Phase II study to evaluate the response to 2 induction courses (12 intravesical instillations) of Bacillus Calmette-Guérin (BCG) for high risk superfici al bladder cancer

PROTOCOL FACE PAGE FOR
MSKCC THERAPEUTIC/DIAGNOSTIC PR)TOCOL

Principal Investigator/Department:	Harry W. Herr, MD	Dept of Surgery – Urology
Co-Principal Investigator(s)/Department:	S. Machele Donat, MD	Dept of Surgery – Urology
Investigator(s)/Department:	Bernard H. Bochner, MD	Dept of Surgery – Urology
	Eugene K. Cha, MD	Dept of Surgery – Urology
	Jonathan A. Coleman, MD	Dept of Surgery – Urology
	Guido Dalbagni, MD	Dept of Surgery – Urology
	Timothy Donahue, MD	Dept of Surgery – Urology
	Alvin Goh, MD	Dept of Surgery – Urology
	Ari Hakimi, MD	Dept of Surgery – Urology
	Vincent P. Laudone, MD	Dept of Surgery – Urology
	Eugene Pietzak, MD	Dept of Surgery – Urology
	Paul Russo, MD	Dept of Surgery – Urology
	Jaspreet S. Sandhu, MD	Dept of Surgery – Urology
	Robert Charles Smith, MD	Dept of Surgery – Urology
	Hikmat Al-Ahmadie, MD	Pathology
	Oscar Lin, MD	Pathology
	Daniel D. Sjoberg, MS	Epidemiology and Biostatistics
Consenting Professional(s)/Department:	Harry W. Herr, MD	Dept of Surgery – Urology
	S. Machele Donat, MD	Dept of Surgery – Urology
	Bernard H. Bochner, MD	Dept of Surgery – Urology
	Eugene K. Cha, MD	Dept of Surgery – Urology
	Jonathan A. Coleman, MD	Dept of Surgery – Urology;
	Guido Dalbagni, MD	Dept of Surgery – Urology
	Timothy Donahue, MD	Dept of Surgery – Urology
	Alvin Goh, MD	Dept of Surgery – Urology
	Ari Hakimi, MD	Dept of Surgery – Urology
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	Eugene Pietzak, MD	Dept of Surgery – Urology
	Paul Russo, MD	Dept of Surgery – Urology
	Jaspreet S. Sandhu, MD	Dept of Surgery – Urology
	Robert Charles Smith, MD	Dept of Surgery – Urology

Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program

OneMSK Sites	
Manhattan	Westchester
Basking Ridge	Monmouth
Commack	

Memorial Sloan-Kettering Cancer Center
1275 York Avenue
New York, New York 10065

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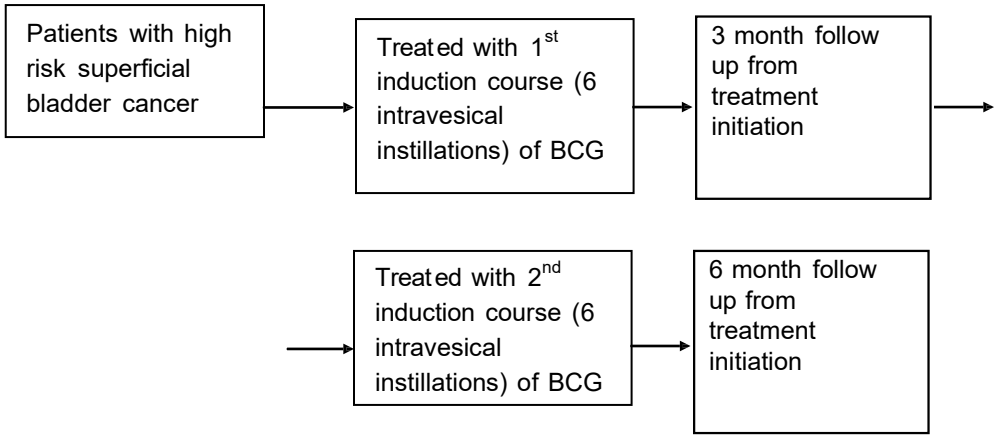
1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Title: Phase II study to evaluate the response to 2 induction courses (12 intravesical instillations) of Bacillus Calmette-Guérin (BCG) for high risk superficial bladder cancer

