A Single Arm Phase II Trial of the Intraoperative Intravesical Instillation of Mitomycin C During Nephroureterectomy for Urothelial Carcinoma of the Upper Urinary Tract

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Keywords: urothelial carcinoma; mitomycin c; upper urinary tract; nephroureterectomy

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ABBREVIATIONS

AE	adverse event
ALT	alanine transaminase (also SGPT)
ANC	absolute neutrophil count
AST	aspartate transaminase (also SGOT)
BTR	bladder tumor recurrence
BUN	blood urea nitrogen
CBC	complete blood count
CI	confidence interval
CRF	case report form
CRO	Clinical Research Office
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	clinical trials management system
DISC	Data Integrity and Safety Committee
DNA	deoxyribonucleic acid
eCRF	electronic case report form
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
HR	hazard ratio
HRT	hormone replacement therapy
ICF	informed consent form
ICH	International Conference on Harmonization

IND	Investigational New Drug
IRB	Institutional Review Board
MMC	mitomycin C
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NSAE	non-serious adverse event
PI	principal investigator
PMO	Project Management Office
POD0	post-operative day zero
POD1	post-operative day one
PS	performance status
RBC	red blood cells
RNU	radical ureteronephrectomy
SAE	serious adverse event
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvate transaminase
TUR	transurethral resection
UF	University of Florida
UFHCC	University of Florida Health Cancer Center
US	United States
WBC	white blood cell
WHO	World Health Organization
WOCBP	Women of Childbearing Potential

Protocol Signature Page

A Single Arm Phase II Trial of the Intraoperative Intravesical Instillation of Mitomycin C During Nephroureterectomy for Urothelial Carcinoma of the Upper Urinary Tract

Principal Investigator Protocol Signature Page

_____
Signature of Investigator Date (DDMMMYYY)

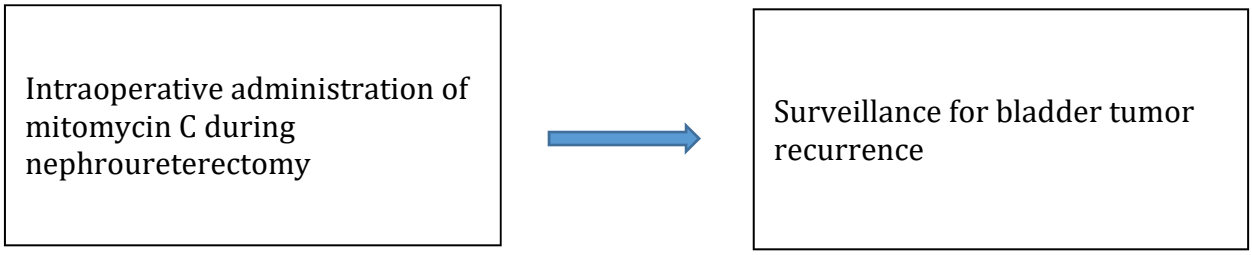
_____
Printed Name of Investigator

_____
Name of Facility

_____
Location of Facility (City/State)

By my signature, I agree to personally supervise the conduct of this study and to ensure its conduct in compliance with the protocol, informed consent, IRB procedures, the Declaration of Helsinki, ICH Good Clinical Practices guidelines, and the applicable parts of the United States Code of Federal Regulations or local regulations governing the conduct of clinical studies.

STUDY SCHEMA



Accrual Goal: 53 subjects

PROTOCOL SYNOPSIS

Title:	**A Single Arm Phase II Trial of the Intraoperative Intravesical Instillation of Mitomycin C During Nephroureterectomy for Urothelial Carcinoma of the Upper Urinary Tract**
Funding Organization:	University of Florida
Investigational Agent Supplier:	Commercial supply
Rationale:	We have recently completed a retrospective review of our experience at the University of Florida of the administration of intraoperative of mitomycin C compared to mitomycin C administered post-operative day one or later. Results of this study suggest that the timing of intravesical mitomycin C may impact bladder tumor recurrence rate following radical nephroureterectomy. This is the first study of its kind to attempt to identify the importance of timing of mitomycin C administration relative to bladder tumor recurrence rate following radical nephroureterectomy.
Objectives:	Primary: • Determine the one-year bladder tumor recurrence rate in patients with urothelial carcinoma of the upper urinary tract following intraoperative administration of mitomycin C Secondary: • Evaluate the time to bladder tumor recurrence in patients with urothelial carcinoma of the upper urinary tract following intraoperative administration of mitomycin • Determine the three-year tumor recurrence rate in patients with urothelial carcinoma of the upper urinary tract following intraoperative administration of mitomycin C
Study Design:	This is a single arm, open label, phase II study.

Accrual Goal:	A total of 53 subjects.
Inclusion Criteria:	Individuals eligible for study participation must meet the following criteria: A. Both males and females ≥ eighteen years of age B. Clinical diagnosis of urothelial carcinoma of the renal pelvis and/or ureter. Clinical diagnosis of urothelial carcinoma may be based upon radiographic, pathologic or cytological findings alone or in combination with one another. No other histology is allowed. C. The TNM stage of the subject's disease (using the American Joint Committee on Cancer [AJCC] Cancer Staging Manual, 8th Edition) must be Tis, Ta, T1, T2, or T3, N0, M0. Subjects may have either a high-grade or low-grade tumor. D. ECOG performance status of 0-2 E. Written informed consent obtained from the subject and the ability for the subject to comply with all the study-related procedures. F. Women of childbearing potential (WOCBP) must be using an adequate method of contraception to avoid pregnancy prior to and for at least three months after mitomycin C instillation to minimize the risk of pregnancy. Prior to study enrollment, women of childbearing potential must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. WOCBP include any woman who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or who is not post-menopausal. Post- menopause is defined as: • Amenorrhea that has lasted for ≥ 12 consecutive months without another cause, or • For women with irregular menstrual periods who are taking hormone replacement therapy (HRT), a documented serum follicle-stimulating hormone (FSH) level of greater than 35 mIU/mL. G. Males with female partners of child-bearing potential must agree to use physician-approved contraceptive methods (*e.g.*, abstinence, condoms, vasectomy) and should avoid conceiving children prior to and for three months following mitomycin C instillation. H. Subjects must have hemoglobin ≥ 9 g/dL and a platelet count ≥ 100,000/μL.

