Protocol Title

A Phase II trial for the use of Intravesical Gemcitabine and Docetaxel (GEMDOCE) in the treatment of BCG naïve Non-muscle invasive Urothelial Carcinoma of the Bladder

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SYNOPSIS

TITLE	**A Phase II trial for the use of Intravesical Gemcitabine and Docetaxel (GEMDOCE) in the treatment of BCG naïve Non-muscle invasive Urothelial Carcinoma of the Bladder**
SHORT TITLE	Phase II study of GEMDOCE in BCG naïve NMIBC patients
PHASE	II
OBJECTIVES	Primary Objectives: • Determine the complete response (CR) rate of NMIBC subjects treated with intravesical gemcitabine/docetaxel Secondary Objectives: • Determine safety of NMIBC subjects treated with intravesical gemcitabine/docetaxel • Determine the 12-month, and 24-month recurrence-free survival (RFS) rates of NMIBC subjects treated with intravesical gemcitabine/docetaxel • Determine the cystectomy free survival rates of NMIBC subjects treated with intravesical gemcitabine/docetaxel • Determine how variant histology attenuates 12-month RFS and surgical upstaging rates among NMIBC subjects treated with intravesical gemcitabine/docetaxel • To assemble a blood, urine, and tissue bank (with pre and post treatment samples) to assess molecular correlates for response to intravesical GemDoce. • Determine how RNA expression changes, including molecular subtypes attenuate 12-month RFS and surgical upstaging rates among NMIBC subjects treated with intravesical gemcitabine/docetaxel • Determine how tumor DNA mutations, rearrangements/fusions, copy number alterations, tumor mutational burden impact clinical outcomes (e.g. CR rate, 12m RFS, surgical upstaging) among NMIBC subjects treated with intravesical gemcitabine/docetaxel

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Determine how tumor mutational burden attenuates 12-month RFS and surgical upstaging rates among NMIBC subjects treated with intravesical gemcitabine/docetaxel
Determine associations between baseline- and post-treatment T lymphocyte subset ratios and 12-month RFS and surgical upstaging rates among NMIBC subjects treated with intravesical gemcitabine/docetaxel

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<tr><td>STUDY DESIGN</td><td>This study is a single arm open label Phase II trial investigating the safety and efficacy of intravesical gemcitabine/docetaxel for patients with non-muscle invasive bladder cancer. A Simon’s 2-stage design will be used with an interim analysis between stage one and stage two. Translational correlates will be derived from prior signatures known to predict systemic chemotherapy response in muscle invasive bladder cancer.</td></tr>
<tr><td>ELIGIBILITY CRITERIA</td><td>
Primary Inclusion Criteria

Subject must meet all of the following applicable inclusion criteria to participate in this study:

1. Histologically confirmed intermediate or high-risk non-muscle invasive urothelial carcinoma of the bladder (Ta, T1, or Tis stage) on TURBT obtained within 90 days of registration defined according to modified EORTC risk criteria summarized as follows
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<tr><th>Risk Group</th><th>Characteristics</th></tr>
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NOTE #1: Low-risk tumors as defined above are not eligible.

NOTE #2: Mixed histologies are permitted, provided a component of urothelial carcinoma is present.

NOTE #3: All patients with HGT1 should undergo a restaging TURBT.

2. ECOG (WHO) performance status 0,1, or 2.
3. Age ≥ 18 years old at time of consent
4. Evidence of post-menopausal status or negative urinary or serum pregnancy test for female pre-menopausal patients is required. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

- Women <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy or hysterectomy).

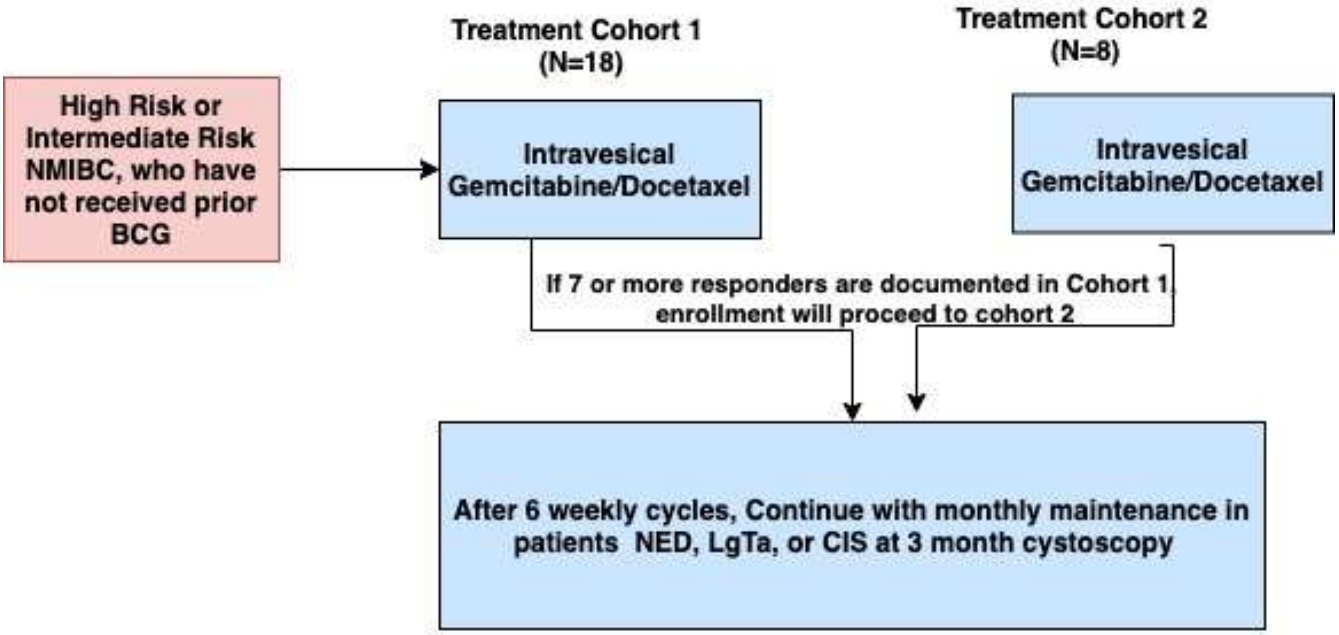
- Women ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

