Pathology will also perform immuno-histochemical staining for the AR in the TURBT specimen, since the maximum AR(-) subjects allowable in either the intermediate risk cohort or high risk+BCG cohort will be 8 subjects in each cohort (1/3 of each cohort). AR(+) status will be assessed according to the German Scoring System, which takes into account both the percentage and intensity of positively staining cells on immuno-histochemical assay, with a cut-off of score of ≥ 2 being used to define AR(+) tumor specimens. Once eligibility criteria is confirmed, the subject will return to the office for dispense of the study drug.

After eligibility for the study has been confirmed by the aforementioned testing, subjects will return to the office approximately 1 month following their original TURBT to begin therapy with Enzalutamide. The study drug will be administered orally at a dose of 160 mg daily for 12 months. Dosing Instructions will be given to all subjects (attached). Study drug compliance will be monitored at intervals throughout the study. Subjects will be monitored for adverse reactions or side effects from Enzalutamide at scheduled office visits and 2 weeks after study drug discontinuance. In order to track adverse events in the study, an Adverse Event form (attached) will be distributed to the subject with verbal instructions for completion and reviewed at scheduled visits. Subjects 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 (attached). Subjects with partners of child-bearing potential will be contacted and reminded about maintaining birth control until 3 months after study drug discontinuance.

- For subjects in the intermediate risk cohort, these visits will occur at 2 months post-operatively (1 month after initiation of Enzalutamide), and then again at post-operative months 3, 6, 9 and 12, as is part of the usual standard of care for these patients (Figure 2A).
- For subjects in the high risk+BCG cohort, office visits will occur on a slightly different schedule to conform to the standard of care for these patients (Figure 2B). Subjects in this cohort typically start their intravesical BCG instillations 4-6 weeks post-operatively. Therefore, subjects in this cohort will still be seen approximately 1 month following their initial TURBT, and they will begin therapy with Enzalutamide at that time as described above. These subjects will need to be on the study drug for at least 7 days prior to initiation of their BCG therapy to ensure adequate blockade of the androgen receptor prior to BCG therapy, which will occur once a week for 6 weeks. Similar to the subjects in the intermediate risk cohort, the subjects receiving BCG will also be seen 1 month after initiation of Enzalutamide therapy to ensure there are no adverse reactions to the study drug. Adverse events will be reviewed during the 6 weekly instillations of BCG at Visits 1, 3, 4, and 6. Following this visit, they will be seen again at the time of their initial post-BCG cystoscopy, which occurs 1 month after their 6th instillation. They will then be seen again at their 3, 6, 9 and 12-month post-BCG cystoscopy office visits.

Subjects will be withdrawn from the study for the following reasons:

1) Weekly BCG treatments delayed more than twice (i.e., adverse events, gross hematuria, urinary tract infections or any other reason BCG treatments cannot be completed at the scheduled office visit)
2) Unable to complete all 6 BCG treatments
3) Development of any serious side effects or significant complications associated with this therapy. This will include development of painful gynecomastia, heart attack, stroke, DVT/PE, elevation of hepatic enzymes, alkaline phosphatase or bilirubin to greater than twice the upper limit of normal, or development of renal insufficiency with eGFR < 30. CBC, CHEM8 and LFTs will be checked 1 month after initiation of Enzalutamide (approximately 2 months post-operatively). For subjects with intermediate risk bladder cancer, these labs will be checked again at 3, 6, 9 and 12 month post-operatively (as per the regularly scheduled office visits, Figure 2A). For the high risk+BCG cohort, these labs will be checked again at the 1, 3, 6 and 9-month post-BCG office visits (per the regularly scheduled office visits for these patients, Figure 2B). EKGs will be obtained at baseline as mentioned above, but will also be re-checked at approximately 6 months (half-way through therapy with Enzalutamide) to ensure there are no signs of worsening cardiac disease while on the study drug.

