Masonic Cancer Center
University of Minnesota

Phase II Trial of Neoadjuvant Nivolumab with Cisplatin and Gemcitabine in Muscle-Invasive Bladder Cancer (MIBC) Patients Undergoing Radical Cystectomy

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Revision History

Revision #	Version Date	Summary of Changes	Consent Revision (y/n)
	03/31/2017	Original to CPRC	n/a
	07/27/2017	In response to CPRC stipulations	n/a
	09/21/2017	In response to Bristol-Myers Squibb's review and other minor edits – initial version to FDA and IRB	n/a
	10/19/2017	In response to FDA request for information dated 10/18/2017: • Section 4.2 and Appendix I - Exclusion criteria: clarify prior treatment prior systemic therapy directed at MIBC is not permitted; however systemic therapy for non-muscle invasive BC is permitted as long as prohibited agents are not used; add cisplatin, gemcitabine, and/or radiation to the bladder as prohibited prior treatments; reorder prior therapies in the exclusion criteria to group together and move higher up in the list, the 1st occurrence of "prior allogeneic stem cell or solid organ transplant was deleted (appeared twice in list). Synopsis updated to match. • Section 6.1– add criteria for permanent discontinuation of study treatment: any Grade 4 drug related AE, any grade neurologic event, any grade pneuomonitis • Section 6.1 last paragraph – clarify that any person receiving at least one dose of study treatment would be included in ITT analysis • Section 6.3 – add additional off treatment criterion of requiring a 2nd treatment delay of more than 2 weeks • Section 9 – add ACTH stimulation test at the final treatment visit to monitor adrenal function • Additional clarifications (not part of the information request) -Section 6. 1 - for split-dose cisplatin leave to physician discretion -Section 13.3 – require all affiliate sites to follow UMN DSMP for monitoring -Section 12 – add definition of clinical deviations and reporting requirements to match current MCC template	yes
1	07/19/2018	Cover page – Add BLASST-1 study number and update fax #, delete Paari Murugan as co-I; Add Key Abbreviations table Edit primary objective for clarity, better define follow-up period for progression free survival Exclusion criteria: clarify that prior intravesical gemcitabine is permitted; however prior IV gemcitabine is not Exclusion criteria: expand definition of systemic antibiotic use	yes

Revision #	Version Date	Summary of Changes	Consent Revision (y/n)
		Exclusion criteria: waive hearing loss exclusion if benefit is felt to outweigh potential hearing loss after discussion with participant Exclusion criteria: expand and clarify additional malignancy exclusion language Section 5 – revise to match current MCC protocol template Sections 6,7, 8, and 9 – expand and edit for clarity Section 12 – update deviation reporting to current MCC protocol template Section 12.2 – clarify grade and expectedness of AEs to be collected Section 12.3 – add a section for early study stopping rule events Section 15.6.2 – add an early stopping rule for excessive Grade 3 and 4 non-hematologic toxicities Add Appendix II – ECOG performance status and NYHA classification Other minor edits and clarifications – all tracked	
2	01/14/2019	Update Schema for clarity and consistency with changes in the protocol body. Section 4.2 - Exclusion criteria #24 and Appendix I - simplify exceptions to “known additional malignancy that is progressing or requiring active treatment” Section 6.1 – permit screening weight to be used for dose 1 drug calculations, allow nivolumab to be given per institutional practice, add nivolumab should be given 60 min (±15 min) after the chemotherapy agent (gemcitabine or cisplatin if using a split-dose) Section 6.2 – clarify that Nivolumab has an Investigator brochure (versus package insert for cisplatin and gemcitabine) Section 6.2 – Add the statement “Use of ≤ 10 mg prednisone or equivalent dose of steroids is allowed for short-term use (< 7 days) as supportive care for issues other than immune-related adverse events.” Section 6.3 – Duration of Treatment section: clarify the End of Treatment visit and Final Study Visit. Section 6.4 – clarify the CT or PET/CT is of chest, abdomen, and pelvis Section 6.5 – clarify that the Final Study Visit is also the assessment point for SAEs or AE that become SAEs to fulfill BMS’s requirement for following patients for 100 days after the last dose of nivolumab	yes update study coordinator

Revision #	Version Date	Summary of Changes	Consent Revision (y/n)
		Section 9 – clarify the timing and purpose of the End of Treatment Visit and Final Study Visit and follow-up, edit x chart for clarity Section 12.2 – reword AE monitoring and documentation to reflect clarification of the End of Treatment Visit and Final Study Visit. For clarity add the statement "Adverse events related to the surgery are not documented unless they are felt to be due to the study treatment." Sections 12.3 and 15.2.6 – clarify that assessment for stopping rules ends with the End of Treatment Visit Section 13.1 – update Data Management language to current template. Sections 13.3 and 13.4 – add possibility of MMC monitoring services performing affiliate site monitoring	
3	04/25/2019	Change Principal Investigator/IND Sponsor from Dr. Gupta who is leaving the institution to Dr. Konety a current co-I	Yes – update PI information

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Key Abbreviations

ADL	activities of daily living
AE	adverse event
BCG	Calmette-Guerin
BID	bis in die (twice a day)
BLASST	Bladder Cancer Signal Seeking Trial-1
BMS	Bristol-Myers Squibb
BSA	body surface area
CNS	central nervous system
CrCl	creatinine clearance
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTO	Clinical Trials Office
DSMC	Data and Safety Monitoring Council
DSMP	Data and Safety Monitoring Plan
ECOG	Eastern Cooperative Oncology Group
e-CRF	electronic case report forms
EOT	end of treatment
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin embedded
GC	gemcitabine-cisplatin
G-CSF	granulocyte colony stimulating factor
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	human immunodeficiency virus
IND	investigational new drug
irAE	immune related adverse event
ITT	intention-to-treat
IV	Intravenous
MCC	Masonic Cancer Center
MIBC	muscle-invasive bladder cancer
OnCore	Online Enterprise Research Management Environment
PaR	pathologic response rate
PCRC	Primary Clinical Research Coordinator
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PET/CT	positron emission tomography–computed tomography
PFS	progression free survival
PHI	personal health information
PO	per os (by mouth)
PS	performance status
SAE	serious adverse event
TURBT	transurethral resection of bladder tumor
ULN	upper limit of normal
UMN	University of Minnesota
WES	whole exome sequencing

Protocol Synopsis

Phase II Trial of Neoadjuvant Nivolumab with Cisplatin and Gemcitabine in Muscle-Invasive Bladder Cancer (MIBC) Patients Undergoing Radical Cystectomy

Study Design:

This is a multi-center Phase II study to determine the safety and efficacy of nivolumab when given in combination with cisplatin and gemcitabine as neoadjuvant treatment in patients with muscle-invasive bladder cancer (MIBC) prior to standard of care radical cystectomy.

Eligible, consenting patients receive neoadjuvant treatment with nivolumab in combination with gemcitabine-cisplatin (GC) every 3 weeks for 4 treatment cycles over 12 weeks followed by standard of care radical cystectomy.

Primary Objective:

To determine the efficacy of nivolumab and GC neoadjuvant therapy for MIBC as measured by the pathologic response rate (PaR) at time of radical cystectomy. PaR is defined as a pathologic down-staging to ≤pT1pN0, which includes pT0, pT1,pTa and pTis.

Secondary Objectives:

- To determine the safety of nivolumab when given with GC as neoadjuvant therapy in patients with MIBC prior to radical cystectomy.
- To determine the progression free survival (PFS) measured from the date of radical cystectomy to date of progression or death from disease recurrence for a maximum of 2 years from surgery.

Exploratory Objectives:

- Evaluate molecular subtypes associated with resistance to platinum-based neoadjuvant chemotherapy in patients with MIBC and evaluate whether addition of nivolumab alters the response to platinum-based neoadjuvant therapy.
- Whole Exome Sequencing (WES) of the pre-treatment bladder cancer biopsy tissue and its correlation with response.
- Determine correlation between PD-L1 expression and response to nivolumab.
- Nanostring pancan immune panel gene expression at baseline and at cystectomy (archival biopsy and any fresh residual tumor at cystectomy).

Key Inclusion Criteria:

- Patients with MIBC (predominantly urothelial carcinoma in cases of mixed histology) with clinical stage T2-T4a and N≤1 disease (solitary lymph node measuring < 2 cm) and M0 deemed eligible for radical cystectomy.
- ECOG PS 0-1.

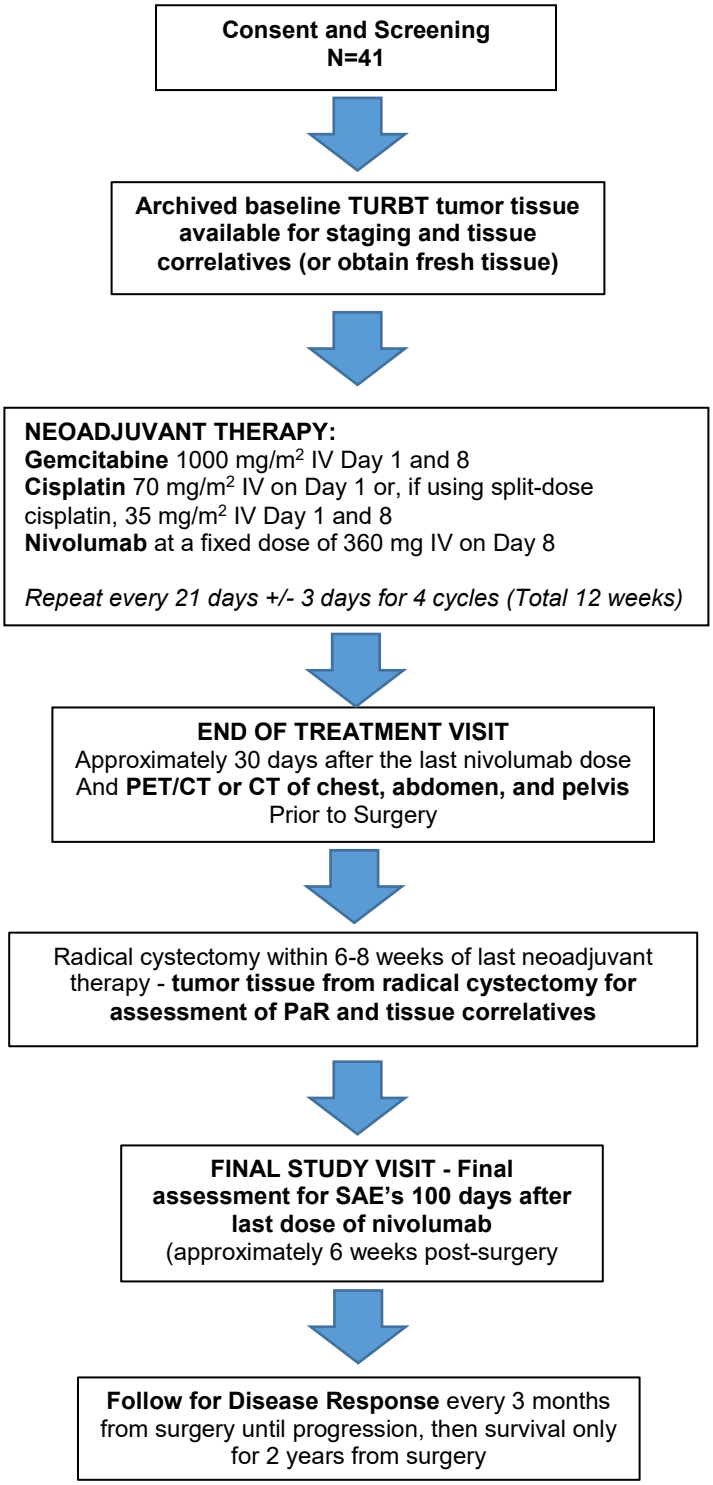
Key Exclusion Criteria:

- Presence of N2-3 or M1 disease.
- Ineligible to receive cisplatin.
- Prior systemic therapy (intravenous) is not permitted. Prior intravesical therapy is including intravesical gemcitabine permitted for non-muscle invasive disease.
- Prior treatment with cisplatin
- Prior treatment with anti-PD-1, and CTLA-4, or anti-a PD-L1 therapeutic antibody or pathway-targeting agents.
- Prior radiation to the bladder.
- History of autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, Wegener's granulomatosis, vascular thrombosis associated with antiphospholipid syndrome, Sjogren's syndrome, Guillain-Barre syndrome, multiple sclerosis, systemic vasculitis, or glomerulonephritis.
- Hepatitis B virus (HBV) or hepatitis C virus (HCV) infection.
- Active infection requiring systemic antibiotics for > 7 days within 3 days of Cycle 1, Day 1.
- Prior allogeneic stem cell or solid organ transplant.
- Concomitant use of systemic corticosteroids at physiologic doses or >10 mg/day of prednisone or equivalent.

