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A Phase II Multicenter Study of Intravesical *bacillus Calmette-Guerin* Followed by Sunitinib for the Treatment of High Risk Non-muscle Invasive Lower Urinary Tract Urothelial Carcinoma of the Urinary Bladder

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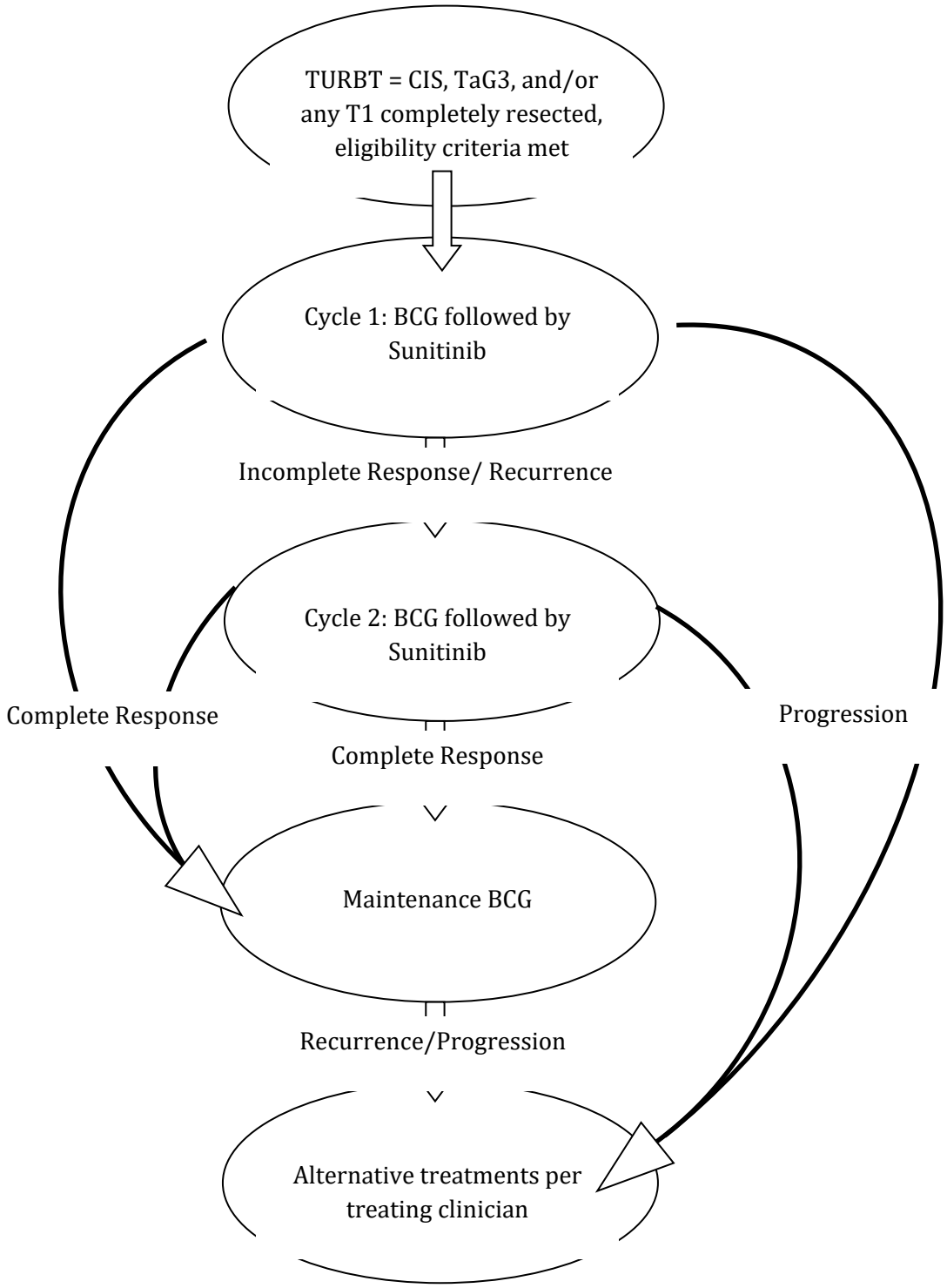
SCHEMA


TURBT = CIS, TaG3, and/or any T1 completely resected, eligibility criteria met
Cycle 1: BCG followed by Sunitinib
Incomplete Response/ Recurrence
Cycle 2: BCG followed by Sunitinib
Complete Response
Progression
Complete Response
Maintenance BCG
Recurrence/Progression
Alternative treatments per treating clinician

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PROTOCOL SUMMARY

1. Objectives:

   The primary objective of this study is to determine the complete response rate (negative bladder biopsy, negative urine cytology, normal exam under anesthesia) at 3 months in high risk non-invasive urothelial carcinoma of the lower urinary tract (bladder, prostatic urethra)

patients treated with a 6-week induction course of intravesical ***bacillus Calmette-Guerin*** (**BCG**) followed by a 2 week rest period and 4 week course of oral **Sunitinib.**

Secondary objectives of the trial:

a. Determine the percentage of patients with high risk non-muscle invasive urothelial carcinoma of the lower urinary tract (bladder, prostatic urethra) with a complete response (negative bladder biopsy, negative urine cytology, normal exam under anesthesia) at 6 months treated with a 6-week induction course of intravesical *bacillus Calmette-Guerin* (BCG) followed by a 4 week course of oral Sunitinib +/- a second course of BCG followed by Sunitinib.

b. To assess the recurrence-free survival of patients treated with BCG followed by Sunitinib at 2 years with an intact bladder.

c. To determine toxicity related to treatment with BCG followed by Sunitinib.

Correlative objectives of trial: To correlate changes in VEGF, VEGFR, p53, and other cytokine expression in the voided urine and/or serum with response in patients treated with **BCG** followed by **Sunitinib.**

2. Rationale:

This study is based on the concept that angiogenesis and vascular endothelial growth factor play a role in disease progression in patients with lower urinary tract non-muscle invasive urothelial carcinoma. Treatment with BCG is likely to target this pathway and consolidating treatment with Sunitinib, a VEGF receptor inhibitor may improve the complete response rate in this population which currently is approximately 45-55% at 3 months.

3. Primary Statistical Endpoint:

The primary endpoint of this phase II trial is to determine the complete response rate at 3 months as assessed by negative bladder biopsy, negative urine cytology, and normal exam under anesthesia of patients treated with a 6 week induction course of BCG followed by a 4-week course of **Sunitinib.**

4. Schedule:

Patients will receive intravesical BCG (50mg TICE BCG in 50 ml normal saline) once weekly for 6 weeks within 6 weeks of bladder biopsy confirming high risk non-muscle invasive urothelial carcinoma. Two weeks after completion of BCG, patients will receive Sunitinib (50 mg daily) continuously for 28 days followed by a two week rest period. Patients will be reassessed with transurethral resection and urine cytology. Those with residual/recurrent

disease will receive a second course identical to the initial protocol. Those with a complete response following initial or second treatment will be placed on maintenance BCG (3 week course every 6 months for 2 years). Those failing (progression, intolerance) initial/secondary treatments will be offered alternative therapy.

1. OBJECTIVES

PRIMARY OBJECTIVE:

The primary objective of this study is to determine the complete response rate ((negative bladder biopsy, negative urine cytology, normal exam under anesthesia) at 3 months in high risk non-invasive urothelial carcinoma of the lower urinary tract (bladder, prostatic urethra) patients treated with a 6-week induction course of intravesical ***bacillus Calmette-Guerin*** (**BCG**) followed by a 6 week course of oral **Sunitinib** (4 weeks on drug, 2 weeks off)**.**

SECONDARY OBJECTIVES OF THE TRIAL:

1. Determine the percentage of patients with high risk non-muscle invasive urothelial carcinoma of the lower urinary tract (bladder, prostatic urethra) with a complete response (negative bladder biopsy, negative urine cytology, normal exam under anesthesia) at 6 months to the study regimen

2. To assess the recurrence-free survival of patients treated with **BCG** followed by **Sunitinib** at 2 years in patients with an intact bladder.

3. To determine toxicity related to treatment with **BCG** followed by **Sunitinib.**

Correlative objectives of trial:

To correlate changes in VEGF, VEGFR, p53, HIF1a and other cytokine expression in the voided urine, serum and/or tissue with response in patient treated with **BCG** followed by **Sunitinib**

2. BACKGROUND

2.1 NON-MUSCLE INVASIVE UROTHELIAL CARCINOMA OF THE LOWER URINARY TRACT

Approximately 67,000 people will be diagnosed with bladder cancer in 2007.[1] Most patients are initially diagnosed with non-muscle invasive bladder cancer. Non-muscle invasive urothelial cancer

of the lower urinary tract is characterized by tumor involving the mucosa or lamina propria of the urinary bladder and/or prostatic urethra. These patients are most commonly treated with initial endoscopic resection. The natural history of non-muscle invasive urothelial carcinoma is one of frequent recurrences. The close surveillance of patients with non-muscle invasive urothelial carcinoma with repeated upper tract imaging (computed tomography, intravenous pyelogram), office cystoscopy (every 3 months initially), and urine cytology combined with the need for frequent return to the operating room for repeat endoscopic resection make bladder cancer one of the most expensive malignancies to treat per individual patient.[2]

This surveillance pattern is driven by the fact that up to 1/3 of patients will progress to more invasive disease. A multitude of both clinical and molecular factors have been studied to attempt to identify which patients are at high risk of progression.[3] To date, the two proven factors associated with risk of progression are grade and stage. Patients with high grade tumors have at least a 50% chance of recurrence. This can range from 50-90% in patients with carcinoma in situ (CIS), a flat high grade mucosal lesion. Both high grade tumors and CIS carry a high risk of progression to muscle invasive and/or metastatic disease. In addition, patients with T1 tumors (invasion into the lamina propria) have a 50-70% chance of recurrence and a high probability of progression to more invasive disease.[4] Once a patient has advanced to muscle invasive disease, they have decreased 5-year survival similar to those patients who present initially with muscle invasive urothelial carcinoma.[5] In addition, the current standard for muscle invasive bladder cancer is radical cystectomy with or without neoadjuvant chemotherapy which is associated with a 1-3% peri-operative mortality ratio, a 20-30% peri-operative complication ratio, and significant alteration in the patient's quality of life.[6, 7] Clinical efforts have focused on the prevention of recurrence and progression for patients with non-muscle invasive urothelial carcinoma.

For those patients with adverse features including tumor recurrence, multifocality, invasion into the lamina propria, sessile architecture, mixed histology, high grade tumor, or tumors associated with carcinoma in situ, endoscopic resection is typically combined with intravesical therapy. There are a variety of current intravesical agents used in the management of non-muscle invasive bladder cancer. Mitomycin is a chemotherapeutic agent that is frequently instilled at the time of endoscopic resection. In several series, mitomycin has been shown to reduce the risk of recurrence when combined with endoscopic resection.[8] However, it does not appear to prevent disease progression which is the predominant factor in overall survival in this population. As a consequence several intravesical agents are used clinically in the peri-operative period to prevent tumor recurrence and progression. To date, the most effective agent is bacillus Calmette Guerin (BCG). In several randomized controlled studies in patients with non-muscle invasive disease, the average percentage of patients with complete response to intravesical chemotherapy was roughly 30% compared to 45-55% for those treated with BCG at 3 months. While the percentage of patients responding at 3 months with CIS is similar to other tumors using intravesical chemotherapy, up to 70% of patients treated with BCG will have a complete response at 3 months.[9] An expected 30% of patients failing initial induction with BCG will respond to a second

course of BCG. However, residual disease following two induction courses of BCG denotes a high risk of tumor progression.