Exclusion Criteria:	Subjects with any of the following will not be eligible for study participation: A. Active urothelial carcinoma of the bladder within 12 months prior to enrollment B. History of adverse reaction to mitomycin C C. Subjects must not have evidence of regional or metastatic disease. D. History of radical cystectomy E. Planned radical cystectomy at the time of nephroureterectomy F. Females or males of childbearing potential who are **unwilling or unable** to use an acceptable method to avoid pregnancy prior to and for at least 3 months after mitomycin C instillation. G. Females who are pregnant or breastfeeding. H. History of any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of protocol therapy or that might affect the interpretation of the results of the study or that puts the subject at high risk for treatment complications, in the opinion of the treating physician. I. Prisoners or subjects who are involuntarily incarcerated. J. Subjects who are compulsorily detained for treatment of either a psychiatric or physical illness. K. Subjects demonstrating an inability to comply with the study and/or follow-up procedures.
Efficacy Assessments:	Patients will be evaluated for bladder tumor recurrence every 3 months for the first two years and then every 6 months for the third year following nephroureterectomy by cystoscopy and urine cytology with UroVysion testing if urine cytology results are atypical or suspicious. Patients with suspected recurrence of urothelial carcinoma within the bladder will require bladder biopsy for histologic confirmation.

Statistical Considerations:	The primary endpoint for this study is the bladder tumor recurrence (BTR) rate at 1-year post-surgery. A one-sided, one sample exact test of proportion will be used to assess the primary endpoint, 1-year BTR rates, with level of significance set at 0.10. Time to BTR will be characterized using Kaplan-Meier plots. Log-rank tests and Cox proportional hazard modeling will be used to examine the impact of baseline characteristics. A p-value of less than 0.05 will be considered statistically significant. In our previous study, there was a 16% recurrence rate for those that received mitomycin C on day 0 and a 33% recurrence rate for those receiving it on day 1 or later. From this we will assume that the underlying proportion of BTR at 1 year is 25% for our population. A sample size of 53 subjects is needed to detect the decrease of 1-year BTR rate from 25% to 12.5% based on Simon's optimal two-stage design and to reach more than 80% power with a one-sided type 1 error rate 0.10. In the first stage, 16 subjects will be recruited and the study will be terminated early if 4 or more BTR happens. If the study proceeds to the second stage, 53 subjects will be studied. If the total number of BTR at 1-year post-surgery is less than 10, the treatment will be considered a success. The sample size was calculated using the PASS 16.
Estimated Enrollment Period:	48 months
Estimated Study Duration:	84 months

1. BACKGROUND

1.1 Urothelial Carcinoma Cancer Therapy

Urothelial carcinoma is projected to be the sixth most common malignancy in the United States in 2017, affecting over 79,000 individuals1. The majority of urothelial carcinoma occurs in the bladder, while urothelial carcinoma involving the upper tract is relatively rare. Upper tract urothelial carcinoma accounts for less than 10% of malignancies of the upper urinary tract2. The incidence of upper tract urothelial carcinoma has slowly increased over the past 30 years, and treatment options continue to evolve3. Radical nephroureterectomy with bladder cuff excision remains the standard surgical management for high-risk upper tract urothelial carcinoma and lower risk tumors not amenable to endoscopic management2, 4. Unfortunately, recurrence in the bladder is common, occurring in 22-47% of cases4.

1.2 Overview of Mitomycin in the Treatment of Urothelial Carcinoma

Mitomycin C (MMC) is an alkylating agent which cross links DNA between adenine and guanine residues thus blocking DNA synthesis and mitosis5. Activity against urothelial carcinoma has been documented for over 50 years, including intravesical instillation.

Intravesical MMC presents potential advantages over systemic use including direct contact of chemotherapeutic agent with the tumor and limited systemic toxicity. MMC is hydrophobic and characterized by a high molecular weight resulting in slow diffusion and low capillary permeability, allowing for a deep penetration and persistent tissue concentration5.

Pharmacokinetic studies suggest there should be little systemic absorption of MMC from an intact bladder6. Drug concentration has been shown to be more important than total dose with duration of exposure and drug concentration being more influential on tumor cell kill than dose7. With the recognized importance of drug concentration on tumor cell kill the recommended concentration of MMC is 1 mg per ml and complete bladder emptying should be performed prior to instillation8.

The standard intravesical dwell time ranges from 60 to 120 minutes. Prior studies have demonstrated a benefit of a 60-minute dwell time over a 30-minute dwell time with a significant reduction in tumor recurrence noted in the 60-minute treatment group9.

The prophylactic efficacy of MMC in decreasing bladder tumor recurrences following transurethral resection of bladder tumors is well documented. It is theorized the decreased recurrence rates are accomplished via both destroying implanted tumor cells after transurethral resection (TUR) and an ablative effect on residual cells at the resection site and on small overlooked tumors. A combined analysis randomized trials including 2535 patients demonstrated a 20% decrease in tumor recurrence in patients receiving a single dose of chemotherapy with TUR compared to TUR alone10. The timing of MMC administration has been documented to be an important factor on the rate of tumor recurrence following TUR. Early drug administration (within 24 hours) was noted to be superior over delayed drug administration (between 7-15 days) in a randomized trial with a 30% reduction in tumor recurrence11.

These results are further supported by Kassien et al. whose trial demonstrated a 50% relative reduction of tumor recurrence when MMC is administered within 24 hours of TUR12. Finally, a meta-analysis of studies evaluating TUR alone and TUR with one immediate instillation of chemotherapy noted a 39% decrease in the odds of recurrence with the addition of a single dose of chemotherapy compared to TUR alone13.

Two separate prospective trials have demonstrated a single dose of adjuvant intravesical chemotherapy with either mitomycin C or pirarubicin reduces the risk of BTR during the first year following radical nephroureterectomy15,16. These results were confirmed in a meta-analysis by Deng et. al in 2014, with a pooled hazard ratio of 0.38 for patients receiving intravesical chemotherapy16. Although the data are strong, the timing of intravesical chemotherapy administration varied significantly across these studies. Additionally, Lu et. al demonstrated underutilization of intravesical chemotherapy and significant heterogeneity of its timing among Society of Urologic Oncology members17. It is clear that there is a paucity of evidence regarding the timing of intravesical chemotherapy on BTR and further investigation is necessary.