Subjects will undergo quarterly cystoscopies as part of the standard of care for bladder cancer follow-up (as detailed in Figure 2A & 2B). Lesions suspicious for tumor recurrence will be biopsied as per usual standard of care. If a recurrence is documented, the subject will be notified at the TURBT post-op visit to discontinue use of Enzalutamide and will be withdrawn from the study at this time. The final pathologic diagnosis of the recurrent tumor will also be noted in order to assess for any potential tumor progression. Subjects who are terminated early from the study (i.e., bladder tumor recurrence, or any other early termination) will receive a telephone call from the study staff 2 weeks after the last dose of study drug to check for any new or ongoing adverse events.

The tissue obtained from the initial TURBT will be sent to Surgical Pathology for diagnosis, staging and grading as is part of the usual standard of care. In addition, slides will be created from this tissue by Surgical Pathology and will undergo histologic analysis to stain for the AR, Estrogen Receptor alpha and beta (ER-a, ER-b), as well as the Vitamin-D Receptor (VDR). TURBT specimens will also be analyzed for the presence of the following cell cycle markers with known prognostic value in NMIBC: FGFR3, p53, pRb and p21[16,17]. TURBT specimens will also be analyzed for the following downstream markers of AR signaling that have been implicated in bladder cancer tumorigenesis: EGFR, ERBB2 and CD24. For those subjects undergoing a 6 week induction course of BCG instillations, we will also check

their pre-instillation urine samples for IL-6 levels at weeks 1, 3 and 6, since previous data has suggested that anti-androgens can augment the induction of IL-6 by BCG, and thereby might increase its therapeutic efficacy[11]. Subjects undergoing BCG therapy will also have their TURBT specimens analyzed for alpha-5-beta-1-integrin and the IL6-receptor (CD126).

<u>Figure 2A</u>:
Expected Clinical Follow-up for Study Subjects with Intermediate Risk Bladder Cancer (NOT Receiving BCG Therapy)