2.2 Angiogenesis and Urothelial Cancer

Angiogenesis is a prerequisite to cancer growth and metastasis. It is regulated by the balance between various angiogenic and antiangiogenic factors released by cancer cells or nonmalignant cells that infiltrate the cancer [10, 11]. Microvessel density (MVD), a measure of tumor angiogenesis, has been shown to correlate with a higher incidence of metastasis and a worse prognosis in various cancers, including bladder carcinoma [12, 13]. Specifically, the development of new vasculature has been associated with progression of urothelial cancer from superficial to muscle invasive disease [14]. Canoglu et al [15] looked at tumor specimens from 77 patients with bladder cancer. They found MVD to correlate with tumor grade, stage and prognosis. Significantly higher MVD was shown in invasive tumors compared to superficial tumors ($p < 0.05$). MVD was also shown to increase with tumor grade and stage ($p < 0.05$) and, high MVD was correlated with risk of clinical progression in both superficial and invasive bladder carcinomas ($p < 0.05$, $p < 0.001$) respectively.

Additional support for angiogenesis in the development and progression of urothelial carcinoma has been shown by way of angiogenic factors and their receptors. Tyrosine-kinase receptors, including many growth factor receptors such as the receptors for fibroblast growth factor (FGF), epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), platelet-derived endothelial cell growth factor (PDGF) and Her2/neu, have been found over expressed in tissue, serum, and urine of patients with bladder cancer [16-18]. For many of these growth factor receptors, the degree of expression has been associated with the progression of cancer and a poor prognosis [19]. Several investigators have reported a positive association between over- expression of EGFR and high-grade, high-stage bladder cancer; identifying the receptor as an independent prognostic factor in patients with advanced bladder cancer by some, but not all investigators [20-23].

Of the angiogenic factors, VEGF has been identified as a crucial regulator of both normal and pathologic angiogenesis. VEGF produces a number of important biologic effects including endothelial mitogenesis and migration, extracellular matrix remodeling via induction of proteinases, increased vascular permeability and maintenance of newly formed vasculature [24]. VEGF exerts its biologic effects through the binding and stimulation of two receptors on the surface of endothelial cells: Flt-1 and KDR. Increased VEGF expression has been measured in most human tumors including those of the bladder [25-27]. In addition to the high expression rate, several investigators have reported a correlation of VEGF expression to higher stage, progression and prognosis in bladder cancers. With the progression of tumor grade and clinical stage, the positive rate of VEGF gene expression significantly increased [26-28]. Serum VEGF levels appear to be significantly associated with tumor stage, grade, vascular invasion and carcinoma in situ.

Another angiogenic factor shown to be important in the pathobiology of urothelial cancer is platelet-derived endothelial cell growth factor (PDGF). Higher PDGF levels have been associated with more invasive and higher grade urothelial carcinoma [29, 30] and appear to predict for recurrence and progression [31]. As described in further detail below, the effect of BCG may be related to VEGF inihibition; therefore, the addition of sunitinib following BCG may improve the complete response rate of patients compared to those receiving BCG alone.

2.3 BACILLUS CALMETTE-GUERIN AND UROTHELIAL CARCINOMA

Molecular Formula and Chemical Name

TICE BCG ((Organon) is an attenuated, live culture preparation of the Bacillus of Calmette and Guerin () strain of Mycobacterium bovis. BCG is grown in a medium consisting of potatoes, glycerine, asparagines, citric acid, potassium phosphate, magnesium sulfate, ferric ammonium citrate, calcium chloride, copper sulfate, and zinc sulfate. Monosodium glutamate is added to the freeze-dried preparation which is delivered in 50 mg. Prior to use, the freeze dried preparation is reconstituted with the diluent (3 ml) containing sodium chloride, sodium phosphate, and Tween 80. A single dose consists of the reconstituted BCG combined with 50 ml of sterile normal saline.

Clinical Studies

Pharmacology/Proposed Mechanism of Action

TICE® BCG induces a granulomatous reaction at the local site of administration. Intravesical TICE BCG has been used as a therapy for, and prophylaxis against recurrent tumors in patients with carcinoma in situ (CIS) of the urinary bladder, and to prevent recurrence of Stage TaT1 papillary tumors of the bladder at high risk of recurrence. The precise mechanism of action is unknown. The fundamentally agreed upon mechanism of action of BCG intravesical therapy for superficial bladder cancer is the generation of a non-specific immune response. It is believed that BCG is internalized by both antigen presenting cells and tumor cells. These antigen presenting cells present BCG antigen to T cells and generate a cellular immune response. These cells produce a wide variety of cytokines (IL-2, Il-12, IFNα, IFNγ, etc...) that recruit mononuclear cells (macrophages, natural killer cells, etc…) that generate a nonspecific tumor kill. Beyond the nonspecific killing of tumor cells from the cellular immune response, the local production of cytokines may have an anti-angiogenic impact.[32]

Clinical Safety and Efficacy

The estimated response rate for patients with high risk non-invasive disease is approximately 50% with patients with isolated carcinoma in situ experiencing response rates of 70%. Based on several randomized controlled trials performed by the Southwest Oncology Group in the early 1990s,

compared to endoscopic resection alone as well as intravesical chemotherapy with mitomycin, thiotepa, and other agent, BCG demonstrates superior delay in time to recurrence.[33, 34] However, delay in recurrence has not definitively translated into a change in overall survival or time to progression.[35]

In an effort to improve the long term effects of BCG, several groups have advocated maintenance BCG for those patients who respond to an initial or second induction course. Results of a randomized controlled study of BCG with or without maintenance therapy demonstrated increased time to disease recurrence compared to a single induction course (77 versus 36 months, log rank test p-value <0.001).[34]

Intravesical BCG is routinely used in Urologic practice and the safety and side effects are well established. The most frequent side effects of BCG include the development of lower urinary tract symptoms during treatment including urgency and frequency. In addition, patients may develop microscopic hematuria during BCG therapy.

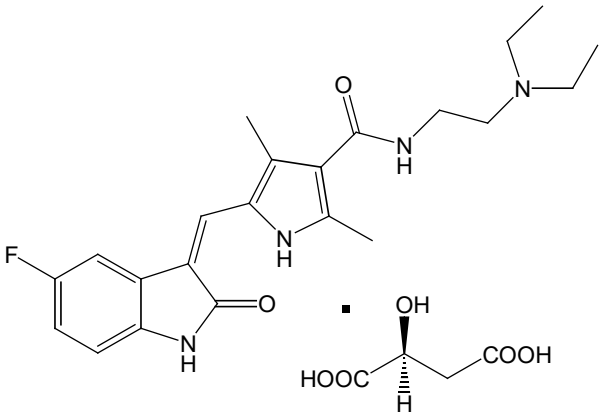
Systemic symptoms may occur with BCG administration including fever, malaise, and fatigue. The most serious side effects related to BCG are infection. Up to 10 % of patients may develop urinary tract infection which is most commonly caused by coliform bacteria. However, local infection of the bladder and prostate may develop which can usually be managed by discontinuation of the BCG and treatment with fluoroquinolone antibiotics. Rare systemic infections related to BCG most commonly occur when BCG is delivered to patients with gross hematuria or following traumatic foley catheterization. This is managed by discontinuation of therapy and treatment with anti-tuberculosis agents in addition to fluoroquinolone antibiotics. This systemic infection may require hospitalization for management of symptoms and initiation of therapy.

2.4 SUNITINIB (SUNITINIB MALATE)

Molecular Formula and Chemical Name

Sunitinib (Sunitinib malate) is a small molecule, multi-targeted receptor tyrosine kinase inhibitor that selectively targets and intracellularly blocks the signaling pathways of receptor tyrosine kinase (RTKs). The free base has a molecular weight of 398.48 and the L-malate salt, the form used in clinical trials. Figure 1), has a molecular weight of 532.57. The chemical name of the L-malate salt is 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethylpyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide, compound with (S)-2-hydroxy-succinic acid 1:1.

Figure 1. The Structural Formula of Sunitinib



Sunitinib drug substance has been identified by NMR spectroscopy as the (Z)-isomer.

Clinical Studies

Pharmacokinetics

Single- and multiple-dose clinical pharmacokinetic studies of Sunitinib over a range of 25 to 100 mg daily have been performed. Regimens have included either a repeated 4-week cycle comprising daily treatment for 2 weeks followed by a 2-week rest period (Schedule 2/2) or a repeated 6-week cycle comprising daily treatment for 4 weeks followed by a 2-week rest period (Schedule 4/2). The C_{max} and AUC of SU0112498 increase in proportion to dose across the range of doses studied. No dose-dependent changes in t_{max} or $t_{1/2}$ have been observed. Sunitinib is metabolized primarily by the cytochrome P450 enzyme, CYP3A4, to produce the active N-desethyl metabolite, SU012662. To date, no other major metabolite has been identified. The terminal elimination half-life of Sunitinib and SU012662 are approximately 40 hours and 80 hours, respectively. Trough plasma drug concentrations plateau during the first 2 weeks of dosing. Accumulation across multiple cycles of treatment has not been observed. Sunitinib may be administered without regard to meals.

Clinical Safety and Efficacy

To date, over 1500 patients with advanced malignancies have been treated with Sunitinib. Multiple phase 1, 2 and 3 studies have been conducted or are underway. The primary dose limiting toxicity in phase 1 studies was fatigue/asthenia, which generally occurred 10 to 15 days after start of daily therapy, and was readily reversible upon discontinuation of Sunitinib treatment. Overall, the most frequent adverse events associated with Sunitinib treatment have been constitutional symptoms (fatigue/asthenia), gastrointestinal effects (nausea, diarrhea, stomatitis, dyspepsia), myelosuppression (eg, neutropenia, thrombocytopenia), and dermatologic effects (e.g., dermatitis, skin discoloration, hair depigmentation). Clinically significant neutropenia has been observed in very few solid tumor patients and febrile neutropenia has rarely been observed in this patient population. The degree of adverse event severity has correlated with higher drug exposure and/or

lower patient performance status for both patients treated with previous chemotherapy and chemotherapy-naïve patients.

In studies evaluating starting doses that ranged from 75 to 100 mg daily, cardiac hypokinesis and clinical signs of congestive heart failure were reported in 4 of 62 advanced acute myeloid leukemia patients. The relationship to Sunitinib exposure was confounded by disease morbidities and prior anthracycline exposure. At the 50-mg dose level, asymptomatic decreases in cardiac ejection fraction have been observed in <3% of solid tumor patients, either with or without a prior history of cardiovascular disease or anthracycline exposure.

The maximum tolerated dose of Sunitinib using the Schedule 4/2 has been defined as 50 mg in Phase 1 clinical studies in patients with advanced solid tumors. Patients receiving this dose of Sunitinib achieved target steady state plasma concentrations of Sunitinib malate plus SU012662 of greater than 50 ng/mL.

Clinically relevant Sunitinib antitumor activity has been demonstrated in Phase 1 patients with advanced malignancies, including individuals with renal cell carcinoma, gastrointestinal stromal tumor, neuroendocrine tumor, sarcoma, thyroid cancer, melanoma and non-small cell lung cancer (NSCLC). The greatest clinical experience with Sunitinib is in solid organ malignancies including metastatic renal cell carcinoma and gastrointestinal stromal tumors. Results of phase II and III studies in this patient population has demonstrated progression free survival ranging from 30.4 to 47.3 weeks and objective response rates from 22 to 48%. In addition, a phase 2 study pivotal study of Sunitinib in patients with cytokine-refractory metastatic renal cell carcinoma demonstrated a response rate of approximately 40% with a TTP of greater than 8 months compared to historical experience of less than 10% and 3 months respectively. Recent data suggests that sunitinib does improve progression free survival in patients with metastatic renal cell carcinoma compared to IFN in a phase III randomized controlled study involving 750 patients. Numerous phase II and III studies in patients with imatinib resistant gastrointestinal stromal tumors (GIST) have demonstrated median progression free survival of 32 weeks (95% confidence interval 25-48) and median overall survival estimated at 88 weeks (95% CI Sunitinib has been or is currently being evaluated in multiple other solid organ tumor settings including neuroendocrine tumors, breast cancer, lung cancer, colorectal cancer, gastric cancer, hepatocellular cancer, prostate cancer, and metastatic bladder cancer.

