A Phase II Open Label Single Arm Study of Adjuvant Nivolumab following Chemo-Radiation in localized Muscle-Invasive Bladder Cancer (NEXT)

Trial ID: HCI100769/IRB# 100769
Drug Manufacturer protocol # CA209-999
NCT#: NCT03171025

Principal Investigator
Sumati Gupta, MD
Huntsman Cancer Institute/University of Utah
2000 Circle of Hope
Salt Lake City, UT 84112
Phone: 801-213-5727
sumati.gupta@hci.utah.edu

Sub-investigator(s)
Neeraj Agarwal, MD
Huntsman Cancer Institute/University of Utah
2000 Circle of Hope, Ste 2123
Salt Lake City, UT 84112
neeraj.agarwal@hci.utah.edu

Benjamin Maughan, MD, PharmD
Huntsman Cancer Institute/University of Utah
2000 Circle of Hope
Salt Lake City, UT 84112
benjamin.maughan@hci.utah.edu

Julia Batten, APRN
Huntsman Cancer Institute/University of Utah
2000 Circle of Hope
Salt Lake City, UT 84112
julia.batten@hci.utah.edu

Jared Thorley, APRN
Huntsman Cancer Institute/University of Utah
2000 Circle of Hope
Salt Lake City, UT 84112
jared.thorley@hci.utah.edu

Tenzin Phunrab, APRN
Huntsman Cancer Institute/University of Utah
2000 Circle of Hope
Salt Lake City, UT 84112
tenzin.phunrab@hci.utah.edu
William Lowrance, MD
Huntsman Cancer Institute/University of Utah
2000 Circle of Hope
Salt Lake City, UT 84112
will.lowrance@hci.utah.edu

Christopher Dechet, MD
Huntsman Cancer Institute/University of Utah
2000 Circle of Hope
Salt Lake City, UT 84112
christopher.dechet@hci.utah.edu

Jonathan Tward, MD
Huntsman Cancer Institute/University of Utah
2000 Circle of Hope
Salt Lake City, UT 84112
jonathan.tward@hci.utah.edu

Brock O’Neil, MD
Huntsman Cancer Institute/University of Utah
2000 Circle of Hope
Salt Lake City, UT 84112
Brock.ONeil@hci.utah.edu

Ken Boucher, PhD (Statistician)
Huntsman Cancer Institute/University of Utah
2000 Circle of Hope
Salt Lake City, UT 84112
Ken.boucher@hci.utah.edu

Ting Liu (Pathology – Correlative Lab)
University of Utah
Department of Pathology
Salt Lake City, UT 84112
ting.liu@hsc.utah.edu

Daniel Albertson (Correlative Lab)
Huntsman Cancer Institute/University of Utah
2000 Circle of Hope
Salt Lake City, UT 84112
daniel.albertson@hsc.utah.edu

James Marvin (Correlative Lab)
University of Utah
Flow Cytometry Lab
Salt Lake City, UT 84112
Version Date: 15AUG2017
Principal Investigator: Sumati Gupta, MD

james.marvin@hsc.utah.edu

Drug Manufacturer
Bristol Myers Squibb

Investigational agent
Nivolumab

IND Number
134,964

Historical Protocol Versions
Version 1: 04MAY2017
Version 2: 06JUL2017
Version 3: 15AUG2017 (current version)
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIST OF ABBREVIATIONS</td>
<td>6</td>
</tr>
<tr>
<td>PROTOCOL SIGNATURE</td>
<td>10</td>
</tr>
<tr>
<td>STUDY SUMMARY</td>
<td>11</td>
</tr>
<tr>
<td>1 OBJECTIVES</td>
<td>13</td>
</tr>
<tr>
<td>1.1 Primary Objectives and Endpoint</td>
<td>13</td>
</tr>
<tr>
<td>1.2 Secondary Objectives and Endpoint</td>
<td>13</td>
</tr>
<tr>
<td>1.3 Exploratory Objectives</td>
<td>14</td>
</tr>
<tr>
<td>2 BACKGROUND</td>
<td>14</td>
</tr>
<tr>
<td>2.1 Bladder cancer</td>
<td>14</td>
</tr>
<tr>
<td>2.2 Localized muscle invasive bladder cancer</td>
<td>14</td>
</tr>
<tr>
<td>2.3 Programmed Cell Death-1</td>
<td>15</td>
</tr>
<tr>
<td>2.4 Role of chemoradiation</td>
<td>15</td>
</tr>
<tr>
<td>2.5 Combining chemo radiation with anti-PD1 antibody</td>
<td>16</td>
</tr>
<tr>
<td>2.6 Rationale for study design primary endpoint</td>
<td>17</td>
</tr>
<tr>
<td>2.7 Rationale for delay between end of chemoradiation and start of adjuvant therapy with nivolumab</td>
<td>17</td>
</tr>
<tr>
<td>2.8 Rationale for patient population</td>
<td>17</td>
</tr>
<tr>
<td>2.9 Rationale for follow up</td>
<td>18</td>
</tr>
<tr>
<td>2.10 Rationale for correlative studies</td>
<td>18</td>
</tr>
<tr>
<td>3 DRUG INFORMATION</td>
<td>18</td>
</tr>
<tr>
<td>3.1 Nivolumab</td>
<td>18</td>
</tr>
<tr>
<td>3.2 Administration</td>
<td>19</td>
</tr>
<tr>
<td>3.3 Recommended Storage and Use Conditions</td>
<td>19</td>
</tr>
<tr>
<td>3.4 Clinical Data</td>
<td>19</td>
</tr>
<tr>
<td>3.5 Dosing Rationale</td>
<td>20</td>
</tr>
<tr>
<td>3.6 Adverse Effects</td>
<td>21</td>
</tr>
<tr>
<td>3.7 Drug-Drug Interaction Potential with the Treatment of Nivolumab</td>
<td>21</td>
</tr>
<tr>
<td>4 STUDY DESIGN</td>
<td>21</td>
</tr>
<tr>
<td>4.1 Description</td>
<td>21</td>
</tr>
<tr>
<td>4.2 Number of Patients</td>
<td>22</td>
</tr>
<tr>
<td>4.3 Number of Study Centers</td>
<td>22</td>
</tr>
<tr>
<td>4.4 Study Duration</td>
<td>22</td>
</tr>
<tr>
<td>5 ELIGIBILITY CRITERIA</td>
<td>23</td>
</tr>
<tr>
<td>5.1 Pre-Chemoradiation Sample Collection Eligibility</td>
<td>23</td>
</tr>
<tr>
<td>5.2 Study Treatment Eligibility</td>
<td>23</td>
</tr>
<tr>
<td>6 DEFINITIVE CHEMORADIATION THERAPY SUMMARY</td>
<td>27</td>
</tr>
<tr>
<td>7 TREATMENT PLAN</td>
<td>27</td>
</tr>
<tr>
<td>7.1 Administration Schedule</td>
<td>27</td>
</tr>
<tr>
<td>7.2 Concomitant Medications</td>
<td>28</td>
</tr>
<tr>
<td>7.3 Duration of Therapy</td>
<td>29</td>
</tr>
<tr>
<td>8 TOXICITIES AND DOSEAGE MODIFICATION</td>
<td>31</td>
</tr>
<tr>
<td>8.1 Dose Modifications</td>
<td>31</td>
</tr>
<tr>
<td>8.2 Dose Delay/Discontinuation</td>
<td>31</td>
</tr>
</tbody>
</table>
LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation or Term</th>
<th>Definition/Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine aminotransferase</td>
</tr>
<tr>
<td>ANCOVA</td>
<td>Analysis of covariance</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
</tr>
<tr>
<td>APTT</td>
<td>Activated partial thromboplastin time</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate aminotransferase</td>
</tr>
<tr>
<td>AV</td>
<td>Atrioventricular</td>
</tr>
<tr>
<td>β-HCG</td>
<td>Beta-human chorionic gonadotropin</td>
</tr>
<tr>
<td>BID</td>
<td>Twice daily</td>
</tr>
<tr>
<td>BLQ</td>
<td>Below limit of quantification</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>BP</td>
<td>Blood pressure</td>
</tr>
<tr>
<td>BUN</td>
<td>Blood urea nitrogen</td>
</tr>
<tr>
<td>Ca++</td>
<td>Calcium</td>
</tr>
<tr>
<td>CBC</td>
<td>Complete blood count</td>
</tr>
<tr>
<td>CFR</td>
<td>Code of Federal Regulations</td>
</tr>
<tr>
<td>CHF</td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>Cl-</td>
<td>Chloride</td>
</tr>
<tr>
<td>CLcr</td>
<td>Creatinine clearance</td>
</tr>
<tr>
<td>Cmax</td>
<td>Maximum observed concentration</td>
</tr>
<tr>
<td>Cmin</td>
<td>Trough observed concentration</td>
</tr>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>CR</td>
<td>Complete response</td>
</tr>
<tr>
<td>CRF</td>
<td>Case report form</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>CTCAE</td>
<td>Common Toxicity Criteria for Adverse Events</td>
</tr>
<tr>
<td>Abbreviation or Term</td>
<td>Definition/Explanation</td>
</tr>
<tr>
<td>---------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>CV</td>
<td>Coefficient of variation</td>
</tr>
<tr>
<td>CYP</td>
<td>Cytochrome P450</td>
</tr>
<tr>
<td>D/C</td>
<td>Discontinue</td>
</tr>
<tr>
<td>ECOG</td>
<td>Eastern Cooperative Oncology Group</td>
</tr>
<tr>
<td>eCRF</td>
<td>Electronic case report form</td>
</tr>
<tr>
<td>DLT</td>
<td>Dose Limiting Toxicity</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>Eg</td>
<td>Exempli gratia (for example)</td>
</tr>
<tr>
<td>FACS</td>
<td>Fluorescence Activated Cell Sorting</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>FDG-PET</td>
<td>Fluorodeoxyglucose (FDG)-positron emission tomography (PET)</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>GFR</td>
<td>Glomerular filtration rate</td>
</tr>
<tr>
<td>GGT</td>
<td>Gamma glutamyl transferase</td>
</tr>
<tr>
<td>GLP</td>
<td>Good laboratory practice</td>
</tr>
<tr>
<td>HBsAg</td>
<td>Hepatitis B surface antigen</td>
</tr>
<tr>
<td>HBV</td>
<td>Hepatitis B virus</td>
</tr>
<tr>
<td>HCO₃⁻</td>
<td>Bicarbonate</td>
</tr>
<tr>
<td>HCV</td>
<td>Hepatitis C virus</td>
</tr>
<tr>
<td>HIV</td>
<td>Human immunodeficiency virus</td>
</tr>
<tr>
<td>HR</td>
<td>Heart rate</td>
</tr>
<tr>
<td>hr</td>
<td>Hour or hours</td>
</tr>
<tr>
<td>IC₅₀</td>
<td>Half maximal inhibitory concentration</td>
</tr>
<tr>
<td>i.e.</td>
<td>Id est (that is)</td>
</tr>
<tr>
<td>IEC</td>
<td>Independent ethics committee</td>
</tr>
<tr>
<td>INR</td>
<td>International normalized ratio</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional review board</td>
</tr>
<tr>
<td>Abbreviation or Term</td>
<td>Definition/Explanation</td>
</tr>
<tr>
<td>---------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>IU</td>
<td>International unit</td>
</tr>
<tr>
<td>IV</td>
<td>Intravenous, intravenously</td>
</tr>
<tr>
<td>LDH</td>
<td>Lactate dehydrogenase</td>
</tr>
<tr>
<td>LLQ</td>
<td>Lower limit of quantitation</td>
</tr>
<tr>
<td>MedRA</td>
<td>Medical Dictionary for Drug Regulatory Activities</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>MRSD</td>
<td>Maximum recommended starting dose</td>
</tr>
<tr>
<td>MTD</td>
<td>Maximum tolerated dose</td>
</tr>
<tr>
<td>NOAEL</td>
<td>No-observed-adverse-effect level</td>
</tr>
<tr>
<td>NOEL</td>
<td>No-observed-effect-level</td>
</tr>
<tr>
<td>PD</td>
<td>Pharmacodynamic(s)</td>
</tr>
<tr>
<td>PFS</td>
<td>Progression Free Survival</td>
</tr>
<tr>
<td>PK</td>
<td>Pharmacokinetic(s)</td>
</tr>
<tr>
<td>PO</td>
<td>Per os (administered by mouth)</td>
</tr>
<tr>
<td>PR</td>
<td>Partial response</td>
</tr>
<tr>
<td>PT</td>
<td>Prothrombin time</td>
</tr>
<tr>
<td>PTT</td>
<td>Partial thromboplastin time</td>
</tr>
<tr>
<td>QC</td>
<td>Quality control</td>
</tr>
<tr>
<td>RBC</td>
<td>Red blood cell</td>
</tr>
<tr>
<td>QD</td>
<td>Once daily</td>
</tr>
<tr>
<td>QTc</td>
<td>QT interval corrected</td>
</tr>
<tr>
<td>QTcF</td>
<td>QT interval corrected using Frederichia equation</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious adverse event</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation or stable disease</td>
</tr>
<tr>
<td>T&lt;sub&gt;1/2&lt;/sub&gt;</td>
<td>Terminal elimination half-life</td>
</tr>
<tr>
<td>T&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Triiodothyronine</td>
</tr>
<tr>
<td>T&lt;sub&gt;4&lt;/sub&gt;</td>
<td>Thyroxine</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Time of maximum observed concentration</td>
</tr>
<tr>
<td>Abbreviation or Term</td>
<td>Definition/Explanation</td>
</tr>
<tr>
<td>---------------------</td>
<td>--------------------------------------------</td>
</tr>
<tr>
<td>TID</td>
<td>Three times daily</td>
</tr>
<tr>
<td>TSH</td>
<td>Thyroid-stimulating hormone</td>
</tr>
<tr>
<td>ULN</td>
<td>Upper limit of normal</td>
</tr>
<tr>
<td>ULQ</td>
<td>Upper limit of quantitation</td>
</tr>
<tr>
<td>UV</td>
<td>Ultraviolet</td>
</tr>
<tr>
<td>WBC</td>
<td>White blood cell</td>
</tr>
<tr>
<td>WOCBP</td>
<td>Women of childbearing potential</td>
</tr>
<tr>
<td>WONCBP</td>
<td>Women of nonchildbearing potential</td>
</tr>
</tbody>
</table>