The main objective of this study is to evaluate the response rate to 2 induction courses (12 intravesical instillations) of BCG, in patients with high risk superficial bladder cancer, at 6 months after the initiation of therapy. We will enroll BCG naïve patients, as well as patients previously treated with BCG who completed therapy 12 months prior to enrollment in this study. The current standard of care for patients with high risk superficial bladder cancer is 1 induction course (6 intravesical instillations) of BCG, but this treatment course has not been effective in a randomized trial. The goal of the proposed study is to identify a more effective BCG regimen to treat high risk superficial bladder cancer.

Study Design and Treatment plan

Patients will be treated with an induction course (6 intravesical instillations) of BCG followed by a second induction course (6 intravesical instillations), with a recovery period between the 2 treatment courses.



2.1 OBJECTIVES AND SCIENTIFIC AIMS

Primary Objective

- To evaluate the response rate (by cystoscopy and cytology) to 2 induction courses (12 intravesical instillations) of BCG 6 months after the initiation of therapy.

Secondary Objective

- To establish the proportion of patients who progress to muscle invasive disease within 6 months of initiation of a 2-induction course (12 intravesical instillations) of BCG.

3.1 BACKGROUND AND RATIONALE

3.2 Natural History of Bladder Cancer

Of the more than 70,000 cases of bladder cancer diagnosed in the United States each year, approximately 70% are found to be non-muscle invasive tumors, 25% are muscle invasive, and 5% are metastatic [1]. Non-muscle invasive tumors encompass non-invasive papillary (Ta), invasive into the connective tissue (T1), and carcinoma in situ (Tis) tumors, with a 60%, 30%, and 10% occurrence, respectively. Sixty percent to 70% of these tumors will recur within 2 years, whereas 20% to 30% will progress to a higher grade or stage during the patient"s lifetime [2]. High-risk non-muscle-invasive bladder disease excludes Ta low grade tumors because even though these tumors possess a high recurrence rate, they rarely progress to muscle-invasive disease. On the other hand, T1 tumors represent a heterogeneous group: some T1 tumors behave in an indolent fashion, responding to conservative therapy; others behave in a more aggressive manner and progress to muscle-invasive disease, giving them the potential to develop metastatic disease. We currently lack the ability to predict how T1 tumors will behave. What we do know is that recurrence of bladder tumors is dependent on size, site, multifocality, presence of concomitant Tis, grade, and prior history of bladder cancer [3]. At MSK, the current therapy for high-risk non-muscle-invasive tumors includes transurethral resection (TUR) followed by the instillation of BCG weekly for 6 weeks.

3.3 Recurrence

Recurrence of high-risk non-muscle-invasive bladder cancer depends on multiple factors as described above. Thirty percent to 90% of patients treated with TUR alone experience recurrence within 2 years. In a prospective longitudinal study, the National Bladder Cancer Collaborative Group A (NBCCGA) followed 133 patients treated with TUR alone and found that the following factors increased recurrence rates: tumors >5 cm, multiple tumors, grade 3 disease, concomitant Tis, T1 disease, and a positive cytologic finding [4]. The high recurrence rate observed in patients treated with TUR alone has led to the use of intravesical immunotherapy with BCG as a supplement to help decrease recurrence. Furthermore, multiple randomized trials have shown that TUR with BCG has superior recurrence-free rates, compared with TUR alone or TUR with intravesical chemotherapy [5, 6]. Thus, TUR with intravesical BCG has become the standard of care for patients with high-risk non-muscle-invasive bladder tumors and has been incorporated into multiple guidelines [3, 7]. Unfortunately, an audit of 1021 patients at MSK treated with intravesical BCG for high-risk non-muscle-invasive bladder cancer revealed that 13.7% (140/1021) of these patients did not have a response to therapy at 3 months from the start of BCG therapy. Furthermore, 20% (205/1021) and 32% (326/1021) did not have a response at 6 and 12 months, respectively. When patients without a response at 3 months were combined with patients with a recurrence at 6 months, 34% of patients experienced treatment failure at 6 months [8]. Many new treatments, such as intravesical chemotherapies and different dosing regimens of BCG, have attempted to decrease the high rate of treatment failure among patients with non-muscle-invasive bladder cancer; however, none have been successful [9].