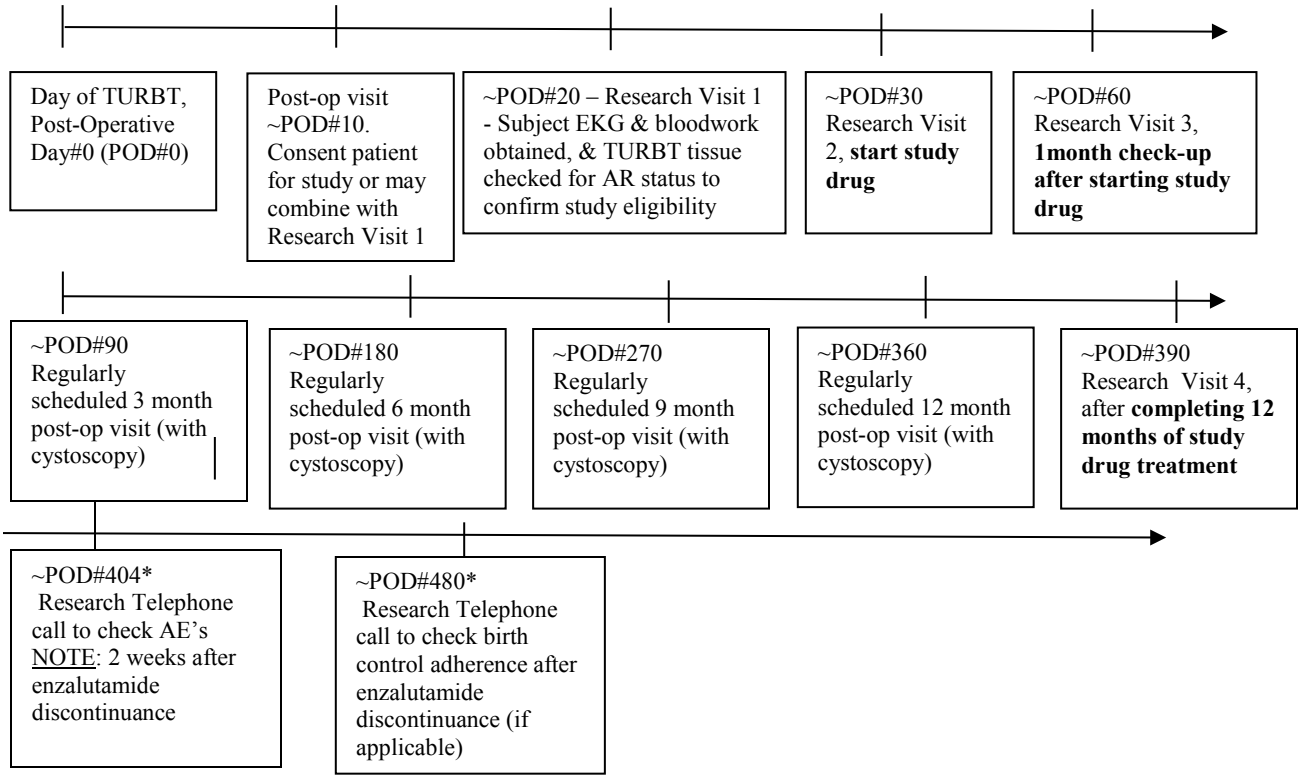
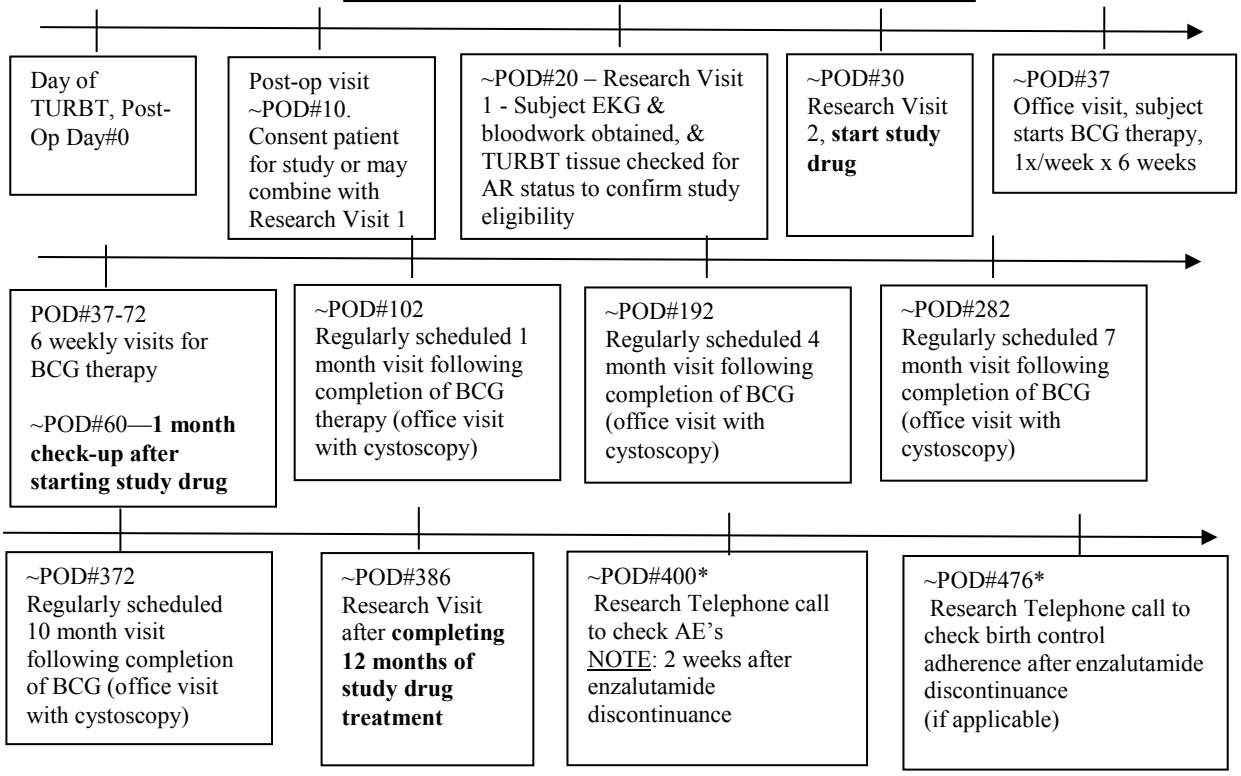


Figure 2B:
Expected Clinical Follow-up for Study Subjects with High Risk Bladder Cancer (Receiving BCG Therapy)