1 All of these abbreviations may or may not be used in protocol.
PROTOCOL SIGNATURE

I confirm that I have read this protocol, and I will conduct the study as outlined herein and according to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable ICH guidelines for good clinical practice, and the applicable laws and regulations of the federal government. I will promptly submit the protocol to the IRB for review and approval. Once the protocol has been approved by the IRB, I understand that any modifications made during the course of the study must first be approved by the IRB prior to implementation except when such modification is made to remove an immediate hazard to the subject.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study treatment, the conduct of the study, and the obligations of confidentiality.

Note: This document is signed electronically through submission and approval by the Principal Investigator in the University of Utah IRB Electronic Research Integrity and Compliance Administration (ERICA) system.
## STUDY SUMMARY

<table>
<thead>
<tr>
<th>Title</th>
<th>A Phase II Open Label Single Arm Study of Adjuvant Nivolumab following Chemo-Radiation in localized Muscle-Invasive Bladder Cancer (NEXT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short Title</td>
<td>Phase II study of Nivolumab adjuvant to chemoradiation in localized bladder cancer</td>
</tr>
<tr>
<td>Protocol Number</td>
<td>IRB # 100769</td>
</tr>
<tr>
<td>IND</td>
<td>IND# 134964</td>
</tr>
<tr>
<td>Phase</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Design</td>
<td>Open Label Single arm</td>
</tr>
<tr>
<td>Study Duration</td>
<td>6-7 years</td>
</tr>
<tr>
<td>Study Center(s)</td>
<td>Single center</td>
</tr>
<tr>
<td>Objectives</td>
<td>The primary objective is to measure the two-year rate of failure-free survival (FFS). The definition of failure will include loco-regional recurrence, and distant metastases.</td>
</tr>
<tr>
<td>Number of Subjects</td>
<td>28</td>
</tr>
<tr>
<td>Diagnosis and Main Eligibility Criteria</td>
<td>Pathologically proven diagnosis of primary carcinoma of the bladder or urethra or lower ureter (adenocarcinoma, transitional cell carcinoma or squamous cell carcinoma). Patients with muscularis propria invasion clinical stages 2 to 4 (T2-4a, N0 or N+, M0 or T1 with N+), who are not candidates for radical cystectomy and have undergone bladder preserving treatment with chemoradiation. Patients may have undergone partial cystectomy for removal of bladder tumor prior to chemoradiation. Patients who have down staged from M1 disease to M0 with prior platinum-based chemotherapy will be eligible. Patients must have received radiosensitizing systemic chemotherapy combined with pelvic radiation therapy for definitive treatment of their localized bladder cancer.</td>
</tr>
</tbody>
</table>

### Inclusion Criteria
- ECOG Performance Status of ≤ 2.
- Age ≥ 18.
- Adequate bone marrow function
- Serum bilirubin and aminotransferase values less than 1.5 times the upper limit of the normal range
- Creatinine clearance of 20 ml/min or greater
- Patients must be willing and able to provide study-specific informed consent prior to study entry
- Able to start study treatment within 90 days of completion of chemoradiation
- All toxicities attributed to prior anti-cancer therapy other than nephropathy, neuropathy, hearing loss, alopecia and
fatigue must have resolved to Grade 1 (NCI CTCAE version 4) or baseline before administration of study drug. Subjects with toxicities attributed to prior anti-cancer therapy which are not expected to resolve and result in long lasting sequelae, such as neuropathy after platinum based therapy, are permitted to enroll.

**Exclusion Criteria**

- Evidence of distant metastases or lymph node metastasis (es) that was not within the radiation field.
- Known additional malignancy that is progressing or requires active treatment. Exceptions include locally curable cancers that have been apparently cured, such as basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or localized early stage cancer that has undergone potentially curative therapy
- Diffuse bladder carcinoma in situ (CIS) that was not able to be encompassed in a boost radiotherapy volume
- Patients with inflammatory bowel disease.
- Patients with active, known or suspected autoimmune disease Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
- Patients with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 day of study drug administration.
- Patients with a known chronic immunocompromised state, HIV infection or active Hepatitis B or Hepatitis C infection
- Patients who are candidates for radical cystectomy
- Pregnancy or women of childbearing potential not willing to use contraception and men who are sexually active and not willing/able to use medically acceptable forms of contraception;
- Severe active co-morbidity as determined by the investigator or principal investigator
- Life Expectancy < 2 years

| Study Product, Dose, Route, Regimen | Nivolumab 480 mg intravenously every 4 weeks until recurrence or discontinuation from study for a maximum of 12 infusions after completion of chemoradiation treatment for localized bladder cancer |
Duration of administration | 1 year
---|---
Reference therapy | Chemoradiation alone

**Statistical Methodology**
The planned sample size for this single arm, open label trial is \(N = 28\). The primary endpoint is failure-free survival (FFS) at two years. Kaplan-Meier methods will be used to plot survival endpoints (FFS, FFS- Intact Bladder (FFSIB), and OS) and cystoscopic local control rates. Provided there is no censoring, exact binomial methods will be used to provide 6 months, 1 year and 2 year estimates for these endpoints. If censoring exists prior to these time points Kaplan-Meier methods will be used to provide 6 month, 1 year and 2 year estimates.

### 1 OBJECTIVES

The primary purpose of this study is to evaluate the ability of checkpoint inhibition with nivolumab to enhance the efficacy of chemoradiation in localized bladder cancer to reduce the rates of loco regional and distant recurrence without added toxicity.

#### 1.1 Primary Objectives and Endpoint

1.1.1 The primary objective is to evaluate the two-year rate of failure-free survival (FFS). The definition of failure will include loco-regional recurrence, and distant recurrence. The primary endpoint of the FFS will be determined based on disease recurrence date defined as the time between the start date of study treatment (nivolumab) and the date of first recurrence or non-cancer related death.

#### 1.2 Secondary Objectives and Endpoint

1.2.1 Evaluate the rate of failure-free survival at two years in patients with intact bladder (FFSIB). This will be measured only in patients who do not have local recurrence requiring radical cystectomy. The endpoint of FFSIB will be determined based on disease recurrence date defined as the time between the start date of study treatment (nivolumab) and the date of first recurrence or non-cancer related death.

1.2.2 Evaluate the rate of acute and late grade 2 or higher treatment-related GU, GI, hematologic, and immune related toxicity. The incidence of adverse events will be collected and tabulated through treatment and follow up.

1.2.3 Evaluate the effect of treatment on Quality of Life. The endpoint will include the completion of quality of life questionnaires as per study calendar.
1.2.4 Evaluate cystoscopic local control at 6 months, 1 year and 2 years post start of study treatment with nivolumab after censoring for distant recurrence. The endpoint will be measurement of local recurrence at 6 months, 1 year and 2 years as determined by cystoscopy.

1.2.5 Evaluate the rate of salvage cystectomy. This will be measured by the endpoint of radical cystectomy for local recurrence during study treatment.

1.2.6 Evaluate the rate of distant failure-free survival at two years in patients with intact bladder and those who discontinue study to undergo salvage cystectomy. This will be measured in patients who do and do not have local recurrence requiring radical cystectomy during study treatment. The endpoint FFS will be determined based on disease recurrence date defined as the time between the start date of study treatment (nivolumab) and the date of first distant recurrence or non-cancer related death.

1.2.7 Evaluate overall survival up to 5 years. This will be measured by the rate of death for up to 5 years from start of study treatment.

1.3 Exploratory Objectives

1.3.1 To assess immunological monitoring on peripheral blood mononuclear cells and other humoral factors collected prior to the initiation of chemoradiation, study therapy, and throughout the study drug administration, to characterize changes in immune cell and immune factor subsets that can be correlated with clinical outcome.

1.3.2 To assess the correlation of response to PD-L1 expression in pretreatment tumor tissue in the study patients.

2 BACKGROUND

2.1 Bladder cancer

Bladder Cancer is the second most common cancer of the genitourinary system with 76,960 cases of bladder cancer and 16,390 deaths predicted in the US for the year 2016 [1]. It is the third most common cancer in men and the eleventh most common cancer in women [2]. Cure is possible in localized disease with a combination of chemotherapy, surgery and / or radiation [3].

2.2 Localized muscle invasive bladder cancer

The 5-year survival for patients with localized muscle invasive bladder cancer who undergo radical cystectomy alone without additional chemotherapy or radiation is 54.2%. Survival is directly related to the final pathological stage. The five year survival rate varies from 94% for stage pT0 to 28% for pT4 disease at the time of RC [4]. The pattern of recurrence at distant sites implicates the presence of occult micrometastases at the time of cystectomy. Currently, the preferred first-line treatment for advanced urothelial carcinoma is cisplatin-based combination chemotherapy [4]. Unfortunately,
30 to 40% of advanced bladder cancers are resistant to cisplatin-based combination chemotherapy and the majority of the patients who do respond initially eventually progress with a median progression-free survival of approximately 9.5 months and a median overall survival of 15.1 months [5].

There is therefore a significant need to combine definitive surgical or radiation therapy for localized disease with systemic chemotherapy for occult metastases. Neoadjuvant chemotherapy with a cisplatin-based combination improves disease specific survival for every pathologic stage of bladder cancer. The risk of death is reduced by 33% upon use of NAC. The median survival improves from 46 months to 77 months [5]. Use of ddMVAC neoadjuvantly has shown survival benefit in muscle-invasive bladder cancer directly correlating with pathologic down staging and reduced risk of distant relapse [3,6].

2.3 Programmed Cell Death-1

Recent trials in bladder cancer have focused on treatment with targeted therapy and immunotherapy. Some early trials show variable and short lived response rates to targeted therapy in bladder cancer indicating the oncogenic versatility of this disease [7]. The T cell receptor programmed death-1 (PD-1) is an immune check point protein that limits the activity of effector T cells in peripheral tissues at the time of inflammatory response to modulate the inflammatory response and limit autoimmunity [8]. Immunotherapy with checkpoint inhibitors targeting the PD-1/PD-L1 axis has shown promise in urothelial malignancies with some dramatic efficacy and little toxicity [9-12] leading to expedited FDA approval of these therapies after decades of lull in treatment for bladder cancer [5]. The response to checkpoint inhibition of the PD-1/PD-L1 axis correlates with tumor mutational burden and degree of PD-L1 expression [9,10]. The Cancer Genome Atlas (TCGA) has classified bladder cancer into luminal and basal subtypes with four cluster subcategories. In a Phase 2 trial of atezolizumab (anti PD-L1 antibody), PD-L1 expression was noted to be more prevalent in Cluster III tumors. PD-L1 blockade is most effective in the cluster II (luminal) subtype of tumors but is effective in all subcategories of tumors [9]. Nivolumab is an anti-PD-1 antibody that has shown a response rate of 19.6% in previously treated locally advanced or metastatic urothelial carcinoma [13]. Responses are observed regardless of PD-L1 expression, with a greater response rate seen with increasing levels of PD-L1 expression.