3.4 Progression

Progression to muscle-invasive disease or development of metastasis occurs in 20 to 30% of patients who present with non-muscle-invasive bladder cancer. The NBCCGA identified tumor grade, T1 disease, and Tis as indicators of progression. Additionally, 45% of patients with grade 3 disease experienced progression, the majority of these progressing within 24 months [4]. Herr et al. reported that 40% of patients with T1 G3 disease experienced progression [10]. Both recurrence and progression are associated with higher grade and stage of disease. Unfortunately, even with these advances in our understanding, we still cannot predict with certainty which tumors will progress. Thus, many trials are currently investigating better ways to treat and control non-muscle-invasive bladder cancer.

3.5 Priming of the Immune System

BCG therapy causes a strong innate immune response, specifically via the activation of CD4+ and CD8+ T lymphocytes [11-13]. This response was shown to be the main factor responsible for eliminating tumor in a mouse model, and a correlation was demonstrated between T cell infiltration and clinical response in patients [14, 15]. *In vivo* studies using urine and blood proteomic and cytometric screens have demonstrated that several instillations of BCG are needed to produce a robust immune response [16]. More specifically, whereas the immune system is activated after the first instillation of BCG, the response is significantly amplified after the third treatment. These findings led to the hypothesis that the effects of BCG therapy are heightened after priming of the immune system. Furthermore, a recent study showed that BCG-specific immunity improved antitumor response in a mouse model of bladder cancer [16]. Mice whose bladders were primed with 3 instillations of BCG, at days 0, 7, and 14, had a more robust T cell bladder wall infiltration when compared to the control group. The authors of this study also observed BCG dissemination to regional lymph nodes and priming of IFN-γ-producing T cells after 1 instillation of BCG and that these responses were more robust after repeated instillations. Finally, the authors demonstrated that patients with preexisting immunity to BCG, those who were PPD-positive, responded significantly better to intravesical BCG, compared with the PPD-negative control group [16]. The authors concluded that patient immunity to BCG should be assessed before initiating therapy. If patient immunity is found to be insufficient, it should be boosted via priming; this action may improve the response to BCG.

3.6 Rationale

1. The standard care for patients with high-risk non-muscle-invasive bladde cancer who do not respond to BCG treatment is radical cystectomy. Surgery with radical cystectomy is associated with a complication rate of up to 60%, as well as with poor self-image owing to external urine collecting devices. There is a need for a more efficient non-surgical approach for patients with these tumors.

2. The current treatment regimen of 6 intravesical treatments with BCG is arbitrary. The proposed study will test the efficacy of a new regimen of BCG treatments.

3. The proposed study will attempt to define the acceptable clinical toxicity profile of intravesical BCG.

4. There is a need to increase the durability of the response to intravesical BCG; the treatment regimen in the proposed study will attempt to address this.

5. The proposed study will incorporate recent data that provided new insight into the T cell activity in response to BCG therapy. Furthermore, we will focus on the idea that priming the immune system will result in a more robust immunologic response against any tumor that is present.

4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.2 Design

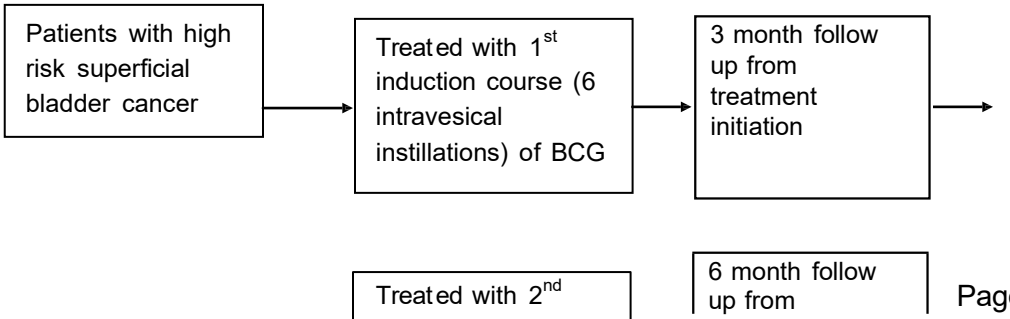
The study will use a single-stage phase II design. We are interested in the 2-induction BCG therapy if the overall response rate is ≥80% and not interested if the overall response rate is ≤66%. The probabilities of a type I error and type II error are set at 0.05 and 0.20, respectively.