1.3 Rationale for Current Study

We have recently completed a retrospective review of our experience at the University of Florida of the administration of intraoperative of mitomycin C compared to mitomycin C administered post-operative day one or later. A total of 51 patients were identified meeting our inclusion criteria. Patients were categorized into two separate groups based on the timing of mitomycin C administration: (1) patients who received mitomycin C on the day of surgery (POD0) and (2) patients who received mitomycin C on post-operative day 1 or later (POD1). Our primary endpoint was BTR rate within the first year after surgery. Our secondary endpoint was overall BTR rate during follow up. Associations between treatment groups and recurrence rates were assessed using Kaplan-Meier plots, log-rank tests, and univariable and multivariable Cox proportional hazard models. Mean length of follow-up for each group was 22.1 and 12.5 months, respectively (p=0.02). There were no statistically significant differences in baseline characteristics of age, gender, race, surgical approach, tumor grade, tumor stage, surgical margins, nodal status, concomitant CIS, or history of bladder cancer.

BTR rates at 1 year for the POD0 and POD1 groups were 16% and 33%, respectively (p=0.09). Overall BTR rates, including time points beyond the first year, were 23% and 33%, respectively (p=0.16). Multivariable analysis noted that the POD0 patients had a significantly lower rate of BTR in the first year postoperatively (HR=0.082, 95% CI=0.01-0.56, p=0.01). Other factors that were associated with a higher rate of BTR within the first year were open surgery (HR=7.9, 95% CI=1.18-53.88, p=0.03), positive surgical margins (HR=37.89, 95% CI=1.74-825.35, p=0.02), and concomitant CIS (HR=10.8, 95% CI=1.08-108.72). Our results suggest that the timing of intravesical mitomycin C administration may affect the rate of BTR following radical nephroureterectomy (RNU) for urothelial carcinoma.

1.4 Rationale for Regimen/Doses/Schedule

This is the first study of its kind to attempt to identify the importance of timing of MMC administration relative to BTR following RNU. Based on these initial results we propose a single arm phase II trial to further evaluate the impact of intraoperative MMC on BTR.

2. OBJECTIVE

2.1 Primary

- Determine the one-year bladder tumor recurrence rate in patients with urothelial carcinoma of the upper urinary tract following intraoperative administration of mitomycin C

2.2 Secondary

- Evaluate the time to bladder tumor recurrence in patients with urothelial carcinoma of the upper urinary tract following intraoperative administration of mitomycin
- Determine the three-year tumor recurrence rate in patients with urothelial carcinoma of the upper urinary tract following intraoperative administration of mitomycin C

3. STUDY DESIGN

3.1 Study Overview

This is a single arm, open-label, phase II study. Subjects with clinically localized urothelial carcinoma of the renal pelvis and/or ureter who are scheduled to undergo nephroureterectomy will be intraoperatively treated with mitomycin C during their nephroureterectomy procedure. Subjects will then be monitored post-operatively for bladder tumor recurrence every three months for the first two years and every six months for the third year after their nephroureterectomy.

Screening data will be reviewed to determine subject eligibility. Subjects who meet all inclusion criteria and none of the exclusion criteria will be entered into the study.

Total duration of subject participation will be approximately three years. Total duration of the study is expected to be seven years.

4. SELECTION OF SUBJECTS

Subjects with a diagnosis of urothelial carcinoma of the renal pelvis and/or ureter who meet the following inclusion and exclusion criteria will be eligible for participation in this study.

4.1 Number of Subjects

A total of 53 subjects will be enrolled on this study.

4.2 Inclusion Criteria

Subjects must meet all of the following criteria to be eligible for study participation:

A. Both males and females ≥ eighteen years of age
B. Clinical diagnosis of urothelial carcinoma of the renal pelvis and/or ureter. Clinical diagnosis of urothelial carcinoma may be based upon radiographic, pathologic or cytological findings alone or in combination with one another. No other histology is allowed.
C. The TNM stage of the subject's disease (using the American Joint Committee on Cancer [AJCC] Cancer Staging Manual, 8th Edition) must be Tis, Ta, T1, T2, or T3, N0, M0. Subjects may have either a high-grade or low-grade tumor.
D. ECOG performance status of 0-2
E. Written informed consent obtained from the subject and the ability for the subject to comply with all the study-related procedures.
F. Women of childbearing potential (WOCBP) must be using an adequate method of contraception to avoid pregnancy prior to and for at least 3 months after mitomycin C instillation to minimize the risk of pregnancy. Prior to study enrollment, women of childbearing potential must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy.
   WOCBP include any woman who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or who is not post-menopausal. Post-menopause is defined as:
   - Amenorrhea that has lasted for ≥ 12 consecutive months without another cause, or
   - For women with irregular menstrual periods who are taking hormone replacement therapy (HRT), a documented serum follicle-stimulating hormone (FSH) level of greater than 35 mIU/mL.
G. Males with female partners of child-bearing potential must agree to use physician- approved contraceptive methods (*e.g.*, abstinence, condoms, vasectomy) should avoid conceiving children prior to and for 3 months following mitomycin C instillation.
H. Subjects must have hemoglobin ≥ 9 g/dL and a platelet count ≥ 100,000/μL.

4.3 Exclusion Criteria

Subjects with any of the following will not be eligible for study participation:

A. Active urothelial carcinoma of the bladder within 12 months prior to enrollment
B. History of adverse reaction to mitomycin C
C. Subjects must not have evidence of regional or metastatic disease.
D. History of radical cystectomy
E. Planned radical cystectomy at the time of nephroureterectomy
F. Females or males of childbearing potential who are **unwilling or unable** to use an acceptable method to avoid pregnancy prior to and for at least 3 months after

mitomycin C instillation.

G. Females who are pregnant or breastfeeding.

H. History of any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of protocol therapy or that might affect the interpretation of the results of the study or that puts the subject at high risk for treatment complications, in the opinion of the treating physician.

I. Prisoners or subjects who are involuntarily incarcerated.

J. Subjects who are compulsorily detained for treatment of either a psychiatric or physical illness.

4.4 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

5. REGISTRATION PROCEDURES

All subjects must be registered with the UF Health Cancer Center prior to participation in this trial. This is not registration into the trial. Subjects failing to meet all study eligibility requirements will not be registered and will be unable to participate in the trial.

6. STUDY PROCEDURES

Please see the Schedule of Events located in Appendix A.

6.1 Screening Evaluations

Written informed consent must be obtained prior to performing any study-specific evaluations or tests. Tests or evaluations performed as standard of care within the specified screening period, but prior to informed consent, may be accepted for this study and need not be repeated.

