Phase II Study of Neoadjuvant Dose Dense Gemcitabine and Cisplatin (DD GC) In Patients with Muscle-Invasive Bladder Cancer

MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

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

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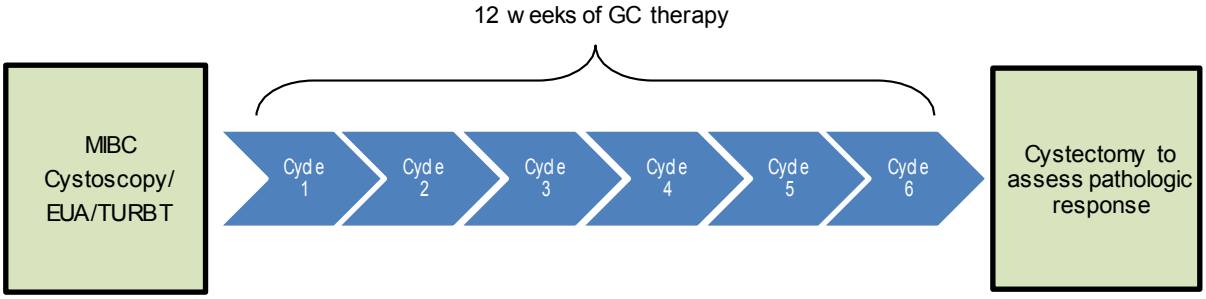
1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This is a Multicenter Phase II study of dose-dense (DD) gemcitabine and cisplatin (GC) neoadjuvant chemotherapy in patients with muscle-invasive bladder cancer (MIBC) who are candidates for radical cystectomy. Patients will receive six cycles of GC administered every 14 days. Gemcitabine 2,500 mg/m^2 will be administered intravenously on day 1 and cisplatin 35 mg/m^2 will be administered intravenously on days 1 and 2 of a 14 days cycle (with Peg G-CSF). A total of six cycles of therapy will be administered followed by radical cystectomy with bilateral pelvic lymph node dissection (PLND). The primary objective of this phase II trial will be to determine the pathologic response rate (< pT2) of this regimen.



2.0 OBJECTIVES AND SCIENTIFIC AIMS

2.1 Primary Objective:

- To define the pathologic response rate (<pT2) of neoadjuvant DD GC regimen in patients with MIBC.

2.2 Secondary Objectives:

- To determine the safety and tolerability of the DD GC regimen in patients with MIBC.
- To determine the progression-free survival in patients with MIBC treated with DD GC followed by radical cystectomy.

3.0 BACKGROUND AND RATIONALE

Bladder cancer is the second most common genitourinary malignancy. The American Cancer Society estimates 69,250 new cases and 14,990 deaths in the United States for the year 2011.[1] The prevalence of bladder cancer is estimated to be approximately 600,000 cases and management of this disease costs $3 billion in healthcare expenditure annually compared with $1 billion for prostate cancer. The most difficult patients to manage are those with muscle-invasive disease; despite surgery with curative intent (radical cystectomy and bilateral pelvic lymph node dissection), approximately 50% of patients with muscle-invasive bladder cancer will develop distant metastases and succumb to their disease.[2] Over the past two decades, attempts to improve outcomes have focused on the addition of perioperative chemotherapy in hopes of eradicating

micrometastatic disease and reducing the risk of relapse. Trials exploring chemotherapy in the adjuvant setting have yielded inconclusive results as these trials were largely underpowered and/or utilized suboptimal chemotherapeutic regimens.[3-5] Neoadjuvant cisplatin-based chemotherapy prior to radical cystectomy has been demonstrated to reduce the risk of relapse and improve overall survival (OS) in multiple clinical trials and a meta-analysis.

3.1 Neoadjuvant Cisplatin-Based Chemotherapy for MIBC Improves Outcomes

Cisplatin is the only chemotherapeutic agent associated with a survival benefit in any urothelial cancer disease state. In the neoadjuvant setting, a survival benefit with cisplatin-based combination chemotherapy has been confirmed in two large randomized clinical trials and a meta-analysis of over 3,000 patients.[6-8] These data clearly establish cisplatin-based neoadjuvant chemotherapy as the standard of care for patients with MIBC who are being considered for radical cystectomy.

The most commonly studied neoadjuvant regimen reported in the literature is MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin), a standard of care for patients with metastatic disease.[9] The Southwest Oncology Group (SWOG)-8710 trial randomized patients with stage T2–T4aN0 bladder cancer to receive either three cycles of MVAC followed by radical cystectomy or radical cystectomy alone.[10] Disease specific survival was superior for patients receiving neoadjuvant MVAC (HR=1.66, 95% CI, 1.22–2.45, p=0.002). There was a trend toward superior OS (HR=1.33, 95% CI, 1.00–1.76) for patients treated with MVAC as compared to patients managed with surgery alone, with an OS of 57% and 43% at 5 years, respectively (p=0.06). Furthermore, pathologic response to neoadjuvant chemotherapy predicted for clinical outcomes. Patients without residual disease (pT0) at cystectomy had an improved 5-year survival (85%) over those who had residual disease, and patients in the MVAC arm more frequently achieved pT0 status (38% vs 15%, p<0.001).[10]

Recently, updated long-term results from the MRC/EORTC randomized Phase III trial of neoadjuvant cisplatin, methotrexate, and vinblastine (CMV) reported improved outcomes associated with neoadjuvant cisplatin, methotrexate, and vinblastine (CMV) prior to definitive therapy for MIBC. Neoadjuvant CMV was associated with a 16% relative improvement in survival (p=0.037) and 23% relative improvement in metastasis-free survival (p=0.001) at 10 years.[11] Notably, the survival benefit observed with neoadjuvant chemotherapy in bladder cancer is similar to the survival benefit observed with adjuvant chemotherapy in early studies performed in breast and colon cancer (Table 1).

Table 1: Summary of Survival Benefit Associated with Perioperative Chemotherapy in Breast, Bladder, and Colon Cancer

	Breast *Lancet 1998*[12]	**Bladder** *Eur Urology 2005*[13]	**Colon** *J Clin Oncology 2004*[14]
	N=17,723	N=3,005	N=3,302
Abs. Difference in Survival (yrs)	7% (10)	5% (5)	7% (5)
HR, Disease-Free Survival	0.77	0.78	0.70

3.2 Role for Gemcitabine and Cisplatin in the Neoadjuvant Setting

The MVAC regimen has long represented a standard of care for the treatment of patients with advanced/metastatic urothelial cancer.[9] With the advent of newer agents, investigators focused on developing regimens with similar efficacy but less toxicity than MVAC. In a large randomized trial, the combination of gemcitabine and cisplatin (GC) proved to have similar efficacy and less toxicity than MVAC and now represents the standard of care for patients with metastatic urothelial cancer.[15] While tolerability of chemotherapy improved with the GC regimen, the efficacy of therapy (response and survival) for patients with metastatic urothelial cancer did not change substantially.

As GC is better tolerated and achieves similar response and survival rates to MVAC in metastatic urothelial cancer, it is frequently used as a substitute for MVAC in the neoadjuvant setting. However, GC has not been prospectively evaluated in the neoadjuvant setting. At MSKCC, pathologic response rate in 42 patients treated with neoadjuvant GC was retrospectively compared to pathologic response rate in 54 patients treated with neoadjuvant MVAC prior to definitive surgery.[16] Pathologic response rate, defined as eradication of muscle invasive disease (<pT2) at cystectomy, was similar for patients receiving GC (15/42; 36%, 95% CI 21-52%) and MVAC (19/54; 35%, 95% CI 23-49). Furthermore, achieving complete pathologic response (pT0) for patients treated with GC (11/42; 26%, 95% CI 14-42) was also similar to MVAC (15/ 54; 28%, 95% CI 16-42).