2.4 Role of chemoradiation

Chemo-radiation for muscle invasive bladder cancer is a treatment modality used in patients who are not candidates for radical cystectomy. Maximal Transurethral Resection of Bladder Tumor (TURBT) followed by chemoradiation is referred to as combined modality treatment and offers excellent loco regional control. If the renal function is adequate the radio-sensitizing chemotherapy regimen may incorporate cisplatin alone or in combination with a second chemotherapy agent such as 5-fluorouracil [14] or paclitaxel [15], the choice depending on the clinical setting and the treating multidisciplinary team. In cisplatin-ineligible patients or patients with
platinum-resistant disease, the regimen incorporates infusional 5-FU and mitomycin [16].

However, radiosensitizing regimens do not target systemic micrometastases and the efficacy of the bladder-sparing approach is more appreciable in loco-regional control than prevention of systemic disease relapse [16,17]. Treatment of localized muscle-invasive urothelial carcinoma with 5-fluorouracil and mitomycin chemo-radiation has a loco-regional control rate of 67% (after censoring for relapse due to distant metastasis) but a disease-free survival of only 50% at 2 years [16].

2.5 Combining chemo radiation with anti-PD1 antibody

High dose ionizing radiation (IR) targeted to tumors results in tumor cell death, release of antigens, and the release of proinflammatory cytokines, thus augmenting tumor specific immunity by creating an in situ vaccine. The adaptive immune responses created by this process mediate tumor regression. The tumor microenvironment also has a population of inhibitory immune cells (such as Tregs) and myeloid-derived suppressor cells (MDSCs) which exert an inhibitory effect on the immune cells leading to immune evasion by tumor. The upregulation of proinflammatory cytokines results in over expression of the PD-1 ligand PD-L1 on tumor tissue. When PD-1 is activated by PD-L1, it results in immune suppression and weakening of IR-induced anti-tumor immunity. This contributes to radioresistance. PD-L1 blockade and IR synergistically amplify the anti-tumor effect in mice studies. A significant abscopal effect is also generated, leading to tumors located in areas distant from the irradiated tumor also shrinking. There is increased systemic activation of tumor specific T cells in the tumor as well as in secondary lymphoid organs. The activation of CD-8 cells also results in apoptosis of MDSCs [18].

In summary, by inhibiting checkpoints in the immune system, radiation induced tumor specific immune response is enhanced both locally and abscopally [19].

A prospective evaluation of circulating immunologic factors was performed in a group of Head and Neck Squamous Cell Carcinoma (HNSCC) patient undergoing definitive radiation therapy (RT) with or without concurrent chemotherapy. Serum cytokine levels, peripheral blood mononuclear cell (PBMC) subsets, T cell receptor (TCR) diversity, and changes in antibody responses were measured prior to and post chemoradiation. A consistent pattern of immune stimulatory and inhibitory effects on anti-tumor immunity were noted. A specific activation of T cell receptor and humoral responses to tumor specific antigens along with an increase in effector CD8+ T cells was offset by increases in regulatory T cells and Myeloid Derived Suppressor Cells (MDSCs). A consistent increase in checkpoint receptor expressing T cells was noted in the majority of patients. Notable increases in PD-1 expressing cells was observed. Immune checkpoint blockade with anti- PD-1 antibody is likely to potentiate the anti-tumor efficacy of chemoradiation [20]. Angiogenic cytokine levels also change in HNSCC patients over the course of chemoradiation. Decreases in VEGF caused by radiation may represent one mechanism of potential synergy with immunotherapy. Increases in Ang2 and PLGF are interesting given their link to tumor associated angiogenesis and poor prognosis. Additional studies are needed to explore synergies
between anti-angiogenic treatments, immunotherapy, and chemoradiation in HNSCC [21].

In summary, the loco-regional response to chemoradiation is likely to be enhanced with the addition of nivolumab due to an abscopal effect on immunotherapy. Also, chemoradiation is likely to enhance the systemic effects of immunotherapy due to antigen release and inflammation from tumor cell death [22].

2.6 Rationale for study design primary endpoint

Targeting localized bladder cancer and systemic micrometastases with nivolumab after completion of chemoradiation would offer an additional disease-free survival rate of at least 20 % at 2 years compared to chemo-radiation alone. The hypothesized efficacy of this bladder preserving approach matches the efficacy of the current front line treatment approach utilizing neoadjuvant chemotherapy followed by radical cystectomy. The inclusion of non-urothelial pathology mirrors the approach taken by James et al [16].

2.7 Rationale for delay between end of chemoradiation and start of adjuvant therapy with nivolumab

Adjuvant chemotherapy for urothelial carcinoma after radical cystectomy may begin 90 days post operatively [23]. This allows time for recovery from surgery. Similarly, adjuvant therapy with nivolumab post chemoradiation may begin up to 90 days after completion of last dose of radiation to allow recovery from side effects of chemoradiation.

2.8 Rationale for patient population

The median age of diagnosis for bladder cancer is 65 years and medical comorbidities are a frequent consideration in patient management. The clinical spectrum of bladder cancer can be divided into 3 categories that differ in prognosis, management and therapeutic aims. The first category consists of non-muscle invasive tumors for which treatment is directed at reducing recurrences and preventing progression to a more advanced stage. The second group encompasses the muscle-invasive lesions and the goal of therapy is to provide cure and long term survival. A combination of systemic and localized treatment is generally recommended. The third group with metastatic disease is treated with the aim to prolong quantity and quality of life [24].

Due to advanced age, comorbidities and compromised renal function, patients with localized muscle invasive bladder cancer are not candidates for neoadjuvant cisplatin based chemotherapy or radical cystectomy. Currently, chemoradiation with 5-FU and mitomycin is used with a significant risk of disease relapse at 2 years. There is a need to target systemic disease with a potent tolerable agent in this class of patients.

Nivolumab is not renally cleared and is relatively well tolerated in this class of patients. The relative lack of drug interactions and the ease of administration are also beneficial. The PD-L1 expression and tumor mutational burden are tumor characteristics which are likely to change with chemoradiation and so the study population will not be selected based on these biomarkers [25].
2.9 Rationale for follow up

The greatest risk of disease recurrence after chemoradiation for muscle invasive localized bladder cancer is within the first two years of treatment. The risk goes down considerably after 5 years. Hence, the primary endpoint of failure-free survival is at 2 years and overall study follow up will be for 5 years.

2.10 Rationale for correlative studies

Archival tissue will be analyzed by genomic characterization of the tumor and evaluated for immunogenicity. Any subsequent tumor tissue obtained from biopsied recurrence or cystectomy will be analyzed to elucidate the mechanisms of resistance. Tumor characteristics will be correlated with failure-free survival. Peripheral blood will be collected and analyzed for correlative studies. These include flow cytometry of peripheral blood mononuclear cells (PBMCs), assessment of humoral responses and genomic characterization of response.

3 DRUG INFORMATION

3.1 Nivolumab

Nivolumab (also referred to as BMS-936558 or MDX1106) is a human monoclonal antibody (HuMAb; immunoglobulin G4 [IgG4]-S228P) that targets the programmed death-1 (PD-1) cluster of differentiation 279 (CD279) cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes. Binding of PD-1 to its ligands, programmed death-ligands 1 (PD-L1) and 2 (PD-L2), results in the down-regulation of lymphocyte activation. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens. Nivolumab is expressed in Chinese hamster ovary (CHO) cells and is produced using standard mammalian cell cultivation and chromatographic purification technologies. The clinical study product is a sterile solution for parenteral administration.

Nivolumab is approved for use in multiple countries including the United States (US, Dec-2014), the European Union (EU, Jun-2015), and Japan (Jul-2014).

Physical and Chemical Properties: Nivolumab is a soluble protein consisting of 4 polypeptide chains, which include 2 identical heavy chains and 2 identical light chains. The physical and chemical properties of nivolumab are provided below:

<table>
<thead>
<tr>
<th>Property</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMS Number</td>
<td>BMS-936558-01</td>
</tr>
<tr>
<td>Other Names</td>
<td>Nivolumab, BMS-936558, MDX1106, ONO-4538, anti-PD-1</td>
</tr>
<tr>
<td>Molecular Weight</td>
<td>146,221 daltons (143,619.17 daltons, protein portion)</td>
</tr>
<tr>
<td>Appearance</td>
<td>Clear to opalescent, colorless to pale yellow liquid, light (few) particulates may be present</td>
</tr>
<tr>
<td>Solution pH</td>
<td>5.5 to 6.5</td>
</tr>
</tbody>
</table>
Pharmaceutical Properties and Formulation: Nivolumab Injection, 100 mg/10 mL (10 mg/mL), is a clear to opalescent, colorless to pale yellow liquid, which may contain light (few) particulates. The drug product is a sterile, non-pyrogenic, single-use, isotonic aqueous solution formulated at 10 mg/mL in sodium citrate, sodium chloride, mannitol, diethylenetriaminepentacetic acid (pentetic acid), and polysorbate 80 (Tween80), pH 6.0, and includes an overfill to account for vial, needle, and syringe holdup. It is supplied in 10-cc Type I flint glass vials, stoppered with butyl rubber stoppers and sealed with aluminum seals. The only difference between the two drug product presentations is the vial fill volume.

3.2 Administration

Nivolumab injection is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding (polyethersulfone membrane) in-line filter at the protocol-specified doses and infusion times. It is not to be administered as an IV push or bolus injection. Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP, to protein concentrations as low as 0.35 mg/mL. When the dose is fixed (e.g., 240 mg, 360 mg, or 480 mg flat dose), nivolumab injections can be infused undiluted or diluted so as not to exceed a total infusion volume of 120 mL.

During drug product preparation and handling, vigorous mixing or shaking is to be avoided. Instructions for dilution and infusion of nivolumab injection may be provided in the clinical protocol, pharmacy binder, pharmacy manual, or pharmacy reference sheet. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent. Nivolumab infusions are compatible with polyvinyl chloride (PVC) or polyolefin containers and infusion sets, and glass bottles.

3.3 Recommended Storage and Use Conditions

Vials of Nivolumab Injection, 100 mg/10 mL (10 mg/mL) must be stored at 2°C to 8°C (36°F to 46°F) and protected from light and freezing.

Undiluted Nivolumab Injection and Diluted Nivolumab Injection in the IV Container. 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. Please refer to IB for additional details regarding infusion times. For the dosing of 480 mg intravenously, a 60 minute infusion duration will be used.

3.4 Clinical Data

The PK, clinical activity, and safety of nivolumab have been assessed in approximately 70 clinical studies (see investigator brochure). These studies include approximately 12,300 subjects who have received nivolumab monotherapy in
single- or multiple-dose Phase 1/2/3 studies or studies with nivolumab in combination with other therapeutics (ipilimumab, cytotoxic chemotherapy, anti-angiogenics, and targeted therapies). Results from the ongoing studies are preliminary and are subject to change.

Nivolumab has demonstrated clinical activity in NSCLC, melanoma, RCC, cHL (approved indications), and other tumor types as monotherapy or in combination with ipilimumab. The majority of responses were durable and exceeded 6 months. In randomized, controlled studies, nivolumab monotherapy demonstrated statistically significant improvement in OS over standard of care in subjects with advanced or metastatic melanoma, in subjects with advanced or metastatic NSCLC, and in subjects with advanced RCC.

3.5 Dosing Rationale

The safety and efficacy of 240 mg Q2W flat dose of nivolumab is expected to be similar to 3 mg/kg Q2W dosing regimen. A flat dose of nivolumab 240 mg Q2W was selected since it is identical to a dose of 3 mg/kg for subjects weighing 80 kg, the observed median body weight in nivolumab treated cancer patients. Using a PPK model, the overall distributions of nivolumab exposures ($C_{avgs}$, $C_{mins}$, $C_{maxss}$ and $C_{min}$) are comparable after treatment with either 3 mg/kg or 240 mg nivolumab. The predicted range of nivolumab exposures (median and 90% prediction intervals) resulting from a 240 mg flat dose across the 35 to 160 kg weight range is maintained well below the corresponding exposures observed with the well tolerated 10 mg/kg nivolumab Q2W dosage. Across the various tumor types in the clinical program, nivolumab has been shown to be safe and well tolerated up to a dose level of 10 mg/kg, and the relationship between nivolumab exposure produced by 3 mg/kg and efficacy and safety has been found to be relatively flat. Given the similarity of nivolumab PK across tumor types and the similar exposures predicted following administration of 240 mg flat dose compared to 3 mg/kg Q2W regimen, it is expected that the safety and efficacy profile of 240 mg Q2W nivolumab will be similar to that of 3 mg/kg nivolumab. Hence, a flat dose of 240 mg nivolumab is under investigation.