Enrollment Plan:

41 patients will be enrolled. This study will be conducted at 3 sites with an estimated accrual of 13-14 patients at each site over 2 years.

Study Schema



1 Study Objectives

1.1 Primary Objective

To determine the efficacy of nivolumab when administered with GC as neoadjuvant therapy for MIBC as measured by the pathologic response rate (PaR) at time of radical cystectomy. PaR is defined as pathologic down-staging to ≤pT1pN0, which includes pT0, pT1,pTa and pTis.

1.2 Secondary Objectives

- To determine the safety of nivolumab when given with GC as neoadjuvant therapy in patients with MIBC prior to radical cystectomy.
- To determine the progression free survival (PFS) measured from the date of radical cystectomy to date of progression or death from disease recurrence for a maximum of 2 years from surgery.

1.3 Exploratory Objectives

- Whole Exome Sequencing (WES) of the pre-treatment bladder cancer biopsy tissue and its correlation with response.
- Evaluate molecular subtypes associated with resistance to platinum-based neoadjuvant chemotherapy in patients with MIBC and evaluate whether addition of nivolumab alters the response to platinum-based neoadjuvant therapy.
- PD-L1 expression in tumor tissue at baseline and correlation with response to therapy.
- Nanostring pancan immune panel gene expression at baseline and at cystectomy (archival biopsy and any fresh residual tumor at cystectomy)

2 Background and Significance

Cisplatin based neoadjuvant chemotherapy is standard of care in muscle-invasive bladder cancer (MIBC) based on two phase III studies have shown improvement in overall survival in patients who received cisplatin-based chemotherapy prior to cystectomy compared with cystectomy alone. [1,2] A meta-analysis of 3005 patients with MIBC showed a significant survival benefit with platinum-based neoadjuvant chemotherapy prior to cystectomy.[3,4] Methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) is an established standard neoadjuvant regimen 1 In metastatic urothelial carcinoma, dose-dense MVAC (DD-MVAC)[5] and gemcitabine plus cisplatin (GC)[6] have demonstrated similar overall survival rates compared to MVAC. Given the favorable safety profile of GC over MVAC in metastatic setting,6 GC is not only increasingly used in this setting, but also in the neoadjuvant setting. [7]

The survival benefit in the neoadjuvant clinical trials correlated with pathologic response (complete response (pCR) or to ≤ pT1N0M0). [1,2,8,9] Strategies to improve pathologic response at cystectomy are urgently needed to improve outcomes in MIBC patients receiving cisplatin-based chemotherapy, while limiting toxicity and combination of chemotherapy with immunotherapy agents, especially anti-PD-1/PD-L1 agents may be a promising approach.

Significant activity of various anti-PD-1/PD-L1 therapies in patients with locally advanced and metastatic urothelial carcinoma (UC) progressing on a platinum-containing regimen has been established.[10-15]

Atezolizumab, an anti-PD-L1 antibody was approved by the FDA in May 2016 based on the results from the IMvigor 210 trial of 315 patients in which atezolizumab showed significant objective response rate (ORR) and durability of responses in patients with advanced or metastatic UC progressing after a platinum-based therapy.[12] Several other checkpoint inhibitors, including nivolumab, pembrolizumab, avelumab, and durvalumab have now been approved for platinum-refractory advanced UC. In addition, atezolizumab and pembrolizumab are approved in the 1st-line metastatic cisplatin-ineligible UC patients.

Nivolumab, a fully human IgG4 monoclonal antibody against PD-1 and currently approved in melanoma, Hodgkin lymphoma, non-small cell lung cancer, head and neck cancer, renal cell cancer, and advanced urothelial carcinoma (UC) after failure of platinum-based therapy. The approval in UC was based on the CheckMate 275 study in 270 patients with advanced locally advanced or metastatic UC who had disease progression during or following platinum-containing chemotherapy, or whose disease progressed within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.[15] Nivolumab showed an ORR of 19.6%; the median time to response was 1.9 months, and the median duration of response was not reached at the time of analysis.[15] Median progression-free survival was 2 months (1.87 months in patients with <1% PD-L1 expression (n = 143) and 3.55 months in patients with PD-L1 expression of >1% (n = 122)). Median overall survival was 8.74 months (5.95 months in patients with PD-L1 <1% and 11.3 months in patients with PD-L1 expression of >1%) 16. ORR was 28.4% in patients expressing PD-L1 >5% and 15.8% in patients expressing PD-L1 <5%. Nivolumab was very well tolerated with Grade 3-4 adverse events occurring in 18% of patients with fatigue and diarrhea being most common, each occurring in 2% of patients. In addition, there was improvement in quality of life from baseline.[15]

The promising efficacy and safety of nivolumab in advanced and refractory UC[13,15], provide a rationale to study its efficacy and safety in as neoadjuvant treatment in MIBC prior to cystectomy, in combination with GC.

While conventional chemotherapy directly targets tumor cell replication, there is preclinical evidence that the antitumor effects of cytotoxic chemotherapy also occur through modulation of the immune system.[16] Preclinical evidence suggests that platinum agents utilize signaling pathways leading to immunogenic cell death, resulting in uptake and processing of tumor antigens.[17] In addition, gemcitabine inhibits B-cell proliferation and selectively depletes immunosuppressive myeloid-derived suppressor cells and regulatory T cells in mouse models of malignant mesothelioma and lung cancer, implying it is not detrimental to specific antitumor cellular immunity and may be useful in combination with immunotherapy agents. [17]

Based on the population pharmacokinetic modeling, established flat exposure-response relationships for efficacy and safety, and clinical safety, the benefit-risk profile of flat dose

nivolumab 240 mg Q2 week dosing was comparable to 3 mg/kg Q2 week dosing and the 240 mg IV Q week dose is approved across majority of indications. Nivolumab 360 mg Q3 week dose has been combined safety with platinum-based chemotherapy doublets in metastatic lung cancer and the combination showed encouraging synergy and activity. [18]

In addition, several ongoing trials are utilizing nivolumab dosing of 360 mg intravenously every 21 days alone or with chemotherapy or other agents in a variety of cancers including bladder cancer. (www.clinicaltrialsgov; NCT03101566, NCT03117309, NCT03081689, NCT03081689, NCT01454102).

Given the favorable safety profile of nivolumab and non-overlapping toxicities with GC, this combination is expected to be well-tolerated in MIBC patients receiving neoadjuvant therapy. For this study, we will utilize the 360 mg every 21 day dosing of nivolumab along with GC regimen which is administered every 21 days.

This study would provide crucial information on whether addition of immunotherapy to chemotherapy improves outcomes in MIBC, which in turn would translate into long-term improved outcomes. Furthermore, the exploratory genomics data from the tissues in this trial would provide information on correlation between genomic and immunologic changes in tumor tissues with clinical outcomes.

3 Study Design

This is a multi-center Phase II study to determine the safety and efficacy of nivolumab when given in combination with gemcitabine/cisplatin (GC) as neoadjuvant treatment in patients with muscle-invasive bladder cancer (MIBC) prior to standard of care radical cystectomy.

This study is open to patients diagnosed with MIBC who are medically eligible for neoadjuvant GC and for whom a radical cystectomy is planned. Eligible, consenting patients receive neoadjuvant treatment with nivolumab in combination with GC every 21 days for 4 treatment cycles over 12 weeks followed by standard of care radical cystectomy.

The outcomes of the surgical procedure will not be evaluated as a part of this study other than related to pathology.

The primary efficacy endpoint of pathologic response rate (PaR) will be evaluated in a one-arm, single stage design. Forty-one (41) subjects will be enrolled and the treatment will be worthy of further study (and the null hypothesis rejected) if pathologic response is seen at the time of cystectomy in more than 19 patients.

4 Patient Selection

Study entry is open to patients 18 years and older regardless of gender, race, or ethnic background. Enrollment in this study is expected to be no different than other similar studies at the University of Minnesota and other participating institutions.

4.1 Inclusion Criteria

1. Diagnosis of MIBC (predominantly urothelial carcinoma, except for small-cell variants) with clinical stage T2-T4a and N≤1 disease (solitary lymph node measuring < 2 cm) and M0 and deemed eligible for radical cystectomy.
2. Age ≥ 18 years.
3. ECOG Performance Status of 0 or 1 (Appendix II).
4. Required initial laboratory values within 14 days of study enrollment:
    - Absolute Neutrophil Count ≥ 1500 cells/mm^3
    - Platelets ≥ 100,000 cells/mm^3
    - Hemoglobin ≥ 9.0 g/dL
    - Bilirubin ≤ 1.5 times the upper limit of normal (ULN) for the institution (For patients with known Gilbert's disease: bilirubin ≤ 3 x ULN)
    - Aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 3.0 x ULN for the institution
    - Creatinine clearance ≥ 50 ml/min by Cockcroft-Gault formula (CrCl = [140-age (years)] x actual weight (kg) / [72 x serum Cr (mg/dL)] - if patient is female multiply the above by 0.85) or 24 hour urinary creatinine clearance.
    - Alkaline phosphatase ≤ 2.5 x ULN for the institution
    - INR and aPTT ≤ 1.5 x ULN if not on therapeutic anticoagulation. Patients receiving therapeutic anticoagulation will be allowed if maintained on a stable dose.
5. Females of childbearing potential and males who are not surgically sterile and with partners of childbearing potential must agree to use effective contraception during study treatment for 5 months for females and 7 months for males after the last dose of nivolumab.
6. Patient must agree to submission of archived tumor (20-25 formalin-fixed paraffin embedded (FFPE) slides of 5-10 microns in thickness) from TURBT and radical cystectomy tissues. If archived samples are not available fresh tissue will be used.
7. Ability to provide written consent prior to the initiation of any research related procedures.

4.2 Exclusion Criteria

1. Presence of N2-3 or M1 disease.
2. Ineligible to receive cisplatin by meeting one or more of the following criteria:
    - creatinine clearance of < 50 mL/min,
    - hearing loss of 25 dB at two contiguous frequencies with testing required if a patient has hearing loss – At the investigator's discretion, and after discussion with the patient, this exclusion may be waived if the potential benefit of cisplatin therapy is felt to outweigh the risk of further hearing loss.
    - CTCAE v4 Grade 2 or higher peripheral neuropathy,
    - New York Heart Association Class III or IV heart failure (Appendix II),

- ECOG performance status 2 or higher (Appendix II).

3. Prior systemic therapy (intravenous) is not permitted. Prior intravesical therapies including intravesical gemcitabine is permitted for non-muscle invasive disease (i.e. T1 or lower).
4. Prior treatment with cisplatin for bladder cancer.
5. Prior treatment with anti-PD-1, CTLA-4, or anti-PD-L1 therapeutic antibody or pathway-targeting agents.
6. Prior therapeutic radiation to the bladder.
7. Major surgical procedure within 28 days prior to Cycle 1, Day 1 or anticipation of need for a major surgical procedure during the course of the study.
8. Any of the following within the 6 months prior to study drug administration:
   - myocardial infarction,
   - severe/unstable angina,
   - symptomatic congestive heart failure (New York Heart Association Class III or IV),
   - stroke, serious cardiac arrhythmia.
9. Human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS)-related illness.
10. Pregnancy, lactation, or breast-feeding. Women of childbearing potential must have a negative urine pregnancy test at screening.
11. History of autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, Wegener's granulomatosis, vascular thrombosis associated with antiphospholipid syndrome, Sjogren's syndrome, Guillain-Barre syndrome, multiple sclerosis, systemic vasculitis, or glomerulonephritis.
12. History of idiopathic pulmonary fibrosis, pneumonitis (including drug induced), organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia, etc.), or evidence of active pneumonitis on screening chest computed tomography (CT) scan, history of radiation pneumonitis in the radiation field (fibrosis) is permitted.
13. Active hepatitis B virus (HBV, chronic or acute, defined as having a positive hepatitis B surface antigen [HBsAg] test at screening) or hepatitis C antibody. Patients with past HBV infection or resolved HBV infection (defined as the presence of hepatitis B core antibody [HBc Ab] and absence of HBsAg) are eligible. HBV DNA must be obtained in these patients prior to Cycle 1, Day 1 and confirmed to be negative. Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.
14. Active tuberculosis or BCG infection
15. Active infection requiring systemic antibiotics for more than 7 days within 3 days prior to Cycle 1, Day 1. Prophylactic short-term antibiotics will be allowed.
16. Administration of intravesical bacillus Calmette-Guerin (BCG) within 4 weeks before Cycle 1, Day 1.
17. Administration of a live, attenuated vaccine within 4 weeks before Cycle 1, Day 1 or anticipation that such a live attenuated vaccine will be required during the study.