A comprehensive medical history, physical exam, and assessment of ECOG performance status will be performed within 60 days pre-operatively. The following laboratory assessments will be performed within 60 days pre-operatively, with the exception of a urine pregnancy test, which will be performed the day of surgery in appropriate patients. Radiographic disease staging will be performed within 90 days preoperatively:

- Laboratory evaluations
    - Complete blood count (CBC), including red blood cell count (RBC), white blood cell count (WBC), platelets, hemoglobin, and hematocrit
    - Basic metabolic panel (BMP), including sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine, and glucose
    - Urinalysis

- Radiographic disease staging
    - CT scan or MRI or PET CT of the abdomen and pelvis
    - Chest X-ray or chest CT or PET CT of chest

6.2 On Study Procedures/Evaluations

Subjects will undergo a single instillation of mitomycin C during their nephroureterectomy as described in section 7.1. An adverse event assessment will be performed before and after instillation of mitomycin C the day of nephroureterectomy, as well as within 30 days following mitomycin C instillation, during a clinic visit.

6.3 Follow up/Survival Evaluations

Subjects will have a follow-up visit every three months (+/- 3 weeks) post-operatively for two years to assess for bladder tumor recurrence. Subjects will have a follow-up visit every six months (+/- 3 weeks) post-operatively the third year to assess for bladder tumor recurrence.
Subjects will have the following procedures at each of these visits:

- Urinalysis
- Surveillance cystoscopy

Urine cytology with reflex UroVysion. UroVysion testing will be performed if urine cytology result is atypical or suspicious. If recurrence of urothelial carcinoma within the bladder is suspected at any point, a subject will undergo a bladder biopsy to confirm recurrence. Once recurrence has been confirmed, the subject will no longer be followed for purposes of this study.

7. STUDY TREATMENT

All subjects entering the screening phase will receive a unique subject number. This number will be used to identify the subject throughout the study. Subjects withdrawn from the study will retain their subject number.

7.1 Treatment Schedule/Administration

A urethral catheter will be placed in a sterile fashion in the operating room and all urine will be drained. 40 mg of mitomycin C in 40 mL of sterile water will then be administered intravesically via a urethral catheter immediately following catheter placement. Immediately following mitomycin C instillation, the urethral catheter will be clamped for one hour. The nephroureterectomy procedure will start even while the urethral catheter is clamped. After this hour has elapsed, the mitomycin C will be drained from the bladder and the urethral catheter will be flushed with 100mL-200 mL (as clinically indicated) of sterile saline and drained. The urethral catheter will remain in place for the remainder of the surgical procedure. Timing of urethral catheter removal after the completion of the nephroureterectomy will be based on surgeon discretion.

7.2 Specific Supportive Care

7.2.1 Concomitant Therapy

Relevant medical history should be obtained at screening and include prior medications and treatment history. All medications taken within two weeks prior to screening will be collected.

During the study, only concomitant medications used to treat side effects from the Mito-C installation will be collected. Standard of care medications used during surgery through discharge will not be recorded.
However, if another course of anti-cancer therapy is initiated prior to the thirty -day follow-up period visit; a record of concomitant medications will no longer be performed.

If the use of any concomitant treatments (medications or procedures) becomes necessary, the treatment must be recorded, including the name of the drug or treatment, dose, route, date, indication for use, expected duration, and frequency of treatment.

7.2.2 Allowed Concomitant Therapy

Supportive measures consistent with optimal patient care will be given throughout the study.

Bladder spasms:	Anticholinergics should be administered per institutional guidelines for treatment or urethral catheter related bladder spams if bothersome to the patient.
Dysuria:	Medications for urinary pain relief should be administered per institutional guidelines for pain associated with urination. Urinary tract infection should be evaluated with a urinalysis prior to starting medications to treat the symptom of dysuria.
Nausea:	Anti-emetics should be administered per institutional guidelines.
Diarrhea:	Subjects should be provided with instructions on use of loperamide (Imodium) in the event of diarrhea, as well as instructions to contact the treating physician. Other anti-diarrheals are also allowed. Subjects should be given mouth care instructions per institutional guidelines.

7.2.3 Prohibited Concomitant Therapy

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol

- Investigational agents other than the study drug in this trial
- Radiation therapy
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial.
  - Examples of live vaccines include but are not limited to: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine.
  - Seasonal influenza vaccines for injection are generally killed by virus vaccines and are permitted. However, intranasal influenza vaccines (e.g. Flu-Mist ®) are live attenuated vaccines and are not permitted.

7.3 Dose Modifications

The National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events Version 4 (CTCAE) will be used to grade toxicity (http://evs.nci.nih.gov/ftp1/CTCAE/About.html).

7.3.1 Dose Modification Table

No dose modification to the single 40 mg intravesical instillation of mitomycin C will be included in the study. No dose reduction is required based on intravesical administration and elimination via catheter drainage. Additionally, dose reduction is not anticipated based on results of prior randomized trials and published retrospective trials.

7.3.2 Supportive Care Guidelines

Subjects should receive full supportive care, including transfusions of blood and blood products, antibiotics, antiemetics, antidiarrheals, analgesics, etc., when appropriate.

7.3.3 Trial Stopping Criteria

The Stopping Criteria for the study will be based on the occurrence of clinically significant and causally related serious adverse reactions higher than Grade 3 (as defined by the CTCAE criteria) which are life-threatening and require urgent medical intervention. The UFHCC DISC will monitor the study and will meet at regular intervals or as events dictate to review any emerging safety data. If serious adverse reactions as highlighted do occur, then the UFHCC DISC will be consulted with respect to stopping the clinical trial.

Stopping rule for efficacy corresponds with Simon optimal two-stage design as described in section 11.1. An interim analysis will be conducted when 16 subjects are enrolled and completed evaluation of the primary endpoint. If 4 or more BTR at 1-year post-surgery are observed, the study will be terminated early.

8. TREATMENT DISCONTINUATION

8.1 Removal of Subjects from Study

Subjects who discontinue participation in the clinical study on their own or subjects who are withdrawn by the investigator, for reasons other than completion of treatment or toxicity, will be defined as premature withdrawals.
Subjects who are not initiated on study drug, but sign informed consent and undergo at least some of the screening procedures will be considered screening failures. A record of these subjects will be maintained by the study site.