We will enroll continue enrolling patients until 75 patients have completed their second cystoscopy on study.. On completion of the trial, if ≥52 patients had a response, the regimen will be declared effective and of interest.

4.3 Intervention

Rationale: The current regimen of 6 intravesical instillations of BCG for high risk superficial bladder cancer is arbitrary. No randomized trials have been performed to identify the optimal number of intravesical BCG instillations needed to obtain the lowest recurrence rates.

Treatment Plan: Patients with high risk superficial bladder cancer will be treated with 2 induction courses (12 intravesical instillations total) of BCG. Patients will undergo a diagnostic TUR which will include a urine cytology when possible to evaluate their bladder tumor/tumors, a past TURBT and urine cytology within 60 days of treatment initiation will also suffice. If the pathological characteristics of the tumors result in the patient being deemed eligible, they will be asked to enroll in the study. A prior/current history and physical examination will also be evaluated. After the first induction course (6 intravesical instillations) of BCG, patients will be scheduled for a cystoscopy at 3 months (+/- 4 weeks). During this 3 month cystoscopy appointment patients will again submit a urine cytology prior to the procedure. If worsening tumor is found a TURBT will be scheduled at the physicians discretion. All enrolled patients will be evaluated for the primary endpoint, as defined in section 14.0, of the study, regardless of whether they received the full course of treatment.



5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

Agent: BCG for Intravesical Use

Source of supply: TICE

Licensing agreement:

Mechanism of Action: BCG induces a granulomatous reaction at the local site of administration. The exact mechanism of action is unknown.

Formulation, Packaging, and Storage: BCG is supplied in a box containing 1 vial. Each vial contains 1 to 8 × 10^8 CFU, which is equivalent to approximately 50 mg (wet weight), as lyophilized (freeze-dried) powder. The intact vials should be stored refrigerated, at 2° to 8°C (36° to 46°F), and should be protected from direct sunlight. The product should not be used after the expiration date printed on the label.

Dosage Regimen and Administration: BCG will be administered at a dose of 1 vial (50 mg) per instillation. The suspension should be prepared using aseptic technique. The administration instructions are as follows: Draw 1 mL of sterile saline (0.9% sodium chloride injection USP) at 4° to 25° into a small syringe (e.g., 3 mL) and resuspend 1 vial of BCG. Gently swirl until a homogenous suspension is obtained. Avoid forceful agitation, which may cause clumping of the mycobacteria. Dispense the cloudy BCG suspension into the top end of a catheter-tip syringe that contains 49 mL of saline diluent, bringing the total volume to 50 mL. Gently invert the syringe to mix. After the bladder has been drained, using a Foley catheter, gently instill the 50 mL mixture into the patient‟s bladder.

6.1 CRITERIA FOR SUBJECT ELIGIBILITY

- Age eligibility: 18 years and older
- Sex eligibility: Both
- Accepts healthy volunteers: No

6.2 Subject Inclusion Criteria

- Patients must have high risk non-muscle invasive urothelial bladder carcinoma (Tis, TaHG, or T1) that is pathologically confirmed by the Memorial Sloan Kettering Department of Pathology or a documented history of TaHG or T1 non-muscle invasive urothelial bladder tumors.
- All visible papillary lesions must be macroscopically resected within 60 days of treatment initiation.