18. Persisting toxicity from prior therapy (NCI CTCAE v4.03 Grade >1); however alopecia or other Grade ≤2 AEs not constituting a safety risk, based on Investigator's judgement, are acceptable.
19. History of or active bone marrow disorders expected to interfere with study therapy (e.g. acute leukemias, accelerated/blast-phase chronic myelogenous leukemia, chronic lymphocytic leukemia, Burkitt lymphoma, plasma cell leukemia, or non-secretory myeloma).
20. Prior allogeneic stem cell or solid organ transplant.
21. Known primary central nervous system (CNS) malignancy.
22. Patients with eczema, psoriasis, lichen simplex chronicus of vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis would be excluded) are permitted but patients with psoriasis require a baseline ophthalmologic exam to rule out ocular manifestations. Rash must cover less than 10% of body surface area (BSA) and must be well controlled at baseline and only requiring topical steroids.
23. Any other chronic medical condition or psychiatric condition, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk from treatment complications
24. Known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin or in situ cervical cancer that has undergone potentially curative therapy. Patients on androgen deprivation therapy as part of adjuvant therapy after radiation for prostate cancer or patients on adjuvant hormonal therapies for breast cancer will be allowed if they are being considered for curative intent for bladder cancer.
25. Treatment with systemic immunostimulatory agents (including but not limited to interferon-a or interleukin-2) within 4 weeks or five half-lives of the drug (whichever is shorter) prior to Cycle 1, Day 1
26. Concomitant use of systemic corticosteroids at physiologic doses or >10 mg/day of prednisone or equivalent.
27. Concomitant use of another investigational agent and/or treatment with an investigational agent within 4 weeks prior to Cycle 1, Day 1 (or within five half-lives of the investigational product, whichever is longer).
28. Use of bisphosphonate therapy for osteoporosis will be allowed if started prior to study enrollment.

5 Patient Screening and Enrollment

Written consent must be obtained prior to the performance of any research related tests or procedures. Consent is obtained before eligibility is confirmed.

5.1 Enrollment with the University of Minnesota Clinical Trials Office

Any patient who has been consented is to be entered in OnCore by the site Primary Clinical Research Coordinator (PCRC) or designee. If a patient is consented but is not enrolled, the patient's record is updated in OnCore as a screen failure and reason for exclusion recorded.

Complete enrollment information is found in the study's Procedures Manual for Affiliate Sites.

Affiliate sites only: Affiliates are responsible for fulfilling any local registration requirements.

5.2 Patient Enrollment in OnCore

To be eligible for study enrollment, the patient must sign the treatment consent and meet each inclusion criteria and none of the exclusion criteria on the eligibility checklist (Appendix I) based on an eligibility assessment documented in the patient's medical record.

The Primary Clinical Research Coordinator (PCRC) or designee enters the study arm and adds the on treatment date in OnCore.

5.3 Patients Who Do Not Begin Study Treatment

If a patient is registered to the study and is later found unable to begin study treatment the patient will be removed from study and treated at the physician's discretion. The study staff will update OnCore of the patient's non-treatment status (off study). The reason for removal from study prior to starting study treatment will be clearly indicated in OnCore. The patient will be replaced to complete enrollment.

6 Treatment Plan

6.1 Study Drug Administration

Treatment will be administered on an outpatient basis. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's cancer. Patients will receive neoadjuvant treatment with cisplatin, gemcitabine and nivolumab every 21 days for 4 cycles over 12 weeks prior to radical cystectomy.

The sequence and time between gemcitabine and cisplatin administration is per institutional usual practice. On Day 8, nivolumab should be given after the chemotherapy with the time from the end of the chemotherapy and the start of the nivolumab infusion per institutional usual practice.

The patient's weight will be obtained on Day 1 or within the 3 days prior of each cycle. For Cycle 1 Day 1, the screening weight may be used. The patient's weight used for Day 1 dose calculation may also be used for Day 8 dosing. The adjustment of doses of gemcitabine and cisplatin based on weight change from Cycle 1 Day 1 weight can be done per Institutional standards.

For cycle 2 and beyond, Day 1 treatment may be given using a ± 3 day window.

Cisplatin is given at 70 mg/m^2 IV over 30 minutes on Day 1 every 21 days; however, based on treating physician's discretion, split-dose cisplatin can be given at 35 mg/m^2 IV Day 1 and Day 8 every 21 days for 4 cycles. Recommended dose of prophylactic dexamethasone (Decadron) up to 8 mg IV or PO on day of cisplatin treatment followed by up to 4 mg PO BID for 3 days. Other antiemetics may be given per the investigator's discretion and institutional guidelines.

Gemcitabine is given at 1000 mg/m^2 IV over 30 minutes on Day 1 and Day 8 every 21 days for 4 cycles. There should be a minimum of 7 days between gemcitabine doses with a + 3 day window for Day 8 treatment.

Nivolumab is given at a fixed dose of 360 mg IV over 30 minutes or per institutional practice on Day 8 after the chemotherapy (gemcitabine, and, if given, cisplatin) every 21 days for 4 cycles. Nivolumab should be given 60 min (±15 min) after the chemotherapy agent (gemcitabine or cisplatin if using a split-dose).

Prophylactic granulocyte colony stimulating factor (G-CSF) support will be allowed as standard of care based on treating physician's discretion.

Study treatment is permanently discontinued for any of the following situations:

- Any Grade 4 drug related adverse event – without exceptions
- Any grade neurologic event
- Any grade pneumonitis
- Recurrent Grade 2 or 3 immune-related adverse event (refer to Section 8 – Nivolumab Related Toxicity Management)

6.1.1 Criteria to Begin a New Treatment Cycle and Required Delays

The following criteria must be met prior to starting Day 1 of any cycle based on lab work performed on the day of treatment or up to 3 days prior to Day 1 treatment:

- ANC ≥ 1500 cells/mm^3 for Cycle 1 Day 1 only, ANC ≥ 1000 cells/mm^3 for Day 1 of all subsequent cycles.
- Hemoglobin ≥ 9 g/dl
- Platelet ≥ 100,000/mm^3
- Bilirubin ≤ 1.5 x ULN (≤ 3 x ULN if Gilbert's disease)
- Creatinine clearance ≥ 50 ml/min (beginning with Cycle 2, if CRCL ≥ 45, but < 50 ml/min with other criteria for treatment met, treatment may be administered with cisplatin/gemcitabine given at 75% dose per Section 7.2). Creatinine clearance is

calculated by the Cockcroft-Gault formula (CrCl = [140-age (years)] x actual weight (kg) / [72 x serum Cr (mg/dL)] (if patient is female multiply the above by 0.85). 24 hour urinary clearance can be obtained as well and the results from this can be used instead.

In addition, the patient must not have experienced unacceptable toxicity since Day 1 of the previous treatment cycle (defined as Grade 4 nivolumab related adverse event, any grade neurologic event, any grade pneumonitis or Recurrent Grade 2 or 3 immune-related adverse event) per Section 6.1.2.

For Cycle 2 and beyond, if any of the above criteria is not met, treatment is delayed 1 week and the patient re-evaluated. Treatment may be delayed for up to 3 weeks for a given cycle start. If after a 3 week delay the patient is still unable to restart treatment, the patient will be discontinued from study treatment. If a patient who has had a previous treatment cycle delay, requires a delay of more than 2 weeks in a subsequent cycle, the patient will be discontinued from study treatment.

6.1.2 Discontinuation of Treatment Due to Toxicity

Study treatment is permanently discontinued for any of the following:

- Any Grade 4 drug related adverse event – without exceptions
- Any grade neurologic event
- Any grade pneumonitis
- Recurrent Grade 2 or 3 immune-related adverse event (refer to Section 8 – Nivolumab Related Toxicity Management)

For Cycle 2 and beyond, if a patient is unable to receive nivolumab due to any of the above, the patient may continue to receive future cycles of cisplatin and gemcitabine on the study, if meet the criteria for receiving those drugs.

For Cycle 2 and beyond, if a patient cannot receive cisplatin and gemcitabine due to toxicities or patient refusal, the patient will be taken off study treatment and treated at the discretion of the medical provider.

Any patient receiving at least one dose of study treatment (nivolumab) will be included in the study's intention-to-treat (ITT) analysis.

6.2 Concomitant Medications and Supportive Care

Medications to prevent or reduce the severity of expected side effects for cisplatin, gemcitabine, and nivolumab, may be given per the package insert (Investigator Brochure for nivolumab) or institutional standards. Recommended dose of prophylactic dexamethasone (Decadron) up to 8 mg IV or PO on day of cisplatin treatment followed by up to 4 mg PO BID for 3 days. Other antiemetics can be given per Investigator's discretion and Institutional guidelines.

Hydration prior to cisplatin will be given using institutional guidelines and may include mannitol, electrolytes, or furosemide according to institutional practices.

Prophylactic granulocyte colony stimulating factor (G-CSF) support will be allowed as standard of care based on treating physician's discretion.

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care. During the study, supportive therapy can include antibiotics, analgesics, pain control, transfusions, psychotherapy, growth factors, hydration or any other symptomatic therapy as clinically indicated.

Steroids will be allowed to treat any immune-related adverse events from nivolumab as outlined in Section 8 for management of immune-relates adverse events. Use of ≤ 10 mg prednisone or equivalent dose of steroids is allowed for short-term use (< 7 days) as supportive care for issues other than immune-related adverse events.

6.3 Duration of Study Treatment and the End of Treatment Visit

Treatment consists of four 21 day treatment cycles of nivolumab in combination with gemcitabine and cisplatin given over approximately 12 weeks unless one of the following occurs:

- Patient experiences unacceptable toxicity as defined in Section 6.1.2
  - Any Grade 4 drug related adverse event
  - Any grade neurologic event
  - Any grade pneumonitis
  - Recurrent Grade 2 or 3 immune-related adverse event (refer to Section 8 – Nivolumab Related Toxicity Management)
- Patient is unable to receive nivolumab after at least 1 treatment cycle. In such situations, the patient may continue GC on treatment, provided they meet the criteria to continue.
- More than 3 weeks delay occurs between 2 treatment cycles OR requires a 2nd treatment delay between 2 cycles of more than 2 weeks
- Continuation of therapy is no longer in the best interest of the patient in the opinion of the treating investigator
- Patient withdraws consent or is non-compliant

An End of Treatment (EOT) visit will occur approximately 30 days after the last dose of nivolumab to assess for ongoing treatment related toxicity. However, per Section 12.7 serious adverse events (SAEs) or adverse event (AEs) that become SAEs must be assessed through the Final Study Visit (approximately 100 days after the last dose of nivolumab).

Any patient leaving the study prior to completing 4 treatment cycles will be treated as the physician's discretion. The patient is still considered on study (unless consent is

withdrawn) and will follow the study plan of pre-operative imaging and obtaining tissue samples at the time of surgery per Section 10.

6.4 Pre-Operative Imaging and Radical Cystectomy

After the completion of the treatment, but prior to the surgery, the patient will undergo a PET/CT or CT of the chest, abdomen and pelvis.