2.5 RATIONALE

Despite a complete response of 45-55% in patients with non-muscle invasive urothelial carcinoma involving the lower urinary tract at 3 months, many patients suffer from multiple recurrences and progression in up to 1/3 of patients. In fact, there is little evidence demonstrating that BCG therapy prevents disease progression and the underlying hope of the therapy is that a delay in recurrence will translate into death from competing causes in this population before progression can occur. While

radical cystectomy is an effective local therapy for patients with high risk non-invasive disease, roughly 15% of patients will still develop progression.[36] More importantly, the morbidity of radical cystectomy as described above represents a barrier to treatment in some individuals. Thus, there is a real need to identify newer therapies that reduce morbidity and improve outcomes in patients with non-invasive urothelial cancer. While multiple drug regimens have been the standard for many forms of cancer including invasive bladder cancer, few reports exist on multidrug regimens for non-invasive bladder cancer. BCG combined with intravesical interferon alpha is the most commonly used multidrug regimen for patients failing standard BCG therapy. This regimen likely allows dose reduction of BCG without significant gains over BCG therapy alone.[37]
The fundamentally agreed upon mechanism of action of BCG intravesical therapy for superficial bladder cancer is the generation of a non-specific immune response. It is believed that BCG is internalized by both antigen presenting cells and tumor cells. These antigen presenting cells present BCG antigen to T cells and generate a cellular immune response. These cells produce a wide variety of cytokines (IL-2, Il-12, IFNα, IFNγ, etc...) that recruit mononuclear cells (macrophages, natural killer cells, other inflammatory cells) that generate a nonspecific tumor kill. Beyond the nonspecific killing of tumor cells from the cellular immune response, the local production of cytokines may have an anti-angiogenic impact.[32]

Overexpression of vascular endothelial growth factors (VEGF) is well described in invasive as well as superficial bladder cancer.[27] It has also been demonstrated that p53 abnormalities (very common in aggressive bladder cancer) can result in increased VEGF expression due to failure of regulation of p53 as a transcription factor.[38] IFNα has been shown to down regulate VEGF expression. As a consequence, the production of cytokines (specifically IFN) indirectly generated by BCG treatment may target a critical pathway in which superficial bladder cancer becomes invasive.[39] This mechanism of tumor progression has been targeted clinically by combining BCG and interferon intravesically for BCG failures. While the results of this data are mixed, the addition of IFN does allow for similar clinical results with the reduction of BCG dose further strengthening the concept of the role of IFN in BCG effectiveness.

Recent reports demonstrate clinical response in patients with metastatic bladder cancer treated with sunitinib after recurrence following standard chemotherapeutic regimens.[40] The addition of sunitinib following BCG in order to consolidate VEGF inhibition may result in superior 3 month complete response rates. We know that patients who have a complete response to BCG at 3 months have improved disease control and an attempt to improve the complete response rate in this early phase may improve recurrence free survival in this population.

2.6 CORRELATIVE STUDIES BACKGROUND

Multiple clinical trials are attempting to either understand the role of cytokines in the response to BCG and/or combine BCG with systemic agents to provide a multidrug regimen to target this disease. These studies are including urine based markers which may allow a better prediction of

who will respond to BCG and patients more likely to fail BCG therapy. However, to date visual inspection with cystoscopy combined with biopsy is the standard method to detect response to BCG. Identification of a marker to predict or assess response would allow clinicians to guide patients toward intravesical therapy versus more aggressive forms of therapy in the case where BCG was not likely to have an effect.

The only current multi-drug regimen with clinical data is BCG combined with IFN. The rational as outlined above for this regimen is that both treatments have downstream effect on VEGF inhibition. Recent evidence shows that VEGF expression is prominent in the bladder urothelium and may be altered by inflammation. [46] However, there have been mixed results of BCG + IFN with the addition of IFN allowing a reduction in BCG dose with a similar outcome to BCG alone. A potentially more powerful combination could be following BCG therapy with Sunitinib for a synergistic blockade of the VEGF pathway as VEGF is a well recognize target of Sunitinib.[41, 42]

As described above, VEGF inhibition is likely important in BCG's effect on bladder cancer. VEGF receptors are present in the normal urothelium and are also upregulated during inflammation such as that occurring in interstitial cystitis. BCG is known to cause bladder inflammation and therefore may cause upregulation of VEGFR receptors in normal as well as malignant bladder cells.[27] Thus the combination of BCG followed by sunitinib may sensitize bladder tumors to respond to BCG by blocking the VEGF receptor pathway. Alternatively, tumor cells not affected by BCG may be targeted by sunitinib thus providing an opportunity to consolidate complete response to therapy.

Additionally, other tissue markers may provide important information for patient stratification. For example, p53 mutation, which is common even in non-muscle invasive bladder cancer [32], may also be involved in regulated angiogenesis and response to hypoxia [33] Thus, the p53 status of patients may alter responses to sunitinib. Another important tissue marker is HIF1a, a marker upregulated with tissue hypoxia. Elevated tissue levels of HIF1a may indicate activation of the VEGF pathway, and thus indicate patients who would be more likely to respond to treatment [35] Each of these additional hypotheses can be tested using formalin-fixed, paraffin-embedded tissues subjected to immunoperoxidase staining after antigen retrieval [34].

Urine represents an ideal medium to evaluate response to therapy in patients with localized bladder cancer as it may directly indicate the response to therapy. . We will investigate the effect of BCG and sunitinib therapy on urinary VEGF and VEGFR levels. Additionally, As there are no known biomarkers of response to therapy of non-muscle invasive bladder cancer to BCG and/or sunitinib we will utilize urine, serum and tissue obtained in this study to identify potential biomarkers that may be predictive of response to treatment,

3. PATIENT SELECTION

3.1 INCLUSION CRITERIA

3.1.1. Patients must have histologically confirmed urothelial carcinoma confined to the urinary bladder and/or prostatic urethra by bladder biopsy within 6 weeks of study enrollment.
- Patients are eligible if there biopsy was done within 3 months of enrollment and a cystoscopy demonstrates no gross disease within 6 weeks of enrollment.

3.1.2. Tumor histology with >50% transitional cell carcinoma histology

3.1.3. Tumor stage ≤ T1 confirmed by pathology report
- Patients with a T1 tumor will require a restaging TURBT confirming no higher stage tumor prior to study enrollment

3.1.4. High grade tumor as defined by the WHO/ISUP 1998 classification system. (Presence of carcinoma in situ constitutes a high grade tumor)

3.1.5. No BCG within 12 months of enrollment
- Patients are allowed to have received a single dose of intravesical chemotherapy (excluding BCG) in the operating room following transurethral resection documenting non-muscle invasive urothelial carcinoma of the lower urinary tract.
- Patients are allowed to have received a previous 6 week cycle of any standard intravesical chemotherapy if > 3 months prior to enrollment.

3.1.6. Age ≥18 years.

3.1.7. ECOG performance status 0 or 1 **(see Appendix A)**

3.1.8. Patients must have adequate organ and marrow function as defined below:

X	absolute neutrophil count	≥1,500/mcL
X	Platelets	≥100,000/mcL
X	total bilirubin	≤ 1.5 upper limit of
X	AST(SGOT)/ALT(SGPT)	≤2.5 X institutional upper limit of normal
X	Serum creatinine	< 2.0 mg/dl
X	MUGA scan	within institutional normal limits

3.1.9. Timing guideline for pre-study labs and measurements:
- All pre-study labs required for determination of eligibility are to **be completed within 6 weeks prior to registration.**
- X-rays and/or scans to determine disease status **are to be completed within 6 months prior to registration** (or the next business day if falls on a weekend or holiday)**.**

3.1.10. All patients must be informed of the investigational nature of this study and must sign an informed consent in accordance with institutional and federal guidelines.

3.2 EXCLUSION CRITERIA

3.2.1. Patients with a prior history of radiation for bladder cancer
- Patients with a prior history of radiation for prostate cancer are eligible for the study

3.2.2. ≥ T2N0M0 transitional cell carcinoma of the bladder on current pathology or in the past. Patients with a prior history of upper tract urothelial carcinoma are eligible for participation in the study as long as there is no evidence of disease for 6 months prior to study enrollment

3.2.3. Patients with other malignancies are eligible for enrollment in the study but should not be on active treatment for this malignancy within 12 months of study enrollment. Patients with prior history of local treatment for prostate cancer are eligible for participation in the study

3.2.4. Patients cannot have received Sunitinib or other anti-angiogenic therapy for at least 12 months prior to enrollment in the study

3.2.5. History of allergic reactions attributed to compounds of similar chemical or biologic composition to BCG and Sunitinib
- Patients with prior systemic infection with BCG are not eligible for the study
- Patients with prior intolerance to BCG may be considered

3.2.6. Major incisional surgery within 4 weeks of study enrollment

3.2.7. Bleeding diathesis or unresolved gross hematuria after bladder biopsy

3.2.8. Known HIV – positive patients may not participate. This is to avoid additional complications that immune suppression and HIV infection may cause due to treatment with BCG, which is a live attenuated bacteria that is known to cause systemic infection in patients who are immunocompromised.

3.2.9. Patients taking agents that result in immunosuppresion are not eligible for the study due to the potential for the increased risk of systemic infection in those patients receiving BCG

3.2.10. Any of the following within the 6 months prior to study drug administration: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, **symptomatic congestive heart failure (CHF)**, cerebrovascular accident or transient ischemic attack, or pulmonary embolism.

3.2.11. Ongoing cardiac dysrhythmias of NCI CTCAE grade ≥2.

3.2.12. Patients with history of or who are suspected to have CHF can be included as long as they are asymptomatic and have an ejection fraction that is equal to or above the institutional lower limit of normal by baseline MUGA (obtained within 28 days of registration or the next business day if falls on a weekend or holiday).

3.2.13. QTc interval > 500 msec on baseline EKG (to be done within 6 weeks prior to registration or the next business day if falls on a weekend or holiday).

3.2.14. Hypertension that cannot be controlled by medications (>150/100 mm Hg despite optimal medical therapy).

3.2.15. Patient may not have unresolved bacterial infection.
3.2.16. Patients with hypothyroidism that cannot be adequately controlled with medication will be excluded. All patients will be monitored at trial initiation with a TSH.
3.2.17. Concurrent treatment on another clinical trial. Supportive care trials or non-treatment trials, e.g. QOL, are allowed.
3.2.18. Pregnancy or breastfeeding. Female subjects must be surgically sterile or be postmenopausal, or must agree to use effective contraception during the period of therapy. All female subjects with reproductive potential must have a negative pregnancy test (serum or urine) prior to enrollment. Male subjects must be surgically sterile or must agree to use effective contraception during the period of therapy. The definition of effective contraception will be based on the judgment of the principal investigator or a designated associate.
3.2.19. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration, or may interfere with the interpretation of study results, and in the judgment of the investigator would make the subject inappropriate for entry into this study.

3.3 INCLUSION OF WOMEN AND MINORITIES

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

4.0 PRETREATMENT EVALUATION

Pre-enrollment screening tests and evaluations will be used to determine the eligibility of each candidate for study inclusion. All enrollment evaluations must be assessed within the interval specified prior to treatment. All dates are specified below but may occur on the following day if it falls on a weekend or holiday.

4.1 CLINICAL: (within 6 weeks prior to registration)

4.1.1 Complete history and physical examination.
4.1.2 Height, weight, and ECOG Performance Status.
4.1.3 Baseline evaluation of symptoms and medications. Patients medication list will be reviewed and compared to the list in Appendix F. Medication adjustment will be performed to eliminate the possibility of interaction with Sunitinib.