5. Subjects who give a written informed consent obtained according to local guidelines

Primary Exclusion Criteria

	1. Subjects with muscle-invasive (i.e. T2, T3, T4), locally advanced unresectable, or metastatic urothelial carcinoma as assessed on baseline radiographic imaging obtained within 90 days prior to study registration. The required radiographic imaging includes: • Abdomen/Pelvis – CT scan • Chest – chest x-ray or CT scan 2. Subjects with concurrent upper urinary tract (i.e. ureter, renal pelvis) urothelial carcinoma of any stage. (**NOTE:** Subjects with history of non-invasive (Ta, Tis) upper tract urothelial carcinoma that has been definitively treated with at least one post-treatment disease assessment (i.e. cytology, biopsy, imaging) that demonstrates no evidence of residual disease are eligible). 3. Subjects with another active second malignancy with an estimated overall survival from the second malignancy of < 12 months. Subjects with another second active malignancy that are deemed to have an estimated overall survival of ≥12 months are eligible. 4. Subjects who have received the last administration of an anti-cancer therapy including chemotherapy, immunotherapy, and monoclonal antibodies ≤ 4 weeks prior to starting study drug, or who have not recovered from the side effects of such therapy 5. Subjects who have had radiotherapy ≤ 4 weeks prior to starting study drug, or who have not recovered from radiotherapy toxicities. 6. Pregnant or breast-feeding women 7. Subjects unwilling or unable to comply with the protocol. 8. Patients with prior systemic gemcitabine or docetaxel use for a non-bladder malignancy may enroll and receive treatment.
STATISTICAL CONSIDERATIONS	**Study Design/Endpoints** Simon's two-stage design (Simon, 1989) will be used. The null hypothesis that the true 3 month complete response rate is 35% will be tested against a one-sided alternative. In the first stage, 18 patients will be accrued. If there are 6 or fewer responses in these 18 patients, the study will be stopped. Otherwise, 8 additional patients will be accrued for a total of 26. The null hypothesis will be rejected if 14 or more responses are observed in 26 patients. This design yields a type I error rate of 0.0377 and power of 80% when the true response rate is 60%. Standard life table methods will be used to analyze RFS for each arm of the study and for each sub-type within arms of the study separately. We will report 3, 6, 12 and 24-four month RFS with 90% confidence bounds.

	The proportion of toxicities by type and grade according to the revised Common Terminology Criteria for Adverse Events (CTCAE) v5 will be reported with exact 95% confidence intervals. All patients who receive at least one dose of the study drug(s) will be evaluable for toxicity.
TOTAL NUMBER OF SUBJECTS	N = 26
ESTIMATED ENROLLMENT PERIOD	Estimated 24 months
ESTIMATED STUDY DURATION	Estimated 36 months



Primary Endpoint: 3 month complete response rate

Key Secondary Endpoints: Safety, cystectomy free survival, progression free survival molecular predictors of response

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1 BACKGROUND AND RATIONALE

1.1 Study Disease

1.1.1 Non-muscle Invasive Urothelial Carcinoma of the Bladder (NMIBC)

Bladder cancer is the 5th most common cancer in the United States, with an estimated 80,470 individuals newly diagnosed in 2019.(1) 70% of patients will harbor an early stage at diagnosis, defined by non-muscle invasive disease (NMIBC) with invasion limited to the mucosal epithelium (Ta, Tis) and immediate connective tissue layer beneath the mucosa (T1). High risk NMIBC, affecting more than 30,000 patients each year, is defined by carcinoma in situ (CIS), high grade Ta or T1 tumors. Intermediate risk bladder cancer is defined by recurrent, large (>3cm), or multifocal low-grade bladder cancer.

1.1.2 Current Management of Initial NMIBC

Transurethral resection of bladder tumor (TURBT) followed by intravesical bacillus Calmette-Guerin (BCG) immunotherapy is the standard 1st line treatment. While up to 35% of patients have long term sustained remissions with intravesical BCG, 40-60% will have tumor recurrence within 2 years.(2) Ultimately, 40% of these high risk NMIBC patients will progress to muscle invasive stages and require radical cystectomy, or complete bladder removal. Progression to metastatic disease and ultimately bladder cancer death occurs in 20-30% of these patients.(3,4) In 2019, 17,670 are estimated to die of bladder cancer, with many of these patients beginning with early stage disease.(1)

1.1.3 Issues with BCG supply

In July 2012, Sanofi Pasteur announced that it was halting production of the Connought strain of BCG, after inspectors identified manufacturing problems in the only plant in which it was produced. In 2016, Sanofi announced that the BCG program would be shut down permanently.(5) In the United States, United Kingdom, and several other countries, this left oncoTICE BCG, produced by Merck, as the only available strain and producer of BCG. This monopoly over production and distribution became catastrophic for patients when increased demand and manufacturing issues led to a worldwide shortage of BCG in 2014-2015. The British department of health noted that 6000 British patients would be affected by the shortage of BCG, and recommended switching to intravesical chemotherapy if BCG is in low supply. (6,7) During the shortage thousands of patients were left with inadequate BCG dosing regimens without evidence-based alternatives in their place. This left many patients at our institution and nationally with increased uncertainty and anxiety regarding the best steps towards treating their cancer, as evidenced by numerous patient blogs and articles written at that

time(8–10). Since February 2018, we are in the midst of another ongoing global TICE® **(Merck)** shortage, with many institutions with limited or no BCG supply. Given the tenuous supply of BCG worldwide, the formal study of alternatives is essential for patients.

1.2 Rationale for Intravesical Chemotherapy in Non-Muscle Invasive Bladder Cancer

Thus far, attempts to discover alternatives to BCG have primarily rested on studies involving single agent intravesical chemotherapy instillations. Most recently, a randomized controlled trial was performed comparing intravesical chemohyperthermia with intravesical mitomycin C (MMC) versus BCG for patients with intermediate and high risk NMIBC. Although the study closed prematurely and was underpowered, in the analysis of per-protocol treated patients, 2 year recurrence free survival (RFS) approached 81.8% among those receiving hyperthermic MMC compared to 64.8% among those receiving BCG.(11) This study demonstrated the potential non-inferiority of chemotherapy when given through a novel delivery platform and when given with a maintenance program.

Intravesical gemcitabine and cisplatin take their intellectual justifications from their use as the 1st line systemic agents in advanced bladder cancer.(12) Similarly, systemically administered taxane therapies (both paclitaxel and docetaxel) have been combined with gemcitabine and cisplatin to treat metastatic disease.(13–15) As these drugs are all currently employed in combination regimens for systemic disease, and all have been previously tested intravesically in prior human trials, there is a strong rationale to investigate the clinical efficacy and safety of intravesical chemotherapy regimens combining these agents.

Gemcitabine, a deoxycytidine analogue, inhibits DNA synthesis and is a commonly used drug in metastatic bladder cancer patients. Intravesical gemcitabine has been studied in multiple Phase I and II trials. It appears to have very little systemic absorption, with plasma levels immeasurable or quite low, and metabolite difluorodeoxyuridine levels that reach at most 5 μM in the blood, suggesting that low levels of the drug reach systemic circulation.(16) Thus, although myelosuppression is a serious side effect when gemcitabine is used intravenously, it has a very favorable toxicity profile when administered intravesically. Due to the reported efficacy and low toxicity profile, gemcitabine has been favorably compared to other intravesical agents such as mitomycin C (MMC), and has shown improved or similar efficacy to BCG in other settings.(17,18) In a Phase II study of 30 patients with NMIBC who had failed BCG treatment (2 or more induction courses) and refused cystectomy, 15 (50%) had complete responses following intravesical gemcitabine treatment, though durable response were limited with 1yr RFS of 21% among those with initial CR.(19) Additionally, in a prospective, randomized trial of patients (n=120) with intermediate risk NMIBC, no differences between gemcitabine and 1/3 strength