Patients treated with GC received 4 cycles of therapy on one of two 21-day dosing schedules for 12 weeks: 1.) a standard single dose schedule with gemcitabine 1000 mg/m^2 and cisplatin 70 mg/m^2 on day 1 and gemcitabine 1000 mg/m^2 on day 8; or 2.) a "split-dose" schedule with gemcitabine 1000 mg/m^2 and cisplatin 35 mg/mg^2 on day 1 and day 8. Under these two dosing schedules, the achieved median dose delivered for cisplatin was 91% and for gemcitabine was 90%. Treatment was well-tolerated. These data support the use of a 21-day schedule of GC in the neoadjuvant setting for MIBC. Unfortunately, despite the use of better tolerated neoadjuvant chemotherapy, outcomes have not significantly changed and a large proportion of patients ultimately recur. Novel neoadjuvant treatment strategies are needed to improve outcomes.

3.3 Rationale for Dose Dense Chemotherapy

Potential incremental benefits in disease-free survival (DFS) and OS have been observed in clinical trials utilizing higher doses (dose intense) and more frequent administration (dose dense) of chemotherapeutic agents.[17] This is especially true for women with high-risk breast cancer, where dose dense therapy has become a mainstay in the adjuvant setting.[18]

The Cancer and Leukemia Group B (CALGB) 9741 phase III randomized trial evaluated a dose-dense chemotherapy approach using concurrent doxorubicin and cyclophosphamide followed by paclitaxel in the adjuvant treatment of women with lymph node-positive early-stage breast cancer.[19] This trial demonstrated a significant improvement in DFS and OS in the dose-dense chemotherapy arm, which has subsequently become the adjuvant treatment standard for patients with early-stage breast cancer.[18]

Bonilla, et al. conducted a meta-analysis of randomized trials investigating dose-dense chemotherapy in non-metastatic breast cancer. Ten trials met the inclusion criteria and were classified into two categories based on trial methodology. Three trials enrolling 3,337 patients compared dose-dense chemotherapy with a conventional chemotherapy schedule using similar chemotherapeutic agents. Patients who received dose-dense chemotherapy

had longer OS (HR=0.84, 95% CI 0.72-0.98, p=0.03) and longer DFS (HR=0.83, 95% CI=0.73-0.94, p=0.005) than patients receiving similar chemotherapy on a conventional schedule. Seven trials enrolling 8,652 patients compared dose-dense chemotherapy with regimens that use standard intervals but with different agents and/or dosages in the treatment arms. Similar results were obtained for these trials with respect to OS (HR=0.85, 95% CI 0.75-0.96, p=0.01) and DFS (HR=0.81, 95% CI 0.73-0.88, p< 0.001).[18]

3.4 Higher Dose Density of Cisplatin May be Associated with Improved Outcomes in Advanced Urothelial Cancer.

In metastatic urothelial cancer, Sternberg, et al. were first to report a potential benefit of high dose intensity chemotherapy in a phase III randomized trial of high dose MVAC (HD MVAC) plus G-CSF versus conventional MVAC.[20] In actuality, the doses of MVAC were identical in both arms, but the "high dose" arm was administered at 2 week intervals rather than 4 week intervals for standard MVAC. After a median follow up of 7.3 years, HD MVAC was associated with a significant relative reduction in the risk of progression (p= 0.017) and death (p=0.042) compared to MVAC.[21]

Bamias, et al. recently reported the results of a phase III randomized trial evaluating dose dense MVAC (DD MVAC) versus DD GC in patients with inoperable or recurrent urothelial cancer.[22] Patients were randomized to receive MVAC (30 mg/m^2; 3 mg/m^2; 30 mg/m^2; 70 mg/m^2) or GC (gemcitabine 2500 mg/m^2 day 1 plus cisplatin 35 mg m^2 days 1 and 2 with G-CSF) every two weeks for a planned 6 cycles. Overall response rate and survival were similar for both treatment arms: 65% and median 18.4 months respectively for patients treated with DD GC and 63% and median 18.0 months respectively for patients treated with DD MVAC. However, DD GC was better tolerated than DD MVAC, leading the authors to conclude DD GC could represent another treatment standard for advanced disease. Importantly, the OS reported for both arms in this trial using two dose dense regimens appears to be substantially better than previously reported with other cisplatin-based regimens administered in standard schedules, suggesting a benefit to dose dense chemotherapy.[15]

These data suggest that higher dose density cisplatin may be associated with improved response rate and survival in advanced urothelial cancer, and thus, supports its study in the neoadjuvant setting (Table 2).

Table 2. Comparison of Cisplatin-Based Studies Utilizing Different Dose Densities in the Treatment of Metastatic Bladder Cancer

Regimen	Dose Density of Cisplatin (mg/m^2/week)	N=	Overall Response Rate (%)	Median OS (months)
GC[15]	17.5	203	49.4	14
MVAC[15]	17.5	202	45.7	15.2
MVAC[21]	17.5	129	58	14.9
GC[23]	17.5	315	46	12.8
DD MVAC[21]	35	134	72	15.1
DD MVAC[24]	35	118	62.7	18.4
DD GC[24]	35	57	65.3	18.0

3.5 Neoadjuvant Dose Dense Cisplatin-Based Chemotherapy in MIBC

To date, no prospective trials have evaluated dose dense chemotherapy in the neoadjuvant setting in MIBC. However, two retrospective experiences using MVAC were recently presented at the 2011 ASCO Genitourinary Cancers Symposium and the 2011 ASCO Annual Meeting that suggest a dose dense approach may improve clinical outcomes (Table 3).

Table 3. Retrospective Experiences Using Dose-Dense MVAC

Study	Regimen	Cisplatin Dose Density (mg/m^2/week)	N=	CR	2 year DFS
Blick et al. 2011 GU ASCO[25]	DD MVAC x 3-4 cycles	35	80	43%	65%
Elmongy et al 2011 ASCO[26]	DD MVAC x 4-6 cycles	35	12	50%	100%

These retrospective data suggest that neoadjuvant dose dense chemotherapy may increase response rate (43-50% CR rate for DD MVAC vs 38% for standard MVAC), in a manner similar to that observed with its use in advanced disease, further strengthening the rationale for the prospective approach outlined in this clinical trial.

3.6 Rationale for Neoadjuvant DD GC in MIBC

Neoadjuvant GC is similar to MVAC with regards to pathologic response rates and offers an advantage with respect to tolerability. Administering standard doses of cisplatin-based chemotherapy over a shorter period of time (i.e. higher dose density) potentially improves response rate and offers a survival advantage without compromising safety or tolerability.

The current trial seeks to explore the intensified regimen of gemcitabine and cisplatin in the neoadjuvant setting in patients with MIBC. This trial is supported by the following rationale:

- Neoadjuvant cisplatin-based therapy has improved survival over cystectomy alone in patients with MIBC.
- Since the survival benefit is greatest in patients achieving response to chemotherapy, strategies to increase response rates of active regimens is warranted.
- Dose-dense cisplatin chemotherapy increases response rate for patients with metastatic bladder cancer.
- DD GC is the best tolerated dose dense regimen.
- DD GC is a logical candidate for prospective study in the neoadjuvant setting.