Nivolumab 480 mg administered once every 4 weeks (Q4W) is currently under investigation. The less frequent dosing regimen is designed to afford more convenience to the target patient populations. The nivolumab dose of 480 mg Q4W was selected based on clinical data and modeling and simulation approaches using PPK and exposure-response analyses of data from studies in multiple tumor types (melanoma, NSCLC, and RCC) to provide an approximately equivalent dose of nivolumab 3 mg/kg Q2W. Exposures following nivolumab 480 mg Q4W regimen are predicted to be within the exposure ranges observed at doses up to 10 mg/kg Q2W used in the nivolumab clinical program, and are not considered to put participants at increased risk.
3.6 Adverse Effects

All available data suggest that nivolumab monotherapy has a consistent AE profile across tumor types. The safety profile is generally consistent across completed and ongoing clinical trials, with no maximum tolerated dose (MTD) reached at any monotherapy dose tested up to 10 mg/kg. Across all studies conducted to date, drug-related AEs have included pulmonary toxicity, renal toxicity (including acute renal failure), endocrine abnormalities, GI toxicity, dermatologic toxicity (including rash), and hepatotoxicity. For nivolumab monotherapy and combination therapy, the majority of these AEs have been managed successfully with supportive care and, in more severe cases, a combination of dose delay, permanent discontinuation, and/or use of corticosteroids or hormone replacement therapy (endocrinopathies) (see investigator brochure).

3.7 Drug-Drug Interaction Potential with the Treatment of Nivolumab

Although monoclonal antibodies are not direct inhibitors/inducers of metabolizing enzymes, recent literature reports suggest that therapeutic proteins that are modulators of cytokines may indirectly affect expression of cytochrome (CYP) enzymes. The indirect drug-drug interaction potential of nivolumab was assessed using systemic cytokine modulation data for cytokines known to modulate CYP enzymes, at single and multiple doses of 0.3 to 10 mg/kg Q3W from CA209009. There were no meaningful changes in cytokines known to have indirect effects on CYP enzymes across all dose levels of nivolumab (0.3, 2 and 10 mg/kg) during the course of treatment. This lack of cytokine modulation suggests that nivolumab has no or low potential for modulating CYP enzymes, thereby indicating a low risk of therapeutic protein-drug interaction.

Nivolumab is an IgG4 monoclonal antibody, which is eliminated by mechanisms similar to that of other antibodies, namely by non-specific catabolism (mainly by enzymes in the reticuloendothelial system). These enzymes are not known to be inhibited or induced by drugs, and therefore it is unlikely that other drugs will have an impact on the PK of nivolumab.

4 STUDY DESIGN

4.1 Description

This is a phase 2, single arm, open label trial to evaluate the rate of failure-free survival at 2 years after start of study treatment with adjuvant nivolumab in adult subjects who undergo chemoradiation for localized bladder cancer. Nivolumab at a dose of 480 mg will be administered as an IV infusion over 60 minutes every 4 weeks until disease recurrence or discontinuation due to unacceptable toxicity for a maximum of 12 treatments over an expected duration of 1 year.

The study will consist of four phases:
1. **Pre-chemoradiation specimen collection (optional):** Patients who present for the treatment of localized muscle invasive bladder cancer who are deemed appropriate for treatment with chemoradiation followed by treatment on the NEXT trial will be offered information about the trial. Pre-chemoradiation consent will allow peripheral blood draw for assessment of correlative biomarkers prior to start of radiation.

2. **Screening Phase:** Patients who have completed part or all of their chemoradiation for localized bladder cancer will be evaluated for eligibility for enrollment for the treatment phase of the NEXT trial. Correlative studies will be performed using archival tissue and peripheral blood at baseline.

3. **Treatment Phase:** Patients who have consented to be on study and who are deemed eligible for the study based on screening will start treatment with nivolumab until disease recurrence or unacceptable toxicity or end of treatment with up to 12 infusions of nivolumab.

4. **End of Treatment Follow-up:** All patients should return to the clinic 28 days after the last treatment dose for an end of treatment visit. From the start of nivolumab treatment, patients will be followed for disease assessment every 12 weeks for the first two years, semi-annually for the third year, and annually for the fourth and fifth years. Adverse event reporting will continue until 120 (±7) days after the last dose of study drug.

4.2 **Number of Patients**

A total of 28 patients will be enrolled in the study. Patients who have received at least one infusion of nivolumab on the study and are available for follow-up until the primary endpoint of failure-free survival (recurrence) will be considered evaluable for response.

4.3 **Number of Study Centers**

This will be a single center study conducted at the Huntsman Cancer Institute.

4.4 **Study Duration**

Assuming an average accrual rate of 3 subjects per month, the accrual will take approximately 10 to 12 months. The total duration of study from start of treatment of the first patient to enroll to the final analysis for 2 year FFS will be approximately 12 + 24 = 36 months. Additional disease assessments and survival follow-up will continue until distant relapse or discontinuation from study (whichever occurs later) for a maximum of 5 years from start of study treatment. The total study duration is expected to be 6 to 7 years.
5 ELIGIBILITY CRITERIA

5.1 Pre-Chemoradiation Sample Collection Eligibility

This eligibility checklist is used to determine patient eligibility FOR PRE-CHEMORADIATION SAMPLE COLLECTION ONLY and must be filed with signature in the patient research chart.

Patient No. ______________________
Patient’s Initials: (L, F, M) _________________

5.1.1 Inclusion Criteria
Yes/No (Response of “no” = patient ineligible)

5.1.1.1 _____ Patients with muscularis propria invasion clinical stages 2 to 4 (T2-4a, N0 or N+, M0 or T1 with N+), who are not candidates for radical cystectomy.
  • Patients may have undergone partial cystectomy for removal of bladder tumor prior to chemoradiation. Patients who have down-staged from M1 disease to M0 with prior platinum-based chemotherapy will be eligible.
  • Staging is determined prior to chemoradiation.

5.1.1.2 _____ Patients must have histologically proven primary carcinoma of the bladder or urethra or lower ureter (adenocarcinoma or transitional or squamous-cell carcinoma).

I certify that this patient meets all inclusion and exclusion criteria for enrollment onto this study.

_____________________________  ___________  ______
Investigator Signature              Date       Time

5.2 Study Treatment Eligibility

This eligibility checklist is used to determine patient eligibility FOR STUDY TREATMENT and must be filed with signature in the patient research chart.

Patient No. ______________________
Patient’s Initials: (L, F, M) _________________

5.2.1 Inclusion Criteria
Yes/No (Response of “no” = patient ineligible)

5.2.1.1 _____ Patients with muscularis propria invasion clinical stages 2 to 4 (T2-4a, N0 or N+, M0 or T1 with N+), who are not candidates for radical cystectomy.
- Patients may have undergone partial cystectomy for removal of bladder tumor prior to chemoradiation. Patients who have down-staged from M1 disease to M0 with prior platinum-based chemotherapy will be eligible.
- Staging is determined prior to chemoradiation.

5.2.1.2 Patients must have histologically proven primary carcinoma of the bladder or urethra or lower ureter (adenocarcinoma or transitional or squamous-cell carcinoma).

5.2.1.3 Tumor tissue from the most recently resected site of disease (preferable) or from the transurethral resection that yielded the initial muscle invasive diagnosis must be provided for biomarker correlative analyses. Enrollment is permitted if adequate archived tissue is unavailable.

5.2.1.4 Patients must have received systemic radiosensitizing chemotherapy with definitive pelvic radiation therapy (see Section 6 for detailed requirements). Patients may have received partial amount of chemotherapy and radiation (both) to be eligible.

5.2.1.5 Platinum-based chemotherapy prior to chemoradiation is permitted but not mandatory.

5.2.1.6 ECOG Performance Status of ≤ 2 (see appendix 3).

5.2.1.7 Age ≥ 18.

5.2.1.8 Adequate bone marrow function: WBC ≥ 2000 /µl, neutrophils ≥ 1500 /µl, Hemoglobin ≥ 9.0 g/dl.

5.2.1.9 Serum bilirubin and aminotransferase values less than 1.5 times the upper limit of the normal range.

5.2.1.10 Creatinine clearance of 20 ml/min or greater as measured by the Cockroft-Gault formula.

5.2.1.11 Able to start study treatment in less than or equal to 90 days after completion of chemoradiation.

5.2.1.12 Female subject of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
5.2.1.13 Female subjects of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 7 months after the last dose of study medication. Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

5.2.1.14 Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 7 months after the last dose of study therapy.

5.2.1.15 All toxicities attributed to prior anti-cancer therapy other than nephropathy, neuropathy, hearing loss, alopecia and fatigue must have resolved to Grade 1 (NCI CTCAE version 4) or baseline before administration of study drug. Subjects with toxicities attributed to prior anti-cancer therapy which are not expected to resolve and result in long lasting sequelae, such as neuropathy after platinum based therapy, are permitted to enroll.

5.2.1.16 Able to provide informed consent and willing to sign an approved consent form that conforms to federal and institutional guidelines.

5.2.2 Exclusion Criteria

Yes/No (Response of “yes” = patient ineligible)

5.2.2.1 Evidence of distant metastases or lymph node metastasis(es) that was not within the radiation field.

5.2.2.2 Known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin. A history of localized early stage malignancy that has undergone potentially curative therapy or is low grade and does not require active treatment is allowed.

5.2.2.3 Diffuse bladder carcinoma in situ (CIS) that was not able to be encompassed in a boost radiotherapy volume.

5.2.2.4 Patients with inflammatory bowel disease.

5.2.2.5 Patients with active, known, or suspected autoimmune disease. Subjects with vitiligo, type 1 diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
5.2.2.6 _____ Patients with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 day of study drug administration. Inhaled, ocular, intraarticular, intranasal, and topical steroids are permitted.

5.2.2.7 _____ Patients with a known chronic immunocompromised state, HIV infection, or active Hepatitis B or C infection.

5.2.2.7.1 _____ Patients who desire and are candidates for radical cystectomy.

5.2.2.7.2 _____ Pregnant women, women of childbearing potential not willing to use contraception, men who are sexually active and not willing/able to use medically acceptable forms of contraception, and breast-feeding women not willing to stop breast feeding during the study.

5.2.2.8 _____ Severe active co-morbidity as determined by the investigator or principal investigator.

5.2.2.9 _____ Life expectancy less than 2 years.

I certify that this patient meets all inclusion and exclusion criteria for enrollment onto this study.

_____________________________  ____________  ________
Investigator Signature        Date              Time
6 DEFINITIVE CHEMORADIATION THERAPY SUMMARY

Radiosensitizing chemotherapy regimens may be based on cisplatin or 5-fluorouracil and the choice would depend on the clinical setting and the treating multidisciplinary team.

A definitive course of chemoradiation therapy will be defined as 20 to 35 fractions of 1.8 to 2.75 Gy per fraction. Shorter fractionation schemes will have a higher dose per fraction. The volumes covered can include the bladder only in select cases or the bladder, prostate, and regional lymph nodes which can include the internal, external, common iliac, and obturator nodal chains. When nodal chains are treated, the bladder will be treated to a higher dose than the nodal chains. This can be accomplished either by simultaneous integrated boost or cone-down. IMRT or 3D-conformal radiation therapy are acceptable. Treatment of whole bladder or partial bladder to full dose will be at the discretion of the treating physician.

7 TREATMENT PLAN

7.1 Administration Schedule

Subjects will receive treatment with nivolumab as a 60-minute IV infusion on Day 1 of a treatment cycle every 4 weeks (28 days), for a maximum of 12 doses or until recurrence, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first. The first dose must be administered within 90 days after completion of the last dose of radiation.

There are no pre-medications recommended on the first cycle. If an acute infusion reaction is noted, subjects should be managed according to Section 8. At the end of the infusion, flush the line with a sufficient quantity of dextrose or normal saline.

**Treatment**

Nivolumab 480 mg intravenously on day 1 of each cycle.

1 cycle = 28 days.

Repeat for a total of 12 cycles.

7.1.1 How Supplied, Stored, Packaged and Labeled

Nivolumab Injection, 100 mg/10 mL (10 mg/mL) is a clear to opalescent colorless to pale yellow liquid which may contain light (few) particulates. The drug product is a sterile, non-pyrogenic, single-use, isotonic aqueous solution formulated at 10 mg/mL in sodium citrate, sodium chloride, mannitol, diethylenetriaminepentacetic acid (pentetic acid), and polysorbate 80 (Tween80), pH 6.0, and includes an overfill to account for vial, needle, and syringe holdup. It is supplied in 10-cc Type I flint glass vials, stoppered with butyl rubber stoppers and sealed with aluminum seals.

**Recommended Storage and Use Conditions:** vials of nivolumab injection must be stored at 2°C to 8°C (36°F to 46°F) and protected from light and freezing.
Undiluted Nivolumab Injection and Diluted Nivolumab Injection in the IV Container: 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 4 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 4-hour period under room temperature and room light conditions includes the product administration period.