BCG were observed.(20) This study is particularly relevant in the current era of BCG shortage as 1/3 dosing is a common strategy to conserve BCG at many centers. There is also evidence that gemcitabine may be as or more efficacious than BCG for patients who recur after 1 course of BCG. In a multicenter prospective randomized trial of patients with NMIBC who recurred after 1 course of intravesical BCG, gemcitabine was associated with a 1 yr recurrence-free survival rate of 47% compared to only 13% for patients who underwent a 2nd course of BCG.(21) While this study was hypothesis generating, its results were not incorporated into guidelines or clinical practice due to the study's significant limitations, notably its small scale (40 patients/group), and 2 year recurrence free survival rates of 19% with gemcitabine vs 3% for BCG. These RFS rates were far lower than any prior trial, and thus the validity of the study was questioned in the absence of larger patient cohorts and further studies validating its results.(22)

In 2006, the first phase I trial (n=18) investigating intravesical docetaxel for the treatment of NMIBC with BCG failure was completed.(23) All patients failed BCG with a mean of 3 prior intravesical induction treatments. In a second clinical trial of intravesical docetaxel (n=13), it was found that monthly maintenance therapy extended the durability of response to induction treatment for a selected group of patients with BCG-refractory NMIBC, and might decrease the overall risk of recurrence in high-risk NMIBC.(24) One and 3-year recurrence-free survival rates for the entire cohort were 40% and 25%, respectively.(25) There is thus a promising clinical efficacy for intravesical docetaxel in a population heavily pretreated (mean 3 inductions) with BCG, and justification to study this therapy when there is tumor recurrence after the 1st BCG induction.

In 2015, Steinberg et. al. published the first known study of sequential gemcitabine and docetaxel (GEM/DOCE) as salvage therapy for patients with NMIBC, and demonstrated a 54% 1 year and 34% 2 year recurrence free survival, in addition to a 66% recurrence free survival at first surveillance.(26) At our institution, GEM/DOCE has been administered following the treatment protocol established by Steinberg et. al. since 2013. The 25 BCG unresponsive/relapsing patients treated at our institution have had a 49% 1-year high grade recurrence free survival (HG-RFS) and 34% 2-year HG-RFS with a median HG-RFS was 6.5 months.

At our institution, among patients undergoing BCG treatment who have already recurred after 1 course of BCG, 2 year recurrence free survival is 33%--this is much different than the 50-70% 2 yr RFS after the 1st induction course, and is more on par with other 2nd line intravesical chemotherapies that are typically studied after 2 or more BCG associated recurrences. There is likely a biologic mechanism that explains this response pattern, however, the exact mediators of BCG resistance are not clear. Similarly, while deleterious DNA mutations in genes responsible for DNA damage repair (DDR) have been associated with response to systemically administered cisplatin in muscle-invasive bladder cancer patients, predictors of response or resistance to intravesical

chemotherapy treatments including gemcitabine and docetaxel are uncertain. Identifying predictive biomarkers of intravesical BCG and chemotherapy response is an area our group is actively studying. Our plan is to seek funding from another organization for a translational component of this trial that compares responders and nonresponders to each treatment (BCG vs chemotherapy) and assesses whether there is a molecular signature characteristic of those that respond to BCG immunotherapy vs chemotherapy.

Given the encouraging preliminary efficacy data in BCG relapsed and unresponsive populations, the critical need to develop non-BCG therapy approaches, and the improved opportunity for biomarker discovery in a more homogenous patient population, we aim to move combination intravesical GEM/DOCE chemotherapy up in the treatment algorithm to those who are naïve to BCG.

1.3 Rationale for a Single Arm Two-Stage Clinical Trial Design

A Simon's single arm two-stage study design was chosen for several reasons. At the time of this writing (March 2020), a worldwide BCG shortage was underway and one of the central purposes of this trial is to provide patients with a reasonable, on-protocol alternative. Secondly, in order to fully ensure that the proposed Gem/Doce regimen is non-inferior to BCG, a 1st stage analysis to determine efficacy or futility is appropriate.

1.4 Summary

In summary, a strong rationale exists to study combination intravesical gemcitabine/docetaxel in BCG naïve high risk nonmuscle invasive bladder:

1) NMIBC represents a common, sizeable patient population.

2) Intravesical BCG therapy, which has been the accepted standard of care in NMIBC patients, is fraught with frequent drug shortages.

3) Recent monotherapy intravesical chemotherapy trials have demonstrated similar outcomes between BCG and chemotherapy.

4) Intravesical gemcitabine/docetaxel is a commonly used, safe therapy for BCG unresponsive NMIBC and for BCG naïve NMIBC in times of shortage, with efficacy approaching that of BCG in retrospective series.

5) Safety and efficacy data from this trial will prove helpful in assessing development strategies for a larger scale randomized trial with practice-changing impact in the BCG-naïve population.

6) Urine cytology and bladder tumor biopsies are usually considered standard in the baseline evaluation and follow-up care of patients with NMIBC. As such, this trial presents a unique environment by which to discover and validate biomarkers to predict intravesical chemotherapy response and understand mechanisms of resistance.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

- Determine the complete response (CR) rate of NMIBC subjects treated with intravesical gemcitabine/docetaxel

2.1.2 Secondary Objectives:

- Determine safety of NMIBC subjects treated with intravesical gemcitabine/docetaxel
- Determine the 12-month, and 24-month recurrence-free survival (RFS) rates of NMIBC subjects treated with intravesical gemcitabine/docetaxel
- Determine the cystectomy free survival rates of NMIBC subjects treated with intravesical gemcitabine/docetaxel
- Determine how variant histology attenuates 12-month RFS and surgical upstaging rates among NMIBC subjects treated with intravesical gemcitabine/docetaxel
- To assemble a blood, urine, and tissue bank (with pre and post treatment samples) to assess molecular correlates for response to intravesical GemDoce.
- Determine how RNA expression changes, including molecular subtypes attenuate 12-month RFS and surgical upstaging rates among NMIBC subjects treated with intravesical gemcitabine/docetaxel
- Determine how tumor DNA mutations, rearrangements/fusions, copy number alterations, tumor mutational burden impact clinical outcomes (e.g. CR rate, 12m RFS, surgical upstaging) among NMIBC subjects treated with intravesical gemcitabine/docetaxel
- Determine how tumor mutational burden attenuates 12-month RFS and surgical upstaging rates among NMIBC subjects treated with intravesical gemcitabine/docetaxel
- Determine associations between baseline- and post-treatment T lymphocyte subset ratios and 12-month RFS and surgical upstaging rates among NMIBC subjects treated with intravesical gemcitabine/docetaxel

2.2 Endpoints

2.2.1 Primary Endpoint

- The complete response (CR) rate of BCG-naive NMIBC subjects treated with intravesical gemcitabine/docetaxel is defined as the proportion of patients who demonstrate no evidence of recurrent high grade urothelial carcinoma of the bladder of any stage at the 3-month post-treatment disease assessments.