3.7 Pathologic Response to Chemotherapy as an Endpoint of Clinical Efficacy

3.7.1 Pathologic Response (<pT2)

Muscle-invasive bladder cancer, defined as pathologic evidence of muscle invasion (pT2) on biopsy specimen, is the major indication for neoadjuvant chemotherapy prior to radical cystectomy. Pathologic response to neoadjuvant chemotherapy can be defined as absence of any residual muscle invasive disease at the time of cystectomy (< pT2) and includes pT1, pTcis, pTa, and T0 disease. Due to the multi-focal nature of this disease, it is very common at both pre-chemotherapy and post-chemotherapy evaluations to see pre-existing and/or residual superficial transitional cell carcinoma such as Tcis, Ta or T1 disease (frequently collectively defined as < pT2). The likelihood of residual superficial disease is also directly related to the extent of the TURBT prior to neoadjuvant chemotherapy. Superficial disease, and in particular Tcis, is typically unresponsive to chemotherapy, non-life threatening, and frequently included within the definition of major chemotherapy response. The prognostic value of defining response to neoadjuvant chemotherapy in MIBC as <pT2 in contrast to solely pT0 (complete pathologic response) was first shown in an analysis by Splinter et al. of 147 patients treated with neoadjuvant chemotherapy prior to radical cystectomy at eight different centers.[27] This study demonstrated that patients with MIBC who achieved < pT2 (including pT0, pTcis, pTa, and pT1) after neo-adjuvant chemotherapy achieved 75% survival at 5 years in contrast to 20% survival for those whose tumors still harbored continued muscle-invasion ($\geq$ pT2 residual disease).

The comparable survival rates of patients achieving pathological complete response (pT0) and patients achieving partial pathologic response (<pT2) has been validated in a prior, independent study at MSKCC.[28] In a trial of 111 patients treated with neo-adjuvant MVAC at MSKCC, outcome analysis showed a similar survival benefit from chemotherapy for those patients achieving < pT2 (pT0, pTa, pTcis, and pT1) after neoadjuvant chemotherapy and for those achieving the status of pT0. This experience confirms the findings of Splinter et al.

3.7.2 Rationale for Response Rates used in Study Design

This trial will aim to test a 20% improvement on the average pathologic response rate reported with conventional schedule cisplatin-based neoadjuvant chemotherapy regimens of approximately 35%. Thus, a "promising" pathological response rate for DD GC of 55% would warrant further study of this regimen. The average pathologic response rate associated with conventional schedule cisplatin-based chemotherapy was determined by data from a prior MSKCC retrospective study and two large intergroup randomized neoadjuvant trials.[6,8,29] At MSKCC, the pathological response rate (<pT2) was 36% for patients treated with neoadjuvant GC and 35% for patients treated with neoadjuvant MVAC. In the MRC/EORTC trial, the pathologic response rate was 27% (95% CI 21-33) for the 246 patients receiving neoadjuvant chemotherapy by an intent-to-treat analysis. In the SWOG 8710 trial, the pathologic response rate was 32% (95% CI 25-40) for the 153 patients randomized to neoadjuvant MVAC chemotherapy, also using an intent-to-treat analysis.

It is well known that pathologic response rate can be subject to the completeness of the initial transurethral resection of the bladder tumor (TURBT) at diagnosis, and thus, can vary based on the surgeon performing the procedure. For example, in the SWOG 8710 randomized trial, 15% of patients randomized to surgery alone had a complete pathologic response at the time of cystectomy. Thus, the pathologic response rate after neoadjuvant chemotherapy can also similarly vary based on the completeness of the initial TURBT.

However, the MSKCC experience reported by Dash et al. demonstrates similar pathologic outcomes to those reported by prospective randomized studies.

This protocol, like our prior MSKCC neoadjuvant studies and those at other centers, will examine pathologic response (<pT2) after chemotherapy as the endpoint of efficacy.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This is a multicenter phase II study of neoadjuvant DD GC in patients with MIBC prior to radical cystectomy. Patients with biopsy proven MIBC who are candidates for radical cystectomy will be enrolled and will receive six 14-day cycles of DD GC. Toxicity and interval response will be assessed during treatment. Following treatment, patients will undergo radical cystectomy and bilateral pelvic lymph node dissection and the surgical specimens will be assessed for pathologic response to therapy. Patients will be followed for five years or until disease recurrence/progression.

4.2 Intervention

Patients will receive six cycles of GC administered every 14 days followed by radical cystectomy. Gemcitabine 2,500 mg/m^2 will be administered intravenously on day 1 and cisplatin 35 mg/m^2 will be administered intravenously on days 1 and 2 every 14 days for 6 cycles (for a total of 12 weeks) with G-CSF support. The primary objective of this phase II trial will estimate the pathologic response rate of this regimen.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1 Gemcitabine (GEMZAR®):

5.1.1 Gemcitabine is a pyrimidine analogue of deoxycytidine in which the deoxyribose moiety contains 2 fluorine atoms at the 2'position. The drug acts as an inhibitor to ribonucleotide reductase and inhibition of DNA synthesis may result in perturbations of deoxynucleotide pools and interference with DNA chain elongation. The drug is cell-cycle specific and blocks cells in the G1/S interface. Cytotoxicity is schedule dependent and increases with increasing duration of exposure. The drug is rapidly eliminated from plasma, owing mainly to deamination. Renal clearance of drug is less than 10% of parent drug.

5.1.2 Availability
The drug is supplied as either a 200 mg or 1 gram lyophilized powder in a 50mL sterile single vial for reconstitution.

5.1.3 Administration
The drug is administered via a freely running intravenous catheter per local institutional guidelines.

5.1.4 Toxicity
Toxicities include nausea, vomiting, alopecia, stomatitis, anorexia, fatigue, elevations of hepatic transaminases, rash, flu-like symptoms, edema, constipation, paresthesias, hypersensitivity reactions, phlebitis, proteinuria, hematuria, reversible myelosuppression, rarely interstitial pneumonitis and ARDS, and rarely kidney damage.

5.2 Cisplatin:

5.2.1 Cisplatin is a planar inorganic metal salt that function as an alkylating agent. In aqueous solution, the drug is equated to a diaquo species as the two chloride groups leave the molecule. The reactive diaquo species binds to N7 residues of guanine bases on DNA resulting in strand scission, and intra- and inter-strand crosslinking.

5.2.2 Availability
Cisplatin is commercially supplied as a lyophilized powder in 10 mg and 50 mg vials, and stored at room temperature. The drug should be reconstituted using 10 ml and 50 ml respectively of sterile water for injection, USP, to yield a concentration of 1 mg/ml. Prereconstituted multidose vials of 100 mg are also available. Once the multidose vial has been entered, the remaining cisplatin is stable for 28 days when protected from light.

5.2.3 Administration
Route of Administration: Cisplatin should be given IV drip per local institutional guidelines. Needles and IV sets using aluminum should not be used in the administration of cisplatin.

5.2.4 Toxicity
Potential side effects from cisplatin include cumulative nephrotoxicity, myelosuppression, nausea, and vomiting. Ototoxicity, manifested by tinnitus and/or high frequency hearing loss, is significant. Anaphylactic-like reactions to cisplatin have been reported. Facial swelling, bronchospasm, tachycardia, and hypotension may occur within minutes of cisplatin administration. Other side effects include fatigue, anorexia, weight loss, diarrhea, serum electrolyte disturbances including hyponatremia, hypomagnesemia, and hypocalcemia, edema of the lungs or extremities, vascular toxicities, neurotoxicity including cerebral infarction, seizures and dizziness, ocular toxicity with visual disturbances, peripheral neuropathy, autonomic neuropathy, infertility, muscle cramps, and hepatic toxicity. Other rare side effects include cardiac abnormalities, hiccoughs, elevated serum amylase, rash, and alopecia. Local soft tissue injury has been reported following extravasation of cisplatin. Based on reported toxicities from completed/ongoing trials utilizing NCI Common Toxicity Criteria.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