Nivolumab infusion will be labeled consistently with individual institutional practices.

7.1.2 Preparation and Administration

Visually inspect the drug product solution for particulate matter and discoloration prior to administration. It should be a clear to opalescent, colorless to pale-yellow solution. Discard the vial if the solution is cloudy, discolored, or contains extraneous particulate matter other than a few translucent-to-white, proteinaceous particles. Do not shake the vial.

Preparation: withdraw the required volume of Nivolumab and transfer into an intravenous container. Dilute Nivolumab with either 0.9% Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP, to prepare an infusion with a final concentration ranging from 1 mg/mL to 10 mg/mL. Mix diluted solution by gentle inversion. Do not shake. Discard partially used vials or empty vials of Nivolumab.

Administration: administer the infusion over 60 minutes through an intravenous line containing a sterile, non-pyrogenic, low protein binding in-line filter (pore size of 0.2 micrometer to 1.2 micrometer). Do not co-administer other drugs through the same intravenous line. Flush the intravenous line at end of infusion.

7.1.3 Accountability and Compliance

Drug return and destruction are done according to institutional guidelines. Drug disposition should be recorded on an investigational drug accountability form. Drug can be destroyed on site if proper accountability of the destructions is maintained (number of vials, expiration date, lot number, etc.) as well as documentation that the drug was destroyed according to the institution’s SOP.

7.2 Concomitant Medications

Concomitant medications are recorded at baseline, throughout the treatment phase of the study, and at the end of treatment visit, and are captured in the appropriate section of the CRF. All medications (prescriptions or over the counter medications) continued at the start of the study or started during the study and different from the study drug must be documented in the concomitant therapy section of the CRF.

7.2.1 Prohibited Concomitant Medications

The following medications are prohibited during the study:

- Immunosuppressive agents (except to treat a drug-related adverse event).
• Systemic corticosteroids > 10 mg daily prednisone equivalent (except as stated in Section 7.2.2 or to treat a drug-related adverse event).

• Any concurrent antineoplastic therapy (i.e., chemotherapy, hormonal therapy, immunotherapy, standard or investigational agents, surgery or radiation therapy for treatment of cancer).

• Alternative systemic or topical therapy (herbal supplements, alternative treatments, essential oils, vitamin or mineral doses exceeding FDA recommended daily allowance) unless deemed medically appropriate by the investigator.

7.2.2 Permitted Concomitant Medications

Supportive care for disease-related symptoms may be offered to all subjects on the trial. Subjects are permitted the use of topical, ocular, intra-articular, intranasal and inhalational corticosteroids (with minimal systemic absorption). A brief course of corticosteroids for prophylaxis (e.g., for contrast dye allergy) or for treatment of non-autoimmune conditions (e.g., delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.

Intravitreal injections of vascular endothelial growth (VEGF) inhibitors are permitted if used according to the approved ocular indication, such as macular degeneration.

7.2.3 Other Restrictions and Precautions

Imaging: it is the local imaging facility’s responsibility to determine, based on subject attributes (e.g., allergy history, diabetic history and renal status), the appropriate imaging modality and contrast regimen for each subject. Imaging contraindications and contrast risks should be considered in this assessment. Subjects with renal insufficiency should be assessed as to whether or not they should receive contrast and if so, what type and dose of contrast is appropriate.

The ultimate decision to perform MRI and/or upper tract imaging with retrograde pyelogram in an individual subject in this study rests with the site.

7.3 Duration of Therapy

Patients will continue to receive drug at day 1 of each 28 day cycle for a total of 12 cycles. Delays in dosing are allowed and will lengthen the total duration of treatment which should not exceed two years. A maximum interval of 84 days (12 weeks) between doses is allowed (see section 8 for additional details).

Subjects must be withdrawn from the study treatment for the following reasons:

• Subject withdraws consent from the study treatment and/or study procedures. A subject must be removed from the trial at his/her own request or at the request of his/her legally acceptable representative. At any time during the trial and without giving reasons, a subject may decline further participation. The subject will not suffer any disadvantage as a result.
- Any clinical adverse event (AE), laboratory abnormality, or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study treatment is not in the best interest of the subject.
- Recurrence as defined in Section 11.1. (see note below).
- Subject is lost to follow-up.
- Death.
- Any protocol-specified reason for discontinuation as outlined in Section 8.
- Clinical deterioration (see note below).

Note: accumulating clinical evidence indicates that the emergence of objective responses to agents that activate anti-tumor immune responses may follow delayed kinetics of weeks or months, and can be preceded by initial apparent progression of disease with the appearance of new lesions or some enlarging of lesions while certain index lesions are regressing (“mixed response”). Therefore, it is reasonable to allow patients who experience apparent progression to continue to receive treatment until progression is confirmed at the next imaging assessment. These considerations should be balanced by clinical judgment as to whether the patient is clinically deteriorating and unlikely to receive any benefit from continued treatment. Such deterioration will be assessed to have occurred after a clinical event that, in the Investigator’s opinion, is attributable to disease progression and is unlikely to reverse with continued study treatment and cannot be managed by the addition of supportive care. The decision to continue treatment should be discussed with the Sponsor–Investigator or designee. Examples of events that in the Investigator’s opinion, indicate a lack of clinical benefit include but are not limited to the following:

- Eastern Cooperative Oncology Group (ECOG) score increase of at least 2 points from baseline (e.g. from 0 to 2).
- Habitual changes such as changes in activities and symptoms including reduction in appetite and/or sleep, altered awareness, and increased pain-related symptoms due to cancer.
- Any setting where the initiation of new anti-neoplastic therapy has been deemed beneficial to the patient even in the absence of any such documented clinical events.

Subjects may also be withdrawn from the study for the following reasons:

- The subject is non-compliant with study drug, trial procedures, or both. This includes the use of anti-cancer therapy not prescribed by the study protocol.
- If, in the investigator's opinion, continuation of the trial would be harmful to the subject's well-being.
- The development of a second cancer.
- Development of an intercurrent illness or situation which would, in the judgment of the investigator, significantly affect assessments of clinical status and trial endpoints.
- Deterioration of ECOG performance status to 4.
8 TOXICITIES AND DOSAGE MODIFICATION

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.0 for adverse event and serious adverse event reporting.

8.1 Dose Modifications

There will be no dose modifications (dose escalations or reductions) allowed for the management of toxicities of individual subjects.

**Dosing window:** subjects may be treated no less than 26 days between doses and no more than 7 days after the scheduled dosing date. If a dose is given outside of the +7-day window it is considered a dose delay. A maximum interval of 84 days (12 weeks) between doses is allowed.

8.2 Dose Delay/Discontinuation

Nivolumab administration should be delayed/discontinued as per Table 1:

**Table 1: Recommended Dose Delays/Discontinuation for Nivolumab**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Severity per NCI CTCAE v4</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colitis</td>
<td>Grade 2 diarrhea or colitis</td>
<td>Withhold dose&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Grade 3 diarrhea or colitis</td>
<td>Withhold dose&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Grade 4 diarrhea or colitis</td>
<td>Permanently discontinue</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>Grade 2 pneumonitis</td>
<td>Withhold dose&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Grade 3 or 4 pneumonitis</td>
<td>Permanently discontinue</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 3 x ULN and ≤ 5 x ULN or total bilirubin ≥ 1.5 x ULN and ≤ 3 x ULN</td>
<td>Withhold dose&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>AST or ALT ≥ 5 x ULN or total bilirubin ≥ 3 x ULN</td>
<td>Permanently discontinue</td>
</tr>
<tr>
<td>Hypophysitis</td>
<td>Grade 2 or 3 hypophysitis</td>
<td>Withhold dose&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Grade 4 hypophysitis</td>
<td>Permanently discontinue</td>
</tr>
<tr>
<td>Adrenal Insufficiency</td>
<td>Grade 2 adrenal insufficiency</td>
<td>Withhold dose&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Grade 3 or 4 adrenal insufficiency</td>
<td>Permanently discontinue</td>
</tr>
<tr>
<td>Type 1 Diabetes Mellitus</td>
<td>Grade 3 hyperglycemia</td>
<td>Withhold dose&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Grade 4 hyperglycemia</td>
<td>Permanently discontinue</td>
</tr>
<tr>
<td>Nephritis and Renal Dysfunction</td>
<td>Serum creatinine ≥ 1.5 x baseline</td>
<td>Withhold dose&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Serum creatinine ≥ 6 x ULN</td>
<td>Permanently discontinue</td>
</tr>
</tbody>
</table>
Dose Delay/Discontinuation Criteria

Dose delays are allowed to address any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Subjects who require a nivolumab dose delay should be re-evaluated every two weeks or more frequently if clinically indicated and resume nivolumab dosing when re-treatment criteria are met.

After a dose delay, treatment will continue as the next cycle and no cycles will be skipped (e.g., if dose is held for > 4 weeks after cycle 6 the next cycle will still be cycle 7 regardless of the duration of the dose delay). **Scans and other assessments on treatment will occur every 12 weeks regardless of dose delay.**

For patients who experience dose delays due to adverse events and who remain eligible to complete up to 12 infusions of nivolumab, study treatment may not be extended beyond the second year since the start of therapy.

For patients requiring surgery, study treatment may resume after adequate recovery from surgery.

Subjects with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters should have treatment permanently discontinued.

Additional criteria to discontinue treatment:
- Any dosing delay lasting > 12 weeks from the last dose with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 12 weeks from the last dose, the sponsor-
investigator must be consulted. Tumor imaging assessments should continue as per protocol (every 12 weeks) even if dosing is interrupted.

- Dosing delays > 12 weeks from the last dose that occur for non-drug-related reasons may be allowed if approved by the Sponsor-Investigator. Tumor imaging assessments should continue as per protocol (every 12 weeks) even if dosing is interrupted.

- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing.

Tumor assessments for all subjects should continue until non-urothelial tract recurrence as per protocol even if study drug dosing is discontinued. Tumor assessments, QoL questionnaires collection and correlative sampling should continue as per protocol even if dosing is omitted.

8.3 Dose Interruption

The term “interruption” is reserved for interruption of the actual IV infusion during administration. The terms delay and interruption should not be used synonymously when completing the CRF forms.

8.4 Supportive Care

All supportive measures consistent with optimal patient care will be given throughout the study, with observation of concomitant medication restrictions (Section 7.2.1). Additional supportive care guidelines are as follows

8.4.1 Adverse Event Management Algorithms for Immuno-Oncology Agents

- Gastrointestinal
- Renal
- Pulmonary
- Hepatic
- Endocrinopathies
- Skin
- Neurological

In order to standardize the management of adverse events for all subjects, treatment management algorithms recommended for utilization in this study are from the current IB and included in Appendix 3 of the IB. These algorithms might be considered for individual cases. Some subjects may require prolonged treatment with high-dose corticosteroids or alternative immunosuppressants for the treatment of nivolumab-related AEs. For subjects expected to require more than 4 weeks of corticosteroids or other immunosuppressants to manage an adverse event, consider recommendations provided in Appendix 3 of the IB.

Rare cases of opportunistic infections have occurred in subjects treated with immunosuppression. It is rare for a patient receiving immunosuppression for
nivolumab-related AEs to develop an opportunistic infection. Subjects with inflammatory events of any organ category expected to require more than 4 weeks of corticosteroid or other immunosuppressive agents to manage the AE should be considered for antimicrobial/antifungal prophylaxis, per institutional guidelines, to prevent opportunistic infections such as *P. jiroveci* (formerly *P carinii*) and fungal infections. Early consultation with an infectious disease specialist should be considered. Depending on the presentation, consultation with a pulmonologist for bronchoscopy or a gastroenterologist for endoscopy may also be appropriate. In addition, a concomitant opportunistic infection should be considered in the differential diagnosis if a patient develops recurrent AEs in the setting of ongoing or prior immunosuppressive use. Nivolumab should not be used in subjects with active autoimmune disease given the mechanism of action of the antibody.

8.4.2 Criteria to Resume Treatment

Subjects may resume treatment with study drug when the drug-related AE(s) resolve to Grade ≤ 1 or baseline value, with the following exceptions:

- Subjects may resume treatment in the presence of Grade 2 fatigue.
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- Subjects with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT OR total bilirubin.
- Drug-related pulmonary toxicity, diarrhea, or colitis, must have resolved to baseline before treatment is resumed.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment.
- Patient who are treated with high dose steroids for immune related adverse events as referenced in Section 8.4.1 must be on immunosuppression tapered down to prednisone 10 mg or equivalent prior to resuming treatment with nivolumab.