Note: All patients will receive a total of 12 months of Enzalutamide therapy unless they terminate the study drug prematurely.
*The 2-week and 3-month telephone call will take place when the subject discontinues Enzalutamide use (i.e., completes study or early withdrawal)

Number of subjects: We anticipate enrolling 50 subjects with confirmed NMIBC. 25 subjects will be patients classified as having "intermediate-risk" bladder cancer, and 25 subjects will be patients classified as having "high-risk" bladder cancer, as per the EAU guidelines for non-muscle invasive bladder cancer[21]. As mentioned above, only subjects with high-risk bladder cancer who undergo therapy with BCG will be eligible for study enrollment.

Gender of subjects: Only male subjects will be enrolled in this study. Although women and their bladder tumors both express androgen receptors, we will limit this study to men primarily because of the low overall number of subjects we expect to enroll, and because the side effects of Enzalutamide at the dose to be used are not as well known in women as they are in men.

Age of subjects: All subjects will be adults 18 years of age and older. Given the epidemiology of bladder cancer, the vast majority of our subjects will be greater than 60 years old.

Racial and Ethnic Origin: The intended racial and ethnic distribution of the study population would be approximately 90% Caucasian with the remaining 10% being African American, Hispanic, or Asian. This represents the demographics typical of this patient population in this geographic area. Further, it has been found that BC is roughly twice as common in Caucasians as in African Americans and Hispanics.

Objectives:

1) The primary endpoint of the study will be to evaluate the 1-year rate of recurrence in NMIBC subjects treated with ADT via Enzalutamide, for comparison with historical rates of BC recurrence without ADT.
2) A secondary endpoint will be to estimate the rate of tumor *progression* in NMIBC subjects treated with Enzalutamide, for comparison with historical rates of progression without ADT.
3) Another secondary endpoint will be to assess for cancer-specific and patient-specific factors (such as tumor grade and stage, AR status, FGFR3 mutation status, and baseline hormonal status) that may affect any response to Enzalutamide in terms of bladder tumor recurrence and/or progression.

Duration of Enrollment:

We estimate that 18-24 months of patient accrual will be necessary to meet the goal accrual of 50 subjects. Subjects will ultimately be followed for approximately 13 months after study entry, and they will be assessed as described above for any tumor recurrences during that 1 year time period while on the study drug.

Inclusion Criteria:

1) Males, age 18 or greater

2) Subjects with histologically confirmed NMIBC who have undergone their TURBT.

3) Per the European Association of Urology (EAU) guidelines, only subjects with "Intermediate" or "High risk" bladder cancer will be enrolled[21]:

Low-risk tumours	Primary, solitary, Ta, G1 (low grade), < 3 cm, no CIS
Intermediate-risk tumours	All tumours not defined in the two adjacent categories (between the category of low and high risk)
High-risk tumours	Any of the following: • T1 tumour • G3 (high grade) tumour • CIS • Multiple and recurrent and large (> 3 cm) Ta G1G2 tumours (all conditions must be presented in this point)

For patients with "high risk" bladder cancer, only those who undergo BCG therapy following their TURBT will be eligible for enrollment.

4) Subjects who receive BCG instillations post-operatively will be eligible for enrollment.

5) Subjects whose tumors are AR(+) as well as AR(-) will be included, but we will restrict inclusion of AR(-) subjects so that they represent no more than 1/3 of the total study population, or any single cohort (ie. the intermediate or high-risk groups).

6) Subjects with partners of child-bearing potential must agree to 2 acceptable forms of birth control and be continued for at least 3 months after study drug is discontinued.

Exclusion Criteria:

1) Subjects with "low risk" bladder cancer, as defined by the EAU guidelines[21], will be ineligible for enrollment.
2) Subjects with "high risk" bladder cancer who do not undergo BCG therapy following their TURBT will be ineligible for enrollment.
3) Subjects who have "failed" BCG therapy in the past (had a recurrence of bladder cancer despite prior use of BCG) will be ineligible for enrollment.
4) Subjects who receive an immediate post-TURBT single instillation of intravesical chemotherapy will be ineligible for enrollment.
5) Subjects who receive a post-operative induction course of intravesical chemotherapy (ie. more than just a single immediate post-operative dose of intravesical chemotherapy) will be ineligible for enrollment.
6) Subjects who undergo blue-light/fluorescence cystoscopy will be ineligible for enrollment.