2.2.2 Secondary Endpoints

- The 12-month relapse-free survival (RFS) rates of BCG-naive NMIBC subjects treated with intravesical gemcitabine/docetaxel is defined as the proportion of patients with no evidence of recurrent high grade urothelial carcinoma of the bladder of any stage at the post-treatment tumor assessments performed at least 12 months after the initiation of study treatment

- The 24-month relapse-free survival (RFS) rates of BCG-naive NMIBC subjects treated with intravesical gemcitabine/docetaxel is defined as the proportion of patients with no evidence of recurrent high grade urothelial carcinoma of the bladder of any stage at the post-treatment tumor assessments performed at least 24 months after the initiation of study treatment

- The safety profile of BCG-naive NMIBC subjects treated with intravesical gemcitabine/docetaxel will be assessed by NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.

- The association between 1) DNA and RNA based genomic changes, 2) tumor mutational burden, 3) immune cell populations and RFS will be assessed from DNA and RNA derived from pre treatment bladder tumor.

3 ELIGIBILITY CRITERIA

3.1 Primary Inclusion Criteria

Subject must meet all of the following applicable inclusion criteria to participate in this study:

1. Histologically confirmed intermediate or high-risk non-muscle invasive urothelial carcinoma of the bladder (Ta, T1, or Tis stage) on TURBT obtained within 90 days of registration defined according to modified EORTC risk criteria summarized as follows

Risk Group	Characteristics
Low-risk Tumors	Initial or recurrent tumor > 12 months after resection with all of the following: • Solitary tumor • Low-grade • < 3 cm • No CIS
Intermediate-Risk Tumors	All tumors not defined in the two adjacent categories (between the category of low- and high-risk)
High-risk Tumors	Any of the following: • T1 tumor • High-grade • CIS • Multiple and recurrent and large (> 3 cm) Ta low-grade tumors (all conditions must be met for this point on Ta low-grade tumors)

NOTE #1: Low-risk tumors as defined above are not eligible.

NOTE #2: Mixed histologies are permitted, provided a component of urothelial carcinoma is present.

NOTE #3: All patients with HGT1 should undergo a restaging TURBT.

2. ECOG (WHO) performance status 0,1, or 2.

3. Age ≥ 18 years old at time of consent

4. Evidence of post-menopausal status or negative urinary or serum pregnancy test for female pre-menopausal patients is required. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

    - Women <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy or hysterectomy).

- Women ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

5. Subjects who give a written informed consent obtained according to local guidelines

3.2 Primary Exclusion Criteria

1. Subjects with muscle-invasive (i.e. T2, T3, T4), locally advanced unresectable, or metastatic urothelial carcinoma as assessed on baseline radiographic imaging obtained within 90 days prior to study registration. The required radiographic imaging includes:

    - Abdomen/Pelvis – CT scan

    - Chest – chest x-ray or CT scan
2. Subjects with concurrent upper urinary tract (i.e. ureter, renal pelvis) urothelial carcinoma of any stage. (**NOTE:** Subjects with history of non-invasive (Ta, Tis) upper tract urothelial carcinoma that has been definitively treated with at least one post-treatment disease assessment (i.e. cytology, biopsy, imaging) that demonstrates no evidence of residual disease are eligible).
3. Subjects with another active second malignancy with an estimated overall survival from the second malignancy of < 12 months. Subjects with another second active malignancy that are deemed to have an estimated overall survival of ≥12 months are eligible.
4. Subjects who have received the last administration of an anti-cancer therapy including chemotherapy, immunotherapy, and monoclonal antibodies ≤ 4 weeks prior to starting study drug, or who have not recovered from the side effects of such therapy
5. Subjects who have had radiotherapy ≤ 4 weeks prior to starting study drug, or who have not recovered from radiotherapy toxicities.
6. Pregnant or breast-feeding women
7. Subjects unwilling or unable to comply with the protocol.
8. Patients with prior systemic gemcitabine or docetaxel use for a non-bladder malignancy may enroll and receive treatment.

4 SUBJECT REGISTRATION

All subjects must be registered through the dedicated JHH GBCI RedCap database, with this trial marked as “registered”. A subject is considered registered when an “On Study” date is entered into RedCap.

Subjects must be registered prior to starting protocol therapy. Subjects must begin therapy **within 60 days** of registration.

5 TREATMENT PLAN

5.1 Induction Drug administration

Upon successful screening and registration, subjects will undergo the following treatment.

GEM/DOCE induction is given intravesically in sequential order once a week for six consecutive weeks. One gram of gemcitabine in 50 ml of sterile water is slowly instilled into the bladder via a Foley catheter and the catheter is clamped for 60 minutes. The bladder is then drained and 40 mg of docetaxel in 50 ml of NSS is then slowly instilled via the Foley catheter into the bladder. The catheter is again clamped for 60 minutes. The docetaxel is then drained and catheter removed and the patient is questioned regarding discomfort, instructed to remain well-hydrated and to notify a physician with any adverse reactions, questions, or concerns. The patient may have the option of leaving the urology clinic with the docetaxel instilled with the understanding that it must remain in the bladder for 60 minutes. The patient is instructed to put a capful of bleach in the toilet prior to urinating and flushing the toilet.

Gemcitabine and docetaxel are given per standard of care. As such, if the standard of care guidelines should change, there is allowance for adjustment in the dosing of gemcitabine and docetaxel under the discretion of the investigator.

5.2 Maintenance Drug administration

For patients with a CR, CIS, or LgTa histologies after induction therapy, the maintenance program will be monthly GEM/DOCE instillations for up to 2 years from time of diagnosis on pathology, with cystoscopic and cytologic evaluations every 3 months.

Any deviations from the standard GEM/DOCE induction or maintenance schedule will be recorded in the study database.

5.3 Allowed Concomitant Medications

Use of full-dose anti-coagulation (i.e. warfarin, enoxaparin, rivaroxaban, etc.) is permitted at the site investigator’s discretion.

Use of antibiotics concurrent with study drugs is allowed.

5.4 Contraception

5.4.1 Female patient of child-bearing potential

Females of childbearing potential who are sexually active with a non-sterilized male partner must use at least 1 **highly** effective method of contraception as described in the table below from the time of screening and must agree to continue using such precautions for 90 days after the last dose of GEM/DOCE combination therapy. Non-sterilized male partners of a female patient must use male condom plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Not engaging in sexual activity for the total duration of the drug treatment and the drug washout period is an acceptable practice; however, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control. Female patients should also refrain from breastfeeding throughout this period.

5.4.2 Male patients with a female partner of childbearing potential

Non-sterilized males who are sexually active with a female partner of childbearing potential must use a male condom plus spermicide from screening through 90 days after receipt of the final dose of GEM/DOCE combination therapy. Not engaging in sexual activity is an acceptable practice; however, occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male patients should refrain from sperm donation throughout this period.

5.4.3 Female partners (of childbearing potential) of male patients

Female partners (of childbearing potential) of male patients must also use a highly effective method of contraception throughout this period (see table below).

5.4.4 Definition of Childbearing Potential

Females of childbearing potential are defined as those who are not surgically sterile (i.e., bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or post-menopausal. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

- Women <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the

institution or underwent surgical sterilization (bilateral oophorectomy or hysterectomy).

- Women ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

5.4.5 Classification of Contraceptive Options

Highly effective methods of contraception, defined as one that results in a low failure rate (i.e., less than 1% per year) when used consistently and correctly are described below. Note that some contraception methods are not considered highly effective (e.g. male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non-copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action [excluding Cerazette/desogestrel which is considered highly effective]; and triphasic combined oral contraceptive pills).