8.2 Criteria for Study Treatment Discontinuation

A subject will be discontinued from protocol therapy under the following circumstances:

- Any adverse event which, in the Investigator's opinion, requires termination of the study medication.
- Substantial non-compliance with the requirements of thestudy.
- The subject presents with a beta-HCG test consistent with pregnancy. Pregnancy will be reported along the same timelines as a serious adverse event.
- The subject uses illicit drugs or other substances that may, in the opinion of the Investigator, have a reasonable chance of contributing to toxicity or otherwise interfering with results.
- The development of a second malignancy that requires treatment, which would interfere with this study.
- The subject is lost to follow-up.
- Development of an intercurrent illness or situation which would, in the judgment of the investigator, affect assessments of clinical status and the study endpoint to a significant degree.

The Investigator will make every reasonable effort to keep each subject in the study unless it is in the subject's best interests to discontinue participation. A description of the reason(s) for withdrawal from the study must be recorded on the case report form (CRF).

Relevant visit data should be entered on the CRF and any unused study medication will be accounted for and returned for all subjects participating in the study, even for a brief period of time. Subjects who discontinue following entry will have relevant information completed and recorded on the CRF. All subjects who discontinue because of adverse events or clinically significant laboratory abnormalities should be followed up until they recover or stabilize, and the subsequent outcome will be recorded. If any subject should die during the trial or within 30 days of stopping study treatment, the Investigator will inform the UF Health Data Integrity and Safety Committee.

8.3 Replacement of Subjects

Subjects will be replaced if they do not receive the single intravesical instillation of mitomycin C or if the nephroureterectomy is not completed in the protocol for any reason, or if the subject wishes to discontinue participation in the protocol, but is not discontinued for toxicity or any of the reasons listed in section 8.2.

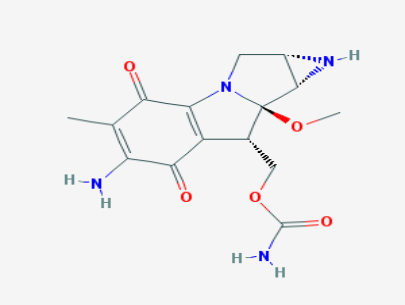
9. STUDY DRUG INFORMATION

9.1 Study Drug Name

Mitomycin C

9.1.1 Identification

Chemical name: 7-amino-9-methoxymitosane Chemical structure:



Molecular formula: 15H18N4O5 Molecular weight: 334.33 daltons

Physical description: Mitomycin C is a blue-violet crystalline powder that is heat-stable and that is freely soluble in organic solvents.

9.1.2 Packaging and Labeling

Mitomycin C is packaged in sterile, single use vials. Each vial contains a sterile mixture of mitomycin and mannitol in a 1:2 ratio. Each vial contains either 5 mg mitomycin C and 10 mg mannitol, 20 mg mitomycin C and 40 mg mannitol, or 40 mg mitomycin C and 80 mg mannitol.

9.1.3 Drug Supply

Mitomycin C will be supplied commercially for this study.

9.1.4 Storage, Handling and Dispensing

Unreconstituted mitomycin C powder should be stored at controlled room temperature, 15 to 30°C (59 to 86°F). Mitomycin C powder should also be protected from light. To reconstitute mitomycin C powder for administration, add of 40 mL sterile water to 40 mg mitomycin C powder and shake to dissolve. If mitomycin C powder does not dissolve immediately, let stand at room temperature until solution is obtained. Protect mitomycin C solution from light.

9.1.5 Contraindications

Mitomycin C is contraindicated in patients who have had a hypersensitivity reaction to it in the past.
Mitomycin C is FDA pregnancy category D and is contraindicated for pregnant women because it can cause fetal harm if administered during pregnancy. Females of childbearing potential should be advised to avoid becoming pregnant and should be

informed of the potential for harm to the fetus.
It is unknown whether mitomycin C is excreted in human milk. For this reason, women who are breast-feeding should not receive mitomycin C.
Mitomycin C is also contraindicated for use in patients with thrombocytopenia, bleeding disorders, or an increased tendency for bleeding due to other causes.

9.1.6 Special Warnings and Precautions for Use

Mitomycin C should not be administered intravesicularly to patients with a known or suspected bladder perforation.

9.1.7 Adverse Event Profile

Common side effects of intravesicular treatment with mitomycin C can include bladder irritation/inflammation, dysuria, fever, flu-like symptoms, skin rash, malaise, hematuria, urinary incontinence, urinary frequency, urine discoloration, and urinary urgency.
Bladder fibrosis and contraction has also been reported following intravesicular treatment with mitomycin C, which in rare cases has required cystectomy. Potential complications that could result from intravesicular treatment with mitomycin C can include urinary tract infection, fever > 101.3
°F (> 38.5 °C), epididymitis, orchitis, abscess formation, hematuria with clot retention, myelosuppression, neutropenia, ureteral obstruction, pneumonitis, and hepatitis.

10. ADVERSE EVENTS

10.1 Definitions

10.1.1 Adverse Event

The term “adverse event” (AE) includes any sign, symptom, syndrome, or illness that appears or worsens in a subject during the period of observation in the clinical study and that may impair the wellbeing of the subject. The term also covers laboratory findings or results of other diagnostic procedures that are considered to be clinically significant (*e.g.*, that requires unscheduled diagnostic procedures or treatment measures, or result in withdrawal from the study). An AE is therefore any unfavorable and unintended symptom or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product.
The adverse event may be:

- A new illness/condition;
- Worsening of a sign or symptom of the condition under treatment, or of a concomitant illness/condition;
- An effect of the study drug; or
- A combination of 2 or more of these factors.

No causal relationship with the study drug or with the clinical study itself is implied by the use of the term “adverse event.”

The Investigator will probe, via discussion with the subject, for the occurrence of AEs during each subject visit and record the information in the site's source documents. AEs will be recorded in the subject CRF. AEs will be described by duration (start and stop dates and times), severity, outcome, treatment and relation to study drug, or if unrelated, the cause.

Surgical procedures themselves are not adverse events; they are therapeutic measures for conditions that require surgery. The condition(s) for which the surgery is required may be an adverse event. Planned surgical measures permitted by the clinical study protocol and the condition(s) leading to these measures are not adverse events.

When a clear diagnosis is available that explains the abnormal objective findings, this diagnosis will be recorded as an adverse event and not the abnormal objective findings (*e.g.*, viral hepatitis will be recorded as the adverse event and not the transaminase elevation). If a definitive diagnosis is not available, then the sign(s) (*e.g.*, clinically significant elevation of transaminase levels) or symptom(s) (*e.g.*, abdominal pain) will be recorded as the adverse event.