- Absence of urothelial carcinoma involving the upper urinary tract (documented by radiological imaging or biopsy) preferably within 12 months from the start of treatment. Should the imaging or biopsy be performed outside this window it will be up to the physicians discretion to re-scan/biopsy.
- Patients who have received a single dose of mitomycin C following staging TUR.

6.3 Subject Exclusion Criteria

- Currently being treated or scheduled to have radiation treatment for bladder cancer during the study.
- Treatment with intravesical BCG or chemotherapy for a patient"s current <T2 tumor during the 12 months prior to the current diagnosis.
- Currently being treated or scheduled to have treatment with any systemic or intravesical chemotherapeutic agent during the study.
- Currently being treated with or having been treated in the last 12 months with any investigational drug for high risk superficial bladder cancer.
- Currently being treated for metastatic transitional cell carcinoma.
- Scheduled to have surgery for bladder cancer during the study.
- Presence of clinically significant infections or congenital or acquired immunodeficiency.

7.0 RECRUITMENT PLAN

All MSK patients with a diagnosis of high risk superficial bladder cancer (TaHG, T1, Tis) who have not received any treatment within 12 months of the current diagnosis or who have a new diagnosis will be offered participation in the protocol. Both sexes and all racial and ethnic groups will be eligible to participate in this clinical trial, provided all the other eligibility criteria are met. Eligible research subjects will be identified by a member of the patient"s treatment team, one of the protocol investigators, or the research team at MSK. If the investigator is a member of the treatment team, he or she will screen their patients" medical records for suitable research study participants. When a potential participant is identified, the investigator will inform the patient about this study and discuss the possibility of enrolling. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study.

The principal investigator may also screen the medical records of patients with whom he or she does not have a treatment relationship, for the limited purpose of identifying patients who would be eligible to enroll in the study. The principal investigator would record appropriate contact information so that these patients could be approached regarding the possibility of enrolling in the study.

If a patient meets the eligibility criteria defined in section 6.0 and agrees to participate in the study, one of the Consenting Professionals listed on page 1 will conduct the Informed Consent process with the patient.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of the patient‟s MSK medical records to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

In most cases, the initial contact with the prospective subject will be conducted by either the treatment team, investigator, or research staff working in consultation with the treatment team. The recruitment process outlined above presents no more than minimal risk to the privacy of the patients who are screened, and minimal protected health information (PHI) will be maintained as part of a screening log. For these reasons, we seek a (partial) limited waiver of authorization for the purposes of (1) reviewing medical records to identify potential research subjects and to obtain information relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling of PHI contained within those records and provided by the potential subjects; and (4) maintaining information in a screening log of patients approached (if applicable).

Patients will not be paid to participate in this study. Study participants will be responsible for some or all costs associated with the cancer treatment they receive during the study.

8.1 PRETREATMENT EVALUATION

Screening

- Informed Consent

Pre-Treatment Evaluation

- History and physical exam
- TUR or biopsy of bladder tumor (within 60 days of treatment initiation)
  - Urine cytology will be included with this TURBT whenever possible.

9.1 TREATMENT/INTERVENTION PLAN

Patients enrolled in the study will receive 6 consecutive intravesical BCG treatments. After the 3 month follow-up cystoscopy appointment, patients will undergo another set of 6 intravesical BCG treatments. Each set of BCG treatments will include 6 injections within a recommended 6 weeks, a regimen that is within the standard of care. Any delay of treatment will be allowable per standard of care BCG treatment procedures. Such disruptions may include but are not limited to unforeseen circumstances, institutional holidays, or patients‟s schedule.

9.2 BCG suspension and administration procedures

Study participants will undergo intravesical treatment with approximately 1 to 8 $x10^8$ CFU of BCG (1 vial), which is equivalent to approximately 50 mg (wet weight), lyophilized (freeze-dried) powder.

The suspension will be prepared using aseptic technique. The steps are as follows:

1. Draw 1 mL of sterile saline (0.9% sodium chloride injection USP) at 4° to 25° into a small syringe (e.g., 3 mL) and resuspend 1 vial of BCG.
2. Resuspend 1 vial of BCG by gently swirling until a homogenous suspension is obtained. Avoid forceful agitation, as this may cause clumping of the mycobacteria.
3. Dispense the cloudy suspension into the top end of a catheter-tip syringe that contains 49 mL of saline diluent, bringing the total volume to 50 mL.
4. Gently invert the syringe to mix.