Radical cystectomy will be scheduled per surgeon's discretion as standard of care procedure, preferably within 6-8 weeks after completion of neoadjuvant chemotherapy. Tissue samples will be acquired for research related testing per Section 10.

6.5 Final Study Visit/Assessment 100 Days Post Nivolumab

A Final Study Visit occurs after surgery. Most visits will occur approximately 6 weeks post-surgery, but a visit outside of this timeframe is permissible. This visit also serves as the final assessment for nivolumab related serious adverse events (SAEs) or adverse event (AEs) that become SAEs through 100 days after the last dose of nivolumab per Section 12.7. After the final study visit, patients will be followed by record review until disease progression and then for survival only for 2 years from the time of cystectomy.

7 Dose Modifications and Delay Guidelines

No dose modifications are permitted for nivolumab but the dose may be skipped based on occurrence of significant immune-related AE as described in Section 8.

Management of toxicities from gemcitabine and cisplatin will be per the package insert and standard institutional guidelines.

The below dose modification guidelines serve as a general guideline only. The treating physician's discretion can be used to further modify the dose of cisplatin and gemcitabine. If a treatment cycle is delayed, all drugs should be delayed. In addition, after Cycle 1, cisplatin may be changed to split-dose schedule if, in Investigator's judgement, it would be better tolerated by patient.

7.1 Hematologic Toxicity (Cisplatin and Gemcitabine)

Day 1 Cycle 2 and subsequent cycles				
ANC		**Platelet count**	**Gemcitabine**	**Cisplatin**
≥1000/mm^3	and	≥100,000/mm^3	Give 100% dose	Give 100% dose
< 1000/mm^3	and/or	<100,000/mm^3	Delay new cycle start by 1 week per Section 6.1.1	Delay new cycle start by 1 week per Section 6.1.1

Day 8 of Cycle 1 and Subsequent Cycles*				
ANC		**Platelet count**	**Gemcitabine**	**Cisplatin (if using split-dose cisplatin)**
≥1,000/mm^3	and	≥ 75,000/mm^3	Give 100% dose	Give 100% dose
≥1,000/mm^3	and	50,000-74,999	Give 75% dose	Give 100% dose
<1,000/mm^3	or	< 50,000/mm^3	Skip treatment. Reduce dose by 25% for next treatment.	Skip treatment

*If a Day 8 gemcitabine/cisplatin is withheld due to hematologic toxicity the dose will not be made up. Only nivolumab will be administered on Day 8, unless criteria are met in Section 8 to also skip that dose.

G-CSF should be considered with subsequent cycles if a patient develops neutropenic complications in the immediate previous cycle.

If febrile neutropenia requiring antibiotic therapy or Grade 4 thrombocytopenia occurs, the cisplatin and gemcitabine dose will be reduced by 25% for subsequent treatment cycles.

7.2 Renal Impairment (Cisplatin and Gemcitabine)

Day 1 and Day 8 (after Cycle 1 Day 1)		
CrCl	**Gemcitabine**	**Cisplatin**
≥50 ml/mil	Give 100% dose	Give 100% dose
≥45 but <50 ml/min	Day 1: give 75% dose if all other criteria to start a new cycle is met per Section 6.2.1 Day 8: give 75% dose	Day 1: give 75% dose if all other criteria to start a new cycle is met per Section 6.2.1 Day 8 (if split dose): give 75% dose
<45 ml/min	Day 1: delay cycle start per Section 6.2.1 Day 8: skip treatment*	Day 1: delay cycle start per Section 6.2.1 Day 8 (if split dose): skip treatment*

**If a Day 8 gemcitabine/cisplatin is withheld due to renal impairment the dose will not be made up. Only nivolumab will be administered on Day 8, unless criteria are met in Section 8.2 to also skip that dose.

The weight from Day 1 can be used to calculate creatinine clearance on Day 8.

Cisplatin may be changed to split-dose schedule if, in Investigator's judgement, it would be better tolerated by patient.

7.3 Hepatic Impairment

No dose adjustments are required for cisplatin or gemcitabine.

Nivolumab does not need to be held for hepatic dysfunction, unless immune related hepatic AEs are suspected from nivolumab, then follow the Nivolumab related toxicity management as outlined in Section 8.

Discontinuation of treatment should be considered if drug induced liver injury is suspected (cisplatin, gemcitabine or nivolumab)

- ALT or AST >8 × ULN
- ALT or AST >5 × ULN for more than 2 weeks
- ALT or AST >3 × ULN and total bilirubin >2 × ULN or INR >1.5 (if INR testing is applicable/evaluated)
- ALT or AST >3 × ULN with the appearance of symptoms suggestive of liver injury (e.g. right upper quadrant pain or tenderness) and/or eosinophilia (>5%)

These treatment discontinuation recommendations are based on the FDA Guidance for Industry (Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009).

8 Nivolumab Related Toxicity Management

Immune-related adverse events (irAEs) from nivolumab will be managed depending on severity (NCI CTCAE V4.0 grading) as outlined below.

Note: if Nivolumab cannot be given on Day 8 of a cycle, dosing will be skipped for that cycle. Nivolumab dosing may be resumed no sooner than Day 8 of the next cycle.

Immune-Related (ir) Adverse Events Management – General Guidelines

Grade 1 to 2: Treat symptomatically or with moderate dose steroids, more frequent monitoring.

Grade 1 to 2 (persistent): Manage similar to Grade 3 to 4 irAE

Grade 3 to 4: Treat with high dose corticosteroids, typically 1-2 mg/kg of prednisone or IV steroid equivalent and

Grade 4 irAEs permanently discontinue treatment with nivolumab

Grade 3 irAEs requires withholding nivolumab except for any of the following: Transient (≤ 6 hours) Grade 3 flu-like symptoms or fever, which is controlled with medical management, transient (≤ 24 hours) Grade 3 fatigue, local reactions, headache, nausea, emesis that resolves to Grade ≤ 1 and single laboratory values out of normal range (excluding Grade ≥ 3 liver function test increase) that are unlikely related to study treatment according to the Investigator, do not have any clinical correlate, and resolve to Grade ≤ 1 within 7 days with adequate medical management

Any Grade 2 irAEs should be managed as follows:

If a Grade 2 irAE resolves to Grade ≤ 1 by the next planned cycle, treatment may continue.

If a Grade 2 irAE does not resolve to Grade ≤ 1 by the next planned cycle, treatment should be withheld at next cycle. If at the end of the following cycle the event has not resolved to ≤ Grade 1, the subject should permanently discontinue treatment with nivolumab (except for hormone insufficiencies, that can be managed by replacement therapy).

Upon the recurrence of the same Grade 2 irAE (except for hormone insufficiencies that can be managed by replacement therapy) in the same subject, treatment with nivolumab should be permanently discontinued.

Treatment of gastrointestinal, dermatological, pulmonary, hepatic and endocrine irAEs should follow guidelines in the following table.

GI irAEs		
Severity of Diarrhea/Colitis	**Management**	**Follow-up**
Grade 1 Diarrhea: < 4 stools/day over baseline Colitis: asymptomatic	Continue nivolumab therapy Symptomatic treatment (for example, loperamide)	Close monitoring for worsening symptoms Educate subject to report worsening immediately If worsens: Treat as Grade 2 or 3 to 4
Grade 2 Diarrhea: 4 to 6 stools per day over baseline; IV fluids indicated < 24 hours; not interfering with ADL Colitis: abdominal pain; blood in stool	Withhold nivolumab for the current cycle Symptomatic treatment	If improves to Grade ≤1: Resume nivolumab on Day 8 of the next cycle If worsens: treat as Grade 3 to 4
Grade 3 to 4 Diarrhea (Grade 3): ≥ 7 stools per day over Baseline; incontinence; IV fluids ≥ 24 hrs.; interfering with ADL Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs Grade 4: life-threatening, perforation	Grade 3: Withhold nivolumab for the current cycle Grade 4 or recurrent Grade 3: permanently discontinue nivolumab Begin methylprednisolone 1.0 to 2.0 mg/kg/day IV or equivalent Add prophylactic antibiotics for opportunistic infections Consider colonoscopy if needed	If improves, continue steroids until Grade < 1, then taper over at least 1 month, Resume nivolumab on Day 8 of the next cycle If worsens, persists > 3 to 5 days, or recurs after improvement, add infliximab 5 mg/kg (if no contraindication), Note: Infliximab should not be used in cases of perforation or sepsis
Dermatological irAEs		
Grade of Rash	**Management**	**Follow-up**
Grade 1 to 2 Covering for Grade 3 30% body surface area	Symptomatic therapy (for example, antihistamines, topical steroids) Continue nivolumab	If persists > 1 to 2 weeks or recurs: Consider skin biopsy Consider methylprednisolone 0.5 to 1.0 mg/kg/day IV or oral equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections. If worsens. treat as Grade 3 or 4
Grade 3 to 4 Covering > 30% Grade 4: body surface area; life threatening consequences	Grade 3: Skip nivolumab for the current cycle Grade 4 or recurrent Grade 3: Permanently discontinue nivolumab Consider skin biopsy Dermatology consult methylprednisolone 1.0 to 2.0 mg/kg/day IV or IV equivalent	If improves to ≤ Grade 1, taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections Resume nivolumab therapy Day 8 of next cycle for Grade 3

Pulmonary irAEs		
Grade of Pneumonitis	**Management**	**Follow-up**
Grade 1 Radiographic changes only	Permanently discontinue nivolumab per Section 6.1.2 Monitor for symptoms every 2 to 3 days Consider pulmonary and Infectious disease consults	If worsens, treat as Grade 2 or 3 to 4
Grade 2 Mild to moderate new symptoms	Permanently discontinue nivolumab per Section 6.1.2 Pulmonary and Infectious Disease consults Monitor symptoms daily, consider hospitalization methyl-prednisolone 1.0 mg/kg/day IV or oral equivalent Consider bronchoscopy, lung biopsy	When symptoms improve to Grade ≤1, taper steroids over at least 1 month If not improving after 2 weeks or worsening, treat as Grade 3 to 4
Grade 3 to 4 Severe new symptoms; New / worsening hypoxia; life-threatening	Permanently discontinue nivolumab per Section 6.1.2 Hospitalize Pulmonary and Infectious Disease consults methyl-prednisolone 2 to 4 mg/kg/day IV or IV equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	When symptoms improve to Grade ≤ 1, taper steroids over at least 1 month If not improving after 48 hours or worsening:, add additional immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil)
Hepatic irAEs		
Grade of Liver Test Elevation	**Management**	**Follow-up**
Grade 1 Grade 1 AST or ALT > ULN to 3.0 x ULN and/or total bilirubin > ULN to 1.5 x ULN	Continue nivolumab	Continue liver function monitoring If worsens, treat as Grade 2 or 3 to 4
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and / or total bilirubin > 1.5 to ≤ 3 x ULN	Skip nivolumab for the current cycle Increase frequency of monitoring to every 3 days	If returns Grade ≤ 1, resume routine monitoring, resume nivolumab on Day 8 of the next cycle If elevations persist > 7 days or worsens, methylprednisolone 0.5 to 1 mg/kg/day or oral equivalent and when LFT returns to Grade ≤ 1 taper steroids over at least 1 month, resume nivolumab on Day 8 of next cycle
Grade 3 to 4 AST or ALT > 5 x ULN and / or total bilirubin > 3 x ULN	Permanently discontinue nivolumab Increase frequency of monitoring to every 1 to 2 days methylprednisolone 1.0 to 2.0 mg/kg/day IV or IV equivalent Consult gastroenterologist Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted	If returns to Grade ≤1, taper steroids over at least 1 month If does not improve in > 5 days, worsens or rebounds, add mycophenolate mofetil 1 gram (g) twice daily If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines

Cardiac irAEs		
Myocarditis	**Management**	**Follow-up**
New onset cardiac signs/symptoms and/or new laboratory cardiac biomarker elevations (e.g. troponin, CK-MB, BNP) or cardiac imaging suggestive of myocarditis	Skip nivolumab for the current cycle Hospitalize. Cardiology consult to establish etiology and rule-out immune-mediated myocarditis, consider myocardial biopsy	If symptoms improve and immune-mediated etiology is ruled out, resume nivolumab Day 8 of next cycle. If symptoms do not improve or worsen, and immune-mediated etiology is suspected or confirmed manage as immune-mediated myocarditis.
Immune-mediated myocarditis	Permanently discontinue nivolumab Methylprednisolone 1 to 2 mg/kg/day.	Once improving, taper steroids over at least 1 month If no improvement or worsening, consider additional immunosuppressants (e.g. azathioprine, cyclosporine A)
Endocrine irAEs		
Endocrine Disorder	**Management**	**Follow-up**
Asymptomatic TSH abnormality	Continue nivolumab If TSH < 0.5 x LLN, or TSH > 2 x ULN, or consistently out of range in 2 subsequent measurements: include T4 at subsequent cycles as clinically indicated; consider endocrinology consult	
Hypophysitis **Grade 2 or 3**	Evaluate endocrine function Consider pituitary scan Withhold nivolumab 1 mg/day prednisone equivalents Initiate appropriate hormone therapy as indicated Consider Endocrinology consult	If improves (with or without hormone replacement): Taper steroids over at least 1 month Resume nivolumab on Day 8 of next cycle
Grade 4	Permanently discontinue nivolumab	
Adrenal Insufficiency **Grade 2**	Withhold nivolumab Evaluate endocrine function Consider Endocrinology consult	If improves to Grade ≤1, Resume nivolumab Day 8 of next cycle
Grade 3 or 4	Permanently discontinue nivolumab Consider Endocrinology consult prednisone 1 to 2 mg/kg/day or equivalents	

9 Schedule of Tests and Procedures

For Cycle 2 and beyond, Day 1 treatment may be given using a ±3 day window. Gemcitabine should be given on Day 1 and Day 8 of each cycle and there should be a minimum of 7 days between gemcitabine doses, with a + 3 day window for Day 8 treatment. The lab work for Day 1 may be performed the day of treatment or up to 3 days before.

The End of Treatment (EOT) may be performed any time prior to surgery but is targeted for approximately 30 days after the last dose of nivolumab. This visit also serves as the end of assessment for safety stopping rule events per Section 12.3.

A Final Study Visit occurs after surgery. Most visits will occur approximately 6 weeks post-surgery, but a visit outside of this timeframe is permissible. This visit also serves as the end of 100 day post-nivolumab monitoring for serious adverse events (SAEs) and adverse events (AE) that became serious per Section 12.7.

After the Final Study Visit, follow-up visits with disease assessments are per standard of care. Patients are followed for response until disease progression, and then survival status only for up to 2 years after surgery. This information may be obtained by in person visits, record review or other methods of obtaining disease and survival status.

	Screening within 28 days of Cycle 1 Day 1	**Every Treatment Cycle**		**End of Treatment visit** prior to surgery (~ 30 days after last nivo dose)	**Final Study Visit and Final SAE Assessment** at time of SOC post-surgery (~120 day after last dose nivo)	**Follow-up every 3 months**[13] from surgery per SOC until PD, then survival only for 2 years from surgery
		Day 1	**Day 8**			
REQUIRED ASSESSMENTS						
Informed Consent	X					
Medical history	X					
Eligibility Confirmation	X					
Prior treatment	X					
Physical exam	X	X	X	X	X	
Weight (Height also during screen)	X	X[1]				
Concomitant medications	X	X	X	X	X	
ECOG performance status	X	X		X	X	
ECG –single, at rest	X					
Audiology Assessment (refer to Section 4.2 #2)	X					
Assessment of AEs		X	X	X	X[2]	
Assessment for safety stopping rule events		X	X	X		
LABORATORY ASSESSMENTS						
Complete Blood Count with diff (CBC)	X	X[3]	X	X	X	
Comprehensive Metabolic Profile (CMP)[3]	X	X[3]	X	X	X	
LDH, phosphorus, Mg	X	X	X		X	
ACTH stimulation test				X[11]		
TSH	X				X	
INR, aPTT	X				X	
Hepatitis B, C, HIV serology	X					
Creatinine clearance	X	X	X[12]			
Pregnancy test (urine) WOCBP	X[5]	X[6]				
RESPONSE ASSESSMENT AND SURVIVAL STATUS						
CT of chest, abdomen and pelvis or PET/CT	X			X	X (optional – if performed for SOC)	X
Survival status						X
TREATMENT EXPOSURE						
Gemcitabine		X	X[1]			
Cisplatin		X	X[1,7]			
Nivolumab			X			
CORRELATIVE STUDIES						
Blood and tissue collection (TURBT)[8]	X					
GenomeDx from TURBT[9] (SOC)	X					
Tissue collection[10]	X				X	

1. Weight from Day 1 (or within 3 days prior or screening weight if Cycle 1) may be used to calculate the doses of the Day 8 gemcitabine and if given, cisplatin. No adjustment in dose is required if < 10% weight change from Cycle 1 Day 1 weight.
2. Per Section 12.4 BMS requires monitoring for Serious Adverse Events (SAEs) through 100 days of discontinuation of nivolumab dosing.
3. If screening (baseline) labs were performed within 7 days of Day 1 of treatment, these do not need to be repeated; For Cycle 2 or later, lab work may be performed up to 3 days prior to Day1
4. CMP to include sodium, potassium, chloride, creatinine, blood urea nitrogen; liver function tests (LFTs) to include AST, ALT, total bilirubin, alkaline phosphatase
5. For women of childbearing potential (WOCBP): urine pregnancy test within 14 days prior to study enrollment. If a urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
6. Women of childbearing potential must get a pregnancy test at each Cycle.
7. Cisplatin will be given on Day 1, unless using split-dose when it will be given on Day 1 and Day 8
8. Whole blood (5 cc in EDTA tube for germline DNA extraction) and archival tissue from TURBT or fresh tissue will be collected for WES and shipped to UMN (Section 10.2)
9. The archival tissue from TURBT will be sent for molecular subtyping using Deciper testing from Genome Dx directly from all sites.
10. 20-25 formalin-fixed paraffin embedded (FFPE) slides of 5-10 microns in thickness from TURBT and radical cystectomy tissues will be stored for future correlative studies
11. Required of all patients at the final End of Treatment visit (pre-surgery); if abnormal, manage as medically appropriate
12. Estimated creatinine clearance by Cockcroft-Gault formula (use cycle's Day 1 actual weight for calculating Day 8) or by 24 hour collection urine collection
13. Follow-up after the final treatment visit is by in person visits, record review or other methods of obtaining disease and survival status

Refer to the Laboratory Manual for complete details of research sample handling and shipping.

10 Correlative Research Studies

10.1 Molecular Subtyping of Bladder Cancer Using Decipher® Bladder Cancer Classifier

We will evaluate molecular subtypes associated with resistance to platinum-based neoadjuvant chemotherapy in patients with MIBC and evaluate whether addition of nivolumab alters the response to neoadjuvant therapy. Decipher® Bladder is a Genomic Subtyping Classifier (GSC) that uses whole transcriptome oligonucleotide microarrays interrogating the RNA expression of 149 gene-level biomarkers. The test provides a molecular genomic classification of Muscle Invasive Bladder Cancer Tumors (MIBC) from TURBT samples. The tissue is classified into one of four molecular subtypes namely, (a) Basal, (b) Basal Claudin-Low (c) Luminal, and (d) Luminal Infiltrated, based on the functional molecular pathways. These molecular subtypes may predict response to neoadjuvant cisplatin-based chemotherapy in bladder cancer patients. Decipher® Bladder, which is based on the consensus of two previously established classification systems UNC (Damrauer et al 2014) and TCGA (Cancer Genome Atlas Research Network 2014), was developed as a single sample classifier from TURBT specimens of 223 muscle invasive bladder cancer patients treated with neoadjuvant chemotherapy and radical cystectomy from five different institutions. Independent validation was performed in 82 MIBC patients from two institutions.[19] Luminal tumors had the best OS independent of neoadjuvant chemotherapy, and patients with tumors classified as UNC basal, MDA basal and TCGA cluster III experienced the greatest improvement in overall survival after neoadjuvant chemotherapy compared to surgery alone. Tumors assigned as UNC claudin-low had the worst overall survival irrespective of treatment regimen. This data provides an insight into benefit form neoadjuvant cisplatin-based chemotherapy. We will be studying for the 1st time whether addition of immunotherapy to cisplatin-based chemotherapy alters the impact on outcomes in different molecular subtypes. [19]

The following work plan will be used for performing the molecular subtyping using Decipher® Bladder Cancer Classifier

Specimen selection

Select the TURBT specimen that was used to make the decision to treat the patient with radical cystectomy and contains tumor within the muscularis propria. Re-evaluate the H&E slide most representative of the blocks current tissue level and select the appropriate block with:

a) Tumor invading the muscularis propria bladder wall
b) Largest area of representative muscularis propria invasive tumor
c) Tumor focus with at least 50% tumor cell content

Pathology sampling

Tissue sampling will be performed according to the pathology instructions detailed in the Study's Laboratory Manual. Briefly, for each patient specimen 2 X 1.5 mm in diameter punch (e.g., as obtained with a tissue microarray coring device or GenomeDx provided

punch tools) will be sampled and placed in separate Eppendorf microfuge tubes. Alternatively, 9 x 5um sections and 1 x HE representative of the block may be provided for macrodissection. Tissue punches/sections must be stored at 4°C until shipment (and then shipped with cold gel packs).

Note: Tissue blocks may be submitted to GenomeDx pathology department to perform the appropriate sampling.

Tissue logistics

All blocks, tissue cores or sections will be sent to the GenomeDx Biosciences CAP/CLIA certified laboratory located in San Diego, CA. The punch cores or sections will be used for the transcriptome-wide expression analysis. RNA will be extracted from a single 1.5 mm punch. For situation where not enough RNA or QC failures, the second 1.5mm punch will be extracted.

Transcriptome-wide analysis of FFPE specimens

The transcriptome-wide expression analysis will be performed using GenomeDx's clinical-grade high-density oligonucleotide microarray expression platform and cloud-based informatics pipeline. The extracted RNA will be used as template for whole transcriptome amplification and hybridization to 1.4 million feature gene expression microarrays. GenomeDx will perform quality control on the raw microarray data. Samples that fail array QC will be re-amplified from a second aliquot of RNA. After generation of all the array data and QC analysis, the Decipher® Bladder algorithm is applied. Decipher® Bladder detects the expression of 149 pre-specified gene-level biomarkers and uses a generalized linear model with elastic net regularization (GLMNET) to derive probability scores for each of the subtypes. For each patient sample, four scores will be generated. The score, represented by a value between 0% and 100%, indicates the likelihood of the sample belonging to each of the four subtypes. While the subtype with the highest probability is designated as the 'true' subtype, the probabilities for each subtype will also be reported.

Unused tissue specimens or tissue derivatives (e.g., RNA) will be returned by GenomeDx to the submitting institution.

Sampling Instructions for affiliate sites will be provided in the Laboratory Manual Tissue will be shipped directly from affiliate sites to GenoneDx.

10.2 Whole Exome Sequencing (WES)

We will sequence tumor (FFPE or fresh) and matched normal samples (obtained from a peripheral blood sample) from patients enrolled in the trial. DNA extracted from tumor samples will be sequenced to an average depth of 150X and the DNA extracted from the matched normal tissue (peripheral blood) to a mean depth of 50X. Bioinformatics analysis will be conducted to eliminate germline variants and construct an index of mutational load based on the number of somatic single nucleotide substitutions and short indels. The mutational load will likely be defined iteratively based on the percentage of tumor cells that harbor particular mutations to identify an optimal mutational load index.

Samples are shipped the day of the collection (Monday-Thursday) for next day delivery to Dr. Bharat Thyagarajan's lab at the University of Minnesota. The archival tissue and whole blood is shipped with the pre-treatment blood sample. Refer to the Laboratory Manual for Dr. Thyagarajan's lab address and additional details.

10.3 PD-L1 Testing of Baseline Pre-Treatment Tumor Tissue

Tumor tissue slides from TURBT will be sent out to Quest Diagnostics to evaluate PD-L1 status using IHC 28-8 pharmDx immunohistochemistry test, available through Dako. We will determine correlation between PD-L1 expression and response to nivolumab.