- Muscle invasive urothelial carcinoma of the bladder histologically confirmed at MSKCC or participating site. (Urothelial carcinoma invading into the prostatic stroma with no histologic muscle invasion is allowed, provided the extent of disease is confirmed via imaging and/or EUA.)
- Clinical stage T2-$T4_a$ $N_{0/X}$ M0 disease
- Medically appropriate candidate for radical cystectomy, as per MSKCC or participating site Attending Urologic Oncologist
- Karnofsky Performance Status ≥ 70%
- Age ≥ 18 years of age
- Required Initial Laboratory Values:
  - Absolute Neutrophil Count ≥ 1000 cells/mm^3
  - Platelets ≥ 100,000 cells/mm^3
  - Hemoglobin ≥ 9.0g/dL
  - Bilirubin ≤ 1.5 the upper limit of normal (ULN) for the institution

- Aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 2.5 x ULN for the institution
- Alkaline phosphatase ≤ 2.5 x ULN for the institution
- Serum creatinine ≤ 1.5 mg/dL
- Estimated glomerular filtration rate ≥ 60 ml/min/1.73m^2 using the CKD-EPI equation: eGFR = 141 x min(Scr/k, 1)^a x max(Scr/k, 1)$^{-1.209}$ x 0.993^{Age}
  - x 1.018 [if female] x 1.159 [if black]
    Scr is serum creatinine, k is 0.7 for females and 0.9 for males, a is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/k or 1, and max indicates the maximum of Scr/k or 1
- If female of childbearing potential, pregnancy test is negative

6.2 Subject Exclusion Criteria

- Prior systemic chemotherapy (prior intravesical therapy is allowed)
- Prior radiation therapy to the bladder
- Evidence of NYHA functional class III or IV heart disease
- Serious intercurrent medical or psychiatric illness, including serious active infection
- Preexisting sensory grade ≥ 2 neuropathy
- Preexisting grade ≥ 2 hearing loss
- Major surgery or radiation therapy < 4 weeks of starting study treatment
- Concomitant use of any other investigational drugs
- 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, cerebrovascular accident, or transient ischemic attack
- Ongoing cardiac dysrhythmias of NCI CTCAE Version 4.0 grade ≥ 2
- Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness or other active infection
- Concurrent treatment on another clinical trial; supportive care trials or non-treatment trials, e.g. QOL, are allowed
- Pregnancy or breast-feeding. Patients must be surgically sterile, postmenopausal, 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. Male patients must be surgically sterile or agree to use effective contraception.

7.0 RECRUITMENT PLAN

Eligible patients with urothelial carcinoma of the bladder will be recruited from the Genitourinary Oncology and Urology Services at MSKCC, University of North Carolina at Chapel Hill, and New York University. Every attempt will be made to recruit women and minorities to participate in this study. Participation is voluntary. The consenting physician will inform patients of their diagnosis, current treatment options including standard treatment, and the risks, benefits, and experimental nature of this treatment program. Approximately a total of 46 evaluable patients will participate in the trial with about 26 patients from MSKCC and 20 from University of Carolina at Chapel Hill and New York University. Accrual goals are feasible because neoadjuvant chemotherapy is the standard of care in our center. MSKCC performs over 200 cystectomies per year (130 in patients with MIBC) and our group has published multiple studies of neoadjuvant chemotherapy in patients with bladder cancer.

8.0 PRETREATMENT EVALUATION

The following studies must be completed within 14 days prior to initiation of treatment (unless otherwise indicated):

- Complete history and physical examination
- Vital signs including temperature, blood pressure, respiratory rate, heart rate, weight, and height
- Karnofsky Performance Status
- Complete blood count (CBC) with differential and platelets
- Comprehensive panel (Na, K, Cl, CO2, BUN, Cr, Ca, glucose, AST, ALT, TP, Albumin, ALP, BT)
- Coagulation profile (PT/INR/PTT)
- Urinalysis
- Pregnancy test in women of childbearing potential
- Chest X-ray (a CT of chest may be performed instead if clinically relevant) within 30 days of enrollment
- EKG
- Baseline CT scan and/or MRI of the abdomen and pelvis within 30 days of enrollment. Diffusion-weighted MRI is preferred.
- Cystoscopy/Transurethral Resection of Bladder Tumor (TURBT) within 60 days of enrollment to define clinical stage. Biopsies from that procedure must have confirmed invasive urothelial carcinoma of the bladder.

9.0 TREATMENT/INTERVENTION PLAN

Dose and Schedule of GC

	2 weeks = 1 cycle		
	Day 1	Day 2	Day 3
Gemcitabine	2,500 mg/m2 IVPB over approximately 1½ - 2 hrs		
Cisplatin	35 mg/m2 IVPB over approximately 30 mins	35 mg/m2 IVPB over approximately 30 mins	
Peg G-CSF			6 mg SC 1-2 liters of normal saline or suitable alternative

Treatment will be administered for a total of 6 cycles with each cycle given at 2 week intervals if criteria for initiation of subsequent cycles are met.

9.1 Gemcitabine and Cisplatin (GC)

Gemcitabine and Cisplatin will be administered on day 1 and Cisplatin will be administered on day 2 of each 14 day cycle as follows:

Day 1: Gemcitabine 2500 mg/m 2 as an IV infusion per local hospital guidelines
Cisplatin 35 mg/m 2 as an IV infusion per local hospital guidelines

Day 2: Cisplatin 35 mg/m 2 as an IV infusion per local hospital guidelines

Day 3: Pegylated G-CSF (6 mg) will be administered subcutaneously per local hospital guidelines
1-2 liters of normal saline (or suitable alternative) will be administered per local hospital guidelines

Suggested delayed emesis and hydration regimens are provided in Appendix 1.

9.2 Toxicities Requiring Treatment Interruption for GC

Toxicities requiring treatment interruption include one or more of the following hematologic or non-hematologic criteria:

Hematologic:

- Platelet count <100,000 cells/mm^3
- Requirement for platelet transfusion and/or other methods to increase platelet count
- Febrile neutropenia (ANC <1000/mm^3 concurrent with a temperature $\geq$38.5°C)
- Grade 4 neutropenia without fever of $\geq$7 days duration

Non-Hematologic:

- Any $\geq$ Grade 3 non-hematologic toxicity considered by the investigator to be related to study drug

9.3 Criteria for Continuation of Chemotherapy

At each clinic visit prior to initiating Day 1 of each cycle of chemotherapy, patients must meet the following criteria.

- Absolute neutrophil count ≥ 1000 cells/mm^3
- Platelets ≥ 100,000 cells/mm^3
- Serum creatinine ≤ 1.5 or estimated GFR ≥ 60 mL/min
- Resolution of adverse events to baseline or ≤ grade 2

The initiation of subsequent cycles of chemotherapy beyond the 1st cycle may be delayed up to 14 days from the planned day 1 of the current chemotherapy cycle to allow for resolution of adverse events. If the criteria for re-treatment are not met by 14 days, the patient will discontinue chemotherapy.

9.4 Dose Modifications

Dose Level	Gemcitabine
Starting	2500 mg/m^2
Dose Level -1	2250 mg/m^2
Dose Level -2	2000 mg/m^2
Dose Level -3	1800 mg/m^2

Dose Level	Cisplatin
Starting	35 mg/m^2
Dose Level -1	30 mg/m2
Dose Level -2	25 mg/m2

9.4.1 Maximum Duration of Treatment Delays/Maximum Dose Reductions: Treatment with gemcitabine and cisplatin may be held up to a maximum of 14 days from the scheduled cycle initiation date to await resolution of toxicity according to the guidelines above. If more than 14 days are needed for recovery, the patient will discontinue chemotherapy.

Patients requiring more than 3 dose reductions of gemcitabine or 2 dose reductions of cisplatin will discontinue chemotherapy and be counted as treatment failures. All patients discontinued from chemotherapy for maximum dose reduction will be treated according to physician discretion. Any patients who have completed at least 3 cycles of protocol therapy will be evaluated for the primary endpoint.