Administration:

1. Place a small gauge (i.e., 14fr) Foley catheter and empty the patient"s bladder of any residual urine.
2. Instill the 50 mL of resuspended BCG into the bladder through the Foley catheter.
3. Remove the Foley catheter.
4. The patient will be instructed not to urinate for a minimum of 1 hour.

9.3 Monitoring and compliance

The treatment will be instilled in an outpatient MSKCC facility by a trained professional. After each treatment, the patient will be assessed for toxicity. If patients experience toxicity between the scheduled visits, they will be instructed to contact their physician"s office for further instruction, assessment, or treatment.

Intravesical BCG does not have systemic interactions.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

3 months (+/- 4 weeks) after initiation of therapy

- Urine cytology
- Cystoscopy
- TUR will be scheduled (at physician"s discretion)

6 months (+/- 4 weeks) after initiation of therapy

- Urine cytology
- Cystoscopy
- TUR will be scheduled (at physician"s discretion)

Evaluation	Pretreatment screening	3 months (+/- 4 weeks) after initiation of therapy	6 months (+/- 4 weeks) after initiation of therapy
History and physical	x		

Urine cytology	x	x	x
Cystoscopy		x	x
Trans-urethral resection tumor*	x (within 60 days of treatment initiation)	x (*will be scheduled at physician"s discretion)	x (*will be scheduled at physician"s discreton)

11.1 TOXICITIES/SIDE EFFECTS

- At each follow-up visit, enrolled patients will be evaluated for toxicities and side effects due to therapy. As is standard of care a Nursing Treatment/Assessment form will be used to record any toxicities and side effects. A research assistant will follow the patient and maintain a record of toxicities and side effects that are possibly, probably or definitely related to protocol therapy and will be documented on the CTCAE toxicities form and collected for data entry. Only toxicities that are considered Grade $\geq$ 2, per CTCAE version 4.0 will be captured for this trial.

- Clinically insignificiant symptoms/findings of expected symptoms listed below that may be collected in the Nursing Treatment/Assessment form will not be graded or attributed on the toxicities forms.

    - Symptoms of bladder irritability, which are related to the inflammatory response that is induced by BCG, include urgency and frequency of urination, cystitis, nocturia, and pelvic pain. Symptoms occur in approximately 60% of patients receiving intravesical BCG. Symptoms are usually treated with symptomatic control using medicines such as propantheline bromide, oxybutynin chloride, and acetaminophen. Symptoms are not related to dose.

    - Hematuria is another potential side effect that is also related to the inflammatory response induced by BCG. This occurs in approximately 25% of patients treated with BCG and is usually self-limiting.

    - “Flu-like” symptoms (malaise, fever, and chills) often reflect hypersensitivity reactions to BCG. These symptoms occur in approximately 33% of patients and can be treated symptomatically with medicines such as antihistamines and acetaminophen.

    - The following adverse events were reported in ≤1% of patients: anemia, BCG sepsis, coagulopathy, contracted bladder, diarrhea, epididymitis/prostatitis, hepatic granuloma, hepatitis, leukopenia, neurologic (unclassified) symptoms, orchitis, pneumonitis, pyuria, rash, thrombocytopenia, urethritis, and urinary obstruction.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Patient response/outcome will be assessed by both urine cytology and cystoscopy at 6 months after initiation of therapy.

Patients who have a response are those who have no evidence of disease in their bladder by both urine cytology and cystoscopy.

Patients whose disease remains at the same stage or is downstaged without complete resolution are considered nonresponders and will be documented as having recurred. Any positive result for either cystoscopy or cytology exam will be followed by TURBT at the physician"s discretion.

Patients with worsening tumor, defined as the upstaging from non-muscle invasive to muscle invasive disease, or metastatic disease will be documented as disease progression.