10.4 Nanostring Pancan Immune Panel Gene Expression

Archival/fresh tissue from TURBT and fresh tissue from the radical cystectomy will be stored for future evaluation with Nanostring pancan immune panel gene expression.

11 Drug Formulation, Availability, and Preparation

11.1 Gemcitabine

Refer to the FDA-approved package insert for gemcitabine for product information, extensive preparation instructions, and a comprehensive list of adverse events.

Gemcitabine is a nucleoside analogue in the pyrimidine antimetabolite class which is S-phase specific. Its phosphorylated product is incorporated into DNA and interferes with DNA synthesis. Gemcitabine also exhibits self-potentiation by causing an enzymatically-mediated reduction in the intracellular nucleotide pool.

Availability

Gemcitabine is commercially supplied as a powder for reconstitution in 200 and 1 gram vials.

Storage and Stability

Intact vials containing sterile powder are stored at room temperature. When prepared as directed, reconstituted vials are reportedly stable for 35 days at room temperature and protected from light. Further diluted solutions of gemcitabine are stable for up to 7 days at room temperature when protected from light. However, the manufacturer recommends that solutions be used within 24 hours. The diluted solution should be clear and colorless to light straw-colored solution.

Preparation and Administration

Gemcitabine will be prepared and administered intravenously according to institutional guidelines.

11.2 Cisplatin

Refer to the FDA-approved package insert for cisplatin for product information, extensive preparation instructions, and a comprehensive list of adverse events.

Cisplatin is a platinum-containing heavy metal complex which acts as an alkylating agent. Cisplatin inhibits DNA synthesis by the formation of interstrand and intra-strand DNA crosslinkages, denaturation of the DNA double helix, and covalent binding to DNA bases.

Availability

Cisplatin is commercially available as a 1 mg/mL concentration aqueous injection in multi-dose vials of 50 mL, 100 mL, and 200 mL.

Storage and Stability

Intact vials should be stored at room temperature and be protected from light. Solutions diluted in 0.9% or 0.45% NaCl to a concentration of 0.05-2mg/mL are stable for up to 72 hours at room temperature and protected from light.

Preparation and Administration

Cisplatin is to be administered as an intravenous infusion according to institutional practice. Patients should receive intravenous hydration with at least 1 L of NaCl prior to cisplatin. Needles, syringes, catheters, or IV administration sets containing aluminum parts should not be used, as contact with cisplatin yields a black precipitate.

11.3 Nivolumab

Nivolumab is a PD-1 blocking antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2.

Availability

Nivolumab will be provided as investigational supply for this study by Bristol-Myers Squibb without cost.

Storage and Stability

Nivolumab must be dispensed only from official study sites and to eligible patients under the supervision of the site investigator. Nivolumab should be stored in a secure area according to local regulations. It is the responsibility of the site investigator to ensure that study drug is only dispensed to patients on this study.

Store nivolumab under refrigeration at 2°C to 8°C (36°F to 46°F). Protect nivolumab from light by storing in the original package until time of use. Do not freeze.

The product does not contain a preservative. The administration of nivolumab infusion must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored under refrigeration conditions (2°C to 8°C, 36°F to 46°F) for up to 24 hours, and a maximum of 8 hours of the total 24 hours can be at room temperature

(20°C to 25°C, 68°F to 77°F) and room light. The maximum of 8 hours under room temperature and room light conditions includes the product administration period.

Administration

Refer to the current Investigator Brochure for the most up to date information.

Nivolumab is to be administered as an intravenous infusion over 30 minutes or per institutional practice.

Toxicities

Refer to the current Investigator Brochure for the most up to date information.

The most common (>10%) adverse events reported in patients treated with Nivolumab are: rash, pruritus, cough, upper respiratory tract infection and peripheral edema. Laboratory abnormalities reported in >10% of patients include increased AST, increased alkaline phosphatase, hyponatremia, increased ALT and hyperkalemia.

12 Adverse Event Monitoring, Documentation, and Reporting

Toxicity and adverse events will be classified and graded according to NCI's Common Terminology Criteria for Adverse Events V 4.0 (CTCAE) and reported on the schedule below. A copy of the CTCAE can be downloaded from

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

The following definitions of adverse events (AEs) and serious adverse events (SAEs) will determine whether the event requires expedited reporting via the OnCore SAE Report Form in addition to routine documentation in the OnCore AE case report form (CRF).

12.1 Adverse Event and Deviation Terminology

An AE is any untoward medical occurrence or worsening of a pre-existing medical condition in a subject. AE will be graded using the National Cancer Institute CTCAE version 4.0. A laboratory test abnormality considered clinically relevant, e.g., causing the subject to withdraw from the study, requiring treatment or causing apparent clinical manifestations, or judged relevant by the investigator, should be reported as an AE.

Serious Adverse Event (SAE)

AEs are classified as serious or non-serious. A serious adverse event (SAE) is any AE that is:

1. fatal
2. life-threatening
3. requires or prolongs hospital stay
4. results in persistent or significant disability or incapacity
5. a congenital anomaly or birth defect
6. an important medical event. Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may

jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

Unexpected Event: An AE or SAE or suspected AE is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

The categories for AE attribution are as follows:

- Definite
- Probable
- Possible
- Unlikely
- Unrelated

Major Deviation: A deviation or violation that impacts the risks and benefits of the research; may impact subject safety, affect the integrity of research data and/or affect a subject's willingness to participate in the research. Deviations that place a subject at risk, but do not result in harm are considered to be major deviations.

Minor Deviation: A deviation or violation that does not impact subject safety, compromise the integrity of research data and/or affect a subject's willingness to participate in the research.

12.2 Event Monitoring and Documentation

Adverse event monitoring and documentation begins with the patient's written consent to participate in the study through 30 days after the last dose of nivolumab or the End of Treatment visit, whichever is shorter. Patients will continued to be monitored for Serious Adverse Events (SAEs) through 100 days of discontinuation of dosing of nivolumab (per Section 12.4) or the Final Study visit, whichever is shorter.

Adverse events related to the surgery are not documented unless they are felt to be due to the study treatment.

For the purposes of this study, AE documentation requirements will be determined based on grade, expectedness and relationship to each of the study drug (nivolumab, cisplatin and gemcitabine):

	CTCAE Grade 1	CTCAE Grade 2		CTCAE Grade 3		CTCAE Grade 4 and 5
	Expected or Unexpected	Expected	Unexpected	Expected	Unexpected	Expected or Unexpected
Unrelated Unlikely	Not required	Not required	Not required	Not required	Required	Required
Possible Probable Definite	Not required	Not required	Required	Required	Required	Required

In addition any event meeting the definition of a serious adverse event (SAE) regardless of attribution that occurs during this period will be documented in the source document and recorded in OnCore.

After the End of Treatment visit, monitoring for adverse event will become less frequent based on the schedule in Section 9.

12.3 Safety Stopping Rule Events Documentation and Reporting Requirements

The following events at or prior to the End of Treatment visit count toward an early study stopping rule per Section 15.2.6 and must be reported to the MCC Affiliate Sites Manager using the Early Stopping Rule Form found OnCore under the reports tab:

- Grade 3 or 4 neutropenia
- Grade 3 or 4 thrombocytopenia
- Grade 3 or 4 anemia
- Grade 3 or 4 non-hematologic toxicities

An event that counts toward an early stopping rule does not necessarily constitute a SAE and should be reported as such only if they meet the criteria for reporting as defined in Section 12.6.

12.4 Additional BMS Requirements for Nivolumab

Non-serious Adverse Event Collection and Reporting

The collection of non-serious AE (AE that is not an SAE) information should begin at initiation of study drug. All non-serious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 30 days following the last dose of study treatment.

Non-serious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate.

Laboratory Test Abnormalities

All laboratory test results captured as part of the study should be recorded following institutional procedures. Test results that constitute SAEs should be documented and reported as such.

The following laboratory abnormalities should be documented and reported appropriately:

- any laboratory test result that is clinically significant or meets the definition of an SAE
- any laboratory abnormality that required the subject to have study drug discontinued or interrupted
- any laboratory abnormality that required the subject to receive specific corrective therapy.

Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a non-serious or serious AE, as appropriate, and reported accordingly.

Serious Adverse Events (SAEs)

BMS requires monitoring for Serious Adverse Events (SAEs) that occur following the subject's written consent to participate in the study through 100 days of discontinuation of nivolumab dosing.

12.5 Institutional Event Reporting

The SAE Report Form found in OnCore (not MedWatch) is used for this study. Individual institutional sites are responsible for reporting any event meeting local reporting requirements to their institutional IRB and/or other research oversight committees.

Event Type	Reporting Timeframe	Form in OnCore to Use	Report to
Any event meeting the definition of a SAE within 100 days of discontinuing nivolumab	Within 24 hours of knowledge	SAE Report Form	Masonic Cancer Center (MCC) Affiliate Sites Manager affiliates@umn.edu Local institutional IRB or other entities per institutional policies and guidelines.
Event counting toward the safety stopping rule as defined in Section 12.3	Within 24 hours of knowledge	Stopping Rule Event Form	
Major Deviations, as defined in Section 12.1.	Within 5 working days of knowledge	Deviation Report Form	
Minor Deviations, as defined in Section 12.1.	Per Institutional Policy	n/a (record in Deviations Tab) but it is not necessary to report the event to MCC	For UMN MCC only: minor deviations are reported to the UMN IRB by the study's regulatory specialist per IRB reporting requirements. For Affiliate Sites: minor deviations are not reportable to the Masonic Cancer Center. Report to local institutional IRB or other entities per institutional policies and guidelines.

12.6 MCC Reporting Requirements

As the study sponsor, the Masonic Cancer Center has the following expedited reporting responsibilities for events reported in Section 12.5.

Agency	Criteria for reporting	Timeframe	Form to Use	Submission address/ fax numbers
UMN IRB (UMN patients only)	Unanticipated death of a locally enrolled subject(s); New or increased risk; Any adverse event that require a change to the protocol or consent form – refer to the IRB website for complete details Deviations that occur at MCC meeting the IRB's reporting requirements.	5 Business Days	IRB Report Form	irb@umn.edu
FDA	Unexpected and fatal or unexpected and life threatening suspected adverse reaction	no later than 7 Calendar Days	MedWatch Form 3500A	Submit to FDA as an amendment to IND with a copy to BMS and each affiliate institution
	1) Serious and unexpected suspected adverse reaction or 2) increased occurrence of serious suspected adverse reactions over that listed in the protocol or investigator brochure or 3) findings from other sources (other studies, animal or in vitro testing)	no later than 15 Calendar-Days		
BMS	Refer to Sections 12.7			
Masonic Cancer Center SAE Coordinator	Events that count toward the early study stopping rule.	At time of reporting	Stopping Rule Event Form	mcc-saes@umn.edu

In each IND safety report, the sponsor must identify all IND safety reports previously submitted to the FDA concerning a similar suspected adverse reaction and must analyze the significance of the suspected adverse reaction in light of the previous, similar reports or other relevant information.

12.7 BMS Reporting Requirements

NOTE for Affiliate Sites: All reports are submitted to the University of Minnesota Masonic Cancer Center (MCC) Affiliate Sites Manager (affiliates@umn.edu) who will be responsible for forwarding reportable events to BMS and other entities as applicable.

- All Serious Adverse Events (SAEs) that occur following the subject's written consent to participate in the study through 100 days of discontinuation of dosing must be reported to BMS Worldwide Safety (worldwide.safety@bms.comaebusinessprocess@bms.com.
- Medwatch or CIOMS should be used to report SAEs. The BMS protocol ID number must be included on whatever form is submitted by the Sponsor/Investigator.
- Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, are collected, including those thought to be associated with protocol-specified procedures. The investigator should report any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure.