9.5 Algorithm for Dose Modification and Interruption

9.5.1 Dose Modifications for Hematologic Toxicity

If the criteria for treatment on Day 1 are not met, treatment will be held one week and the CBC will be rechecked before proceeding. The following dose modifications of gemcitabine will be based on blood counts within 1 day prior to day 1 of each cycle of therapy. Only the gemcitabine dose will be reduced for hematologic toxicity.

Table 4: Dose Interruption and Modification for Hematologic Toxicity Based on Day 1 Counts.

ANC (x10^9/L)		Platelets (x10^9/L)	If previous dose level of gemcitabine was:	Day 1 level of gemcitabine:
< 1.0	or	< 100	Level 0*	Level -1
< 1.0	or	< 100	Level -1*	Level -2
< 1.0	or	< 100	Level -2*	Level -3
< 1.0	or	< 100	Level -3	Off-Study

*Hold therapy for 1 week and recheck CBC

9.5.2 Non-Hematologic Toxicity

Renal Insufficiency/ Nephrotoxicity

If on day 1 of any cycle, the serum creatinine > 1.5 and calculated estimated GFR < 60 ml/min/m^2, treatment will be held for one week and creatinine/eGFR will be rechecked. If recovery to serum creatinine $\leq$ 1.5 or eGFR $\geq$ 60 cc/min occurs, the patient will be retreated with a cisplatin dose 1 level lower than the prior cycle. Additional hydration should be considered on the day of treatment or on the day following treatment.

Neurologic Toxicity:
If neurologic toxicity ≥ grade 2 occurs at any point of the cycle, then gemcitabine and cisplatin should be held for one week. If resolution to grade 1 occurs, patient will be retreated with a cisplatin dose 1 level lower than prior cycle.

Ototoxicity:
If ototoxicity is suspected, audiometry will be performed to assess hearing. For loss of greater than 30 db in two consecutive hearing frequencies, therapy will be held for 1 week, and audiometry assessment will be repeated. If hearing loss is resolved, then the patient will be retreated with a cisplatin dose 1 level lower than prior cycle.

Cardiovascular Toxicity:
If during any cycle of therapy a patient develops ≥ grade 3 cardiovascular toxicity, then treatment should be permanently discontinued and the PI or Co-PI contacted.

Pulmonary Toxicity:
If during any cycle of gemcitabine and cisplatin therapy a patient develops ≥ grade 3 pulmonary toxicity, then the patient should discontinue chemotherapy and the PI or Co-PI should be contacted.

Hepatic Dysfunction:
If bilirubin > 1.5 (in the absence of Gilbert's disease) or transaminases >2.5 X upper limit or normal, evaluate for progressive disease. If drug toxicity suspected, hold until toxicity < grade 2 and resume gemcitabine at 1 dose level lower.

Gastrointestinal Toxicity:
Patients who develop nausea, vomiting, or diarrhea that persists at Grade 3 or 4 should be treated with maximal medical therapy and treatment should be withheld until the patient's recovery. Once fully recovered, therapy at the same dose and schedule can resume with appropriate prophylactic medications.

Other Non-Hematological Toxicities:
For any grade 3 or 4 toxicity not mentioned above, the treatment should be withheld until the patient's recovery and the possibility of resumption of therapy should be discussed with the Study PI or Co-PI.

Patients who develop a symptomatic grade 4 venous thromboembolic event will not be eligible for retreatment.

9.6 Concomitant Medications
Radiation therapy is not allowed during the study. Administration of other chemotherapy, immunotherapy, or anti-tumor hormonal therapy during the study is not allowed. Supportive care, including but not limited to anti-emetic medications, may be administered at the discretion of the Investigator.

No other investigational drug may be used during treatment on this protocol. Other concomitant therapies considered necessary for the patient's well being may be prescribed at the investigator's discretion. Included are antiemetics, antidiarrheals, hematopoietic growth factors, anti-inflammatory agents, analgesics, etc.

Concomitant medication data for all patients will be collected until the time of protocol specified surgery.

9.7 Ideal Body Weight Modification

The total chemotherapy dose for GC may be modified for patients with obesity (e.g. male with body surface area (BSA) ≥ 2.1 or female with BSA ≥ 2.0), after consultation with the Principal Investigator. The modification will be calculated as follows:

$$\text{Adjusted BSA} = \frac{\text{Ideal BSA} + \text{Actual BSA}}{2}$$

The ideal body weight is calculated according to the formula:
Women = 45.5kg + .9kg/cm over 152
Men = 50kg + .9kg/cm over 152

Note: In patients with severe obesity, the investigator may elect to dose based on the ideal BSA alone.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

	Baseline	Cycle 1 (2 weeks[3])			Cycle 2 (2 weeks[3])			Cycle 3 (2 weeks[3])			Cycle 4 (2 weeks[3])			Cycle 5 (2 weeks[3])			Cycle 6 (2 weeks[3])			Post Chemo Follow-Up	Surgery	Post Treatment Follow-Up[4]
	Day -14 to 0	D1	D2	D3	D1	D2	D3	D1	D2	D3	D1	D2	D3	D1	D2	D3	D1	D2	D3	~2-4 wks after chemotherapy	~4-8 weeks after chemotherapy	X[4]
History/Physical	X	X			X			X			X			X			X			X		
Vital signs, KPS, Height and Weight[1]	X	X			X			X			X			X			X			X		
Toxicity Assessment		X			X			X			X			X			X			X		
Laboratory																						
CBC[2]	X	X			X			X			X			X			X			X	X	
Comprehensive panel[2]	X	X			X			X			X			X			X			X		
BHCG (pregnancy test)	X																					
PTT/PT/INR	X																					
EKG	X																					
UA	X																					
Staging																						
Chest X-ray[5]	X												X[5]							X		
CT/MRI of Ab/Pelvis[6]	X												X[6]							X		
Cystoscopy+/- EUA[7]	X																					
Treatment																						
Gemcitabine		X			X			X			X			X			X					
Cisplatin		X	X		X	X		X	X		X	X		X	X		X	X				
G-CSF				X[8]			X[8]			X[8]			X[8]			X[8]			X[8]			
Cystectomy																					X	

[1] Height and KPS will be performed only at baseline.
[2] CBC must be performed and resulted within 1 day of planned treatment.
[3] Each 2 week cycle clinic assessment and treatment should occur within a +/- 5 day window.
[4] Standard follow up evaluations and imaging will occur as determined by the investigator (i.e. every 3 months for the first 18 months, every 6 months for the next 18 months, and then yearly) until 5 years from the time of surgery or disease recurrence/progression.
[5] A Chest X-ray (CXR) can be omitted if a chest CT is performed. Follow-up imaging will be performed after completion of cycle 4 treatment, prior to initiating cycle 5.
[6] The baseline CT or MRI must be performed within 30 days of enrollment. Follow-up imaging will be performed after completion of cycle 4 treatment, prior to initiating cycle 5.
[7] Within 60 days of enrollment, patients must have undergone a cystoscopy and had confirmation of muscle-invasive urothelial carcinoma by pathologic review at MSKCC or participating site
[8] 1-2 liters of normal saline (or suitable alternative per institutional guidelines) will be administered for renal protection.

10.1 Clinical Evaluation During Treatment

Patients must undergo a complete history, physical exam, and toxicity assessment on day 1 of each cycle. Weight and vital signs must be recorded. Height and KPS will only be assessed at baseline. All clinical assessments should occur within +/- 5 days of the intended cycle start date.

10.2 Laboratory Studies During Treatment

Complete blood count (CBC) with differential and platelets and comprehensive panel (Na, K, Cl, CO2, BUN, Cr, Ca, glucose, AST, ALT, TP, Albumin, ALP, BT) must be performed on day 1 of each cycle.