13.0 CRITERIA FOR REMOVAL FROM STUDY

If at any time the patient develops progressive disease or experiences an unacceptable toxicity, the patient will be referred to receive standard treatment. An unacceptable toxicity is defined as severe frequency, dysuria or pain. Patients that cannot tolerate BCG instillations and refuse due to side effects are also defined as unacceptable toxicity. These patients will be evaluable for the primary endpoint of the study.

Patients with progressive disease will be considered to have experienced treatment failure, and patients with toxicities will have their outcomes ascertained 6 months after the initiation of the first BCG treatment. The number of patients, who do not complete therapy, and the reasons for not completing therapy, will be included in the final study report.

If at any time the patient is found to be ineligible for the protocol as designated in the section on Criteria for Patient/Subject Eligibility (i.e., a change in diagnosis), the patient will be removed from the study.

Patients who are removed from the study due to withdrawal of consent or who are lost to follow-up will not be considered evaluable and will be replaced.

14.0 BIOSTATISTICS

A detailed explanation of the study design including the rational for the research can be found in section 3.0 of the protocol.

Primary endpoint

The study will employ a single-stage design. We are interested in the 2-induction BCG therapy if the overall response rate is ≥80% after the initiation of the first BCG therapy and not interested if the overall response rate is ≤66%. The probabilities of a type I error and type II error are set at 0.05 and 0.20, respectively. We will continue enrolling patients until 75 patients have completed their second cystoscopy on study. On completion of the trial, if ≥52 patients had a response, the regimen will be declared effective and of interest. All patients who meet the eligibility criteria for the study and enroll in it will be included in the analysis, regardless of whether they completed the full 2 BCG induction courses.

Secondary endpoints

We will also assess the proportion of patients whose disease progresses at 6 months. The 6 month progression rate will be presented along with a 95% confidence interval based on the binomial distribution.

Accrual

We estimate 3-5 patients per month will be accrued to this protocol.

15.1 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.2 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

The individual signing the Eligibility Checklist is confirming that the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

16.1 DATA MANAGEMENT ISSUES

A research study assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordination of the activities of the protocol study team. The data collected for this study will be entered into Caisis, a secure departmental database. A minimal data set will be added to CRDB. Source documentation will be available to support the computerized patient record.

16.2 Quality Assurance

Monthly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period, and potential problems will be brought to the attention of the study team for discussion and action. Random-sample data quality and protocol compliance audits will be conducted by the study team at a minimum of once every 6 months, and more frequently if indicated.

16.3 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled “Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials” which

can be found at: http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM Plans at MSKCC were established and are monitored by the Clinical Research Administration. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: *http://mskweb2.mskcc.org/irb/index.htm*

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center"s Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

17.1 PROTECTION OF HUMAN SUBJECTS

17.2 Privacy

MSKCC"s Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

The recruitment process presents no more than minimal risk to the privacy of the patients who are screened and minimal protected health information (PHI) will be maintained as part of a screening log. For these reasons, we seek a (partial) limited waiver of authorization for the purposes of (1) reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling of PHI contained within those records and provided by the potential subjects; and (4) maintaining information in a screening log of patients approached (if applicable).

17.3 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death

- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant signs consent. SAE reporting is required for 30-days after the participant"s last investigational treatment or intervention. Any events that occur after the 30-day period and that are at least possibly related to protocol treatment must be reported.

If an SAE requires submission to the IRB office per IRB SOP RR-408 „Reporting of Serious Adverse Events", the SAE report must be sent to the IRB within 5 calendar days of the event. The IRB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office as follows:

For IND/IDE trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to saemskind@mskcc.org.

For all other trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to sae@mskcc.org.

The report should contain the following information:

Fields populated from CRDB:

- Subject"s initials
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment (drug, device, or intervention)

- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
    - A explanation of how the AE was handled
    - A description of the subject"s condition
    - Indication if the subject remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

The PI"s signature and the date it was signed are required on the completed report.

For IND/IDE protocols: The CRDB SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the SAE staff through the IND Office

18.1 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form will meet the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature, objectives, potential risks, and potential benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

19.0 REFERENCES

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20.0 APPENDICES

There are no appendices.