7) Subjects with a history of heart attack within the previous 12 months or who have unstable cardiovascular status will be ineligible for enrollment.
8) Subjects 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.
9) Subjects with a history of venous thrombo-embolism (DVT/PE) within the past 3 years.
10) Subjects with a history of seizure disorders, or those with a history of stroke or transient ischemic attacks (TIA) within the previous 12 months will be ineligible.
11) Subjects 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.
12) Subjects with kidney disease with an estimated glomerular filtration rate (eGFR) < 30 will be ineligible.
13) Subjects with neutropenia (< 3,000/μL) will be ineligible.
14) Subjects with clinical hypogonadism, those on androgen replacement therapy, or those with prostate cancer or other diseases treated with various forms of hormonal therapy (not including 5-alpha reductase inhibitors) will also be ineligible for study enrollment.
15) Subjects who have undergone treatment for any malignancy other than bladder cancer within the past 2 years except for non-melatomatas skin cancers and basal and squamous cell carcinomas of the skin.
16) Subjects who have undergone treatment for bladder cancer in the past 1 year.
17) Subjects with prior histories of prostate cancer treated by definitive local therapy > 5 years ago will only be eligible if they have had no clinical or biochemical evidence of recurrent prostate cancer.
18) Subjects taking an investigational drug within 3 weeks of enrollment into this study.

Data Analysis and Monitoring:

A password-protected file will be generated using the RedCap software program to store and maintain the data generated during this study in accordance with the scope of the project. The following variables will be recorded for each subject:

1) Age, race and ethnic origin
2) Total testosterone level, dihydro-testosterone levels, and estradiol levels
3) 25-Hydroxyvitamin D2 and D3 levels
4) Complete blood counts, liver function tests and basic metabolic panel results will be recorded from scheduled office visits as outlined above.

5) Tumor grade and stage, as well as AR, ER-a, ER-b and VDR staining intensity of the tumor specimens. AR, ER-a/b and VDR staining intensity will be assessed using the German Scoring System, which combines the percentage of positive staining cells with overall staining intensity.
6) Use of other adjunctive therapies for bladder cancer, such as BCG.

Subjects will undergo quarterly cystoscopies as part of their BC follow-up protocol. They will require histologic confirmation from bladder biopsies to document BC recurrence, and they will not continue on the study drug once recurrence is documented. In this fashion, we will calculate the BC recurrence rate of our study population at 13 months following their TURBT, and compare this to the expected rate of recurrence from historical control data. Subset analyses will also be performed to determine if patients with high risk bladder cancer who undergo BCG and/or patients with AR(+) tumors have significantly decreased rates of BC recurrence on Enzalutamide as compared to intermediate risk patients or AR(-) patients.

Power Analysis and Statistical Data Analysis:

(1) ***Power analysis***. The historical data shows that without administration of Enzalutamide, the risk of recurrence of NMIBC in the first year following TURBT for our selected patient population (ie. intermediate risk BC as well as high risk BC+BCG) is approximately 30%. We project that with Enzalutamide, we will be able to achieve a 15% overall risk reduction in BC recurrence (our primary objective). In the power analysis we calculated the required sample sizes with a wide range of projected risk. Our calculation shows that a sample size of 49 subjects achieves 81% power to detect an absolute risk difference of 15% using a one-sided binomial test (with significance level 0.05). It should be noted that we have not performed separate statistical analyses and power calculations for our secondary objectives (as outlined above), as these will remain exploratory at this time and will be used to help guide potential future areas of study.

(2) ***Statistical data analysis.*** For continuous variables, the means and standard deviations will be calculated. For categorical variables, the frequencies will be calculated. Multiple logistic regression analysis (with model section) will be used to study the effects of some covariates (such as tumor stage and grade) on the risk of recurrence of NMIBC within the first year following TURBT.