Adverse events fall into the categories "serious" and "non-serious."

10.1.2 Serious Adverse Event

A serious adverse event is one that at any dose of the study drug or at any time during the period of observation:

- Results in death
- 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 or causes prolongation of existing hospitalization (see note below for exceptions)
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event, defined as a medical event that may not be immediately life-threatening or result in death or hospitalization but, based on 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 above. Examples of such events include but are not limited to intensive treatment in an emergency department or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization. "Medically important" should be marked only if no other serious criteria are met.

An "unexpected SAE" is any SAE for which the nature, specificity or severity is not consistent with the currently known adverse event profile of the investigational agent(s).

NOTE: The following hospitalizations are not considered SAEs in UFHCC clinical studies:

- a visit to the emergency room or other hospital department lasting less than 24 hours that does not result in admission (unless considered an "important medical event" or a life-threatening event)
- elective surgery planned before signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- medical/surgical admission for purpose other than remedying ill health state that was planned before study entry. Appropriate documentation is required in these cases.
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative).

Clarification of the difference in meaning between "severe" and "serious"

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). Any grade ≥ 3 adverse events per CTCAE are generally considered severe AEs.

This is not the same as "serious," which is based on the outcome or action criteria usually associated with events that pose a threat to life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

10.1.3 Non-Serious Adverse Event

A non-serious adverse event is any adverse event not meeting any of the serious adverse event criteria.

10.2 Period of Observation

Following the subject's written consent to participate in the study, all SAEs must be collected, including those thought to be associated with protocol-specified procedures. Collection of all SAEs must continue until the postoperative clinic visit which will occur within 30 days after mitomycin C instillation. If applicable, SAEs must be collected that relate to any later protocol- specified procedure (e.g., a follow-up skin biopsy). The investigator should notify the DISC of any SAE occurring after this time period that is believed to be related to the investigational product or protocol-specified procedure.

The investigator will begin collecting non-serious adverse event (NSAE) information once administration of the investigational product is initiated. This NSAE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects. Treated subjects, including those who were prematurely discontinued from the study, will be followed for any adverse events that occur during the study until 30 days following mitomycin C instillation. However, if another course of anti-cancer therapy is initiated prior to the

end of this period, collection of adverse events will no longer be performed, with the exception of events that may be possibly, probably, or definitely related to the investigational agent or are clinically significant.

10.3 Documenting and Reporting of Adverse Events by Investigator

All adverse events must be fully recorded in the subject's case record form. Documentation must be supported by an entry in the subject's file. A laboratory test abnormality considered clinically relevant, e.g., causing the subject to withdraw from the study, requiring treatment or causing apparent clinical manifestations, or judged relevant by the investigator, should be reported as an adverse event. Each event should be described in detail along with start and stop dates, severity, relationship to investigational product, action taken and outcome.

Every attempt should be made to describe the adverse event in terms of a diagnosis that encompasses the component signs and symptoms. If only nonspecific signs or symptoms are present, then these should be recorded as separate diagnoses on the pages of the case report form.

All subjects who have adverse events, whether considered associated with the use of study drug or not, must be monitored to determine the outcome. The clinical course of the adverse event will be followed according to accepted standards of medical practice, even after the end of the period of observation, until a satisfactory explanation is found or the Principal Investigator considers it medically justifiable to terminate follow-up. Should the adverse event result in death, a full pathologist's report should be supplied, if possible.

10.3.1 Assessment of Causal Relationship of Study Drug

The Investigator will provide an assessment of the potential causal relationship between adverse events and study medication by determining whether or not there is a reasonable possibility that the event was caused by the study medication. The relationship or association of the adverse event to the study medication will be characterized as not related, probably not related, possibly related, probably related, or related:

Not Related: There is not a temporal relationship to the study drug administration or the adverse event is clearly due only to the progression of the underlying disease state, intercurrent illness, concomitant medication, concurrent therapy, or other known cause.

Probably Not Related: There is little or no chance that the study drug administration caused the adverse event; the event is most likely due to another competing cause, including intercurrent illness, disease progression, or expression of the disease state, or a reaction to a concomitant medication or concurrent therapy appearing to explain the reported adverse event.

Possibly Related: The association of the adverse event with the study drug administration is unknown; however, the adverse event is not reasonably attributed

to any other condition.

Probably Related: When a reasonable temporal relationship exists between the adverse event and the study drug administration; significant symptoms abate upon discontinuation of the study drug and there is a reasonable explanation based on known characteristics of the study drug and there is no clear association with preexisting disease or therapy, intercurrent illness, concurrent therapy or other factor(s).

Related: When the adverse event is a known side effect of the study drug or there is a temporal relationship to the administration of the study drug; or the adverse event reappears upon re- administration of the study drug (rechallenge); or the significant symptoms of the adverse event

abate upon discontinuation of the study drug (dechallenge).

10.3.2 Intensity of Adverse Events

The intensity of adverse changes in physical signs or symptoms will be graded according to the CTCAE version 4. For all other adverse events not described in the CTCAE, the intensity will be assessed by the Investigator using the following categories:

Mild (Grade 1) – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required.

Moderate (Grade 2) – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required.

Severe (Grade 3) – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible.

Life-threatening (Grade 4) – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable.

Death (Grade 5) – the event resulted in death.

10.3.3 Action Taken with Study Drug

The action the Investigator took with study drug as a result of the event should be recorded as one of the following:

None – No action was taken with regard to the study drug as a result of the adverse event.
Interrupted – Study drug was stopped due to the adverse event, but was later resumed at the same dose.
Dose decreased – The dose of study drug was decreased as a result of the adverse event.
Permanently discontinued – The subject was withdrawn from the study due to the adverse event.

Only one item should be chosen. If multiple actions apply, the following "worst case" scenario hierarchy should be used to determine the preferred entry: Discontinued > dose decreased > therapy interrupted.

10.3.4 Definition of Outcome

The outcome of the AE should be recorded as one of the following:

Resolved without sequelae – The subject fully recovered from the adverse event with no observable residual effects.
Resolved with sequelae – The subject recovered from the adverse event with observable residual effects.
Not resolved – The adverse event was present at the time of last observation.
Death – The subject died as a result of the adverse event.

10.4 Immediately Reportable Events

10.4.1 Serious Adverse Events

The UFHCC Protocol Management Office (PMO) must be notified of the SAE within **24 hours** of knowledge of the event by email at PMO@cancer.ufl.edu.