Highly effective methods of contraception (<1% failure rate)

Barrier/Intrauterine methods	Hormonal Methods
• Copper T intrauterine device • Levonorgestrel-releasing intrauterine system (e.g., Mirena®)[a]	• Etonogestrel implants: e.g., Implanon or Norplan • Intravaginal device: e.g., ethinylestradiol and etonogestrel • Medroxyprogesterone injection: e.g., Depo-Provera • Normal and low dose combined oral contraceptive pill • Norelgestromin/ethinylestradiol transdermal system • Cerazette (desogestrel)

[a] This is also considered a hormonal method

5.4 Prohibited Concomitant Medications and Other Restrictions and Precautions

Any medicinal herbal preparation unless prescribed by the site investigator. All concomitant medications including prescribed medicinal herbal preparations must be documented.

Any administration of any anti-cancer therapies (investigational or approved) within 12 weeks prior to study drug is prohibited.

Alcohol consumption while on study is strongly discouraged due to the potential to confound interpretation of hepatotoxic events.

6 TOXICITIES AND DOSE DELAYS/DOSE MODIFICATIONS

The NCI Common Terminology Criteria for Adverse Events (CTCAE) v5 will be used to grade adverse events. Subjects enrolled in this study will be evaluated

clinically and with standard laboratory tests before and at regular intervals during their participation in this study as specified in Study Calendar & Evaluations.

Subjects will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation as specified in Study Calendar & Evaluations.

6.1 Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions

Guidelines for dose modifications and management of immune-mediated adverse events are outlined in the following tables.

General Guidelines

Dose Modifications	Toxicity Management
Drug administration modifications of study drug/study regimen will be made to manage potential immune-related AEs based on severity of treatment-emergent toxicities graded per NCI CTCAE v5. In addition to the criteria for permanent discontinuation of study drug/study regimen based on CTC grade/severity (table below), permanently discontinue study drug/study regimen for the following conditions: • Recurrence of a previously experienced Grade 3 treatment-related AE following resumption of dosing **Grade 1** No dose modification **Grade 2** Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. If toxicity worsens, then treat as Grade 3 or Grade 4. Study drug/study regimen can be resumed once event stabilizes to Grade ≤1. **Grade 3** Depending on the individual toxicity, study drug/study regimen may be permanently discontinued. Please refer to guidelines below. **Grade 4** Permanently discontinue study drug/study regimen.	

AE Adverse event; CTC Common Toxicity Criteria; CTCAE Common Terminology Criteria for Adverse Events; IV intravenous; NCI National Cancer Institute; PO By mouth.

Intravesical Treatment Reactions

Severity Grade of the Event (NCI CTCAE version 5)	Dose Modifications	Toxicity Management
Any Grade	Note: Dose modifications are not required for AEs not deemed to be related to study treatment (i.e., events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.	Treat accordingly, as per institutional standard.
Grade 1	No dose modifications.	Treat accordingly, as per institutional standard.
Grade 2	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline. Specifically, for hematuria or dysuria in the absence of infection the study drug may be given,	Treat accordingly, as per institutional standard.
Grade 3	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline. For AEs that downgrade to ≤Grade 2 within 7 days or resolve to ≤Grade 1 or baseline within 14 days, resume study drug/study regimen administration. Otherwise, discontinue study drug/study regimen.	Treat accordingly, as per institutional standard.
Grade 4	Discontinue study drug/study regimen (Note: For Grade 4 labs, decision to discontinue should be based on accompanying clinical signs/symptoms, the Investigator's clinical judgment, and consultation with the Sponsor.).	Treat accordingly, as per institutional standard.
Note: As applicable, for early phase studies, the following sentence may be added: "Any event greater than or equal to Grade 2, please discuss with Study Physician." AE Adverse event; CTCAE Common Terminology Criteria for Adverse Events; NCI National Cancer Institute.		

6.2 Protocol Therapy Discontinuation

In addition to discontinuation from therapy related to toxicities, a subject will also be discontinued from protocol therapy and followed per protocol under the following circumstances outlined below. The reason for discontinuation of protocol therapy will be documented on the electronic case report form (eCRF)

- Documented disease progression, as defined by:
  - Evidence of progression to muscle invasive disease on transurethral biopsy.

- Documented disease recurrence, as defined by:
  - Evidence of HGT1 disease on transurethral biopsy at the 3 month post-treatment evaluation.
  - Evidence of any high grade bladder cancer (including CIS, HgTa, or HGT1) at the 6 month post treatment evaluation or any timepoint thereafter.
  - Note that patients with HgTa or CIS at the 3 month post treatment evaluation may stay on study at the discretion of the treating physician.
  - Similarly, patients with low grade Ta disease at any timepoint may stay on study at the discretion of the treating physician.

- Investigator determines a change of therapy would be in the best interest of the subject

- Subject requests to discontinue protocol therapy, whether due to unacceptable toxicity or for other reasons

  - In a subject decides to prematurely discontinue protocol therapy (“refuses treatment”), the subject should be asked if he or she may still be contacted for further scheduled study assessments. The outcome of that discussion should be documented in both the medical records and in the eCRF.

- Female subject becomes pregnant

- Protocol induction therapy is interrupted for ≥ 21 days.

6.3 Protocol Discontinuation

If a subject decides to discontinue from the protocol (and not just from protocol therapy) all efforts should be made to complete and report study assessments as thoroughly as possible. A complete final evaluation at the time of the subject’s protocol withdrawal should be made with an explanation of why the subject is withdrawing from the protocol. If the reason for removal of a subject from the study is an adverse event, it will be recorded on the eCRF.

7 STUDY CALENDAR & EVALUATIONS

Study Day	Screening (0-60 days pre-study)	Induction						Maintenance Instillation				
		Day 1	Day 8	Day 15	Day 22	Day 29	Day 35	3 months	6 months	9 months	12 months[14]	24 months/ End of Study Visit [12, 13, 14]
Medical history	X											
Physical examination	X											
Vital signs to include BP, weight, ECOG PS; height at screening only	X											
AEs & concomitant medications	X	X	X				X	X			X	
CBC w/differential	X	X[8]						X[8]			X[8]	
CMP	X											
GEM/DOCE instillation		X[3,5]	X	X	X	X	X	monthly[5]				
Urinalysis	X	X	X	X	X	X	X	monthly				
Urine pregnancy test	X[5]											
Chest X-ray or if clinically indicated, CT chest	X[11]											
CT or MRI abdomen/pelvis	X[11]											
Cystoscopy	X[1]							X[9]	quarterly			
Urine cytology	X[2]							X	quarterly			
Bladder Biopsy/TURBT	X[1]							X[9]	At urologist discretion			
Blood sample (Plasma, Serum, PBMC)	X[4]							X[6]			X[6]	
Urine sample	X[4]							X[6]			X[6]	
Tumor Tissue	X[1]							X[9]			X[10]	

[1] Cystoscopy with TURBT at screening should be performed within 90 days of study registration.

[2] Urine cytology sample at screening should be performed within 90 days of starting study therapy.