Patient Safety & Adverse Event Reporting

Study Investigators will conduct continuous review of data and patient safety. The Investigator will submit semi-annualprogress reports of these data to the Wilmot Cancer Center's Data Safety Monitoring Committee (DSMC) for review. The review will include for each treatment arm: the number of subjects enrolled, withdrawals, significant toxicities as described in the protocol, serious adverse events both expected and unexpected, and responses observed. The *Principal Investigator* (PI) maintains a database of all adverse events with toxicity grade and information regarding treatment required complications or sequelae. The *Investigator* will submit a copy of the adverse events (AE) spreadsheet along with the Progress Report to the DSMC for review.

- Any serious adverse event that is serious, related AND unexpected must be reported within 10 calendar days to both the DSMC and the Research Subjects Review Board (see RSRB guidelines).

- Serious adverse events that are related AND expected or unrelated AND unexpected will be reported to the DSMC for review at the quarterly meeting. Serious AE reports are expected to include sufficient detail so that the DSMC can determine the severity, toxicity grade, expectedness, treatment required, and a follow up report documenting resolution or if there are sequelae. Unless otherwise specified in the protocol, serious adverse events that require detailed reports (but not necessarily expedited) are expected, related, non-hematologic toxicities of grades 3, 4 or 5.

The DSMC provides 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 and is assigned by the Wilmot Cancer Center's Protocol Review Committee at the time of their initial review and approval. The DSMC will monitor all adverse event rates utilizing a cumulative spreadsheet listing of all events submitted along with progress reports by the PI. All serious adverse events that have occurred in the prior 3 months will be reviewed at the regular quarterly meeting of the DSMC in order 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 Safety Coordinator. The DSMC Chair will determine whether further action is required, and when patient safety is of concern, an interim meeting may be called.

Reporting of only SAEs will be sent to Astellas for their own internal review. Per Astellas protocols, within 24 hours of awareness of a serious adverse event, whether or not related to the study drug, the Investigator will complete and submit a Medwatch 3500A Form to FDA, containing all required information (reference 21 CFR 312.32). The Investigator will submit a copy of this MedWatch 3500A form to Astellas by either e-mail or fax, within the same timeframe (Appendix 3).

The effect of Enzalutamide in pregnant and lactating women is not known, and the exposure of a fetus or nursing infant is considered a potential risk. Enzalutamide can cause fetal harm when administered to a pregnant woman based on its mechanism of action. Subjects receiving Enzalutamide are advised to use 2 acceptable methods of birth control (one of which must include a condom as a barrier method of contraception) starting at the time of screening for an Enzalutamide study and continuing throughout the course of treatment and for at least three months after Enzalutamide is discontinued (See Appendix 3 for full protocol related to handling of exposure of Enzalutamide to a fetus or lactating woman).

The safety of Enzalutamide at the dosage and frequency used in this study has already been demonstrated in the initial Phase 1 and Phase 2 studies conducted for its original use with castration-resistant prostate cancer. Per these studies, the most common grade 3-4 AE was dose-dependent fatigue (11% patients), which generally resolved after dose reduction[23]. Please also refer to Appendix 2 which includes the package insert for Enzalutamide.

Furthermore, per discussions with the University of Rochester's Department of Regulatory Support and per Section V, Part A.1 of the FDA's Guidance for Industry Document for IND Exemptions for Studies of Lawfully Marketed Drug or Biologic Products for the Treatment of Cancer (Appendix 4), our proposed clinical study should be exempt from the filing of an IND application. We will be utilizing the same dose and schedule for Enzalutamide as those already approved for the treatment of prostate cancer. We expect no difference in AE's from those already described in the original studies for the use of Enzalutamide for the treatment of prostate cancer and already outlined in the drug package insert[23, Appendix 2]. Lastly, the use of Enzalutamide in this study will be in addition to the current standard of care, and therefore, no proven effective therapies will be withheld from the study population.