Subjects who require delay of nivolumab should be re-evaluated every two weeks or more frequently if clinically indicated and resume nivolumab dosing when re-treatment criteria are met.

8.4.3 Treatment of Nivolumab-Related Infusion Reactions

Since nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. Infusion reactions should be graded according to NCI CTCAE (version 4.0) guidelines. Treatment recommendations are provided below (Table 2) and may be modified based on local treatment standards and guidelines as appropriate: Severe
Infusion reactions have been reported in less than 1.0% of patients in clinical trials of Nivolumab.

**Table 2: Infusion Reaction Treatment Guidelines**

<table>
<thead>
<tr>
<th>NCI CTCAE Grade</th>
<th>Treatment</th>
<th>Pre-medications at subsequent dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade 1</strong></td>
<td>Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the site investigator.</td>
<td>None</td>
</tr>
<tr>
<td>Mild reaction; infusion interruption not indicated; intervention not indicated</td>
<td>Stop infusion and monitor symptoms. Additional appropriate medical therapy may include but is not limited to: IV fluids, Antihistamines, NSAIDS, Acetaminophen, Narcotics. Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the site investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate. Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.</td>
<td>Subject may be premedicated 1.5 h (± 30 minutes) prior to infusion of nivolumab with: Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg PO (or equivalent dose of antipyretic)</td>
</tr>
<tr>
<td><strong>Grade 2</strong></td>
<td>Stop Infusion. Additional appropriate medical therapy may include but is not limited to: IV fluids, Antihistamines, NSAIDS, Acetaminophen, Narcotics, Oxygen, Pressors, Corticosteroids, Epinephrine. Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the site investigator. Hospitalization may be indicated. Subject is permanently discontinued from further trial treatment administration.</td>
<td>No subsequent dosing</td>
</tr>
<tr>
<td>Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Grades 3 or 4</strong></td>
<td>Stop Infusion. Additional appropriate medical therapy may include but is not limited to: IV fluids, Antihistamines, NSAIDS, Acetaminophen, Narcotics, Oxygen, Pressors, Corticosteroids, Epinephrine. Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the site investigator. Hospitalization may be indicated. Subject is permanently discontinued from further trial treatment administration.</td>
<td>No subsequent dosing</td>
</tr>
<tr>
<td>Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 4: Life-threatening; pressor or ventilatory support indicated</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms.

In the case of late-occurring hypersensitivity symptoms (e.g., appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine, or corticosteroids).
8.5 Treatment Compliance

Treatment compliance will be monitored by drug accountability as well as the subject’s medical record and electronic CRF (eCRF).

8.6 Destruction of Study Drug

Do not store any unused portion of the infusion solution for reuse. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.
## STUDY CALENDAR

**Cycle = 28 days**

<table>
<thead>
<tr>
<th>Examination</th>
<th>Pre-chemoradiation Preferred, not required⁹</th>
<th>Screening¹</th>
<th>Cycles 1⁴ – 12 Day 1 -2 days, +7 days</th>
<th>Additional procedures for Cycle 4, 7 and 10</th>
<th>End of Treatment visit 28 ± 3 days after last dose of nivolumab</th>
<th>Follow-up ¹¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informed consent</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical history</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiation treatment summary¹⁸</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sEligibility criteria</td>
<td>X¹⁶</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vital signs &amp; weight</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Physical examination</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>ECOG performance status</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Hematology²</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Chemistry³</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>TSH (TSH, T3, T4)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pregnancy test⁴</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT/MRI¹⁵,¹⁹</td>
<td>X</td>
<td>X¹²</td>
<td></td>
<td></td>
<td>X¹²</td>
<td></td>
</tr>
<tr>
<td>RECIST 1.1</td>
<td>X</td>
<td>X¹²</td>
<td></td>
<td></td>
<td>X¹²</td>
<td></td>
</tr>
<tr>
<td>Nivolumab infusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premedication, if any</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Review Adverse Events</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant medications</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cystoscopy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X¹²</td>
</tr>
<tr>
<td>Chart review or phone call¹⁰</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X¹²</td>
</tr>
<tr>
<td>QOL questionnaire¹⁵</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>RTOG Toxicity evaluation¹⁴</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Tissue for correlative studies</td>
<td>X</td>
<td>X⁶</td>
<td></td>
<td></td>
<td></td>
<td>X⁶</td>
</tr>
<tr>
<td>Peripheral blood for correlative studies⁷</td>
<td>X</td>
<td>X⁷</td>
<td>X⁷</td>
<td></td>
<td></td>
<td>X⁸</td>
</tr>
</tbody>
</table>
1. All pre-study/screening procedures should be completed within 4 weeks of study enrollment, with the exception of laboratory tests which need to be completed within 2 weeks prior to study enrollment.

2. Hematology includes CBC with differential and platelets.

3. Chemistry includes Albumin, Alkaline Phosphatase, Aspartate Aminotransferase, Alanine Aminotransferase, Total Bilirubin, Calcium, Carbon Dioxide, Creatinine, Chloride, Glucose, Potassium, Protein, Sodium, Urea Nitrogen. Amylase and Lipase will be collected at screening only.

4. Pregnancy test must be done at screening for all women of childbearing potential and repeated as clinically indicated.

5. Procedures done at screening do not need to be repeated at C1D1 if procedures have been done within 7 days of start of treatment. Subjects may be dosed no less than 26 days between doses and no more than 7 days after the scheduled dosing date. If a dose is given after the 7-day window it is considered a dose delay.

6. Archival tissue will be used for baseline tissue correlative studies. In the event of need for cystectomy or tissue biopsy for treatment or diagnosis, tissue will be obtained for correlative studies after completion of standard care tissue analysis. See section 15 for details.

7. During the Nivolumab treatment period, blood collections will only be obtained after consent. Samples are to be collected prior to chemoradiation and on cycles 1, 4, 7, and 10 prior to infusion. Blood collection will also be taken at disease progression. See section 15 for details.

8. Once treatment is discontinued, follow-up blood collections will take place every three months (from C1D1) until the end of the 2nd year to correspond with CT scans. See section 15 for details.

9. The pre-chemoradiation visit is optional. Patients who agree to participate in blood sampling must sign pre-chemoradiation consent and fulfill inclusion criteria prior to blood collection.

10. If a patient discontinues treatment or follow-up visits for any reason, they will be followed up with a chart review or phone call for overall survival.

11. Follow-up visits should occur every 12 weeks (± 1 week) and correspond with CT scans and cystoscopy (footnote 12).

12. CT scans, cystoscopies, and disease assessments should continue at 12 week (± 1 week) intervals for 2 years following the beginning of treatment. Every 6 months for the third year (± 4 weeks) and annually for years 4 and 5 (± 4 weeks).

13. AEs will be followed for 120 days after the last dose of nivolumab.


15. Appendix 2.

16. Subjects must meet inclusion criteria 5.1.1.1 and 5.1.1.2 prior to chemoradiation to qualify for pre-chemoradiation correlative blood sampling.

17. CT of chest, CT or MRI of abdomen, pelvis, upper urinary tract and all known or suspected sites of disease. Cytology and/or histology are mandatory to confirm recurrence in solitary or in equivocal lesions, any new lesions occurring in the urothelial tract, and lymph nodes unless the lesion is too small to biopsy or the risk of biopsy is substantial.

18. A radiation treatment summary will be documented at baseline. This will include dose, fractionation, and treatment volumes, including cone-downs, if necessary.

19. In case of dose delay, tumor-imaging assessments should continue every 12 weeks per protocol.
10 STUDY PROCEDURES

10.1 Pre-chemoradiation

- Informed pre-chemoradiation consent.
- Subjects must meet inclusion criteria 5.1.1.1 and 5.1.1.2 prior to chemoradiation to qualify for pre-chemoradiation correlative blood sampling.
- Serum and Peripheral blood for correlative studies.

10.2 Screening:

- Informed Consent.
- Physical exam.
- Review of medical history/baseline symptoms.
- ECOG Performance status (see appendix 3).
- A radiation treatment summary will be documented at baseline. This will include dose, fractionation, and treatment volumes, including cone-downs, if necessary.
- Labs:
  - CBC w/diff.
  - CMP – Albumin, Alkaline Phosphatase, Aspartate Aminotransferase, Alanine Aminotransferase, Total Bilirubin, Calcium, Carbon Dioxide, Creatinine, Chloride, Glucose, Potassium, Protein, Sodium, Urea Nitrogen, Amylase and Lipase.
  - Thyroid function – TSH, free T4, total T3.
  - Serum pregnancy test (for women of childbearing potential).
- CT scans.
- Tumor tissue (obtained prior to chemoradiation) for correlative studies.
- Serum and Peripheral blood for correlative studies.

10.3 On-Treatment Evaluations

- Physical Exam.
- ECOG Performance Status.
- Laboratory assessments (do not need to be repeated if screening labs performed within 7 days of C1D1):
  - CBC w/diff.
  - CMP – Albumin, Alkaline Phosphatase, Aspartate Aminotransferase, Alanine Aminotransferase, Total Bilirubin, Calcium, Carbon Dioxide, Creatinine, Chloride, Glucose, Potassium, Protein, Sodium, and Urea Nitrogen.
  - Thyroid function – TSH, free T4, total T3 (at cycles 4, 7 and 10 only).
- Safety assessment - Monitoring and recording all adverse events and serious adverse events using the CTCAE version 4 at every cycle.
- Review of concomitant medications.
- CT scans, cystoscopy and review of response as outlined above (every 12 weeks ± 1 week while on treatment).
- Treatment with Nivolumab.
- Serum and Peripheral blood for correlative studies (collected before study treatment).

10.4 End of Treatment Evaluations
- Physical Exam.
- ECOG Performance Status.
- Labs:
  - CMP – Albumin, Alkaline Phosphatase, Aspartate Aminotransferase, Alanine Aminotransferase, Total Bilirubin, Calcium, Carbon Dioxide, Creatinine, Chloride, Glucose, Potassium, Protein, Sodium, and Urea Nitrogen.
  - Thyroid function – TSH, free T4, total T3.
- Safety assessment - Monitoring and recording all adverse events and serious adverse events using the CTCAE version 4.
- Review of concomitant medications.
- CT scans, cystoscopy, and review of response as outlined above (if they fall in the 12-week window for evaluation – not required for the specific visit).
- Serum and Peripheral blood for correlative studies.

10.5 Follow-up Evaluations
- Physical Exam.
- ECOG Performance Status.
- Labs:
  - CMP – Albumin, Alkaline Phosphatase, Aspartate Aminotransferase, Alanine Aminotransferase, Total Bilirubin, Calcium, Carbon Dioxide, Creatinine, Chloride, Glucose, Potassium, Protein, Sodium, and Urea Nitrogen.
  - Thyroid function – TSH, free T4, total T3.
- CT scans, cystoscopy, and review of response as outlined above. Patients should remain on 12 week (± 1 week) schedule for the first two years from the beginning of treatment. Scans should occur every 6 months (± 4 weeks) for the third year and every 12 months (± 4 weeks) for the years 4 and 5 after the start of treatment.
11 CRITERIA FOR EVALUATION AND ENDPOINT

11.1 Efficacy

Efficacy will be measured primarily by assessment of failure-free survival (including both loco regional and systemic disease).

All patients who receive at least 1 infusion of nivolumab on study and remain on follow-up until the primary endpoint (recurrence) will be considered evaluable for the primary endpoint of failure-free survival at 2 years. Patients who do not meet these criteria will be replaced.

For subjects with residual disease after completion of chemoradiation and while on treatment with nivolumab or local bladder recurrence while on nivolumab, partial cystectomy will be allowed if felt clinically indicated without affecting enrollment on study.

11.1.1 Failure-free Survival

This is defined as the time from start of study treatment to time of disease recurrence (systemic or loco regional) or death from any cause. This will be the primary endpoint of the study.

Disease recurrence is defined as follows:

**Local, Urothelial Tract:** Any high grade or muscle invasive lower or upper urothelial tract recurrence of urothelial carcinoma including intravesical recurrences for subjects with an intact bladder that requires additional treatment other than transurethral resection. Any new urothelial carcinoma lesions requiring cystectomy including those thought to be a second urothelial carcinoma primary will be considered recurrences.

**Local, Non-Urothelial Tract:** Any recurrence in pelvic soft tissue or involving pelvic nodes below the aortic bifurcation

**Distant:** Any non-local recurrence

11.1.2 For patients without measurable disease at screening

The appearance of any measurable disease as described below denotes disease recurrence.

**Measurable Disease per RECIST 1.1**

Measurable lesions must be accurately measured in at least one dimension (longest diameter in the plane of the measurement to be recorded) with a minimum size of:

- Serum and Peripheral blood for correlative studies only if there is disease recurrence.
- Safety assessment - Monitoring and recording all adverse events and serious adverse events using the CTCAE version 4 for 120 days after discontinuing nivolumab.
• 10 mm by CT/MRI scan (CT/MRI scan slice thickness no greater than 5 mm).