[3] Study treatment should begin within 60 days of study registration.

[4] Correlative blood (PBMC, plasma, serum) and urine samples should be obtained after eligibility is confirmed and prior to starting study therapy. They may be obtained prior to or on Day 1 provided they are obtained prior to initiation of study therapy.

[5] All induction treatments may be performed ± 5 days of the intended treatment dates and ± 10 days of the intended treatment dates for maintenance treatments. Patients should receive 6 treatments in 9 weeks. Treatments may be administered anywhere where they are routinely given (ie they do not need to be administered at a study site). If treatments are performed at an outside institution, patients must be assessed every 3 doses for a toxicity evaluation. Assessment can be via telephone.

[6] Post-treatment correlative assessments will occur at the 3-month and 12-month time points within ± 7 days of the cystoscopy or instillation.

[7] Cystoscopy and urine cytology at the 3- and 12-month disease assessments may be performed within ± 14 days of the 3- and 12-months post-initiation of study therapy dates (i.e. 3- and 12-months after Day 1 date).

[8] CBC will be drawn up to 10 days prior to Day 1. If screening CBC was drawn within 10 days prior to Day 1, it does not need to be repeated for Day 1. CBC will be drawn up to 10 days prior to 3- and 12-month maintenance instillation.

[9] Tumor tissue will be collected if biopsy (at urologist's discretion) occurred at 3-month cystoscopy.

[10] Tumor tissue will be collected, if biopsy (at urologist's discretion) occurred at 12-month cystoscopy.

[11] Chest X-ray or if clinically indicated, CT chest, and CT or MRI abdomen/pelvis at screening should be performed within 90 days of study registration.

[12] End of study visit (if applicable) will occur if anytime during the study the patient decides to stop early, relapse, if the doctor decides it is in the patient's best interest to stop, or if it's been 24 months from time of diagnosis on pathology. Urine analysis, cystoscopy, urine cytology, and biopsy (at urologist's discretion) will be performed if applicable.

[13] AEs considered related to study drug(s) will be followed until resolution to Grade ≤ 1 or baseline, deemed clinically insignificant, and/or until a new anti-cancer treatment starts, whichever occurs first. All SAEs should be followed until resolution, until the subject returns to baseline status, or until the condition has stabilized with the expectation that it will remain chronic, even if this extends beyond study participation. Refer to Section 11.2 for additional details.

[14] If the patient should exit the study prior to the 12 month and 24 month timepoint from the start of the initial instillation treatment, the patient will be followed for information regarding survival outcome (i.e. disease progression and death) and the tumor assessments performed at least 12 months and 24 months after the initiation of study treatment.

Note: In order to minimize the need for research-only in-person visits, telemedicine visits may be substituted for in-person clinical trial visits or portions of clinical trial visits where determined to be appropriate and where determined by the investigator not to increase the participants risks. Prior to initiating telemedicine for study visits the study team will explain to the participant, what a telemedicine visit entails and confirm that the study participant is in agreement and able to proceed with this method. Telemedicine acknowledgement will be obtained in accordance with the Guidance for Use of Telemedicine in Research. In the event telemedicine is not deemed feasible, the study visit will proceed as an in-person visit. Telemedicine visits will be conducted using HIPAA compliant method approved by the Health System and within licensing restrictions.

8 BIOSPECIMEN STUDIES AND PROCEDURES

8.1 Tumor Tissue Studies

20 unstained 5 micron thick sections (as tissue availability permits) from both the pre- and post-treatment tumor samples will be cut unto slides for correlative investigations.

If available, three to five individual 1.0 mm diameter cores containing at least approximately 75% tumor cellularity will be obtained (as tissue availability permits) from representative pre- and post-treatment formalin fixed paraffin embedded (FFPE) tissue blocks. FFPE block coring kit supplies, methodology, and shipping instructions are detailed in the study Clinical Lab Manual. Some of the cores from each case will be incorporated in tissue microarrays (TMAs) with subsequent sections from these TMAs being stained with H&E and IHC; while other cores from each case with utilized for DNA and RNA.

For all correlative studies analyzing sample DNA or RNA, if sufficient DNA/RNA is not available from the core biopsy samples, and as tissue availability permits, additional tumor and immune cells may be enriched from the subject's pre- and post-treatment tumor slides by macro-dissection under the direction of Dr. Andres Matoso.

Tissue samples will be transferred to Veracyte for DNA/RNA sequencing. De-identified clinical outcome data (i.e. responder/non-responder) correlating to each sample will be shared with Veracyte. An MTA will be secured between JHU and Veracyte prior to transfer and sharing.

8.2 Immunohistochemistry Analyses

IHC analyses may be performed on tumor tissues with recurrent disease. For correlative IHC analyses, IHC on TMA cores will be performed using antibodies acquired from commercial sources at the IHC pathology core facility as follows: Immunohistochemistry (IHC) for PD-1 (Cell Marque, Rocklin, CA; dilution 1:100), PD-L1 (Spring Bioscience, Pleasanton, CA for clone SP142 dilution 1:100 - DAKO, Santa Clara, CA for clone 22C3 predilute) and markers of tumor infiltrating lymphocytes (TILs) CD3 (DAKO, dilution 1:100), CD8 (CellMarque; predilute), CD4 (Ventana; predilute), FoxP3 (Abcam, Cambridge, MA; dilution 1:100), will be performed on 4 µm thick paraffin sections of the tissue microarray masterblock on the Ventana Discovery Autostainer (Ventana Medical Systems), Ventana Benchmark Ultra Autostainer (Ventana). Staining will be scored in blinded manner with respect to BCG response status by a GU pathologist. As tissue availability permits and new data emerges, additional IHC stains of relevance may be performed in addition to those listed above.

8.3 Gene Expression Analyses

All of these procedures will be performed in the Johns Hopkins Greenberg Bladder Cancer Institute's (GBCI's) dedicated Genomics Core (Director: Woonyoung Choi,

PhD). Sequential extraction of total RNA and DNA is performed using a modified version of a protocol jointly developed by the Southwest Oncology Group's Tissue Bank and TCGA. Briefly, RNA is isolated using the High Pure FFPE miRNA isolation kit (Roche) according to the manufacturer's instructions. The key variable in the protocol is time in proteinase K (3 hours), which promotes optimal RNA quality and yield. The pellets created after the proteinase K digestion step are then used for total DNA purification using the QIAmp DNA FFPE kit (Thermo Fisher). RNA and DNA purity and integrity are measured by NanoDrop ND-1000 and Agilent Tapestation. Whole transcriptome RNA sequencing and panel DNA are performed using Ion Torrent's AmpliseqRNA platforms (Thermo Fisher, Inc). The GBCI's panel was developed in consultation with Peter Black and Alex Wyatt at the University of British Columbia, consists of 50 of the most frequently mutated genes in NMIBCs and MIBCs, and contains the DDR mutations highlighted in previous studies. Dr. Wyatt has also developed a strategy to estimate total mutational burden (TMB) from the results generated with this panel(27). Libraries are prepared using 10-20 ng purified RNA or 20-40 ng purified DNA according to the manufacturer's instructions, and libraries are sequenced on an Ion S5 XL sequencer in the Genomics Core. Primary analyses of the data are performed using Torrent Suite Software package provided on the S5 XL's server. Aligned and normalized data are downloaded directly from the server, and the total time from library preparation to data analysis is approximately 48 h for 16 samples. As tissue availability permits and new data emerges, additional gene expression platform analyses of relevance may be performed (e.g. Nanostring, HTG EdgeSeq, etc.) in addition to those listed above.