4.2 LABORATORY: (within 6 weeks prior to registration)

4.2.1 Hematology: Complete blood count, differential and platelet count.

4.2.2Comprehensive panel: sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, AST, ALT, alkaline phosphatase, bilirubin, total protein and albumin.
4.2.3TSH
4.2.4Urine cytology

4.3 IMAGING AND DIAGNOSTIC STUDIES: (within 6 months prior to registration)

4.3.1Computed tomography scan (with contrast), intravenous pyelogram, or magnetic resonance imaging of the abdomen and pelvis.
4.3.2A non-contrasted CT combined with renal/bladder ultrasound can be obtained for those patients with a contra-indication to CT and/or MRI

4.4 ELECTROCARDIOGRAM. (within 3 months of registration)

4.5 MUGA SCAN (within 6 weeks of study enrollment)

5.0 REGISTRATION PROCEDURES

5.1 GENERAL GUIDELINES

Eligible patients will be recruited from the University of Michigan, Department of Urology Clinics. Patients signing informed consent and meeting eligibility criteria will be registered on study by the Study Coordinator. Once registration is complete, the registrar will provide the registering individual a study subject identification number.
Following registration, patients should begin protocol treatment within 3 weeks. Issues that would cause treatment delays should be discussed with the Principal Investigator.

6. 0 TREATMENT PLAN (Treatment must begin within 6 weeks after registration)

6.1 BCG

6.1.1 DOSE LEVELS: Dose Levels for TICE BCG

Dose Levels for TICE BCG

Dose Level	Weekly Dose/ Route	Dispensed As	Schedule
Starting dose level: 0	50 mg reconstituted in 50 ml normal saline/intravesical	vial	1day/week x 6 weeks

–1	25 mg reconstituted in 50 ml normal saline/intravesical	½ vial	1day/week x 6 weeks
–2	12.5 mg reconstituted in 50 ml normal saline/intravesical	¼ vial	1day/week x 6 weeks

6.1.2 BCG ADMINISTRATION

- Patients will undergo urinalysis in clinic and the decision to proceed with BCG therapy will be based on standard clinic procedures (Appendix B).
- BCG is delivered via a 12-16 French Red Robinson catheter by a clinical nurse. Patients are encouraged to decrease fluid intake for up to 6 hours prior to administration. BCG is retained in the urinary bladder for two hours following administration. Patients are requested to void sitting down to avoid contamination and requested to disinfect the toilet with bleach after as well as for any voids up to 6 hours after treatment.
- Study drug TICE BCG will be administered by a nurse in clinic as 50 mg reconstituted in 50 ml sterile normal saline 1 time/week for a total of 6 weeks. Patients without a complete response after the initial cycle will be offered a second identical cycle.
- The Study drug dose may be adjusted according to individual patient tolerance as outlined below in section 10. The BCG can be diluted in ½ to ¼ the original dose.
- Induction and/or maintenance BCG may be administered by a local urologist at the approval of the principal investigator
    - Induction BCG protocol by local urologist will be verified by the principal investigator to ensure compliance with study protocol
    - Maintenance BCG will be administered following the study calendar.
        - Deviations to the maintenance BCG schedule will be reported to the study coordinator along with reason. Ultimately, the administration of maintenance BCG and its timing are at the discretion of the treating physician.
        - Records will be obtained from the local urologist to document dose, dates of administration and completion of course for a length of 2 years following completion of induction course of BCG.

6.1.3 CONCOMITANT MEDICATION(S)

Intravesical BCG is not metabolized. Because BCG works by stimulating the immune system, patients on immunosuppressive agents (corticosteroids) or immunocompromised (HIV infection, transplant patients on immunosuppressive regimens) should not be given BCG. In addition, antimicrobial therapy should be avoided during BCG administration due to the potential antimicrobial effect on the BCG itself. **(PLEASE REFER TO CONCOMINANT MEDICATION SECTION IN REGARD TO SUNITINIB)**

6.1.4 DOSE REDUCTIONS: **Please refer to Section 11.**

6.1.5 SUPPORTIVE CARE GUIDELINES:

- Irritative bladder symptoms occur in 50% of patients
    - For patients with bothersome symptoms, medications such as pyridium, propantheline bromide, oxybutynin and acetaminophen can be used
- "Flu-like" symptoms (malaise, fever, chills)
    - Are related to the immune and hypersensitivity response and can be managed with ibuprofen, acetaminophen, and antihistamines
- Occular symptoms (uveitis, conjunctivitis, iritis, keratitis, granulomatous choreoretinitis) alone or in combination with joint symptoms (arthritis, arthralgia), urinary symptoms, and/or skin rash have been reported. Patients positive for HLA-B27 appear to be at elevated risk
    - Dose reduction will be attempted
    - If persistent, BCG will be halted although patients will be allowed to continue to the Sunitinib portion of the study.
- Infection: Urinary tract infection, prostatitis, orchitis/epidydimitis have all rarely been reported with BCG. Serious disseminated infections to the lung, liver, bone, bone marrow, kidney, and regional lymph nodes have been reported in case reports in the literature. Finally, sepsis has been reported with associated mortality.
- If a patient develops persistent fever (> 38.5 C) or experiences an acute febrile illness consistent with BCG infection, BCG will be immediately discontinued and the patient will be evaluated for BCG infection
- Local infections may often be managed with discontinuation combined with a fluoroquinolone antibiotic such as ciprofloxacin or levofloxacin. However, rare cases of epidydimitis and orchitis have not been successfully managed and may require antituberculosis therapy and/or orchiectomy
- More serious infections will be evaluated and might require one of the following actions:
    - Hospital admission with urine and blood cultures
    - Supportive therapy
    - Infectious disease physician consultation
    - Initiation of anti-tuberculosis therapy including isoniazid, rifampin, and/or ethambutol (not pyrazinimide)

6.2 SUNITINIB (Treatment with Sunitinib will occur according to the study calendar)

6.2.1 DOSE LEVELS: Dose Levels for Sunitinib

Dose Level	Daily Dose/ Route	Dispensed As	Schedule
Starting dose level: 0	50 mg, PO	1 x 50-mg capsules	4 weeks on and 2 weeks off, Q 6 weeks

–1	37.5 mg, PO	1 x25 mg capsule and 1x 12.5 mg capsule	4 weeks on and 2 weeks off, Q 6 weeks
–2	25 mg, PO	1 x 25-mg capsules	4 weeks on and 2 weeks off, Q 6 weeks

6.2.2 SUNITINIB ADMINISTRATION

- Study drug (Sunitinib) will be given at 50 mg/day as a single agent for 4 consecutive weeks followed by a 2-week rest period to form a complete cycle of 6 weeks. Study drug will be orally self administered once daily without regard to meals.
- The Study drug dose may be adjusted according to individual patient tolerance as outlined below in section 10.
- Patients must be provided with a diary to document compliance, (Appendix C).
- Patients will be required to return all bottles of study medication at the beginning of each cycle. The number of capsules remaining will be documented and recorded.

6.2.3 CONCOMITANT MEDICATION(S)

Sunitinib is metabolized primarily by liver enzymes, in particular CYP3A4. Caution is recommended when administering study drug with inhibitors or inducers of the CYP3A4 family (see appendix G).

6.2.4 DOSE REDUCTIONS: **Please refer to Section 11.**

6.2.5 SUPPORTIVE CARE GUIDELINES:

- Diarrhea
  - Lomotil or Imodium may be used by patients developing diarrhea during treatment.
- Hypertension
  - Blood pressure should be well controlled before starting study drug.
  - Standard blood pressure medications should be used for patients that develop hypertension during treatment.
  - Diltiazem and verapamil should be avoided if possible as they are potential inhibitors of the CYP3A4 pathway (see section 6.2.3).
  - If hypertension develops or worsens while on study drug, treatment should first be with optimizing standard anti-hypertensive agents. If refractory, study drug dose modifications can be made.
  - In cases of severe hypertension (>200 mmHg systolic or 110 mmHg diastolic) temporary suspension of study drug is recommended until hypertension is controlled.
- Fatigue
  - For intolerable fatigue, the next cycle of treatment may be delayed by one week.

7.0 DURATION OF THERAPY

7.1 BCG

- Patients will receive within either 6 weeks of bladder biopsy or within 3 months of bladder biopsy and a cystoscopy within 6 weeks of enrollment confirming no visible tumor a 6 week course of BCG as described above.
- Please see section 10 for dosing delays and modifications. Patients unable to complete an induction course of BCG will be removed from the study and replaced with a new subject. The removed subject will be offered alternative treatment options.
- After completion of a 6 week course of BCG, patients will undergo a 2 week rest period before initiating sunitinib
- All patients will be assessed at 3 months after enrollment with repeat bladder biopsy done at the study institution and urine cytology regardless of completion of the study drugs as this is standard of care.
- Patients demonstrating residual disease at 3 months will receive a second complete cycle of the study drugs (BCG followed by sunitinib) if the tumor remains non-muscle invasive. However, patients may elect to proceed to alternative treatments if there is residual non-muscle invasive disease. Patients completing at least one cycle of the study treatment will be assessed for primary and secondary endpoints where applicable.
- Patients with evidence of muscle invasive disease on restaging bladder tumor biopsy will be withdrawn from the study and offered standard alternative treatment options.
- Any patients with a complete response to BCG followed by sunitinib at 3 months or 6 months will be placed on maintenance BCG therapy which is the current standard of care. The maintenance BCG schedule is outlined in Calendar 2. Calendar 2 represents an idealized version of maintenance therapy and actual maintenance therapy varies according to individual physician practice pattern. As such, we will recommend that patients follow the study calendar but the actual administration will be at the discretion of the treating physician based on practice pattern and medical decision making. In addition, surveillance cystoscopy and history and physical is dictated by maintenance schedule and will ultimately be at the discretion of the treating physician. Records of each maintenance treatment (dose, timing, and delays), surveillance, cystoscopy, history and physical, urine studies, imaging, and pathologic data (if obtained) will be collected by the study coordinator and documented for a total of 2 years following completion of the initial or second induction course of BCG to assess for treatment response. Please see section 10 for dose modification and reduction.

7.2 SUNITINIB

- Patients will receive a single 6 week cycle of sunitinib 2 weeks following a 6 week course of intravesical BCG. Complete responders as determined by no cancer on endoscopic biopsy

AND no evidence of cancer on urine cytology will be placed on maintenance BCG by their treating physician as described in the study calendar.

- Patients with residual disease will receive a second course of treatment identical to the first cycle (BCG followed by sunitinib) assuming a normal MUGA scan (see study calendar).
- Patients demonstrating evidence of objective progression by endoscopic biopsy will offered alternative treatments

8.0 CRITERIA FOR REMOVAL FROM STUDY:

8.1Protocol therapy will be discontinued and patients will be removed from study based on any of the following criteria (Patients clinical course will be followed for two years.):

- Patients wishes.
- Disease progression as documented by 3 month or 6 month bladder tumor biopsy documenting progression to muscle invasive bladder cancer.
- Clinician and patient determine that alternative treatment plan should be pursued. Reason for pursuing alternative therapy will be documented.
- Intercurrent illness that prevents further administration of treatment.
- Unacceptable adverse event(s) that may or may not be directly related to BCG and/or sunitinib but that in the judgment of the treating physician make it dangerous for the patient to be retreated.
- General or specific changes in the patient's condition that render the patient unacceptable for further treatment in the judgment of the investigator.

8.2As an excessive rate of withdrawals can render the study un-interpretable, unnecessary withdrawal of patients should be avoided.

8.3When a patient discontinues treatment early, the Investigator will make every effort to contact the patient and to perform a final evaluation. The reason(s) for withdrawal will also be recorded. The reason for terminating therapy should be clearly recorded.