10.3 Radiographic Studies During Treatment

Follow-up imaging (CT Chest or CXR; CT or MR of the abdomen and pelvis) must be performed after completion of cycle 4 treatment, prior to initiating cycle 5. Diffusion-weighted MRI is preferred, if available.

10.4 Surgery

Patients will undergo standard surgery consisting of radical cystectomy and bilateral pelvic lymph node dissection, as determined by their attending surgical urologic oncologist. Surgery will be performed, if possible, 4-8 weeks after completing chemotherapy.

10.5 Post-Treatment Follow-Up

Standard follow-up evaluations and imaging will occur as determined by the investigator (i.e. every 3 months for the first 18 months, followed by every 6 months for the next 18 months, followed by yearly scans from the time of surgery). Follow-up will occur until 5 years from the time of surgery or until disease recurrence/progression.

11.0 TOXICITIES/SIDE EFFECTS

Cisplatin Toxicity

Potential side effects from cisplatin include cumulative nephrotoxicity, myelosuppression, nausea, and vomiting. Ototoxicity, manifested by tinnitus and/or high frequency hearing loss, is significant. Anaphylactic-like reactions to cisplatin have been reported. Facial swelling, bronchospasm, tachycardia, and hypotension may occur within minutes of cisplatin administration. Other side effects include fatigue, anorexia, weight loss, diarrhea, serum electrolyte disturbances including hyponatremia, hypomagnesemia, and hypocalcemia, edema of the lungs or extremities, vascular toxicities, neurotoxicity including cerebral infarction, seizures and dizziness, ocular toxicity with visual disturbances, peripheral neuropathy, autonomic neuropathy, infertility, muscle cramps, and hepatic toxicity. Other rare side effects include cardiac abnormalities, hiccoughs, elevated serum amylase, rash, and alopecia. Local soft tissue injury has been reported following extravasation of cisplatin. Based on reported toxicities from completed/ongoing trials utilizing NCI Common Toxicity Criteria.

Gemcitabine Toxicity

Nausea, vomiting, alopecia, stomatitis, anorexia, fatigue, elevations of hepatic transaminases, reversible myelosuppression, rash, flu-like symptoms, edema, constipation, paresthesias, hypersensitivity reactions, phlebitis, proteinuria, hematuria, and rarely, interstitial pneumonitis, ARDS, and hemolytic uremic syndrome.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

12.1 Pathologic Response

Pathologic response to neoadjuvant DD GC is the primary endpoint of this phase II study and is defined as the absence of muscle invasive carcinoma (<pT2 disease) and the absence of lymph node metastases (N0) on the final cystectomy specimen. Pathologists will assess surgical specimens systematically using criteria agreed upon for all conventional neoadjuvant treatment based on the AJCC TNM staging system.

12.2 Progression Free Survival

Progression-free survival is measured from the time of treatment initiation until the first date that disease progression is objectively documented. Disease progression for this trial is defined as either progression of disease (documented clinically or radiographically) before radical cystectomy, or metastatic or local pelvic recurrence after radical cystectomy. Due to the multifocal nature of transitional cell tumors involving other segments of the genitourinary tract, this definition excludes new primary tumors of the renal pelvis, ureters, or urethra. The assessment of disease recurrence versus development of a second primary tumor will be left to the discretion of the treating physician. If the patient did not progress nor die, the patient will be censored on the date of last follow-up.

12.4 Toxicity

Toxicity will be graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events version 4.0.

13.0 CRITERIA FOR REMOVAL FROM STUDY

If, at any time, the patient develops progressive metastatic disease, he/she will discontinue chemotherapy and be referred for alternative therapy. This will count as a failure for the primary efficacy endpoint.

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

The patient will discontinue chemotherapy if treatment is held for >14 days, or the patient requires more than 3 dose reductions of gemcitabine or 2 dose reductions of cisplatin. These patients will only be considered evaluable for the primary endpoint if they have completed at least 3 cycles of protocol therapy.

The patient will be taken off study and/or discontinue chemotherapy if, at any time, the study doctor believes it is in the patient's best interest to do so.

14.0 BIOSTATISTICS

This is a single arm phase II study of neoadjuvant DD GC in surgical candidates with MIBC prior to radical cystectomy. The primary endpoint is pathologic response, defined as the proportion of patients who achieve absence of muscle-invasive disease at the time of cystectomy (<pT2). The "uninteresting" pathologic response rate is 35%, which is based on a prior retrospective study (Dash et al., 2008) and two prospective randomized clinical trials (MRC/EORTC trial[11] and Intergroup 0080 trial[10]) utilizing a conventional schedule of cisplatin-based neoadjuvant chemotherapy. A total of 46 patients will be accrued to the study to detect an improvement in response rate from 35% to 55%. The study design is based on exact Binomial one-sided test, Type 1 error of 5% and power of 87%. Patients that do not proceed to have surgery due to progression of disease, or discontinue chemotherapy due to excessive treatment delays, dose reductions, or toxicity will be counted as non-responders. Patients will not be considered evaluable for the primary objective if they receive less than 3 completed cycles of protocol therapy and are discontinued from protocol treatment for either withdrawal of consent or adverse events. These patients will be replaced. All patients will remain evaluable for toxicity assessment. At the end of the study, if 22 or more patients will have pathologic response, the treatment regimen will be considered worthy of further investigation. The follow-up time is at least five years for each patient. The accrual rate is 2-3 patients per month, and the study is expected to be completed within 2 years. Since it takes about 5-6 months from the enrollment date to surgery and, therefore, determination of patient's response, the two stage design is not utilized.

Secondary objectives include: 1.) Safety and tolerability, tabulated by NCI CTCAE version 4.0; 2.) Progression free survival, defined as the time from treatment initiation to disease progression, local-regional or metastatic recurrence, or death analyzed using the Kaplan Meier method. Patients who do not proceed to have surgery due to documented disease progression will be counted as progression.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. Registrations must be submitted via the PPR Electronic Registration System (http://ppr/). The completed signature page of the

written consent/RA or verbal script/RA, a completed Eligibility Checklist and other relevant documents must be uploaded via the PPR Electronic Registration System.

15.1.1 For Participating Sites:
Central registration for this study will take place at Memorial Sloan Kettering Cancer Center (MSKCC).

To complete registration and enroll a participant from another institution, the study staff at that site must contact the designated research staff at MSKCC to notify him/her of the participant registration. The site staff then needs to e-mail registration/eligibility documents to the attention of 12-071 Research Staff at medmctcore@mskcc.org.

The following documents must be sent for each enrollment **within 24 hours** of the informed consent form being signed:

- The completed or partially completed MSKCC eligibility checklist
- The signed informed consent and HIPAA Authorization form
- Supporting source documentation for eligibility questions (laboratory results, pathology report, radiology reports, MD notes, physical exam sheets, medical history, prior treatment records, and EKG report).

Upon receipt, the research staff at Memorial Sloan Kettering Cancer Center will conduct an interim review of all documents. If the eligibility checklist is not complete, the patient will be registered PENDING and the site is responsible for sending a completed form within 30 days of the consent.

If the eligibility checklist is complete, participant meets all criteria, all source documentation is received, the participating site IRB has granted approval for the protocol, and the site is in good standing with MSKCC, the MSKCC research staff will send the completed registration documents to the MSKCC Protocol Participant Registration (PPR) Office to be enrolled as stated in section 15.1. The participant will be registered.

Once eligibility has been established and the participant is registered, the participant will be assigned an MSKCC Clinical Research Database (CRDB) number (protocol participant number). This number is unique to the participant and must be written on all data and correspondence for the participant. This protocol participant number will be relayed back to study staff at the registering site via e-mail and will serve as the enrollment confirmation.