8.4 Urine Marker Processing and Analysis

Urine Sample Processing

A clean catch urine sample (20cc) will be collected at baseline and at the 3- and 12-month disease assessment dates from each subject. Urine samples will be banked and stored in the Brady Urology Biorepository. The exact list of urine markers may be modified according to new target identification and emerging translational science, but will likely include metabolomic and gene methylation analyses, as well as immune and T cell profiling. A Streck tube urine sample will also be collected at baseline, 3m, and 12m for ctDNA studies.

Urine samples will be transferred to Predicine for the aforementioned analyses. No data will be transferred with the samples. An MTA will be secured between JHU and Predicine prior to transfer.

8.5 Blood Processing and Analysis

Blood will be collected for germline DNA in order to determine somatic mutations in the tumor tissues. Blood samples will be banked and stored in the Brady Urology Biorepository.

8.6 Confidentiality of Biospecimens

Samples that are collected will be identified by a subject's study number assigned at the time of registration to the trial. Any material issued to collaborating researchers will be anonymized and only identified by the subject's study number.

9 CRITERIA FOR DISEASE EVALUATION

For the purposes of this study, subjects should be evaluated for tumor response at the specified post-treatment time points. Any metastatic progression will be evaluated in this study using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) (see Eisenhauer EA et al. *New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1).* Eur J Can, 2009.45:p.228-247).

9.1 Tumor Response

9.1.1 Evaluable Population Definitions

Evaluable for toxicity. All subjects will be evaluable for toxicity from the time of their first study drug treatment.

Evaluable for tumor response. Only those subjects who have received at least one dose of study therapy, and undergo a restaging cystoscopy with urine cytology will be considered evaluable for tumor response. These subjects will have their tumor response classified according to the definitions stated below. (Note: Subjects who exhibit objective disease progression prior to the end of Cycle 1 will also be considered evaluable.)

Evaluable for Pathologic Staging. Only those patients who have received at least one dose of study therapy, and undergo post-treatment cystectomy will be considered evaluable for pathologic staging. These patients will have their pathologic staging classified according to the definitions stated below.

9.1.2 Methods for Evaluation of Tumor Response

The post-treatment tumor response will be determined based on the cystoscopic and/or bladder biopsy results (if biopsy indicated) and urine cytology results obtained during post-treatment tumor assessments.
NOTE: At time points where bladder biopsies are not required by the protocol, patients with absence of tumor recurrence on cystoscopy and urine cytology will be classified as T0. Patients with high grade UC on urine cytology but T0 stage on bladder biopsy with no evidence of upper tract UC will be classified as Tis.

These categories are summarized below.

Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Non-invasive papillary carcinoma which does not invade the lamina propria
Tis	Carcinoma in-situ
T1	Tumor invades into the lamina propria but not into the muscularis propria
T2	Tumor invades into the muscularis propria

Table 6: Biopsy T-stage

9.1.3 Methods for Evaluating Pathologic Stage

The post-treatment pathologic stage will be determined in patients who undergo a post-treatment cystectomy and will be determined based on the cystectomy pathology staging results. The staging definitions are summarized below.

Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Non-invasive papillary carcinoma which does not invade the lamina propria
Tis	Carcinoma in-situ
T1	Tumor invades into the lamina propria but not into the muscularis propria
T2	Tumor invades into the muscularis propria
T2a	Tumor invades into the inner half of the muscularis propria
T2b	Tumor invades into the outer half of the muscularis propria
T3	Tumor invades into the perivesical tissue
T3a	Tumor microscopically invades the perivesical tissue
T3b	Tumor macroscopically invades the perivesical tissue
T4	Tumor invades into adjacent organs
T4a	Tumor invades the prostatic stroma, uterus, or vagina

T4b	Tumor invades into the pelvic wall or abdominal wall

Table 7: Pathologic T-stage

Nx	Lymph nodes cannot be assessed
N0	No lymph node metastases
N1	Single regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node)
N2	Multiple regional lymph node metastases in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph nodes)
N3	Lymph node metastases to the common iliac lymph nodes

Table 8: Pathologic N-stage

M0	No distant metastasis
M1	Distant metastasis

Table 9: Pathologic M-stage

9.1.4 Tumor Response Definitions

9.1.4.1 Complete Response

Complete response (CR) is defined by a post-treatment cystoscopy with bladder biopsy if clinically indicated with the following T-stages: T0. In addition, patients must demonstrate an absence of high grade urothelial carcinoma on urine cytology. **NOTE:** Patients with urine cytology samples demonstrating urothelial cell atypia but no definitive high grade urothelial carcinoma with an initial post-treatment bladder biopsy tumor stage of T0 are considered complete responders.

9.1.4.2 Incomplete Response

Incomplete response (IR) is defined by the presence of low-grade Ta urothelial carcinoma at the initial post-treatment tumor assessment in subjects with previous baseline high-grade papillary urothelial carcinoma (Ta/T1) or CIS. **NOTE:** Patient's with incomplete response at the initial post-treatment tumor assessment may continue and complete the maintenance therapy portions of the study.

9.1.4.3 Non-Response

Non-response (NR) is defined by persistent high-grade urothelial carcinoma of any T-stage or the presence of low-grade T1 urothelial carcinoma at the initial post-treatment tumor assessment. **NOTE:** Non-response patients with high-grade or low-grade T1 tumors at the initial post-treatment tumor assessment will discontinue study therapy. Non-response patient's with pre-treatment CIS and/or high grade Ta tumors with persistent CIS and/or high grade Ta tumors may continue on study and receive maintenance therapy. Patients with a post-treatment high grade urine cytology with no evidence of tumor recurrence in the bladder (either visually on cystoscopy or by bladder biopsy/TURBT) should have full staging performed including cytology evaluations of the upper urinary tracts and biopsy of the prostatic urethra. If the workup of the upper urinary tracts and the prostatic urethra demonstrates no evidence of high grade disease, the patient may continue on study and receive maintenance therapy.

9.1.4.4 Late Complete Response

Late complete response (LCR) is defined in patients demonstrating IR at the initial post-treatment bladder biopsy who on a subsequent bladder biopsy obtained 6 months after the start of study treatment demonstrate the following T-stages: T0. **NOTE:** Patients with urine cytology samples demonstrating urothelial cell atypia but no definitive high grade urothelial carcinoma with a 6 month post-treatment bladder biopsy tumor stage of T0 are considered late complete responders.

9.1.4.5 Progression to Muscle Invasion

Progression to muscle invasion (pMI) is a post-treatment TURBT with the following T-stages: T2-T4b. For subjects who undergo cystectomy, progression to muscle invasion (pMI) is defined by post-cystectomy tumor stages with the following T-stages: T2-T4b.