9.0 DURATION OF FOLLOW-UP

- Patients will be followed by study calendar
- the clinical course of all patients will be followed for a total of 2 years following completion of 1st or 2nd induction course of the study therapy.

10.0 DOSING DELAYS/DOSE MODIFICATIONS

10.1 TICE BCG

10.1.1 DELAYS

- For patients experiencing bladder related symptoms, all attempts will be used to supportive care to have the patient complete a complete 6 week course at the full dose.
- Patients with gross hematuria and/or evidence of urinary tract infection during treatment as documented by urinalysis and/or confirmed by urine culture will be delayed administration of the dose by 1 week and restarted after confirming absence of gross hematuria and/or lack of nitrite positivity on dipstick urinalysis.
- Those patients with a greater than 3 week delay between doses during the 1st induction course will be removed from the study prior to initiation of sunitinib and be replaced with another eligible patient. Those unable to complete a 2nd induction course of BCG will be offered alternative therapy and followed for secondary endpoints where applicable.
    - Any patient with systemic infection caused by TICE BCG will be withdrawn from further BCG treatment. If this occurs during the first induction course, these subjects will be replaced, otherwise, patients will be offered alternative therapy and followed for applicable secondary endpoints.
    - Patients on maintenance BCG therapy will be given the full dose unless persistent urinary symptoms or systemic side effects (malaise, fever, fatigue) deter treatment. Dose reduction to -1 will be attempted first. Patients will be allowed to decrease dose to -2 if intolerance persists. Those patients who do not tolerate a dose of -2 during (see table in section 6.1). maintenance therapy will be withdrawn from further BCG administration and offered alternative treatment plan at the discretion of the treating clinician.

10.1.2 REDUCTION

- Intrapatient dose reduction by 1, and if needed 2- dose level(s) will be allowed (see Table below) depending on the type and severity of toxicity encountered provided that criteria for patient withdrawal from study treatment have not been met.
- All intra-patient dose reductions are relative to the lowest dose level of the current cycle.
- No more than 2 dose reductions are permitted in any patient. If further dose reduction is required, the patient must be removed from further BCG administration.
- The dosing period may be extended for BCG as outlined in section above
- The below table describes the recommended dose modifications for study treatment associated toxicity.

TABLE: DOSE MODIFICATION FOR BCG BASED ON TOXICITY AND GRADE

* treatment is based on type of infection
# if BCG infection of grade 3 or 4 occurs during the 1st induction course, patients will be withdrawn from the study and replaced. Otherwise, patients will be offered alternative therapy at the discretion of the treating clinician and followed for appropriate endpoints.

10.2 SUNITINIB: In the event of any (CTC version 3) drug related grade 3 or 4 non-hematologic or

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Irritative Bladder symptoms	Continue at the same dose level	Continue at the same dose level.	Dose reduction to -1. If Grade 3 toxicity persists, reduction to -2. Discontinuation will occur at the discretion of the treating clinician.	Dose reduction to -1. If Grade 4 toxicity persists, reduction to -2. Discontinuation will occur at the discretion of the treating clinician.
Fever, chills and "flu-like" symptoms	Continue at same dose level.	Continue at same dose level.	Dose reduction to -1. If Grade 3 toxicity persists, reduction to -2. Discontinuation will occur at the discretion of the treating clinician	Dose reduction to -1. If Grade 4 toxicity persists, reduction to -2. Discontinuation will occur at the discretion of the treating clinician
Occular symptoms +/- joint symptoms	Continue at the same dose level.	Continue at the same dose level.	Dose reduction to -1. If Grade 3 toxicity persists, reduction to -2. Discontinuation will occur at the discretion of the treating clinician	Dose reduction to -1. If Grade 4 toxicity persists, reduction to -2. Discontinuation will occur at the discretion of the treating clinician
Infection	Treat* and continue at same dose after resolution of symptoms within 2 weeks	Treat* and continue at same dose after resolution of infection within 2 weeks	Withdraw BCG treatment#	Withdraw BCG treatment#

grade 4 hematologic adverse event(s) drug should be held until the toxicity resolves to < grade 1 and then the drug should be restarted at -1 dose level (see 6.1).

10.2.1 DOSE REDUCTION FOR SUNITINIB

- Intrapatient dose reduction by 1, and if needed 2- dose level(s) will be allowed (see 6.1) depending on the type and severity of toxicity encountered provided that criteria for patient withdrawal from study treatment have not been met.
- All intra-patient dose reductions are relative to the lowest dose level of the current cycle.
- Recovery to acceptable levels of toxicity must occur within 4 weeks to allow continuation in the study.

- No more than 2 dose reductions are permitted in any patient. If further dose reductions are required, patients will discontinue sunitinib therapy. They will continue to be followed per protocol.
- The following table describes the recommended dose modifications for study treatment associated toxicity.

TABLE: DOSE MODIFICATION OF SUNITINIB BASED ON TOXICITY AND GRADE

Recurring grade 3 toxicity requires dose reduction * Patients who develop grade 3 or 4 hyperlipasemia or hyperamylasemia without clinical or other evidence of pancreatitis, or grade 4 hyperuricemia or grade 3 hypophosphatemia without clinical symptoms may continue study treatment without interruption. *** Patients with recurrent grade 3 lymphopenia and anemia do not require dose modification. Recurring grade 4 neutropenia or grade ≥ 3thrombocytopenia persisting for at least 5 days requires dose reduction in the next cycle. Grade 4 lymphopenia does not require dose reduction.

Management of cardiac ejection fraction.

Toxicity	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Non-hematologic	Continue at the same dose level	Continue at the same dose level.	Withhold dose until toxicity is grade ≤1, or has returned to baseline, then resume treatment at the same dose level or reduce the dose by 1 level at the discretion of the investigator* .	Withhold dose until toxicity is grade ≤1, or has returned to baseline, then reduce the dose by1 level and resume treatment, or discontinue at the discretion of the investigator*.
cardiac toxicity:	Continue at the same dose level.	Continue at the same dose level except in the event of• Non-urgent ventricular paroxysmal dysrhythmia requiring intervention, Withhold dose until toxicity is grade ≤1, then reduce dose by 1 level and resume treatment.	Remove from further therapy, follow for applicable endpoints	Remove from further therapy, follow for applicable endpoints
Neurotoxicity	Continue at the same dose level.	Withhold dose until toxicity is grade ≤1, then continue at same dose level.	Withhold dose until toxicity is grade ≤1, then reduce the dose by 1 level and resume treatment.	Remove from further therapy, follow for applicable endpoints
Fever, chills and "flu-like" symptoms	Continue at same dose level.	Continue at same dose level.	Withhold dose until toxicity is grade ≤2, or has returned to baseline, then resume treatment at the same dose level.	Withhold dose until toxicity is grade ≤2, then reduce the dose by 1 level and resume treatment.
Hematologic	Continue at the same dose level.	Continue at the same dose level.	Withhold dose until toxicity is grade ≤2, or has returned to baseline, then resume treatment at the same dose***.	Withhold dose until toxicity is grade ≤2, then reduce the dose by 1 level and resume treatment***.

All patients will undergo a MUGA scan prior to enrollment in the study. Patients proceeding to a second cycle of therapy (BCG followed by sunitinib) will undergo a MUGA scan prior to initiation of the second cycle. Patients with an ejection fraction lower than the institutional lower limit of normal will not receive further study treatment per protocol and will be offered alternative therapy as directed by the treating clinician.

11.0 PHARMACEUTICAL INFORMATION

11.1 ™ TICE BCG

Formulation and Packaging

TICE BCG Live (intravesical) is a freeze-dried preparation made from the Connaught strain of Bacillus Calmette and Guerin, which is an attenuated strain of Mycobacterium bovis supplied as a vial containing 50 mg of freeze-dried BCG.

Preparation and Dispensing

The preparation of TICE BCG suspension should be done using aseptic technique. To avoid cross-contamination, parenteral drugs should not be prepared in areas where BCG has been prepared. A separate area for preparation of the TICEsuspension is strongly recommended. All equipment, supplies and receptacles in contact with TICE should be handled and disposed of as biohazardous. The individual preparing the TICE should wear gloves, eye protection, and take precautions to avoid contact of BCG with broken skin. If preparation is not performed under a biocontaminant hood, a mask and gown may be worn to avoid inhalation or inadvertent exposure to BCG with broken skin. TICE should not be handled by persons with an immunologic disorder.
Do not remove the rubber stopper from the vial.
(Using Syring Method).
Drawn 1 ml of sterile, preservation-free saline (o.9% Sodium Chloride Injection U.S.P.) at 4-25^{o}C, into a small syringe (e.g., 3 ml) and add to one vial of TICE BCG to resuspend. Gently swirl the vial until a homogenous suspension is obtained. Avoid forceful agitation which may cause clumping of the mycobacteria. Dispense the cludy TICE BCG suspension into the top end of a catheter-tip syringe which contains 49 ml of saline diluent, bringing the total volume to 50 ml. To mix, g ently rotate the syrine.

(Using Reconstituion Accessories)
Reconsitituion Accessories may be provided with each TICE BCG product order. Refer to the Instructions For Use provided with the accessories for a full description of the product reconstitution procedures using these accessories.

Administration

A urethral catheter is inserted into the urinary bladder under aseptic conditions, the bladder is drained and then TICE BCG is instilled slowly by gravity, following which the catheter is withdrawn. The patient should lie prone for the 1st 15 minutes and can be up thereafter. At the end of 2 hours, the patient should void seated and should increase fluid intake to flush the bladder.

Side effects:

The following side effects, as well as their frequency, have been observed in BCG clinical studies:

- Likely (50% or more): dysuria.
- Frequent (10-50%): urinary frequency, malaise, hematuria, fever (>38 C), chills, cystitis, urinary urgency, nausea/vomiting, anemia, urinary tract infection
- Occasional (1-10%): bladder cramps/pain, anorexia, renal toxicity, genital pain, arthralgia/myalgia, urinary incontinence, diarrhea, contracted bladder, leukopenia
- Rare (less than 1%): coagulopathy, abdominal pain, liver involvement, systemic infection, pulmonary infection, cardiac (unclassified), headache, skin rash, tissue in urine, constipation, fatigue, local infection, dizziness, thrombocytopenia, ureteral obstruction, and flank pain.

Procedure for Handling Drug Spills

After use, unused product, packaging and all equipment and materials used for instillation of the product (eg, syringes, catheters) should be placed immediately in a container for biohazardous materials and disposed according to local requirements applicable to biohazardous materials. Spills and/or voided urine during the 6 hours following TICE BCG administration should be disinfected with an equal volume of 5% hypochlorite solution (undiluted household bleach) and allowed to stand for 15 minutes before cleaning or flushing toilet.

OVERDOSAGE

Overdosage occurs if more than one vial of TICE BCG is administered per instillation. If overdosage occurs, the patient should be closely monitored for signs of active local or systemic infection. For acute local or systemic reactions suggesting active infection, an infectious disease specialist experienced in BCG complications should be consulted.

Drug Storage

The reconstituted TICE BCG should be kept refrigerated (2-8° C), protected from exposure to direct sunlight, and used within 2 hours. Unused solution s hould be discarded after 2 hours.

Compliance

Patients will be administered the treatment by a healthcare provider.

11.1.1 AGENT ORDERING

Commercial supplies of BCG will be used.

11.2 PHARMACEUTICAL INFORMATION: SUNITINIB

Formulation and Packaging

SUNITINIB is a small molecule inhibitor of the receptor tyrosine kinases VEGFR, PDGFR, KIT, and FLT3. SUNITINIB will be supplied as hard gelatin capsules containing 12.5-mg, 25-mg or 50-mg equivalents of SUNITINIB free base.