• 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable), 20 mm by chest x-ray.

**Malignant lymph nodes:** to be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

If the measurable disease is restricted to a solitary lesion (visceral or nodal), its neoplastic nature must be confirmed either by cytology/histology or by lesion progression certified on the next CT/MRI examination.

The appearance of new malignant lesions denotes disease recurrence. The finding of a new lesion should be unequivocal, i.e., not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some ‘new’ bone lesions may be simply healing or flare of pre-existing lesions).

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease recurrence. An example of this would be a subject who, while on treatment, has a brain CT or MRI which reveals metastases. The subject’s brain metastases are considered evidence of recurrence even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow up evaluation will clarify if it truly represents new disease. If repeat scans or cytology/histology confirm there is definitely a new lesion (see methods of measurements for confirmation of recurrence), then recurrence should be declared using the date of the initial scan.

**Methods of measurements**

• CT and MRI are an essential part of the work-up to establish recurrence. The following imaging assessments should be performed at pre-specified intervals: CT of chest, CT or MRI of abdomen, pelvis, upper urinary tract and all known or suspected sites of disease (including cystoscopy in subjects who still have bladder intact).

• CT scans should be acquired with 5 mm slices with no intervening gap (contiguous).

• Should a subject have a contraindication for CT IV contrast, a non-contrast CT of the chest and a contrast enhanced MRI of the abdomen and pelvis may be obtained. MRIs should be acquired with slice thickness of < 5 mm with no gap (contiguous).

• Every attempt should be made to image each subject using an identical acquisition protocol on the same scanner for all imaging time points.
PET alone will not be considered for the disease assessment. Complementary CT and/or MRI or biopsy must be performed in such cases.

- Histological or cytological evidence of recurrence should be attempted in all cases except for brain metastases. Cytology and/or histology are mandatory to confirm recurrence in solitary or in equivocal lesions, any new lesions occurring in the urothelial tract, and lymph nodes unless the lesion is too small to biopsy or the risk of biopsy is substantial (e.g., inter-aortal node with risk of bleed after biopsy because of close proximity to the aorta and IVC) in which case the recurrence must be confirmed with a repeat scan.

- For subjects with GU primary tumors (bladder or upper tract) confirmation of a defined lesion on cystoscopy requires transurethral biopsy and, if necessary, retrograde study and biopsy.

- Positive urine cytology (e.g., positive Urovision or similar urine assay) alone does not constitute the basis for recurrence of disease.

- Tumor markers or auto-antibodies alone cannot be used to document recurrence.

11.1.3 For patients with measurable disease at screening

The following definitions and criteria (RECIST version 1.1) should be used for the baseline evaluations of existing disease, and for the ongoing evaluation of tumor responses.

**Measurable lesions** - lesions that can be accurately measured in at least one dimension with longest diameter (LD) ≥ 10 mm using CT, MRI, or caliper measurements or ≥ 20 mm with x-ray.

*Malignant lymph nodes:* to be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

**Non-measurable lesions** - all other lesions including small lesions (LD < 10 mm with CT, MRI, or caliper measurements or < 20 mm with x-ray).

**Documentation of “Target” and “Non-Target” Lesions**

- All measurable lesions up to a maximum of two lesions per organ and five lesions in total, representative of all involved organs, should be identified as *target lesions* and recorded and measured at baseline.

- Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinical assessments).

- A sum of the LD for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as the reference by which to characterize the objective tumor response.
All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

11.1.4 Response Criteria

<table>
<thead>
<tr>
<th>Evaluation of target lesions</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response (CR)</td>
<td>Disappearance of all target lesions (Must persist for a minimum of four weeks)</td>
</tr>
<tr>
<td>Partial Response (PR)</td>
<td>At least a 30% decrease in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started (Must persist for a minimum of four weeks)</td>
</tr>
<tr>
<td>Progressive Disease (PD)</td>
<td>At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions</td>
</tr>
<tr>
<td>Stable Disease (SD)</td>
<td>Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Evaluation of non-target lesions</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response (CR)</td>
<td>Disappearance of all non-target lesions</td>
</tr>
<tr>
<td>Stable Disease (SD)</td>
<td>Persistence of one or more non-target lesion(s)</td>
</tr>
<tr>
<td>Progressive Disease (PD)</td>
<td>Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions</td>
</tr>
</tbody>
</table>

11.1.5 Evaluation of Best Overall Response

The best overall response is the best response observed until progression/recurrence and is determined as indicated in the table below:

<table>
<thead>
<tr>
<th>Target Lesions</th>
<th>Non-Target Lesions</th>
<th>Evaluation of New Lesions</th>
<th>Best Overall Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>CR</td>
<td>No</td>
<td>CR</td>
</tr>
<tr>
<td>CR</td>
<td>SD</td>
<td>No</td>
<td>PR</td>
</tr>
<tr>
<td>PR</td>
<td>Non-PD</td>
<td>No</td>
<td>PR</td>
</tr>
<tr>
<td>SD</td>
<td>Non-PD</td>
<td>No</td>
<td>SD</td>
</tr>
<tr>
<td>PD</td>
<td>Any</td>
<td>Yes or No</td>
<td>PD</td>
</tr>
<tr>
<td>Any</td>
<td>PD</td>
<td>Yes or No</td>
<td>PD</td>
</tr>
<tr>
<td>Any</td>
<td>Any</td>
<td>Yes</td>
<td>PD</td>
</tr>
</tbody>
</table>

11.1.6 Date of Recurrence

The first date when recurrence was observed is taken into account regardless of the method of assessment. Therefore, recurrence will be declared for any lesion when:

- If recurrence is unequivocal (e.g., multiple measurable lesions) confirmation with histology/cytology should be attempted, but not required.
• If recurrence is equivocal, lymph node only, solitary lesion, or in the urothelial tract, confirmation with histology/cytology must be attempted. If the risk of biopsy is too high or the biopsy not feasible, either a follow-up CT or MRI scan showing progressive and measurable disease or PET/CT demonstrating unequivocal FDG uptake must confirm recurrence. The date of initial scan showing recurrence will count as recurrence.

• If “pseudo-progression” is suspected and the patient continues to derive clinical benefit from study treatment, treatment may continue with repeat scans in four to six weeks to confirm progression.

• Any pathological evidence of malignancy denotes recurrence (e.g., if scans never attempted). Positive urine cytology (e.g., positive Urovision or similar urine assay) alone does not constitute the basis for recurrence of disease.

• If both pathology and imaging were done and recurrence/malignancy is confirmed, the date of recurrence is the date of whichever examination came first.

11.2 FFS with intact bladder (FFSIB), rate of distant FFS at two years in patients with intact bladder and those that undergo salvage cystectomy

These will be secondary assessments of FFS analyzed with the additional categories.

11.3 Quality of Life Assessments

All enrolled patients will complete the NCCN-FACT FB1S1 questionnaire at screening, cycle 4, 7 and 10 while on study treatment, and at the End of treatment follow up visit.

11.4 Cystoscopic local control at 6 months, 1 year and 2 years after study treatment and rate of salvage cystectomy

11.5 Overall survival

Overall survival (OS) will be tracked and will be defined as the period from the first dose of Nivolumab until death. Patients will be followed for survival for a period of 5 years following the first dose of the study drug and censored at the last date they were known to be alive.

11.6 Safety

The rate of acute and late grade 2 or higher treatment related GU, GI, hematologic, dermatologic and immune related toxicity will be evaluated.

Routine safety and tolerability will be evaluated from the results of reported signs and symptoms, scheduled physical examinations, vital sign measurements, and clinical laboratory test results. More frequent safety evaluations may be performed if clinically indicated or at the discretion of the investigator.
Physical examination: complete and symptom-directed physical examinations will be performed by a licensed physician (or physician’s assistant or nurse practitioner).

Vital signs and weight: blood pressure, respiratory rate, pulse rate and temperature) will be obtained in the sitting position. Patients should be sitting for 3-5 minutes prior to obtaining vital signs. Weight will be recorded along with vital signs.

Safety laboratory determinations: laboratory evaluations will be performed as noted in the flow chart.

11.7 Stopping Rules

Management of drug-related toxicities will follow the Dose Delay/Discontinuation Table I and Immune Oncology Toxicity Management Algorithms (Appendix 3 of the IB) and Section 8.2

The Study Investigator-Sponsor will discuss such cases with BMS as appropriate to determine further enrollment. IRBs may be notified by the Investigators of all cases and decisions regarding continued enrollment, according to applicable regulatory requirements or institution procedures.

12 STATISTICAL CONSIDERATIONS

This will be an open label single arm phase II trial. The planned sample size for this single arm, open label trial is N = 28. The primary endpoint is failure-free survival (FFS) at two years. Kaplan-Meier methods will be used to plot survival endpoints (FFS, FFSIB, and OS) and cystoscopic local control rates. Provided there is no censoring, exact binomial methods will be used to provide 6 months, 1 year and 2 year estimates for these endpoints. If censoring exists prior to these time points Kaplan-Meier methods will be used to provide 6 months, 1 year and 2 year estimates. The sample size justification is based on the maximum width of a two-sided 95% binomial confidence interval for 2 year FFS. With 28 evaluable subjects and no censored observations, a 95% exact binomial confidence interval, estimated using the method of Clopper-Pearson, will extend no more than 20% from the observed FFS. For example, if the observed FFS is 20/28 (71%), the exact 95% binomial confidence interval will extend from 51% - 87% and will exclude 50%. The number and proportion of subjects with acute and late grade 2 or higher treatment related GU, GI, and hematologic toxicity will be tabulated and 95% exact binomial confidence intervals for the proportions will be calculated. The rate of salvage cystectomy will be reported along with a 95% exact binomial confidence interval. The QOL measures will be tabulated chronologically as assessed on follow up. Baseline tumor characteristics and follow up tissue biopsies will be assessed by immunohistochemistry, molecular studies and bioinformatics analysis. Peripheral blood will be collected at baseline and at the time of periodic assessments to assess for correlative biomarkers of response and markers of resistance.

For Quality of Life assessments, descriptive statistics will be used to assess completion rates and changes in quality of life. The range and median quality of life scores and the range and median of the change in quality of life scores on treatment will be described.
Toxicity assessments performed by CTCAE will be reported in the form of descriptive statistics. The early and late toxicity from chemoradiation as measured by RTOG will be compared to historical reference.

All patients who receive at least 1 infusion of nivolumab on study and remain on follow up until the primary endpoint will be considered evaluable for the primary endpoint of failure-free survival at 2 years.

Patients who participate in the pre-chemoradiation sample collection but are found to be ineligible for treatment with Nivolumab will be replaced.

13 REGISTRATION GUIDELINES

Study related screening procedures can only begin once the patient has signed a consent form.

Patients must meet all of the eligibility requirements listed in Section 5 prior to registration.

Patients will only be registered once:

- Prior to starting chemoradiation for patients who consent and are eligible for the pre-chemoradiation sample collection.
- Prior to starting Nivolumab for patients who only consent and are eligible for the second part of the study.

Patients must be registered before receiving any study treatment (either chemoradiation or Nivolumab) and must being treatment within five working days after registration.

To register eligible patients on study, complete a Clinical Trials Office Patient Registration Form and submit to: CTORegistrations@hci.utah.edu.

14 DATA SUBMISSION SCHEDULE

The Case Report Forms (CRFs) are a set of (electronic or paper) forms for each patient that provides a record of the data generated according to the protocol. CRF’s should be created prior to the study being initiated and updated (if applicable) when amendments to the protocol are IRB approved. **Data capture should be restricted to endpoints and relevant patient information required for planned manuscripts.** These forms will be completed on an on-going basis during the study. The medical records will be source of verification of the data. During the study, the CRFs will be monitored for completeness, accuracy, legibility and attention to detail by a member of the Research Compliance Office. The CRFs will be completed by the Investigator or a member of the study team as listed on the Delegation of Duties Log. The data will be reviewed no less than annually by the Data and Safety Monitoring Committee. The Investigator will allow the Data and Safety Monitoring Committee or Research Compliance Office personnel access to the patient source documents, clinical supplies dispensing and storage area, and study documentation for the
above-mentioned purpose. The Investigator further agrees to assist the site visitors in their activities.

15 SPECIAL INSTRUCTIONS

15.1 Correlative Studies

Correlative studies will be performed using archival tumor tissue, peripheral blood samples and serum samples obtained at baseline and during protocol treatment.

Tissue correlative studies

The patient’s archived bladder tumor tissue will be obtained for general pathological assessment, genomic profiling, and to determine PD-1/PD-L1 status and assess tumor infiltrating lymphocytes.