9.1.4.6 Progression to Metastatic Stage

Progression to metastatic stage (pMet) is a post-treatment subject with the following M-stages at any time point as assessed pathologically, radiologically, or clinically: M1.

9.1.4.7 Rate of Cystectomy

Rate of cystectomy (CystR) is defined as the proportion of subjects who undergo a post-treatment cystectomy for any reason.

9.1.5 Tumor IHC Staining Intensity Definitions

For validated IHC targets, standardized IHC staining intensity cutoffs will be utilized. For all other IHC targets, IHC staining will be categorized as:

0	< 1% cells stained
1+	1 to < 5% cells stained
2+	5 to < 10% cells stained
3+	≥ 10% cells stained

9.2 Survival Analyses

9.2.1 Relapse-Free Survival (RFS)

RFS is defined as the duration of time from start of treatment to time of first documented high grade bladder tumor of any stage, progression or death, whichever occurs first.

NOTE: Low-grade non-muscle invasive bladder tumors detected in follow up do not qualify as a relapse event.

9.2.1.1 12-month Relapse-Free Survival (12m-RFS)

12m-RFS is defined as the proportion of patients alive and with no evidence of high grade bladder tumor of any stage as assessed by post-treatment tumor assessments performed at least 12 months after the initiation of study treatment.

9.2.1.2 24-month Relapse-Free Survival (24m-RFS)

24m-RFS is defined as the proportion of patients alive and with no evidence of high grade bladder tumor of any stage as assessed by post-treatment tumor assessments performed at least 24 months after the initiation of study treatment.

9.2.2 Overall Survival (OS)

OS is defined as the duration of time from start of treatment to time of death.

9.2.3 Cancer-Specific Survival (CSS)

CSS is defined as the duration of time from start of treatment to time of death due to bladder cancer.

10 DRUG ADMINISTRATION

Docetaxel and Gemcitabine are both commonly used pharmaceutical formulations, and their preparation will be according to routine institutional pharmacy protocols.

11 ADVERSE EVENTS

The descriptions and grading scales found in the NCI CTCAE v5 will be utilized for AE assessment. A copy of the CTCAE v5 can be downloaded from the CTEP website at http://ctep.cancer.gov.

11.1 Definitions

11.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence whether or not considered related to the study drug that appears to change in intensity during the course of the study. The following are examples of AEs:

- Unintended or unfavorable sign or symptom
- A disease temporally associated with participation in the protocol
- An intercurrent illness or injury that impairs the well-being of the subject

Abnormal laboratory values or diagnostic test results constitute AEs only if they induce clinical signs or symptoms or require treatment or further diagnostic tests

Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) should not be recorded as an AE.

Disease progression should not be recorded as an AE, unless it is attributable to the study regimen by the site investigator.

11.1.2 Serious Adverse Event (SAE)

A SAE is an adverse event that:

- Results in death. **NOTE:** Death due to disease progression should not be reported as a SAE, unless it is attributable by the site investigator to the study drug(s). Please see additional information regarding reporting death below.

- Is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)

- Requires inpatient hospitalization for >24 hours or prolongation of existing hospitalization. **NOTE:** Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.

- Results in persistent or significant disability/incapacity

- Is a congenital anomaly or birth defect

- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions not resulting in hospitalization; or the development of drug dependency or drug abuse.

11.1.3 Unexpected Adverse Event

For this study, an AE is considered unexpected when it varies in nature, intensity or frequency from information provided in the current IB, prescribing information or when it is not included in the informed consent document as a potential risk. Unexpected also refers to AEs that are mentioned in the IB as occurring with a class of drugs or are anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

11.1.4 Relatedness

AEs will be categorized according to the likelihood that they are related to the study drug(s). Specifically, they will be categorized using the following terms:

Unrelated	Adverse Event is ***not related*** to the study drug(s)
Unlikely	Adverse Event is ***doubtfully related*** to the study drug(s)
Possible	Adverse Event ***may be related*** to the study drug(s)
Probable	Adverse Event is ***likely related*** to the study drug(s)
Definite	Adverse Event is ***clearly related*** to the study drug(s)

11.2 Reporting

11.2.1 Adverse Events

- AEs will be recorded regardless of whether or not they are considered related to the study drug(s).

- All AEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within RedCap.

- AEs should be proactively followed up. Every effort should be made to obtain a resolution for all events, even if the events continue after discontinuation/study completion. AEs considered related to study drug(s) will be followed until resolution to Grade ≤ 1 or baseline, deemed clinically insignificant, and/or until a new anti-cancer treatment starts, whichever occurs first.

11.2.2 Serious Adverse Events (SAEs)

11.2.2.1 Site Requirements for Reporting SAEs

- SAEs will be reported on the SAE Submission Form **within 1 business day** of discovery of the event.

- SAEs include events related and unrelated to the study drug(s).

- All SAEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within RedCap.

- SAEs should be proactively followed up. Every effort should be made to obtain a resolution for all events, even if the events continue after discontinuation/study completion.

- If a subject discontinues from treatment for reasons other than disease progression, and therefore continues to have tumor assessments; drug or procedure-related SAEs must be captured until the patient is considered to have confirmed PD and will have no further tumor assessments.

- The site investigator is responsible for following all SAEs until resolution, until the subject returns to baseline status, or until the condition has stabilized with the expectation that it will remain chronic, even if this extends beyond study participation.

11.2.3 Requirements for Reporting Pregnancy or Maternal exposure

If a patient becomes pregnant during the course of the study, study drug(s) should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study drug under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities or birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

Site investigators (or designees) are responsible for submitting these safety reports to their respective IRBs, as per their IRB policies.

12 STUDY DESIGN AND POWER

Simon's two-stage design (Simon, 1989) will be used. The null hypothesis that the true 3 month complete response rate is 35% will be tested against a one-sided alternative. In the first stage, 18 patients will be accrued. If there are 6 or fewer responses in these 18 patients, the study will be stopped. Otherwise, 8 additional patients will be accrued for a total of 26. The null hypothesis will be rejected if 14 or more responses are observed in 26 patients. This design yields a type I error rate of 0.0377 and power of 80% when the true response rate is 60%.

Standard life table methods will be used to analyze RFS for each arm of the study and for each sub-type within arms of the study separately. We will report 3, 6, 12 and 24-four month RFS with 90% confidence bounds.

The proportion of toxicities by type and grade according to the revised Common Terminology Criteria for Adverse Events (CTCAE) v5 will be reported with exact 95%

confidence intervals. All patients who receive at least one dose of the study drug(s) will be evaluable for toxicity.

13 TRIAL MANAGEMENT

13.1 Monitoring

The SKCCC Compliance Monitoring Program will provide external monitoring for JHU-affiliated sites in accordance with SKCCC DSMP (Version 6.0, 02/21/2019). The SMC Subcommittee will determine the level of patient safety risk and level/frequency of monitoring.

13.2 Data Management

All information will be collected on study-specific case report forms (CRFs) by study staff. These data will be reviewed for completeness and accuracy by the Principal Investigator. Protocol-specified source documents and copies of all study-related documentation will be retained at the site. It is the responsibility of the Principal Investigator to keep all data and essential documentation for a minimum of 5 years after the end of the trial.

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