Preparation and Dispensing

SUNITINIB will be dispensed as capsules at the beginning of each treatment cycle. In case of dose modification, patients will be requested to return all of their previously dispensed medication to the clinic. Capsules will be counted and patients will be dispensed the appropriate number of capsules based on the new dose level.

Administration

Administration will be performed on an outpatient basis. The dose should be taken once daily without regard to meals. Grapefruit and/or grapefruit juice should be avoided during sunitinib administration. The study investigator may implement dose suspension and/or reduction in order to ensure patient safety.

Side effects:

The following side effects, as well as their frequency, have been observed in SUNITINIB clinical studies:

- **Likely (50% or more): fatigue.**
- **Frequent (10-50%): diarrhea, nausea, upset stomach, taste disturbances, stomatitis/mucositis, vomiting, constipation, yellowing of the skin, anorexia, arthralgia and myalgia, hypertension, dermatitis, headache, blisters and/or rash in hands and feet which may be painful, increased lipase and amylase, hair color changes, shortness of breath, edema, dehydration.**
- **Occasional (1-10%): nosebleeds, leucopenia/neutropenia, anemia, thrombocytopenia, insomnia, cough, fever, increased/more frequent eye tearing, alopecia, increase creatinine, increased LFTs, reduced ejection fraction, increased cardiac enzymes.**
- **Rare (less than 1%): bleeding requiring transfusion (including bleeding into the tumor), thrombosis, infection, hypoadrenalism, increased TSH, hypothyroidism, decreased blood flow to the brain, pancreatitis, myocardial infarction, bowel perforation/intestinal fistulae, pneumothorax, seizure, temporary loss of vision. One patient developed thrombosis of the portal vein.**

Procedure for Handling Drug Spills

Following direct contact with skin, the contents of the capsules may cause yellow discoloration of the exposed area. The exposed area should be washed with soap and water immediately.

OVERDOSAGE

No overdose of SUNITINIB was reported in completed clinical studies. In non-clinical studies mortality was observed following as few as 5 daily doses of 500 mg/kg (3000 mg/m2) in rats. At this dose, signs of toxicity included impaired muscle coordination, head shakes, hypoactivity, ocular discharge, piloerection and gastrointestinal distress. Mortality and similar signs of toxicity were observed at lower doses when administered for longer durations. Treatment of overdose with SUNITINIB should consist of general supportive measures. There is no specific antidote for overdosage with SUNITINIB. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage.

Drug Storage

Since SUNITINIB may be light sensitive, the capsules will be stored in the bottles in which they are received to protect the compound from light. Bottles containing SUNITINIB capsules must be stored at controlled room temperature (15-30°C).

Compliance

Patients will be required to return all bottles of study medication at the beginning of each cycle. The number of capsules remaining will be documented and recorded.

11.2.1 Agent Ordering

Sunitinib may be requested by the principal investigator (or their authorized designees). See Appendix E for drug request forms.

11.2.2 Agent Accountability

The investigator, or an approved representative, e.g. pharmacist, will ensure that all investigational products are stored in a secured area, under recommended storage conditions and in accordance with applicable regulatory requirements. All study drug supplies must be kept in a locked limited access room. The study drug must not be used outside the context of the protocol. Under no circumstances should the investigator or other site personnel supply study drug to other investigators, patients, or clinics, or allow supplies to be used other than directed by this protocol. The investigator must maintain adequate records documenting the receipt, use, loss or other deposition of the investigational product, including batch or code numbers, and account for its disposition on patient-by-patient basis, including specific dates and quantities. The prescribed dose should also be recorded in the patient's medical records.

Destruction must be adequately documented.

12.0 CORRELATIVE STUDIES:

Evaluation of biomarkers in tissue, urine, and serum

Serum levels of biomarkers of the vascular endothelial growth factor receptor (VEGF-R) pathway including VEGF and soluble VEGFR-2 (sVEGFR-2) have been serially measured in a Phase I [29] as

well as a phase II [30] study of SUNITINIB in patients with renal cell cancer. In these studies, VEGF was found to be increased and sVEGF-R2 levels decreased by the end of each dosing cycle (day 28). After two weeks off therapy, levels returned to near baseline (day 1). Differences in day 1 and day 28 levels were statistically significant. In addition, in patients with metastatic renal cell carcinoma, when mean marker level changes were correlated with tumor response, larger proportional changes in VEGF and sVEGFR-2 levels were observed in patients exhibiting objective responses compared with those exhibiting stable or progressive disease [31].

As described above, VEGF inhibition is likely important in BCG's effect on bladder cancer. VEGF receptors are present in the normal urothelium and are also upregulated during inflammation such as that occurring in interstitial cystitis. BCG is known to cause bladder inflammation and therefore may cause upregulation of VEGFR receptors in normal as well as malignant bladder cells.[27] Thus the combination of BCG followed by sunitinib may sensitize bladder tumors to response to BCG by blocking the VEGF receptor pathway. Alternatively, tumor cells not affected by BCG may be targeted by sunitinib thus providing an opportunity to consolidate complete response to therapy.

Additionally, other tissue markers may provide important information for patient stratification. For example, p53 mutation, which is common even in non-muscle invasive bladder cancer [32], may also be involved in regulated angiogenesis and response to hypoxia [33] Thus, the p53 status of patients may alter responses to sunitinib. Another important tissue marker is HIF1a, a marker upregulated with tissue hypoxia. Elevated tissue levels of HIF1a may indicate activation of the VEGF pathway, and thus indicate patients who would be more likely to respond to treatment [35] Each of these additional hypotheses can be tested using formalin-fixed, paraffin-embedded tissues subjected to immunoperoxidase staining after antigen retrieval [34].

Urine represents an ideal medium to evaluate response to therapy in patients with localized bladder cancer as it may directly indicate the response to therapy. Further, based on preliminary results described previously, serum levels of biomakers may also be informative. We will investigate the effect of BCG and sunitinib therapy on urinary and serum levels of various VEGFs, soluble VEGF receptors, and cytokines IL8, IL6, interferon gamma, and interferon alpha. Measurements will be performed using commercially-available ELISA kits. Utility of additional biomarkers (e.g., PDGF, [35]) will be evaluated on a pilot basis.

Correlation of changes in VEGF, VEGFR, p53, and other cytokine expression to response will be explored. Markers will be grouped based on terciles of the distribution. Bivariate relationships between the expression level and response status will be assessed with the Mantel-Haenszel chi-square test. Logistic regression will be used to assess the effect of combining markers to predict response. Differences in time to recurrence by expression level will be illustrated by Kaplan-Meier plots and tested using the log-rank test. Due to the sample size and the number of factors we will be statistically testing, these analyses will be considered exploratory until confirmed in a larger, independent, clinical trial.

Procedures and Methods:

- Voided urine and serum will be obtained as outlined on the study calendar. If BCG is given locally no specimens need to be obtained at Week 1 and Week 6 visits. In addition, a bladder biopsy will be obtained at the 3 month endoscopic biopsy to assess response. These specimens will only be obtained for the first study cycle.
- Urine will be kept on ice until it can be centrifuged in the research laboratory. The urine and pellet will aliquoted into separate tubes, codes, and stores at -80^{0}C in the research laboratory.
- Tissue will collected at the time of bladder biopsy at 3 months and processed with formalin fixation and paraffin-embedding in the Pathology Department, following the standard operating procedure of the previously approved University of Michigan Bladder Cancer (Tissue/Blood/Urine/Data) Bank (IRB 1996-0379). Blocks and tissue sections will be stored in research lab until processed.
- Tissue biomarker standardization will be performed by microscopic evaluation in collaboration with a pathologist. Each assay will be performed with positive and negative control tissues from comparisons. Responses will be scored based on the number of cells staining positive and the level of positivity (0-3+).
- Urine biomarker standardization will be based on urine creatinine measurements.

13.0 STUDY CALENDAR:

		Week 1-6 BCG Course 1		Week 8-12† Sunitinib cycle 1			TURBT or bladder biopsy	Therapeutic Plan
Required studies	Pre-study	Week1	Week 6	Week 8	Week 10	Week 12	Week 14	1. **Residual/Recurrent disease without progression**: a. Negative MUGA scan-if positive, proceed to 3. b. 2nd cycle of BCG followed by sunitinib (as per week 1-14) c. alternative treatment plan per treating clinician 2. **No residual disease (Calendar 2)**: patient will proceed to maintenance BCG therapy per institutional standard a. alternative therapy may be chosen on maintenance at patient/physician discretion 3. **Disease progression or patient/clinician desire**: proceed to alternative treatment per standard of care
PHYSICAL								
History and Physical	x			X	X	x		
ECOG performance status	x			X	X	x		
Medication check	x			X	x	x		
Toxicity assessment				X	X	X		
LABORATORY/ STUDIES								
CBCPD	x			X	X	X		
Comprehensive panel	x			X		x		
Magnesium				X		x		
EKG	x							
Dipstick Urine		x	x					
Urine cytology*	x						x	
PT/PTT	x					x		
TSH	x							
MUGA Scan	x							
SPECIMEN SAMPLES								
Urine*		X[1]	X[1]	X		x	x	
Bladder biopsy							x	
Serum		X[1]	X[1]	x		x		
X-RAYS AND SCANS								
Chest radiograph	x							
CT or MRI abdomen/ pelvis or IVP	x							
Cystoscopy or report confirming eligibility	x							
Drug: Sunitnib				X				
Dispense BP log, Study drug info, and medication diary				X				

* voided urine cytology obtained in clinic, instrument urine cytology obtained in operating room

† Medical Oncologist will prescribe sunitinib and monitor for toxicity during treatment

[1] If BCG is given locally no specimens need to be obtained at the Week 1 and Week 6 visits.

Calendar 2: Maintenance BCG/Surveillance Schedule (+/- 3 weeks around each time point allowed)

	Month 3*		Month 6		Month 9	Month 12		Month 18		Month 24	
	Cysto	BCG#	Cysto	BCG#		Cysto	BCG#	Cysto	BCG#	Cysto	BCG#
Required studies											
PHYSICAL											
History and physical	x		x			x		x		x	
Toxicity assessment		x		x			x		x		x
LABORATORY											
Dipstick urine	x	x	x	x		x	x	x	x	x	x
Urine cytology	x		x			x		x		x	
TESTS											
Cystoscopy	x		x		x	x		x		x	

* after CR to BCG at 1st or 2nd induction course, # BCG is a 3 week course

14.0 MEASUREMENT OF EFFECT

For the purposes of this study, patients will be assessed for response at 3 months and 6 months. Continued response assessment during maintenance BCG will be as outlined by the study calendar above. Further imaging evaluation is as clinically indicated. Patients will be followed for a total of 2 years or 2 years following complete response.

14.1 DEFINITIONS

- **Recurrence/Residual disease**
  Recurrcent/residual urothelial carcinoma of the lower urinary tract is defined as any evidence of tumor by biopsy and/or urine cytology within the urinary bladder or prostatic urethra proximal to the striated urethral sphincter. Upper tract urothelial carcinoma (ureters, renal pelvis) does not constitute recurrent disease. Exam under anesthesia at the time of biopsy should be normal. If not consider 3-dimensional axial imaging to evaluate for progression.
- **Progression (to muscle invasive disease)**
  This is defined as any tumor stage > T1 found on scheduled repeat biopsy at 3 or 6 months and any biopsy performed thereafter. Locally advanced disease identified on 3-dimensional axial imaging as tumor extension into the perivesical fat will also constitute disease progression.
- **Metastases**
  Evidence of disease outside the bladder (lymphadenopathy or metastatic site).
- **Urine Cytology**
  - Negative Urine cytology constitutes a negative test result
  - Positive Urine cytology constitutes evidence of disease
  - Any finding other than negative or positive will be considered negative
    - An inadequate specimen will be repeated
- **Cystoscopic biopsy**
  - In the absence of visible disease, random biopsies will be obtained at the discretion of the treating physician. Documentation of any urothelial carcinoma will constitute residual disease. Reactive changes, dysplasia, or other equivocal findings will be reviewed by the study team with the pathologist and treating physician to make a determination of residual disease. A completely negative biopsy will be considered no evidence of residual disease when combined with the results of the urine cytology study.
  - Cystoscopic biopsy should include an exam under anesthesia- if the clinician reports a concerning finding on exam, this should be confirmed by imaging to document recurrent or progressive disease.
- **Exam under anesthesia**
  - Normal: bladder mobile, no palpable bladder mass

- Abnormal may constitute any of the following
  - Fixed bladder
  - Palpable bladder mass
- **Findings on the prostate exam are not considered for normal or abnormal for the purpose of the study unless the clinician determines that abnormal prostate exam constitutes local extension of bladder cancer**

- **Imaging**
  - Follow-up imaging as clinically indicated.