Serious adverse events (SAE's) must be documented on an FDA MedWatch 3500A form. In addition to completing appropriate subject demographic and suspect medication information, the report should include the following information within the Event Description of the MedWatch 3500A form:

- Treatment regimen (dosing frequency, combination therapy)
- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome, if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

The MedWatch form must be emailed to the UFHCC Project Management Office (PMO; pmo@cancer.ufl.edu) and PMO will submit this form to the UFHCC DISC Safety Team within **5 days** of discovery of the event. The original copy of the MedWatch form and any email correspondence must be kept within the Trial Master File at the study site. The site investigator is responsible for informing the IRB and/or the Regulatory Authority of the SAE as per local requirements.

Follow-up information will be emailed or faxed to the UFHCC PMO using an FDA MedWatch 3500A form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the

event has resolved or continues, if and how it was treated, whether the blind was broken or not (if applicable), and whether the participant continued or withdrew from study participation.

10.4.2 Other Events Requiring Immediate Reporting

All pregnancies, regardless of outcome, must be reported to the UFHCC DISC, including pregnancies that occur in the female partner of a male study subject. All pregnancies must be followed to outcome.

Although overdose (dose variance of **10 %**) and cancer are not always serious by regulatory definition, these events should also be reported to the DISC in an expedited manner. In case the overdose did not result in any adverse event, the Investigator should report this as "overdose, no adverse event" on the SAE form and provide the intended amount, as well as the actual amount, of drug administered. In the event of overdose or exaggerated response, appropriate supportive measures should be employed. Actual treatment should depend on the severity of the clinical situation and the judgment and experience of the treating physician.
Pregnancies and overdoses should be documented and reported per the SAE reporting guidelines in section 10.4.1 above.

10.5 IND Safety Reports Unrelated to this Trial

IND safety reports not occurring on this trial but involving the study intervention (outside SAEs) received from outside sources will be submitted to the Institutional Review Board per their guidelines.

11. STATISTICAL METHODS

The sections below provide an overview of the statistical considerations and analyses.

11.1 Sample Size Determination

The primary endpoint for this study is bladder tumor recurrence (BTR) rate at 1-year post-surgery. In our previous study, there was a 16% recurrence rate for those that received mitomycin C on day 0 and a 33% recurrence rate for those receiving it on day 1 or later. From this, we will assume that the underlying proportion of BTR at 1 year is 25% for our population. A sample size of 53 subjects is needed to detect the decrease of 1-year BTR rate from 25% to 12.5% based on Simon optimal two-stage design. A sample size of 53 will allow more than 80% power with one-sided type 1 error rate of 0.10.
In the first stage, 16 subjects will be recruited and the study will be terminated early if 4 or more BTR happen. If the study proceeds to the second stage, a total of 53 subjects will be studied. If the total number of BTR at 1-year post surgery is less than 10, the treatment will be considered a success. Sample size was calculated using PASS 16.

11.2 Analysis of Primary Endpoint

A one-sided, one sample exact test of binomial proportion will be used to assess the primary endpoint, 1-year BTR rates, with level of significance set at 0.10. The proportion with BTR will be estimated, along with a 90% confidence interval.

11.3 Analysis of Secondary Endpoint

Time to BTR will be characterized using Kaplan-Meier plots. Log rank tests and Cox proportional hazard modeling will be used to examine the impact of baseline characteristics. A p-value of less than 0.05 will be considered statistically significant.

12. DATA AND SAFETY MONITORING

12.1 Data Integrity and Safety Committee

This protocol will be reviewed and monitored by the University of Florida Health Cancer Center (UFHCC) DISC in accordance with their policies and procedures. They will review and monitor study progress, toxicity, safety and other data from this trial. Questions about subject safety or protocol performance will be addressed with the sponsor-investigator, statistician, and study team members. Should any major concerns arise; the DISC will offer recommendations regarding whether or not to suspend the trial.

UFHCC DISC data and safety monitoring activities include:

- Review of clinical trial conducted for progress and safety
- Review of all adverse events requiring expedited reporting as defined in the protocol
- Review of reports generated by data quality control review process
- Notification of the sponsor-investigator of recommended action
- Notification of sites coordinated by the UFHCC of adverse events requiring expedited reporting and subsequent committee recommendations for study modifications

12.2 On-site Monitoring

UFHCC monitors will make monitoring visits to the trial sites periodically during the trial to determine if sites are complying with the protocol. Source documents will be reviewed for verification of agreement with data as submitted via the data collection system. The site investigator/institution guarantee access to source documents by UFHCC or its designee and appropriate regulatory agencies.

The trial site may also be subject to quality assurance audit by any collaborating sponsors or their designee as well as inspection by appropriate regulatory agencies.

It is important for the site investigator and their relevant personnel to be available during the monitoring visits and possible audits and for sufficient time to be devoted to

the process.

12.3 Principal Investigator Responsibilities

As part of the responsibilities assumed by conducting this study, the Principal Investigator (PI) agrees to maintain and have available for monitoring adequate case records (accurate source documents and CRFs) for the subjects treated under this protocol.
The PI will be primarily responsible for monitoring of adverse events, protocol violations, and other immediate protocol issues. The study coordinator will collect information on subjects enrolled through the use of electronic or paper adverse event (AE) forms, CRFs, and informed consent forms.

13. EMERGENCY PROCEDURES

13.1 Emergency Contact

In emergency situations, the treating physician should contact the Principal Investigator by telephone at the number listed on the title page of the protocol.

13.2 Emergency Identification of Investigational Products

This is a non-blinded, non-randomized study. Thus, there will be no need for unmasking procedures, and the identification of the investigational product can be made by simple inquiry to the investigational pharmacy.

13.3 Emergency Treatment

During and following a subject's participation in the study, the treating physician and/or institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the study.

14. ADMINISTRATIVE, ETHICAL, AND REGULATORY CONSIDERATIONS

14.1 Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that the Principal Investigator and Co- Investigators abide by Good Clinical Practice (GCP), as described in International Conference on Harmonization (ICH) Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki.
The study will be conducted in compliance with the protocol. The protocol, any amendments, and the subject informed consent will receive Institutional Review Board (IRB) approval before initiation of the study.

The Principal Investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

All potential serious breaches must be reported immediately to the UFHCC DISC and IRB of record, if applicable. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

14.2 Institutional Review Board

Before study initiation, the investigator must have written and dated approval from the IRB for the protocol, consent form, subject recruitment materials/process (e.g., advertisements), and any other written information to be provided to subjects. The investigator should also provide the IRB with a copy of the Investigator Brochure or product labeling, information to be provided to subjects, and any updates. The investigator should provide the IRB with reports, updates, and other information (e.g., amendments, and administrative letters) according to regulatory requirements or institution procedures.