References:

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APPENDIX 1:

European Association of Urology Risk Stratification for Non-Muscle Invasive Bladder Cancer and Projected Risk of Recurrence at 1 Year:

Low-risk tumours	Primary, solitary, Ta, G1 (low grade), < 3 cm, no CIS
Intermediate-risk tumours	All tumours not defined in the two adjacent categories (between the category of low and high risk)
High-risk tumours	Any of the following: • T1 tumour • G3 (high grade) tumour • CIS • Multiple and recurrent and large (> 3 cm) Ta G1G2 tumours (all conditions must be presented in this point)

Recurrence score	Probability of recurrence at 1 year		Probability of recurrence at 5 years		Recurrence risk group
	%	(95% CI)	%	(95% CI)	
0	15	(10-19)	31	(24-37)	Low risk
1-4	24	(21-26)	46	(42-49)	Intermediate risk
5-9	38	(35-41)	62	(58-65)	
10-17	61	(55-67)	78	(73-84)	High risk

APPENDIX 2:

Drug Packet Insert for Enzalutamide (Xtandi®)

APPENDIX 3:

Astellas Protocol for Adverse Event Reporting

1.1 Definition of Adverse Events (AEs)

An adverse event (AE) is defined as any untoward medical occurrence in a subject administered a study drug and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not related to the study drug.

An abnormality identified during a medical test (e.g., laboratory parameter, vital sign, ECG data, physical exam) should be defined as an AE only if the abnormality meets one of the following criteria:

- Induces clinical signs or symptoms.
- Requires active intervention.
- Requires interruption or discontinuation of study medication.
- The abnormality or investigational value is clinically significant in the opinion of the investigator.

All adverse events, whether or not related to the study drug, must be fully and completely documented.

1.2 Definition of Serious Adverse Events (SAEs)

An AE is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Results in death,
- Is life threatening (an AE is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.),
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions,
- Results in congenital anomaly, or birth defect,
- Requires inpatient hospitalization or leads to prolongation of hospitalization (hospitalization for treatment/observation/examination caused by AE is to be considered as serious),
- Other medically important events.

1.2.1 Serious Adverse Event Reporting

Within 24 hours of awareness of a serious adverse event, whether or not related to the study drug, the Investigator will complete and submit a Medwatch 3500A Form to FDA, containing all required information (reference 21 CFR 312.32).

The Investigator will submit a copy of this MedWatch 3500A form to Astellas by either e-mail or fax, within the same timeframe.

If submission of this SAE to FDA or Astellas or is not possible within 24 hours, the Investigator's local drug safety contact (IRB, etc.) should be informed by phone.

The SAE documentation, including the Medwatch 3500A Form and available source records should be emailed or faxed to:

Astellas Pharma Global Development – United States
Email: Safety-us@us.astellas.com
Fax number: (847) 317-1241

The following minimum information is required:

- Study number/IIT regulatory identifier
- Subject number, sex and age
- The date of report
- A description of the SAE (event, seriousness of the event)
- Causal relationship to the study drug

Follow-up information for the event should be sent within promptly (within 7 days) as necessary.

1.2.2 Procedure in Case of Pregnancy

The effect of enzalutamide in pregnant and lactating women is not known, and the exposure of a fetus or nursing infant is considered a potential risk. Enzalutamide can cause fetal harm when administered to a pregnant woman based on its mechanism of action. Subjects receiving enzalutamide are advised to use 2 acceptable methods of birth control (one of which must include a condom as a barrier method of contraception) starting at the time of screening for an enzalutamide study and continuing throughout the course of treatment and for at least three months after enzalutamide is discontinued.

If during the conduct of the clinical trial, a male subject impregnates his partner, the subject should report the pregnancy to the Investigator. The Investigator should report the pregnancy to the Sponsor as an SAE within 24 hours of awareness of the event. The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated fertility date, pregnancy result and neonatal data etc., should be included in this information.

The Investigator should report the outcome of the pregnancy (independent of outcome, eg. full term delivery, pre-term delivery, spontaneous abortion, induced abortion, stillbirth, death of newborn, congenital anomaly [including anomaly in a miscarried fetus, etc] in accordance with the same reporting procedure as for SAEs. The date of outcome of the pregnancy, gestational age, date of birth and neonatal data etc., should be included in this information.

APPENDIX 4:

FDA's Guidance for Industry for IND Exemptions for Studies of Lawfully Marketed Drug or Biologic Products for the Treatment of Cancer