14.2 GUIDELINES FOR DOCUMENTING RESIDUAL DISEASE, RECURRENCE, PROGRESSION, OR METASTASES

Residual/Recurrent disease

- **Will be assessed at 3 and 6 months, as clinically indicated (Exam under anesthesia should be normal- if not see progression)**

Urine cytology*	Cystoscopic Biopsy*	Determination
Negative/other	Negative	No residual disease
Negative/other	Positive	Residual disease
Positive	Positive	Residual Disease
Positive	Negative	Residual disease

Abnormal exam under anesthesia of the bladder requires follow-up imaging

Disease progression or metastases: assessed at 3 and 6 months and as clinically indicated

Cystoscopic biopsy	Exam under anesthesia	Other Tests	Determination
Negative	Negative	N/A	No progression
Negative	Positive	Confirmation by repeat imaging, biopsy or other tests as above	If confirmation negative, then no progression, If +, then progression or metastases depending on location- see defns
Positive ≤ stage T1	Negative	N/A	Residual/recurrent disease, no progression
Positive ≤ stage T1	Positive	Confirmation by repeat imaging, biopsy or other tests as above	If confirmation negative, then residual/recurrent disease, If +, then progression or metastases depending on location-see defns
Positive > T1	Negative	Further imaging may be warranted at the discretion of the treating clinician	Progression
Positive > T1	Positive	Confirmation by repeat imaging, biopsy or other tests as above	Progression or metastases as defined by definition above

14.3 Response Criteria

Complete Response (CR):	Negative/other urine cytology + negative cystoscopic biopsy, negative exam under anesthesia (if positive, imaging must be negative)
Residual Disease:	A positive cytology and/or a positive cystoscopic biopsy, negative exam under anesthesia (if positive, imaging must be negative)
Progressive Disease (PD):	A biopsy demonstrating > stage T1 bladder tumor. A positive exam under anesthesia confirmed by imaging constitutes progression.
Metastases:	A confirmed site of disease by definitions above of urothelial malignancy outside the bladder.

14.4 Duration of Response

- Complete response assessed in every subject receiving at least one dose of sunitinib at 3 months. This will be determined as a percentage of the patients.
- Complete response will be assessed in all those patients undergoing a second cycle of BCG followed by SUNITINIB.
    - Those responding to an initial course and going to maintenance therapy will not be evaluated for CR at 6 months
    - Those patients unable to receive a second induction course of BCG followed by sunitinib will not be evaluated for CR at 6 months
- Recurrence free survival:
    - Recurrence definition as above
    - Assessed from time of study enrollment until recurrence or 2 years
    - Patients receiving a second induction course are assumed to have residual disease, not recurrence
        - Recurrence free survival is therefore assessed from study enrollment until recurrence or two years
    - Assessed in those patients with intact bladder only
    - Assessed only in those completing one induction course of BCG and receiving any sunitinib
- Progression free survival:
    - Progression definition as above
    - Assessed from time of study enrollment until progression or 2 years
    - Patients receiving a second induction course are assumed to have residual disease

        - Progression free survival is therefore assessed from study enrollment until progression or two years
    - Assessed in those patients with intact bladder only
    - Assessed only in those completing one induction course of BCG and receiving any sunitinib
- Metastases free survival
    - Definition above
    - Assessed in those patients completing one induction course of BCG and any sunitinib
    - Assessed from time of study enrollment to disease or two years

15.0 REGULATORY AND REPORTING REQUIREMENTS

- The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 will be utilized for adverse event reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 3.0. A list of adverse events that have occurred or might occur can be found in Sections of Pharmaceutical Information for SUNITINIB and BCG.

- SAE Definition. A SAE is any adverse event, without regard to causality, that is life-threatening or that results in any of the following outcomes: death; in-patient hospitalization or prolongation of existing hospitalization; persistent or significant disability or incapacity; or a congenital anomaly or birth defect. Any other medical event that, in the medical judgment of the Principal Investigator, may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above is also considered an SAE. A planned medical or surgical procedure is not, in itself, an SAE. Also specifically excluded from this definition of SAE is any event judged by the Principal Investigator to represent progression of the malignancy under study, unless it results in death within the SAE Reporting Period.

- SAE Reporting Period. The SAEs that are subject to this reporting provision are those that occur from after the first dose of the study drug through 28 days after discontinuation of study drug(s).

15.1 EXPEDITED ADVERSE EVENT REPORTING

- Expedited reports are submitted via an adverse event reporting form to the IRB which will be created as part of the clinical report forms used for the study. The adverse event will also be reported to Pfizer via fax as well as a Medwatch form. Those AEs that do not require expedited reporting must be reported in routine study data submissions. AEs reported in

expedited review must **also** be reported in routine study data submissions including the Data and Safety Monitoring report.

- Expedited Reporting Guidelines –Reporting Requirements for Adverse Events That Occur Within 28 Days of the Last Dose of the Investigational Agent.

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5[2]	Grades 4 & 5[2]
				Unexpected		Expected			
	Unexpected & Expected	Unex-pected	Expected	with Hospitali-zation	without Hospitali-zation	with Hospitali-zation	without Hospitali zation	Un-expected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	10 Calendar Days

[1] **Adverse events with attribution of possible, probable, or definite that occur greater than 28 days after the last dose of treatment require reporting as follows:**

IRB 24-hour notification followed by complete report within 5 calendar days for:

- Grade 4 and Grade 5 unexpected events

IRB 10 calendar day report:

- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 5 expected events

[2] Although an IRB 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

Note: All deaths on study must be reported using expedited reporting regardless of *causality. Attribution to treatment or other cause should be provided.*

- Expedited AE reporting timelines defined:

➢ "24 hours; 5 calendar days" – The investigator must initially report the AE within 24 hours of learning of the event followed by a complete report within 5 calendar days of the initial 24-hour report.

➢ "10 calendar days" - A complete report on the AE must be submitted within 10 calendar days of the investigator learning of the event.

- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of designation as expected or unexpected and attribution.
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported.
- Use the protocol number and the protocol-specific patient ID provided during trial registration on all reports.
    - **Expected adverse events** are identified in Sections above.
- For **Hospitalization** only – Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitated hospitalization (or prolongation of existing hospitalization) must be reported regardless of designation as expected or unexpected and attribution.

Serious Adverse Event (SAE) Reporting to Pfizer and The University of Michigan

Within 24 hours of first awareness of the event (immediately if the event is fatal or life-threatening), the Principal Investigator at the site of the event will report to the University of Michigan any Serious Adverse Event ("SAE," as defined above) that occurs during the SAE reporting period (from after the first dose of the study drug through 28 days after discontinuation of study drug).

Within 24 hours of first awareness of the event (immediately if the event is fatal or life-threatening), Principal Investigator will report to the Pfizer by facsimile any Serious Adverse Event ("SAE," as defined below) that occurs during the SAE reporting period (as defined below) in a Study subject assigned to receive the Pfizer Product. Principal Investigator will report such SAEs using an FDA MEDWATCH form and the Serious Adverse Event Fax Cover Sheet provided by Pfizer. SAEs should be reported as soon as they are determined to meet the definition, even if complete information is not yet available.

SAE Reporting Period. The SAEs that are subject to this reporting provision are those that occur from after the first dose of the Pfizer Product through 28 days after discontinuation of the Pfizer Product.

Follow-Up Information. Institution will assist Pfizer in investigating any SAE and will provide any follow-up information reasonably requested by Pfizer.

Regulatory Reporting. Reporting an SAE to Pfizer does not relieve Institution of responsibility for reporting it to regulatory authorities, as required.

15.2 DATA REPORTING

- All data must be entered in "real time" such that all data are current. A study database will be created by the Clinical Trials Office of the Department of Urology for this purpose.

Responsibility of the Principal Investigator

- The Principal investigator will be the single liaison with Pfizer. The Principal Investigator is responsible for the coordination, development, submission, and approval of the protocol as well as its subsequent amendments. The protocol must not be rewritten or modified by anyone other than the Principal Investigator. There will be only one version of the protocol.
- All reporting requirements to the IRB / Pfizer are the responsibility of the Principal investigator.
- The Principal Investigator is responsible for the timely review of Adverse Events (AE) to assure safety of the patients.
- The Principal Investigator will be responsible for the review of and timely submission of data for study analysis.
- Any manuscripts reporting the results of this clinical trial will be provided to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 14 days from the date of receipt for review. Copies of abstracts will be provided to Collaborator(s) for courtesy review as soon as possible prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings.

16.0 STATISTICAL CONSIDERATIONS

16.1 STUDY DESIGN/ENDPOINTS

The primary objective of this trial is to estimate the complete response rate in patients with high-risk non-muscle invasive bladder cancer treated with intravesical bacillus Calmette Guerin followed by daily oral sunitinib for 4 weeks as assessed by urine cytology, cystoscopic biopsy, and exam under anesthesia. If the response rate is 55% or less, there would be little interest in pursuing this therapy in further studies. In this case, we would like to terminate the trial early and consider a new therapy. If the response rate is 75% or more, further study would be proposed based on the estimates produced in this trial. To minimize the number of patients treated, the Minimax two-stage accrual design [Controlled Clinical Trials 10:1-10 1989] has been adopted.

We will accrue 24 high-risk non-muscle invasive bladder cancer patients. If less than 16 responses are seen, the trial will stop. If 16 or more responses are seen, an additional 12 patients will be entered. If 25 or more of the 36 evaluable patients achieve a complete response, then further studies will be proposed.

This trial design provides 80% statistical power at the 5% significance level. If the response rate was as low as 55%, there would be a 83% chance of stopping the trial after just 24 patients and only a 4.9% chance of going on to stage two (false positive error). However if the true response rate was 75%, there would only be a 12% chance of stopping the study early and a 19.9% chance of rejecting the therapy (false negative error). Evaluable patients will include all patients who receive at least one dose of sunitinib. Patients who are removed from the study before treatment with sunitinib with be replaced.

16.2 Analyses

The primary endpoint for this study will be the complete response rate. This rate will be reported along with 95% confidence intervals.

This study has several secondary endpoints. Response rates at 6 months will be reported with 95% confidence intervals for patients with an intact bladder. Kaplan-Meier estimates will be used to describe recurrence-free survival, including 2-year recurrence-free survival estimates. Toxicity of this therapy will be described, both overall and by grade. Toxicity rates will be tabulated by type and category.

Correlation of changes in VEGF, VEGFR, p53, and other cytokine expression to response will be explored. Markers will be grouped based on terciles of the distribution. Bivariate relationships between the expression level and response status will be assessed with the Mantel-Haenszel chi-square test. Potential analyses will include logistic regression with an outcome of response and Kaplan-Meier methods for time to recurrence. Differences in time to recurrence by expression level will be illustrated by Kaplan-Meier plots and tested using the log-rank test. Due to the sample size and the number of factors we will be statistically testing, these analyses will be considered exploratory until confirmed in a larger, independent, clinical trial.