15.2 Randomization (if applicable)
Participants will not be randomized for this trial.

16.0 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordination of the activities of the protocol study team.

The data collected for this study will be entered into a secure Clinical Research Database. Source documentation will be available to support the computerized patient record.

16.0.1 Data and Source Documentation for Participating Sites

Data
The participating site(s) will enter data remotely into MSKCC's internet-based Clinical Research Database, termed CRDBi-Multicenter. Standardized Case Report Forms (CRFs) and data entry guidelines have been generated for this study. The site staff will receive CRDB training prior to enrolling its first patient. The participating Site PI is responsible for ensuring these forms are completed accurately and in a timely manner.

Source Documentation
Source documentation refers to original records of observations, clinical findings and evaluations that are subsequently recorded as data. Source documentation should be consistent with data entered. Relevant source documentation to be submitted throughout the study includes:

- Baseline measures to assess pre–protocol disease status (ex. CT, PSA, bone marrow)
- Treatment records
- Grade 3-5 toxicities/adverse events not previously submitted with SAE Reports
- Response designation

16.0.2 Data and Source Documentation Submission for Participating Sites

Participating sites should enter data directly into CRDBi-Multicenter and study-specific paper CRFs . Source documentation should be sent to MSKCC at the contact provided below. Submissions should include a cover page listing relevant records enclosed per participant.

Contact for submission of Source Documentation

E-mail: medmctcore@mskcc.org to the attention of 12-071 Research Staff

16.0.3 Data and Source Documentation Submission Timelines for Participating Site

Data and source documentation to support data should be transmitted to MSKCC according to chart below:

	Baseline	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Post Chemo Follow-Up	Surgery	SAE	Long Term Follow-Up
SUBMISSION SCHEDULE											
Source Documentation	Within 24 hours (see section 15.1.1)	within 14 days of D3 of cycle								Within 3 days of event (see section 17.3); updates to be submitted as available	Within 14 days of visit
CRFs	Within 7 days of visit										
Required Forms											
Demographics Form	X										
Medical History Form	X										
Concomitant Medication Form	X	X	X	X	X	X	X	X			X
Physical Exam Form	X	X	X	X	X	X	X	X			X
Treatment Form		X	X	X	X	X	X		X		
Surgery Form									X		
Laboratory Form	X	X	X	X	X	X	X	X	X		X
Diagnostic Test Form	X				X						
Disease Status Form	X				X						X
Lesion/EOD Form	X				X						X
Adverse Event Form		X	X	X	X	X	X	X		X	X
Patient Status Form	X	X	X	X	X	X	X	X	X		X
Serious Adverse Event Form										X	
Off Study Form											X

16.0.4 Data Review and Queries for Participating Site Data
Research staff at MSKCC will review data and source documentation as it is submitted. Data will be monitored against source documentation and discrepancies will be sent as queries to the participating sites. Queries will be sent by MSKCC Research staff twice a month.

Participating sites should respond to data queries within 14 days of receipt.

16.1 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action.

Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

16.1.1 Quality Assurance for Participating Sites
Each site participating in the accrual of participants to this protocol will be audited by the staff of the MSKCC study team for protocol and regulatory compliance, data verification and source documentation. Audits may be accomplished in one of two ways: (1) selected participant records can be audited on-site at participating sites or (2) source documents for selected participants will be sent to MSKCC for audit. Audits will usually be determined by participant accrual numbers and rate of accrual, but can also be prompted by reported SAEs or request of MSKCC PI.

Audits will be conducted at least once shortly after initiation of participant recruitment at a site, annually during the study (or more frequently if indicated), and at the end or closeout of the trial. The number of participants audited will be determined by available time and the complexity of the protocol.

The audit will include a review of source documentation to evaluate compliance for:

- Informed consent documents and procedures
- Adherence to eligibility criteria
- Protocol defined treatment
- Required baseline, on study and follow-up protocol testing
- IRB documents (submitted amendments, annual continuing review reports, SAEs)
- Case Report Form submissions to MSKCC: timelines and accuracy

A wrap-up session will be conducted at the participating site and preliminary findings will be discussed with the participating site PI and research team. The preliminary results will be sent to the MSKCC PI.

Each audit will be summarized and a final report will be sent to the PI at the audited participating site within 30 days of the audit. The report will include a summary of findings, participant by participant case review, specific recommendations on any

performance and/or shortcomings and request for corrective action, when necessary. When corrective action is required, the participating site must reply within 45 days of receipt of audit report with their corrective action plan.

A copy of the audit report and corrective action plan (if applicable) submitted by the participating site must be sent to the MSKCC IRB/PB, CRQA and maintained in the department's protocol regulatory binder.

16.1.2 Response Review

Since therapeutic efficacy is a stated primary objective, all sites participant's responses are subject to review by MSKCC's Therapeutic Response Review Committee (TRRC). Radiology, additional lab reports and possibly bone marrow biopsies and/or aspirates will need to be obtained from the participating sites for MSKCC TRRC review and confirmation of response assessment. These materials must be sent to MSKCC promptly upon request.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: *http://www.cancer.gov/clinicaltrials/conducting/dsm-guidelines/page1*. . The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: http://inside2/clinresearch/Documents/MSKCC%20Data%20and%20Safety%20Monitoring%20Plans.pdf

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

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

16.3 Regulatory Documentation

Prior to implementing this protocol at MSKCC, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the MSKCC Institutional Review Board/Privacy Board (IRB/PB). Prior to

implementing this protocol at the participating sites, approval for the MSKCC IRB/PB approved protocol must be obtained from the participating site's IRB.

The following documents must be provided to MSKCC before the participating site can be initiated and begin enrolling participants:

- Participating Site IRB approval(s) for the protocol, appendices, informed consent form and HIPAA authorization
- Participating Site IRB approved consent form
- Participating Site IRB membership list
- Participating Site IRB's Federal Wide Assurance number and OHRP Registration number
- Curriculum vitae and medical license for each investigator and consenting professional
- Documentation of Human Subject Research Certification training for investigators and key staff members at the Participating Site
- Participating site laboratory certifications and normals

Upon receipt of the required documents, MSKCC will formally contact the site and grant permission to proceed with enrollment.

16.3.1 Amendments

Each change to the protocol document must be organized and documented by MSKCC and first approved by the MSKCC IRB/PB. Upon receipt of MSKCC IRB/PB approval, MSKCC will immediately distribute all non expedited amendments to the participating sites, for submission to their local IRBs.

Participating sites must obtain approval for all non expedited amendments from their IRB within 90 calendar days of MSKCC IRB/PB approval. If the amendment is the result of a safety issue or makes eligibility criteria more restrictive, sites will not be permitted to continuing enrolling new participants until the participating site IRB approval has been granted.

The following documents must be provided to MSKCC for each amendment within the stated timelines:

- Participating Site IRB approval
- Participating Site IRB approved informed consent form and HIPAA authorization

16.3.2 Additional IRB Correspondence

Continuing Review Approval

The Continuing Review Approval letter from the participating site's IRB and the most current approved version of the informed consent form should be submitted to MSKCC within 7 days of expiration. Failure to submit the re-approval in the stated timeline will result in suspension of study activities.

Deviations and Violations
A protocol deviation on this study is defined as a request to treat a research participant who does not meet all the eligibility criteria, pretreatment evaluation, or who requires alteration in their study plan. If a deviation from this protocol is proposed for a potential or existing participant at MSKCC or a participating site, approval from the MSKCC IRB/PB is required prior to the action. Participating sites should contact the MSKCC PI who will in turn seek approval from the MSKCC IRB/PB.