Archived tissue will be collected for each subject for whom it is available and has given the appropriate consent. One H&E slide and 8 to 10 slides cut at 10 µm and 5 to 15 slides cut at 4 µm will be requested at diagnosis and relapse. A corresponding pathology report should also be included.

Archival tissue from the most recent TURBT prior to start of chemoradiation is preferred. If this is not adequate, then archived tissue from past TURBT will be used. Any tumor tissue obtained subsequently to confirm disease relapse, as part of standard of care, will be requested for similar studies.

The studies planned on archived tissue include genomic characterization of tumor Wholes exome and RNA sequencing via the AVATAR project.

Blood correlative studies

Peripheral blood will be obtained before starting chemoradiation, at C1D1 and every 12 weeks on treatment and every 3 months thereafter for the first two years of study. In addition, peripheral blood will be obtained at the time of disease relapse at any time point falling outside this schedule.

One 6 mL red top tube and four 10 mL purple top K$_2$EDTA tubes will be collected and processed and frozen into aliquots of serum, PBMCs and plasma.

The studies planned on blood products include:

1. Serum cytokine/chemokine/interferon assays.
2. Flow cytometry of PBMCs to assess immune cell subsets.
5. Genomic analysis of immune cells.

Required samples and time points of collection

Detailed instructions will be provided in the laboratory manual.
### 16 ETHICAL AND REGULATORY CONSIDERATIONS

**16.1 Informed consent**

Informed consent will be obtained from all research participants prior to performing any study procedures using the most recent IRB approved version.

**16.2 Institutional Review**

Study will be approved by the Institutional Review Board of University of Utah.

**16.3 Data and Safety Monitoring Plan**

A Data and Safety Monitoring Committee (DSMC) is established at Huntsman Cancer Institute (HCI) and approved by the NCI to assure the well-being of patients enrolled on Investigator Initiated Trials that do not have an outside monitoring review. Roles and responsibilities of the DSMC are set forth in the NCI approved plan. The activities of this committee include a quarterly review of adverse events including SAEs, important medical events, significant revisions or amendments to the protocol, and approval of cohort/dose escalations. If the DSMC and/or the PI have concerns about unexpected safety issues, the study will be stopped and will not be resumed until the issues are resolved. The DSMC also reviews and approves audit reports generated by the Research Compliance Office.

All phase II studies are reviewed by the full committee at each quarterly DSMC meeting. This includes a review of all serious adverse events (SAEs) occurring in patients treated at HCI or its affiliates as well as all grade 3 or greater toxicities for patients on treatment and within 30 day follow-up window (only if possibly, probably or definitely related).

**16.4 Adverse Events / Serious Adverse Events**

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.0 for AE and SAE reporting.
16.4.1 Adverse Events (AE)

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. For the purposes of this study, the terms toxicity and adverse event are used interchangeably. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

Collection of adverse events will begin with the first dose of study drug and end 120 days after the last dose of study drug (or until a new cancer treatment is initiated).

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded and followed as appropriate.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit or phone contact during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade based on CTCAE v.4 (grade 1-5).
2. Its relationship to the study drug(s) (definite, probable, possible, unlikely, not related).
3. Its duration (start and end dates or if continuing at final exam).
4. Action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization).
5. Whether it constitutes an SAE.

All adverse events will be treated appropriately. Such treatment may include changes in study drug treatment as listed in the dose modification section of this protocol (see section 8 for guidance). Once an adverse event is detected, it should be followed until its resolution, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about Nivolumab is described in the Drug Information (section 3) and the most recent Investigator Brochure. This information will be included in the patient informed consent and will be discussed with the patient during the study as needed.

All adverse events will be immediately recorded in the patient research chart.
Adverse Events of Interest

Definition of immune-mediated adverse events (IMAEs): immune-mediated AEs are specific events (that include pneumonitis, diarrhea/colitis, hepatitis, nephritis/renal dysfunction, rash, and endocrine (adrenal insufficiency, hypothyroidism/thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis). IMAEs are limited to subjects who received immunosuppressive medication for treatment of the event, with the exception of endocrine events (hypothyroidism/thyroiditis, hyperthyroidism, hypophysitis, diabetes mellitus, adrenal insufficiency), which are included regardless of treatment since these events are often managed without immunosuppression. IMAEs include events, regardless of causality, occurring within 120 days of the last dose.

Adverse Events considered IMAE should be documented.

16.4.2 Serious Adverse Event (SAE)

Information about all serious adverse events will be collected and recorded. A serious adverse event is an undesirable sign, symptom or medical condition which:

- Is fatal or life-threatening.
- Results in persistent or significant disability/incapacity.
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above.
- Causes congenital anomaly or birth defect.
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (procedures such as central line placements, paracentesis, pain control).
  - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug.
  - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission.
  - Social reasons and respite care in the absence of any deterioration in the patient’s general condition.

The SAE reporting period will begin with the first dose of study drug and end 120 days after the last dose of study drug (or until a new cancer treatment is initiated).

If applicable, SAEs must be collected that relate to any later protocol-specified procedure (e.g., a follow-up skin biopsy).

Any death from any cause while a patient is receiving treatment on this protocol or up to 30 days after the last dose of protocol treatment, or any death which occurs more
than 30 days after protocol treatment has ended but which is felt to be treatment related, must be reported.

Toxicities which fall within the definitions listed above must be reported as an SAE regardless if they are felt to be treatment related or not. Toxicities unrelated to treatment that do NOT fall within the definitions above, must simply be documented as AEs in the patient research chart.

**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. AT (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 AT 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.

**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 in the investigator’s opinion. All occurrences of overdose must be reported as an SAE.

**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 nonserious or serious AE, as appropriate, and reported accordingly.

### 16.5 SAE Reporting Requirements

SAEs must be reported to the DSMC, the FDA, the IRB, and BMS, according to the requirements described below:

A MedWatch 3500A form must be completed and submitted to compliance@hci.utah.edu within 24 hours of first knowledge or notification of event.

DSMC Notifications:

- An HCI Research Compliance Officer (RCO) will process and submit the MedWatch form to the proper DSMC member as necessary for each individual study.
- The RCO will summarize and present all reported SAEs according to the Data
and Safety Monitoring Plan at the quarterly DSMC meeting.

**FDA Notifications:**

Adverse events occurring during the course of a clinical study that meet the following criteria will be promptly reported to the FDA:

- Serious.
- Unexpected.
- Definitely, Probably or Possibly Related to the investigational drug.
- Fatal or life-threatening events that meet the criteria above will be reported within 7 calendar days after first knowledge of the event by the investigator; followed by as complete a report as possible within 8 additional calendar days.
- All other events that meet the criteria above will be reported within 15 calendar days after first knowledge of the event by the investigator.
- The RCO will review the MedWatch report for completeness, accuracy and applicability to the regulatory reporting requirements.
- The RCO will ensure the complete, accurate and timely reporting of the event to the FDA.
- The Regulatory Coordinator will submit the report as an amendment to the IND application.
- All other adverse events and safety information not requiring expedited reporting that occur or are collected during the course of the study will be summarized and reported to the FDA through the IND Annual Report.

**IRB Notification:**

Events meeting the University of Utah IRB reporting requirements ([http://www.research.utah.edu/irb/](http://www.research.utah.edu/irb/)) will be submitted through the IRB’s electronic reporting system within 10 working days.

**Sponsor/Drug Manufacturer Notifications:**

SAEs (whether related or not related to study drug) and pregnancies must be reported to BMS within 24 hours. SAEs must be recorded on a FDA Medwatch 3500A form; pregnancies must be reported on a Pregnancy Surveillance Form.

**SAE Email Address:** [Worldwide.Safety@BMS.com](mailto: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 BMS (or designee) using the same procedure used for transmitting the initial SAE report. All SAEs should be followed to resolution or stabilization.
16.6 Reporting of Pregnancy

Although pregnancy is not considered an adverse event, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject, including the pregnancy of a male subjects’ female partner as an SAE. Pregnancies or lactation that occurs during the course of the trial or with 30 days of completing the trial or starting another new anticancer therapy, whichever is earlier, must be reported to the DSMC, IRB, FDA, and the sponsor as applicable. All subjects and female partners who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events.

16.7 Protocol Amendments

Any amendments or administrative changes in the research protocol during the period, for which the IRB approval has already been given, will not be initiated without submission of an amendment for IRB review and approval.

These requirements for approval will in no way prevent any immediate action from being taken by the investigator in the interests of preserving the safety of all patients included in the trial.

Any amendments to the protocol that significantly affect the safety of subjects, scope of the investigation, or the scientific quality of the study are required to submit the amendment for FDA review.

16.8 Protocol Deviations

A protocol deviation (or violation) is any departure from the defined procedures and treatment plans as outlined in the protocol version submitted and previously approved by the IRB. Protocol deviations have the potential to place participants at risk and can also undermine the scientific integrity of the study thus jeopardizing the justification for the research. Protocol deviations are unplanned and unintentional events.

Because some protocol deviations pose no conceivable threat to participant safety or scientific integrity, reporting is left to the discretion of the PI within the context of the guidelines below. The IRB requires the prompt reporting of protocol deviations which are:

- Exceptions to eligibility criteria.
- Intended to eliminate apparent immediate hazard to a research participant, or
- Harmful (caused harm to participants or others, or place them at increased risk of harm - including physical, psychological, economic, or social harm), or
- Possible serious or continued noncompliance.
16.9 FDA Annual Reporting

An annual progress report will be submitted to the FDA within 60 days of the anniversary of the date that the IND went into effect. (21 CFR 312.33).

16.10 Clinical Trials Data Bank

The study will be registered on [http://clinicaltrials.gov](http://clinicaltrials.gov) and the NCI CTRP (Clinical Trials Reporting Program) by the Clinical Trials Office.

16.11 Record Keeping

Per 21 CFR 312.57, Investigator records shall be maintained for a period of 2 years following the date a marketing application is approved; or, if no application is filed or the application is not approved, until 2 years after the investigation is discontinued and the FDA is notified.

17 BIBLIOGRAPHY


18 APPENDICES

18.1 Appendix 1 - Radiation Therapy Oncology Group (RTOG) toxicity grading system

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>No symptoms</td>
<td>Minor symptoms requiring no treatment</td>
<td>Symptoms responding to simple outpatient management, lifestyle (performance status) not affected</td>
<td>Distressing symptoms altering the patient’s lifestyle (performance status) Hospitalization for diagnosis or minor surgical intervention (such as urethral dilation) may be required</td>
<td>Major surgical intervention (such as laparotomy colostomy, cystectomy) or prolonged hospitalization required</td>
<td>Fatal complications</td>
</tr>
</tbody>
</table>
18.2 Appendix 2 - NCCN-FACT FB1SI questionnaire

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

<table>
<thead>
<tr>
<th>Item</th>
<th>Description</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>GP4</td>
<td>I have pain</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>C2</td>
<td>I am losing weight</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>BL1</td>
<td>I have trouble controlling my urine</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>HI12</td>
<td>I feel weak all over</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>An9</td>
<td>I feel light-headed (dizzy)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GP3</td>
<td>Because of my physical condition, I have trouble meeting the needs of my family</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>C6</td>
<td>I have a good appetite</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Bl5a</td>
<td>(For men only) I am able to have and maintain an erection</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Description</td>
<td>Score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>--------------------------------------------------</td>
<td>-------</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GF5</td>
<td>I am sleeping well</td>
<td>0 1 2 3 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GE6</td>
<td>I worry that my condition will get worse</td>
<td>0 1 2 3 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GE1</td>
<td>I feel sad</td>
<td>0 1 2 3 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GP2</td>
<td>I have nausea</td>
<td>0 1 2 3 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GP1</td>
<td>I have a lack of energy</td>
<td>0 1 2 3 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GP6</td>
<td>I feel ill</td>
<td>0 1 2 3 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CI</td>
<td>I have control of my bowels</td>
<td>0 1 2 3 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GP5</td>
<td>I am bothered by side effects of treatment</td>
<td>0 1 2 3 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GF3</td>
<td>I am able to enjoy life</td>
<td>0 1 2 3 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GF7</td>
<td>I am content with the quality of my life right</td>
<td>0 1 2 3 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Appendix 3 ECOG performance status

<table>
<thead>
<tr>
<th>GRADE</th>
<th>ECOG PERFORMANCE STATUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease performance without restriction</td>
</tr>
<tr>
<td>1</td>
<td>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</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care; confined to bed or chair more than 50% of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled; cannot carry on any self-care; totally confined to bed or chair</td>
</tr>
<tr>
<td>5</td>
<td>Dead</td>
</tr>
</tbody>
</table>