- In accordance with local regulations, BMS will notify investigators of all reported SAEs that are suspected (related to the investigational product) and unexpected (ie, not previously described in the IB). In the European Union (EU), an event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Investigator notification of these events will be in the form of an expedited safety report (ESR).
  - Other important findings which may be reported by the as an ESR include: increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical (eg, animal) study, important safety recommendations from a study data monitoring committee, or sponsor decision to end or temporarily halt a clinical study for safety reasons.
  - Upon receiving an ESR from BMS, the investigator must review and retain the ESR with the IB. Where required by local regulations or when there is a central IRB/IEC for the study, the sponsor-investigator will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.
  - In addition, suspected serious adverse reactions (whether expected or unexpected) shall be reported by BMS to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS within 1 business day of receipt at the University of Minnesota. SAEs and pregnancies must be recorded on a MedWatch or CIOMS Form.
SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: 609-818-3804

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the BMS (or designee) using the same procedure used for transmitting the initial SAE report.

For studies conducted under an Investigator IND in the US, any event that is both serious and unexpected must be reported to the Food and Drug Administration (FDA) as soon as possible and no later than 7 days (for a death or life-threatening event) or 15 days (for all other SAEs) after the investigator's or institution's initial receipt of the information. BMS will be provided with a simultaneous copy of all adverse events filed with the FDA.

SAEs should be reported on MedWatch Form 3500A, which can be accessed at: http://www.accessdata.fda.gov/scripts/medwatch/.

MedWatch SAE forms should be sent to the FDA at:
MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787
Fax: 1-800-FDA-0178 (1-800-332-0178)
http://www.accessdata.fda.gov/scripts/medwatch/

All SAEs should be followed to resolution or stabilization.

- An SAE report should be completed for any event where doubt exists regarding its seriousness.
- For studies with long-term follow-up periods in which safety data are being reported, include the timing of SAE collection in the protocol.
- If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.
- If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)
- If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to BMS using the same procedure used for transmitting the initial SAE report. All SAEs should be followed to resolution or stabilization. All SAEs should be followed to resolution or stabilization.

Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs. Potential drug induced liver injury is defined as:

1) ALT or AST elevation > 3 times upper limit of normal (ULN)
AND

2) Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)
AND

3) No other immediately apparent possible causes of AST/ALT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 5 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety).

The investigator must immediately notify Worldwide Safety @BMS.com of this event via the MedWatch or CIOMS Form in accordance with SAE reporting procedures.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form [provided upon request from BMS].

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE.

13 Study Data Collection and Monitoring

13.1 Data Management

This study will collect regulatory and clinical data using University of Minnesota CTSI's instance of OnCore® (Online Enterprise Research Management Environment).

The OnCore database resides on dedicated secure and PHI compliant hardware consisting of 3 physical servers: dev, DR, and production. All the data servers are managed by the Academic Health Center – Information Systems (AHC-IS) virtual servers which utilize clustered infrastructure to provide real-time failover of virtual servers. All relevant AHC IS procedures related for PHI compliant servers (as required by the Center of Excellence for HIPAA Data) apply to OnCore databases.

The integrated data will be stored in PHI compliant servers managed by AHC IS with access given to those authorized users in the Clinical and Translation Science Institute Informatics team (CTSI BPIC and MCC CISS). The data will be integrated and extracted to researchers through the CTSI Informatics team and will be delivered through secure and compliant mechanisms (e.g. AHC IE data shelter, BOX, sftp, etc). If data de-identification is needed, then compliant AHC IE data de-identification tools will be used. The informatics team will grant the IRB approved study team members access to data.

Key study personnel are trained on the use of OnCore and will comply with protocol specific instructions embedded within the OnCore.

13.2 Case Report Forms

Participant data will be collected using protocol specific electronic case report forms (e-CRF) developed within OnCore based on its library of standardized forms. The e-CRF will be approved by the study's Principal Investigator and the Biostatistician prior to release for use. The Primary Clinical Research Coordinator or designee will be responsible for registering the patient into OnCore at time of study entry, completing e-CRF based on the patient specific calendar, and updating the patient record until patient death or end of required study participation.

13.3 Data and Safety Monitoring Plan (DSMP)

The study's Data and Safety Monitoring Plan will be in compliance with the University of Minnesota Masonic Cancer Center's Data & Safety Monitoring Plan (DSMP), which can be accessed at http://z.umn.edu/dmsp.

For the purposes of data and safety monitoring, this study is classified as high risk (under a locally held IND). Therefore the following requirements will be fulfilled:

- At least quarterly review of the study's progress by the Masonic Cancer Center Data and Safety Monitoring Council (DSMC).
- The University of Minnesota (lead site) Sponsor/Investigator will comply with at least twice yearly monitoring of the study by the Masonic Cancer Center monitoring services.
- The local site PIs will comply with at least twice yearly monitoring of the project by the site's internal monitoring staff or by the Masonic Cancer Center monitoring services.
- The Masonic Cancer Center PI will oversee the submission of all reportable adverse events per Section 12.6 to the Masonic Cancer Center's SAE Coordinator, the University of Minnesota IRB, BMS, and the FDA.
- The PI with the CTO has oversight responsibility for trial monitoring at affiliate sites

IND Annual Reports

In accordance with regulation 21 CFR § 312.33, the Sponsor-Investigator (Dr. Gupta) will submit a progress report annually. The report is to be submitted within 60 days of the anniversary date that the IND went into effect.

13.4 Affiliate Site Monitoring

The PI (Dr. Shilpa Gupta) with the Clinical Trials Office (CTO) has oversight responsibility for trial monitoring at affiliate sites.

Affiliate sites that are a NCI designated cancer center may self-monitor using their institutional Data and Safety Monitoring Plan or monitoring may be done by the Masonic Cancer Center monitoring services. Refer to the University of Minnesota Masonic Cancer Center Data and Safety Monitoring Plan (DSMP - http://z.umn.edu/dmsp) and the CTO Affiliate and Satellite Site Monitoring SOPs for additional details.

The investigator will permit study-related monitoring, audits, and inspections by the study's Principal Investigator and/or IND sponsor and/or any designees, the local IRB, government regulatory bodies, and University of Minnesota compliance groups. The investigator will make available all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data, etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.) will be available for trial related monitoring, audits, or regulatory inspections. Routine teleconferences may be arranged to discuss patient updates with lead and affiliate sites.

13.5 Record Retention

The investigator will retain study records including source data, copies of case report form, consent forms, HIPAA authorizations, and all study correspondence in a secured facility for at least 6 years after the study file is closed with the IRB and FDA.

Please contact the Masonic Cancer Center CTO before destroying any study related records.

14 Study Endpoints

14.1 Primary Endpoint

Pathologic response (PaR) - defined as pathologic downstaging to <pT1pN0, which includes pT0, pT1,pTa and pTis.

14.2 Secondary Endpoints

- To determine the safety of nivolumab when given with gemcitabine/cisplatin as neoadjuvant therapy in patients with muscle invasive bladder cancer prior to radical cystectomy.
- To determine the progression free survival (PFS) measured from the date of radical cystectomy to date of progression or death from disease recurrence based on RECIST.

14.3 Exploratory Endpoints

- Whole Exome Sequencing (WES) of the pre-treatment bladder cancer biopsy tissue and its correlation with response.
- Evaluate molecular subtypes associated with resistance to platinum-based neoadjuvant chemotherapy in patients with MIBC and evaluate whether addition of nivolumab alters the response to platinum-based neoadjuvant therapy.
- PD-L1 expression in tumor tissue at baseline and correlation with response to therapy.
- Nanostring pancan immune panel gene expression at baseline and at cystectomy (archival biopsy and any fresh residual tumor at cystectomy).

15 Statistical Considerations

15.1 Study Design and Sample Size Considerations

This trial will use a single-arm, one-stage design. For the purposes of the design, we specify a null response rate of 0.35 and an alternative hypothesis of 0.55. Historical pathologic response rates of pT1 or less with cisplatin based chemotherapy are around 35%. [1,2,7] We propose that the addition of nivolumab to gemcitabine and cisplatin as neoadjuvant therapy in MIBC patients would lead to an increase in the pathologic response rates to 55% at cystectomy. A total of 41 subjects will be enrolled and we will test the null hypothesis using Fisher's exact test, in which case we will reject the null hypothesis if at least 20 of 41 subjects have a tumor response. This design will provide 83% power to reject the null hypothesis of a response rate of 0.35, assuming an alternative hypothesis of a response rate of 0.55 and a type-I error rate of 0.05.

15.2 Statistical Analysis

15.2.1 General Considerations

The analysis of the primary, secondary and correlation endpoints will be completed using all evaluable patients. Evaluable patients are defined as patients that receive at least one dose of nivolumab. All statistical analyses will be completed using SAS 9.1 (Cary, NC, USA) or the R statistical programming language.[20] P-values less than 0.05 will be considered statistically significant unless otherwise noted.

15.2.2 Analysis of the Primary Endpoint

Pathologic response will be summarized by the pathologic response rate (PAR) as estimated by the sample proportion with exact 95% confidence intervals. Hypothesis testing of the PAR will be completed using Fisher's exact test with a null hypothesis of a PAR less than or equal to 0.35. Secondary analyses of the PAR will involve univariate tests of the association between demographic and baseline clinical covariates and the PAR using Fisher's exact test or the two-sample t-test, as appropriate. Multivariate associations between demographics and baseline clinical covariates will be estimated by logistic regression.

15.2.3 Analysis of Secondary Endpoints

The analysis of secondary endpoints will be primarily descriptive. Binary endpoints (radiological response, adverse events, etc.) will be tabulated and summarized by the sample proportion with exact 95% confidence intervals. Progression free survival (PFS) will be summarized by the Kaplan-Meier curve. In addition, we will also complete secondary analyses to evaluate the univariate and multivariate associations between demographic and baseline clinical covariates and secondary endpoints using logistic regression for binary endpoints (radiological response, adverse events, etc.) or cox proportional hazards regression for survival endpoints (PFS), as appropriate.

15.2.4 Analysis of Exploratory Endpoints

We will evaluate the association between correlative endpoints (whole exome sequencing, molecular subtyping and PD-L1 status) and the primary and secondary endpoints. Univariate and multivariate associations will be evaluating using logistic or Cox proportional hazards regression, as appropriate. This analysis is exploratory and we therefore will not apply a multiple comparison adjustment to the p-values for the analysis of correlative.

15.2.5 Subgroup Analysis

We will complete a pre-planned subgroup analysis of all endpoints by clinical stage (T2 vs. T3 and T4). The analyses within subgroup will follow the analytical approach described in Sections 15.2.2 -15.2.4. Multivariate analysis within subgroups will be dependent on the presence of an adequate sample size within subgroups. This trial is not adequately powered to detect significant differences within subgroup and, therefore, subgroup analyses will be considered exploratory and p-values will not be adjusted for multiple comparisons.

15.2.6 Safety Stopping Rule

The background AE rate for gemcitabine/cisplatin (GC) is high, whereas the rate of Grade 3 and 4 AEs for Nivolumab is 10%. Therefore, our safety stopping rules will be based on the expected rate of toxicity assuming that the two drugs do not act synergistically. Safety stopping will be based on the rate of Grade 3 and 4 neutropenia, thrombocytopenia and anemia and non-hematologic toxicities of Grade 3 or 4.

Hematologic Toxicities:
Pocock-type sequential stopping boundaries will be used to monitor the toxicity rate and accrual will be halted if excessive number of adverse events are observed at or prior to the End of Treatment visit.[21] For neutropenia and thrombocytopenia, we will stop the trial if there is strong evidence that the rate of Grade 3 and 4 AEs exceeds 0.64 and for anemia, we will stop the trial if there is strong evidence that the rate of Grade 3 and 4 AEs exceeds 0.4.

The corresponding stopping boundaries can be found in the table provided below. These rates were chosen based on the published rate of Grade 3 and 4 AEs for GC and assuming a 10% grade 3-4 AE rate for nivolumab. The probability of crossing the stopping

boundaries for neutropenia or thrombocytopenia is 0.05 if the true rate is 0.64 and 0.60 if the true rate is 0.80 and the probability of crossing the stopping boundaries for anemia is 0.05 if the true rate is 0.40 and 0.73 if the true rate is 0.60.