14.3 Compliance with Laws and Regulations

It is intended that the proposed study be conducted according to the International Conference on Harmonization E6 Guideline for Good Clinical Practice (GCP) and the Declaration of Helsinki. Please refer to the International Conference on Harmonization and GCP:

http://www.fda.gov/oc/gcp/guidance.html; Declaration of Helsinki: http://www.fda.gov/oc/health/helsinki89.html; Code of Federal Regulations, Title 21: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch. cfm]

All UF Health Cancer Center investigator-initiated trials, meeting the criteria of the FDAAA's applicable clinical trials, will be registered with ClinicalTrials.gov by the Protocol Development Officer or assigned designee. All studies must be registered no later than 21 days after enrollment of the first participant. The Protocol Development Officer will maintain the responsibility of updating trials registered with ClinicalTrials.gov; per the FDA's updating requirements of information must be updated at least every twelve months and the registry must be updated within thirty days of any changes in recruitment status or completion of the study.

14.4 Delegation of Investigator Responsibilities

The Principal Investigator will ensure that all persons assisting with the study are adequately informed about the protocol, any amendments to the protocol, the study treatments, and their study-related duties and functions.

The Principal Investigator will maintain a list of Co- Investigators and other appropriately qualified persons to whom he has delegated significant study-related duties.

Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks. This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure; debarment). Systems with procedures that ensure the quality of every aspect of the study will be implemented.

14.5 Subject Information and Informed Consent

Before being enrolled in this clinical trial, the subject must consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to him or her. An informed consent document that includes both information about the study and the consent form will be prepared and given to the subject. This document will contain all ICH, GCP, and locally required regulatory elements. The document must be in a language understandable to the subject and must specify the person who obtained informed consent.

After reading the informed consent document, the subject must give consent in writing. The written informed consent will be obtained prior to conducting any study-related procedures or tests. The subject's consent must be confirmed at the time of consent by the personally dated signature of the person conducting the informed consent discussions. A copy of the signed consent document must be given to the subject.

The PI will retain the original signed consent document. The PI will not undertake any measures specifically required only for the clinical study until valid consent has been obtained.

14.6 Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Should direct access to medical records require a waiver or authorization separate from the subject's statement of informed consent, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

Subjects will be told that the IRB, UF Health DISC, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection law.

14.7 Protocol Amendments

Once the study has started, amendments should be made only in exceptional cases. Protocol amendments cannot be implemented without prior written IRB approval except as necessary to eliminate immediate safety hazards to subjects. A protocol

amendment intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, provided the IRB and CRO are notified within five business days.

All amendments will be submitted to the IRB and written verification that the amendment was submitted and subsequently approved is to be obtained.

14.8 Case Report Forms

The Principal Investigator and/or his/her designee will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific Case Report Forms (CRFs) will document safety and treatment outcomes for safety monitoring and data analysis. All study data will be entered into OnCore® via standardized CRFs in accordance with the CTMS study calendar, using single data entry with a secure access account.

An electronic case report form (eCRF) is required and must be completed for each included subject. The completed dataset is the sole property of UFHCC and should not be made available in any form to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from UFHCC.

14.9 Record Retention

Study documentation includes all eCRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed subject consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.
Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

UF Health Cancer Center requires that all study documentation be maintained for at least 6 years from the date of final study publication. No study records may be destroyed without prior authorization from UF.

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16. APPENDICES

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Appendix A: SCHEDULE OF EVENTS

VISIT: / PROCEDURE:	PREOPERATIVE SCREENING (UP TO 60 DAYS BEFORE DATE OF NEPHROURETERECTOMY; RADIOLOGIC ASSESSMENTS MAY BE PERFORMED UP TO 90 DAYS PREOPERATIVELY)	NEPHROURETERECTOMY	POST-OPERATIVE FOLLOW UP[1]
Informed Consent	**X**		
Medical History	**X**		
Physical Exam	**X**		
ECOG Performance Status Assessment	**X**		
CT or MRI or PET CT of the abdomen and pelvis[2]	**X**		
Chest X-Ray or chest CT or PET CT of chest[2]	**X**		
CBC[3]	**X**		
BMP[4]	**X**		
Urinalysis	**X**		**X**
Urine Pregnancy Test[8]	**X**		
Mitomycin C Administration[5]		**X**	
Adverse Event Assessment[e]		**X**	
Surveillance Cystoscopy			**X**
Urine Cytology			**X**
UroVysion Testing (if indicated)[6]			**X**
Bladder Biopsy[7]			**X**

1 Subjects will first be monitored for bladder tumor recurrence every three months (± 3 weeks) for the first two years post-operatively. Subjects will then have a follow-up visit every six months (+/- 3 weeks) for the third year post-operatively to assess for bladder tumor recurrence. Follow up visits will discontinue upon confirmation of bladder tumor recurrence.
2 Radiologic disease staging evaluation will be by CT or MRI or PET CT of the abdomen and pelvis and chest X-Ray or chest C or PET CT of chest.
3 Complete blood count (CBC) is to include red blood cell count (RBC), white blood cell count (WBC), platelets, hemoglobin, and hematocrit will be completed as described in section 6.1.
4 Basic metabolic panel is to include sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine, and glucose will be completed as described in section 6.1.
5 Mitomycin C is to be administered as described in section 7.1.
6 UroVysion will be performed if urine cytology result is atypical or suspicious,
7 A bladder biopsy will be required only if bladder tumor recurrence is suspected based upon cystoscopy or urine testing findings for histologic confirmation of recurrence.
8 Urine pregnancy testing will be completed on the day of the nephroureterectomy prior to the nephroureterectomy.
9 Adverse event assessment will be as described in section 10

Appendix B: PERFORMANCE SCALE

ECOG Performance Status Scale	
Grade	Descriptions
0	Normal activity Fully active, able to carry on all pre-disease performance without restriction
1	Symptoms, but ambulatory Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work)
2	In bed < 50% of the time Ambulatory and capable of all self-care, but unable to carry out any work activities Up and about more than 50% of waking hours
3	In bed > 50% of the time Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	100% bedridden Completely disabled Cannot carry on any self-care Totally confined to bed or chair
5	Dead