16.3 Patient Accrual

Based on previous experience, the accrual to this trial is expected to be 3 eligible patients per month. Thus, the accrual period for the first stage is expected to be 8 months. The second stage is expected to take an additional 3 months to accrue the final 12 patients.

16.4 Reporting and Exclusions

16.4.1 EVALUATION OF TOXICITY. All patients will be assessable for toxicity from the time of their first treatment with study drug.

16.4.2 EVALUATION OF RESPONSE. All eligible patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are taken off study. Evaluation of response will be performed as outlined in Section 14 of the protocol.

All of the patients who met the eligibility criteria and receive at least one dose of sunitinib should be included in the main analysis. All conclusions should be based on all eligible patients. Sub analyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

17. DATA MANAGEMENT AND MONITORING:

17.1 DATA COLLECTION/ENTRY:

Clinical report forms will be developed by the principal investigator and study coordinator for data collection and entered into a password protected database which will be created at the initiation of the trial.

Adverse events, including all toxic effects of treatment, will be tabulated, individually summarized by body system and to severity or toxicity grade. See section 15 for adverse event reporting.

17.2 DATA SECURITY AND CONFIDENTIALITY:

To ensure security and confidentiality, participant names are not part of the research record. Participant initials, date of birth and a study-specific identification number are the sole identifiers. Physical security and systematic backup for the database will occur. Access to data rigorously complies with HIPAA requirements, governed by HIPAA's "minimum necessary" principle. Source documentation will be available to support the computerized database.

17.3 QUALITY ASSURANCE/DATA AND SAFETY MONITORING

The University of Michigan Comprehensive Cancer Center Data and Safety Monitoring Board (UMCCC DSMB) is the DSMB for this study responsible for monitoring the study's scientific progress, and accrual and any serious adverse events.

17.3.1 Data Safety and Monitoring:

There will be scheduled meetings that will be conducted every 3 months or more frequently depending on the activity of the study. These meetings will include the principal investigator, study coordinator and if available the Co-Investigators and study statistician.

During these meetings the investigators will discuss matters related to:

1. Safety of protocol participants (AE reporting).
2. Validity and integrity of the data.
3. Enrollment rate relative to expectation, characteristics of participants
4. Retention of participants, adherence to protocol (potential or real protocol violations).
5. Data completeness.

These meeting are to be documented by the site coordinator, using the Protocol Specific Data and Safety Monitoring Report (DSMR). The reports will be signed by the site principal investigator and submitted to the UMCCC DSMB on a quarterly basis with other pertinent documents. The report generated by the DSMB will be submitted to the IRB according to institutional standards.

The Study Coordinator assigned to the trial will be responsible for completing the Protocol Deviation Form. The reports will be signed by the principal investigator and submitted to the UMCCC DSMB on a quarterly basis with the DSMR.

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APPENDICIES

APPENDIX A: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
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).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active 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.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B: NURSING PROTOCOL FOR ADMINISTRATION OF INTRAVESICAL BCG (BACILLUS CALMETTE-GUERIN)

1. Obtain urinalysis (midstream urine collection) and vital signs (including temperature) before each instillation.
   - urinalysis should be negative for signs of urinary tract infection (wbc, nitrate, bacteria) before instillation
   - gross hematuria is a contraindication to therapy
2. Medication should be ordered from pharmacy once established that patient can proceed with instillation (confirm signed MD order on file prior to patient appointment)
3. Use precautions during instillation – chemo gown, gloves and wear a TB mask. (refer to infection control guidelines)
4. Ensure right patient, route, dose and date prior to instillation
5. Explain procedure to patient before beginning instillation
6. Insert 12 French Coude catheter for men and French straight catheter for females. Drain bladder and document residual.
7. Instill solution of 50cc BCG/Normal Saline into the bladder
8. Remove foley catheter and prevent solution from touching patient's skin as this can cause local irritation.
9. Patient should be instructed to hold medication/urine for 2 hours.
10. Dispose of all contaminated materials in a hazardous waste bucket.
11. Wipe down all surfaces with the Sani-Wipe cloths.
12. Patient should be advised to sit down when he/she urinates (to avoid splashing of urine) for 6 hours post treatment. He /she should place 2 cups of household bleach in the toilet water and allow the bleach to remain for 20 minutes prior to flushing toilet, for 6 hours post treatment. Patient should be advised to cleanse skin with soap and water if incontinent of urine/urine spashes on skin surfaces.
13. Patient should be advised symptoms such as low-grade fever, chills, a flu-like malaise, and joint aches are signs that the body is responding to the BCG. Patients should contact the clinic staff/MD is fever noted above 101.5, rash or cough noted or other abnormal urinary concerns noted.
14. Instillations should be spaced 7 days apart.
15. Document all pertinent information after each instillation including:
    a. Date
    b. Time
    c. Route and catheter size
    d. Dosage
    e. Assessment of patient
    f. Signature

APPENDIX C: MEDICATION DIARY

PATIENT INITIAL /MRN: _____ **CYCLE #:_____**

*Please be sure to fill this out every day and bring this with your study drug bottles (empty or not) to your clinical appointment. Please be sure to **give** this form and the study drug bottles to research nurse or research assistant in the clinic.*

	Date	**# tablets taken**	**Time Taken**
Day 1			
Day 2			
Day 3			
Day 4			
Day 5			
Day 6			
Day 7			
Day 8			
Day 9			
Day 10			
Day 11			
Day 12			
Day 13			
Day 14			
Day 15			
Day 16			
Day 17			
Day 18			
Day 19			
Day 20			
Day 21			
Day 22			
Day 23			
Day 24			
Day 25			
Day 26			
Day 27			
Day 28			

Have you consumed grapefruit juice while taking study drug? _____

Patient Signature: _____ Date: _____

The following pill count should be filled out by the Hospital Staff:

# of study drug capsules remaining in the bottle: _____

Name/Signature of the person doing the pill count: _____

Date of the clinic visit: _____

APPENDIX D: SITE DRUG REQUEST FORM

TO: **Clinical/Scientific Operations – US Oncology**

ATTN: **Taina Lopez, Clinical Study Manager**

FAX: **212.309.0571**

RE: **Sunitinib Malate (SU011248 L-Malate Salt) Drug Request**

Protocol Title: **Phase II study of intravesical bacillus Calmette-Guerin followed by oral sunitinib for the treatment of high risk non-invasive transitional cell carcinoma of the urinary bladder**

Principal Investigator: **Alon Z. Weizer , M.D.**

Pfizer Protocol Number: **GA6181UO**
Institution Protocol Number:
FDA IND Number:

Institution Name: _____

Requestor Name: _____

_____ _____
(Phone) **(Fax)**

Shipping Address: _____

Initial Shipment? ☐ **Yes** ☐ **No** **IRB Approval Date:** _____

Drug and Strength		Number of Bottles
Sunitinib Malate Capsules (30 capsules/bottle)	☐ **50mg**	
	☐ **25mg***	
	☐ **12.5mg***	

** **Date Ordered:** _____

Date Required: _____

* Please note that a **37.5mg** dose should be supplied to the patient as **1 x 25mg cap AND 1 x 12.5mg cap**

** Please allow a minimum of 10-15 business days for initial shipment and 7-10 business days for subsequent shipments. If you have further questions, please call Taina Lopez at (212) 733-9223.

APPENDIX E: SERIOUS ADVERSE EVENT FAX COVER SHEET

Use this fax cover sheet to fax Serious Adverse Events for Investigator-Initiated Research studies.

Fax the completed MedWatch Form FDA 3500A-Mandatory Reporting which can be obtained from the FDA website: www.fda.gov/medwatch/getforms.

The MedWatch Form should include the following information in block 5 of the Adverse Events section:
The complete clinical course of the patient receiving Pfizer drug
The causality assessment for each Serious Adverse Event
The action taken for each study drug and for each Serious Adverse Event
The outcome for each Serious Adverse Event

This cover sheet MUST be attached with each completed MedWatch form. Do not substitute forms/reports or submit additional documentation other than what is required.

Do not fax these forms to any additional fax numbers other than the one listed below.

TO: *Pfizer U.S. Clinical Safety*	
FAX: *1-866-997-8322*	
FROM:	DATE:
TELEPHONE:	FAX:
NUMBER OF PAGES (INCLUDING COVER SHEET):	

PRODUCT	Sutent
PFIZER REFERENCE NUMBER	GA6181UO
STUDY TITLE	*Phase II study of intravesical bacillus Calmette-Guerin followed by oral sunitinib for the treatment of high risk non-invasive transitional cell carcinoma of the urinary bladder*
PATIENT NUMBER	
INVESTIGATOR	Alon Z. Weizer , MD

APPENDIX F: SELECTED POTENTIAL CYP3A4 DRUG INTERACTIONS

SUBSTRATES		INHIBITORS		INDUCERS	
Generic Name	Trade Name	Generic Name	Trade Name	Generic Name	Trade Name
Anti-neoplastics: *e.g.* Docetaxel Gefitinib Irinotecan	Taxotere Iressa Camptosar	Anti-arrhythmics: *e.g.* Amiodarone Diltiazem Quinidine	Cordarone, Pacerone Cardizem, Dilacor XR Cardioquin	Aminoglutethimide	Cytadren
Anti-virals: *e.g.* Amprenivir Rifampin	Agenerase Rifadin	Anti-virals: *e.g.* Amprenavir Indinavir Nelfinavir Ritonavir	Agenerase Crixivan Viracept Norvir	Antibiotics: *e.g.* Rifabutin Rifampin	Rifadin Mycobutin
Anxiolytics: *e.g.* Diazepam Sertraline	Valium Zoloft	Cimetadine	Tagamet	Anticonvulsants: *e.g.* Carbamazapine Phenytoin Pentobarbital Phenobarbital	Tegretol Dilantin Nembutal Luminal
Cyclosporine	Sandimmune	Cyclosporine	Sandimmune	*Hypericum perforatum* (2)	St. John's Wort
Anti-infectives: *e.g.* Erythromycin Tetracycline	Erythrocin Sumycin	Antibiotics: *e.g.* Ciprofloxacin Clarithromycin Doxycycline Enoxacin Isoniazid Telithromycin	Cipro, Ciloxan Biaxin Adoxa, Periostat Penetrex Nydrazid, INH Ketek		
Steroids: *e.g.* Estrogens, conjugated Estradiol Progesterone	Premarin Climara Crinone	Imatinib	Gleevec		
Haloperidol	Haldol	Haloperidol	Haldol		
Cardiovascular agents:*e.g.* Digitoxin Quinidine	Crystodigin Cardioquin	Diclofenac	Cataflam, Voltaren		
Anti-hypertensives: *e.g.* Nicardipine Verapamil	Cardene Calan, Chronovera	Vasodilators: *e.g.* Nicardipine Verapamil	Cardene Calan, Chronovera		
Anesthetics: *e.g.* Ketamine Lidocaine	Xylocaine Diprivan	Anesthetics: *e.g.* Lidocaine Propofol	Xylocaine Diprivan		
Nefazodone	Serzone	Anti-depressants: *e.g.* Nefazodone Sertraline	Serzone Zoloft		
Cocaine		Anti-fungals: *e.g.* Itraconazole Ketoconazole Miconazole	Sporanox Nizoral Lotrimin, Monistat		
Ketoconazole	Nizoral	Caffeine			
Sildenafil	Viagra	Grapefruit juice (1)			
Albuterol	Ventolin				
Carbamazapine	Tegretol				
Lovastatin	Mevacor				

When drugs classified as 'substrates' are co-administered with ***Sunitinib***, there is the potential for higher concentrations of the 'substrate'. When ***Sunitinib*** is co-administered with compounds classified as 'inhibitors', increased plasma concentrations of Sunitinib is the potential outcome. The coadministration of 'inducers' would potentially lower plasma ***Sunitinib*** concentrations.