Number of Subjects	# of Grade 3 and 4 Neutropenia to stop	# of Grade 3 and 4 Thrombocytopenia to stop	# of Grade 3 and 4 Anemia to stop
1	-	-	-
2	-	-	-
3	-	-	-
4	-	-	-
5	-	-	5
6	-	-	6
7	-	-	7
8	-	-	7
9	-	-	8
10	10	10	8
11	11	11	9
12	12	12	10
13	13	13	10
14	13	13	11
15	14	14	11
16	15	15	12
17	16	16	12
18	17	17	13
19	17	17	13
20	18	18	14
21	19	19	14
22	20	20	15
23	20	20	15
24	21	21	16
25	22	22	16
26	23	23	17
27	23	23	18
28	24	24	18
29	25	25	19
30	26	26	19
31	26	26	20
32	27	27	20
33	28	28	21
34	28	28	21
35	29	29	22
36	30	30	22
37	31	31	22
38	31	31	23
39	32	32	23
40	33	33	24
41	34	34	24

*"-" indicates that the stopping boundary cannot be cross for this sample size

Non-Hematologic Toxicities:
We will stop the trial if there is strong evidence that the rate of Grade 3 and 4 AEs observed at or prior to the End of Treatment visit exceeds 0.4.

16 Ethical and Regulatory Considerations

16.1 Good Clinical Practice

The study will be conducted in accordance with the appropriate regulatory requirement(s). Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

16.2 Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The IRB will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The study will only be conducted at sites where IRB approval has been obtained. The protocol, informed consent, written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the investigator.

16.3 Informed Consent

All potential study participants will be given a copy of the IRB-approved consent to review. The investigator or designee will explain all aspects of the study in lay language and answer all questions regarding the study. If the participant decides to participate in the study, he/she will be asked to sign and date the Consent document. Patients who refuse to participate or who withdraw from the study will be treated without prejudice.

17 References

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Appendix I – Eligibility Checklist

Phase II Trial of Neoadjuvant Nivolumab with Cisplatin and Gemcitabine in Muscle-Invasive Bladder Cancer (MIBC) Patients Undergoing Radical Cystectomy (BLASST-1)

CPRC #2017LS039 BMS # 2017-NIV-0823

Patient name or initials: _____ Patient ID17039 ☐☐☐-☐☐

3 letter site code – Seq # (i.e. 01, 02, 03, etc.)

INCLUSION CRITERIA

A "NO" response to any of the following disqualifies the patient from study entry.

<table>
<tr><th></th><th></th><th>Yes</th><th>No</th></tr>
<tr><td>1.</td><td>Diagnosis of MIBC (predominantly urothelial carcinoma except for small-cell variants) with clinical stage T2-T4a and N≤1 disease (solitary lymph node measuring < 2 cm) and M0 and deemed eligible for radical cystectomy</td><td>☐</td><td>☐</td></tr>
<tr><td>2.</td><td>Age ≥ 18 years</td><td>☐</td><td>☐</td></tr>
<tr><td>3.</td><td>ECOG Performance Status of 0 or 1 (Appendix II)</td><td>☐</td><td>☐</td></tr>
<tr><td>4.</td><td>Required initial laboratory values within 14 days of study enrollment:
<table>
<tr><th>Test</th><th>Required value</th><th>Patient's Value</th><th>Date of Testing</th></tr>
<tr><td>Absolute Neutrophil Count</td><td>≥ 1500 cells/mm^3</td><td>☐☐☐☐ cells/mm^3</td><td>☐☐/☐☐/☐☐</td></tr>
<tr><td>Platelets</td><td>≥ 100,000 cells/mm^3</td><td>☐☐☐☐☐☐ cells/mm^3</td><td>☐☐/☐☐/☐☐</td></tr>
<tr><td>Hemoglobin</td><td>≥ 9.0 g/dL</td><td>☐☐.☐ g/dL</td><td>☐☐/☐☐/☐☐</td></tr>
<tr><td>Bilirubin</td><td>≤ 1.5 x ULN*</td><td>☐.☐ mg/dL</td><td>☐☐/☐☐/☐☐</td></tr>
<tr><td>AST</td><td>≤ 3.0 x ULN</td><td>☐☐☐☐</td><td>☐☐/☐☐/☐☐</td></tr>
<tr><td>ALT</td><td>≤ 3.0 x ULN</td><td>☐☐☐☐</td><td>☐☐/☐☐/☐☐</td></tr>
<tr><td>Creatinine clearance**</td><td>≥ 50 ml/min</td><td>☐☐.☐ ml/min</td><td>☐☐/☐☐/☐☐</td></tr>
<tr><td>Alkaline phosphatase</td><td>≤ 2.5 x institutional ULN</td><td>☐☐☐☐☐☐</td><td>☐☐/☐☐/☐☐</td></tr>
<tr><td>INR</td><td>≤ 1.5 x ULN**</td><td>☐.☐</td><td>☐☐/☐☐/☐☐</td></tr>
<tr><td>aPTT</td><td>≤ 1.5 x ULN**</td><td>☐☐.☐ sec</td><td>☐☐/☐☐/☐☐</td></tr>
</table>
* For patients with known Gilbert's disease: bilirubin ≤ 3 x ULN
** By Cockcroft-Gault formula or 24 hour urinary clearance
***if not on therapeutic anticoagulation. Patients receiving therapeutic anticoagulation should be on a stable dose</td><td>☐</td><td>☐</td></tr>
<tr><td>5.</td><td>Females of childbearing potential and males who are not surgically sterile and with partners of childbearing potential must agree to use effective contraception during study treatment and for 5 months for females and 7 months for males after the last dose of nivolumab.</td><td>☐</td><td>☐</td></tr>
<tr><td>6.</td><td>Patient must agree to submission of archived tumor (20-25 formalin-fixed paraffin embedded (FFPE) slides of 5-10 microns in thickness) from TURBT and radical cystectomy tissues. If archived samples are not available fresh tissue will be used.</td><td>☐</td><td>☐</td></tr>
<tr><td>7.</td><td>Ability to provide written consent prior to the performance of any research related procedures.</td><td>☐</td><td>☐</td></tr>
</table>

Phase II Trial of Neoadjuvant Nivolumab with Cisplatin and Gemcitabine in Muscle-Invasive Bladder Cancer (MIBC) Patients Undergoing Radical Cystectomy (BLASST-1)
CPRC #2017LS039 BMS # 2017-NIV-0823

Patient ID17039 ☐☐☐-☐☐

Eligibility Checklist – page 2 of 3

EXCLUSION CRITERIA

A "YES" response to any of the following disqualifies the patient from study entry.

		Yes	No
1.	Presence of N2-3 or M1 disease.	☐	☐
2.	Ineligible to receive cisplatin by meeting one or more of the following: • creatinine clearance of < 50 mL/min, • hearing loss of 25 dB at two contiguous frequencies with testing required if a patient has hearing loss – At the investigator's discretion, and after discussion with the patient, this exclusion may be waived if the potential benefit of cisplatin therapy is felt to outweigh the risk of further hearing loss. • CTCAE v4 Grade 2 or higher peripheral neuropathy, • New York Heart Association Class III or IV heart failure (Appendix II), • ECOG performance status 2 or higher (Appendix II).	☐	☐
3.	Prior systemic therapy (intravenous) is not permitted. Prior intravesical therapy including intravesical gemcitabine is permitted for non-muscle invasive disease (i.e. superficial bladder cancer (T1)	☐	☐
4.	Prior treatment with cisplatin for bladder cancer.	☐	☐
5.	Prior treatment with anti-PD-1, CTLA-4, or anti-PD-L1 therapeutic antibody or pathway-targeting agents.	☐	☐
6.	Prior therapeutic radiation to the bladder	☐	☐
7.	Major surgical procedure within 28 days prior to Cycle 1, Day 1 or anticipation of need for a major surgical procedure during the course of the study	☐	☐
8.	Any of the following within the 6 months prior to study drug administration: myocardial infarction, severe/unstable angina, symptomatic congestive heart failure (New York Heart Association Class III or IV), stroke, serious cardiac arrhythmia	☐	☐
9.	Human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS)-related illness	☐	☐
10.	Pregnancy, lactation, or breast-feeding. Women of childbearing potential must have a negative urine pregnancy test at screening.	☐	☐
11.	History of autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, Wegener's granulomatosis, vascular thrombosis associated with antiphospholipid syndrome, Sjogren's syndrome, Guillain-Barre syndrome, multiple sclerosis, systemic vasculitis, or glomerulonephritis	☐	☐
12.	History of idiopathic pulmonary fibrosis, pneumonitis (including drug induced), organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia, etc.), or evidence of active pneumonitis on screening chest computed tomography (CT) scan, history of radiation pneumonitis in the radiation field (fibrosis) is permitted.	☐	☐
13.	Active hepatitis B virus (HBV, chronic or acute, defined as having a positive hepatitis B surface antigen [HBsAg] test at screening) or hepatitis C antibody. Patients with past HBV infection or resolved HBV infection (defined as the presence of hepatitis B core antibody [HBc Ab] and absence of HBsAg) are eligible. HBV DNA must be obtained in these patients prior to Cycle 1, Day 1 and confirmed to be negative. Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.	☐	☐
14.	Active tuberculosis or BCG infection	☐	☐
15.	Active infection requiring systemic antibiotics for more than 7 days within 3 days prior to Cycle 1, Day 1. Prophylactic short-term antibiotics will be allowed.	☐	☐

Phase II Trial of Neoadjuvant Nivolumab with Cisplatin and Gemcitabine in Muscle-Invasive Bladder Cancer (MIBC) Patients Undergoing Radical Cystectomy (BLASST-1)
CPRC #2017LS039 BMS # 2017-NIV-0823

Patient ID 17039 ☐☐☐-☐☐

Eligibility Checklist – page 3 of 3

EXCLUSION CRITERIA (continued)

A "YES" response to any of the following disqualifies the patient from study entry.

		Yes	No
16.	Administration of intravesical bacillus Calmette-Guerin (BCG) within 4 weeks before Cycle 1, Day 1	☐	☐
17.	Administration of a live, attenuated vaccine within 4 weeks before Cycle 1, Day 1 or anticipation that such a live attenuated vaccine will be required during the study.	☐	☐
18.	Persisting toxicity from prior therapy (NCI CTCAE v4.03 Grade >1); however alopecia or other Grade ≤2 AEs not constituting a safety risk, based on Investigator's judgement, are acceptable.	☐	☐
19.	History of or active bone marrow disorders expected to interfere with study therapy (e.g. acute leukemias, accelerated/blast-phase chronic myelogenous leukemia, chronic lymphocytic leukemia, Burkitt lymphoma, plasma cell leukemia, or non-secretory myeloma).	☐	☐
20.	Prior allogeneic stem cell or solid organ transplant.	☐	☐
21.	Known primary central nervous system (CNS) malignancy.	☐	☐
22.	Patients with eczema, psoriasis, lichen simplex chronicus of vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis would be excluded) are permitted but patients with psoriasis require a baseline ophthalmologic exam to rule out ocular manifestations. Rash must cover less than 10% of body surface area (BSA) and must be well controlled at baseline and only requiring topical steroids.	☐	☐
23.	Any other chronic medical condition or psychiatric condition, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk from treatment complications	☐	☐
24.	Known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin or in situ cervical cancer that has undergone potentially curative therapy. Patients on androgen deprivation therapy as part of adjuvant therapy after radiation for prostate cancer or patients on adjuvant hormonal therapies for breast cancer will be allowed if they are being considered for curative intent for bladder cancer.	☐	☐
25.	Treatment with systemic immunostimulatory agents (including but not limited to interferon-a or interleukin-2) within 4 weeks or five half-lives of the drug (whichever is shorter) prior to Cycle 1, Day 1	☐	☐
26.	Concomitant use of systemic corticosteroids at physiologic doses or >10 mg/day of prednisone or equivalent.	☐	☐
27.	Concomitant use of another investigational agent and/or treatment with an investigational agent within 4 weeks prior to Cycle 1, Day 1 (or within five half-lives of the investigational product, whichever is longer).	☐	☐
28.	Use of bisphosphonate therapy for osteoporosis will be allowed if started prior to study enrollment.	☐	☐

Having reviewed each of the inclusion/exclusion criteria, I verify that this patient is eligible

Signature of enrolling physician Date

Appendix II – ECOG Performance Status and NYHA Classification

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649-655.

New York Heart Association Functional Classification

NYHA Class	Symptoms
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while *at rest*. Mostly bedbound patients.

Ref: The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256.