A protocol violation is anything that occurs with a participant, which deviated from the protocol without prior approval from the MSKCC IRB/PB. For protocol violations that are identified after they occur, the participating site should report to MSKCC as soon as possible. The MSKCC PI will in turn report the violation to the MSKCC IRB/PB.

Participating sites should report deviations and violations to their institution's IRBs as soon as possible per that site's institutional guidelines. Approvals/acknowledgments from the participating site IRB for protocol deviations and violations should be submitted to MSKCC as received.

Other correspondence
Participating sites should submit other correspondence to their institution's IRB according to local guidelines, and submit copies of that correspondence to MSKCC.

16.3.3 Document maintenance
The MSKCC PI and the Participating Site PI will maintain adequate and accurate records to enable the implementation of the protocol to be fully documented and the data to be subsequently verified.

The participating sites will ensure that all participating site IRB correspondence (IRB approval letters referencing protocol version date and amendment number, IRB approved protocol, appendices, informed consent forms, deviations, violations, and approval of continuing reviews) is maintained in the regulatory binder on site and sent to MSKCC.

A regulatory binder for each site will also be maintained at MSKCC; this binder may be paper or electronic.

After study closure, the participating site will maintain all source documents, study related documents and CRFs for 3 years.

16.4 Noncompliance
If a participating site is noncompliant with the protocol document, accrual privileges may be suspended and/or contract payments maybe withheld, until the outstanding issues have been resolved.

17.0 PROTECTION OF HUMAN SUBJECTS

Potential risks to human subjects include drug-related toxicity, pain and discomfort associated with cisplatin, gemcitabine, placement of IV catheters, phlebotomy, and possible psychological discomfort from the stresses associated with obtaining imaging studies (e.g., CT scan). The side effects and potential toxicities of cisplatin and gemcitabine are listed in **section 5.1.4, 5.2.3 and 11.** All efforts will be made to avoid any complication by completely reviewing patients' symptoms, providing appropriate management, and monitoring blood tests. If an adverse medical event occurs, the patient will first contact the primary oncologist or the principal investigator. At nights and weekends, there is an oncology physician on call at all times. Patients may either call or come directly to the urgent care center at Memorial Hospital (or to their local emergency room) to be seen. Patients suffering serious adverse reactions must be carefully followed and all follow-up information recorded.

Alternatives/Options for treatment
Patients can elect to receive standard therapy for muscle invasive urothelial carcinoma with neoadjuvant M-VAC or standard GC. They can also elect to participate in another clinical trial. Participation in a clinical trial is voluntary.

Costs
The patient will be responsible for all costs related to treatment and complications of treatment. Costs to the patient (or third party insurer) will include the cost of hospitalizations, routine blood tests and diagnostic studies, office visits, baseline EKG, other medications such as antibiotics and doctor's fees.

17.1 Privacy

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

17.2 Serious Adverse Event (SAE) Reporting

Serious Adverse Event Definition

A serious adverse event is one that at any dose (including overdose):

- Results in death
- Is life-threatening[1]
- Requires an unplanned inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity[2]
- Is a congenital anomaly or birth defect
- Is an important medical event[3]
- Pregnancy

[1]"Life-threatening" means that the subject was at immediate risk of death at the time of the serious adverse event; it does not refer to a serious adverse event that hypothetically might have caused death if it were more severe.

[2]"Persistent or significant disability or incapacity" means that there is a substantial disruption of a person's ability to carry out normal life functions.

[3]Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. A new diagnosis of cancer during the course of a treatment should be considered as medically important.

Serious Adverse Event Reporting

Any SAE must be reported to the IRB/PB as soon as possible but no later than 5 calendar days. The IRB/PB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office at sae@mskcc.org. The report should contain the following information:

Fields populated from CRDB:

- Subject's name (generate the report with only initials if it will be sent outside of MSKCC)
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
    - A explanation of how the AE was handled
    - A description of the subject's condition
    - Indication if the subject remains on the study
    - If an amendment will need to be made to the protocol and/or consent form.

The PI's signature and the date it was signed are required on the completed report. SAEs will be collected from the time of consent until 30 days following the protocol specified surgery.

17.3 Serious Adverse Event (SAE) Reporting for Participating Sites

Responsibility of Participating Sites

- Participating sites are responsible for reporting all SAEs to their local IRB per local guidelines
- Participating sites are responsible for reporting all SAEs to the MSKCC PI via e-mail within 3 calendar days of learning of the event.
  - SAEs will be collected from the time of consent until 30 days following the protocol specified surgery
- Participating sites should notify the MSKCC PI of any grade 5 event immediately.
- Participating sites should use the SAE Report Form found in MSKCC's internet-based Clinical Research Database, CRDBi-Multicenter, to report SAEs to MSKCC.

SAE contact information for the Coordinating Center is listed below:

Dean Bajorin, MD
bajorind@mskcc.org

12-071 Research Staff
medmctcore@mskcc.org
Ph: 646 888 1007

Responsibility of MSKCC

- The MSKCC Research Staff is responsible for submitting all SAEs to the MSKCC IRB/PB as specified in 17.2
- The MSKCC PI is responsible for informing all participating sites about all unexpected SAEs that are either possibly, probably, or definitely related to the study intervention within 30 days of receiving the stamped SAE from the MSKCC IRB/PB.
- Any report pertaining to a grade 5 event will be distributed to the participating sites as soon as possible.

17.4 Safety Reports

- MSKCC will distribute outside safety reports to the participating sites immediately upon receipt.
- MSKCC must submit outside safety reports to the MSKCC IRB/PB according to institutional guidelines.
- Participating sites must submit safety reports to their institution's IRBs within 30 days of receipt from MSKCC or per participating site guidelines.

18.0 INFORMED CONSENT PROCEDURES

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

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.

3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

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

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

18.1 For Participating Sites

The investigators listed on the protocol cover page and their qualified designees at each participating site may obtain informed consent and care for the participants according to good clinical practice and protocol guidelines.

Signed copies of the informed consent should be distributed as follows: One copy will be given to the participant to be retained for their personal records. One copy will be maintained on file at the MSKCC. The third copy will be confidentially maintained by the participating institution.

A note will be placed in the medical record documenting that informed consent was obtained for this study, and that the participant acknowledges the risk of participation.

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20.0 Appendices

Appendix 1- Suggested Delayed Emesis and Hydration Regimens

Appendix 1: Suggested Delayed Emesis and Hydration Regimens

SUGGESTED DELAYED EMESIS REGIMEN

MEDICATION	Chemo DAY 1	DAY 2	DAY 3
FOSaprepitant	150mg IV in chemotherapy		
Decadron (dexamethasone)	12mg (3 tablets, 4mg each) will be given in chemotherapy	12mg (3 tablets, 4mg each) will be given in chemotherapy	Take 12mg (3 tablets, 4mg each) at home

Zofran (Ondansetron) 8mg **can and should** be taken orally every 8 hours as needed for nausea/vomiting while being treated with chemotherapy.

SUGGESTED HYDRATION REGIMEN

General points:

- It is helpful to weigh patients at the beginning and end of treatment on Days 1 and 2 of each cycle and prior to hydration on Day 3 and record strict I&Os during infusion.
- It is also helpful to have a baseline ECHO to feel more comfortable with fluid shifts, etc.

Days 1 and 2 of each cycle:

Pre-Cisplatin hydration:

- 1000cc normal saline given over 3 hours
- Mannitol 25% (12.5g IV x 1)

Post-Cisplatin hydration:

- Normal saline at 250 ml/hr x 3hrs = total 750 ml

Day 3 of each cycle:

- 500-1000cc normal saline may be given if indicated at the investigator's discretion. This is subject to change due to possible fluid retention on Days 1 and 2 of treatment.