PrE0807 Statistical Analysis Plan (SAP)

Phase Ib Feasibility Trial of Neoadjuvant Nivolumab/Lirilumab in Cisplatin-Ineligible Muscle-Invasive Bladder Cancer

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1. LIST OF ABBREVIATIONS

Abbreviation	Term
ADL	Activities of Daily Living
AE	Adverse Event
AJCC	American Joint Commission on Cancer
ALT	Alanine Aminotransferase
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
BC	Bladder Cancer
BCG	Bacilllus Calmette Guerin
BID	Twice Daily
BMS	Bristol-Myers Squibb
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
C	Celsius
CABG	Coronary Artery Bypass Graft
CBC	Complete Blood Count
cc	Cubic Centimeter
CFR	Code of Federal Regulations

Abbreviation	Term
CHF	Congestive Heart Failure
CR	Complete Response
CrCl	Creatinine Clearance
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating Tumor Deoxyribonucleic Acid
CTLA-4	Cytotoxic T Lymphocyte Antigen-4
CVA	Cerebrovascular Accident
DAB	Diamiobenzidine
DBP	Diastolic Blood Pressure
DEHP	Non-Di-2-Ethylhexyl Phthalate
dL	Deciliter
DNA	Deoxyribonucleic Acid
DSMB	Data Safety Monitoring Board
E-A CBPF	ECOG-ACRIN Central Biorepository Pathology Facility
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
eDC	Electronic Data Capture
FDA	Food and Drug Administration

Abbreviation	Term
F	Fahrenheit
FFPE	Formalin-Fixed Paraffin-Embedded
FT3	Free-Triiodothyronine
FT4	Free-Thyroxine
GCP	Good Clinical Practice
g	Gram
G-CSF	Granulocyte-Colony Stimulating Factor
GI	Gastrointestinal
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIPAA	Health Information Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HPF	High Powered Field
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ID	Infectious Disease
IF	Immunofluorescence

Abbreviation	Term
Ig	Immunoglobulin
IHC	Immunohistochemistry
IL-2	Interleukin-2
IND	Investigational New Drug
I-O	Immuno-Oncology
IRB	Institutional Review Board
IV	Intravenous; Intravenously
IVIG	Intravenous Immunoglobulin
KIRs	Killer Cell Immunoglobulin-Like Receptors
kg	Kilogram
LFT	Liver Function Tests
LLN	Lower Limit of Normal
LN	Lymph Node
mAb	Monoclonal antibody
mg	Milligram
MHC	Major Histocompatibility Complex
MI	Myocardial Infarction
MIBC	Muscle-Invasive Bladder Cancer
min	Minute
mL	Milliliter

Abbreviation	Term
mm	Millimeter
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NA	Not Applicable
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK-Cells	Natural Killer Cells
NKG2D	Natural Killer Group 2, Member D
NMIBC	Non-Muscle-Invasive Bladder Cancer
NS	Normal Saline
NSAID	Nonsteroidal Anti-Inflammatory Drug
NYHA	New York Heart Association
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cell
PBS	Phosphate-Buffered Saline
PD	Progressive Disease (disease progression)
PD-1	Programmed Death-1
PD-L1	Programmed Death-Ligand 1
PET	Positron Emission Tomography

Abbreviation	Term
PK	Pharmacokinetic(s)
PLND	Pelvic Lymph Node Dissection
PO	Orally; By Mouth
PR	Partial Response
PS	Performance Status
Q2W	Every 2 Weeks
Q4W	Every 4 Weeks
RC	Radical Cystectomy
RECIST	Response Evaluation Criteria in Solid Tumors
RFS	Recurrence-Free Survival
RNA	Ribonucleic Acid
RPM	Revolutions Per Minute
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SD	Stable Disease
SITC	Society for Immunotherapy Cancer
SRM	Study Reference Manual
T. Bili	Total Bilirubin
TCGA	The Cancer Genome Atlas
TIA	Transient Ischemic Attack

Abbreviation	Term
TIL	Tumor-Infiltrating Lymphocytes
TMA	Tissue Microarray
TSH	Thyroid Stimulating Hormone
TURBT	Transurethral Resection of Bladder Tumor
UC	Urothelial Carcinoma
ULN	Upper Limit of the Normal Range
US	United States
vs	Versus
WBC	White Blood Cell
WOCBP	Women of Childbearing Potential

2. INTRODUCTION

2.1. Objective of the Statistical Analysis Plan

This statistical analysis plan (SAP) describes the planned analysis of the safety and efficacy data from this study. A detailed description of the planned tables, figures and listings (TFLs) to be presented in the Clinical Study Report (CSR) is provided in the accompanying TFL template document.

The intent of this document is to provide guidance for the analysis of data related to safety and efficacy to describe any applicable statistical procedures. In general, the analyses come directly from the protocol, unless they have been modified by agreement between the Sponsor and Quality Data Services, Inc. (QDS). A limited amount of information concerning this study (e.g., objectives, study design) is summarized to help the reader interpret the accompanying TFL templates. That information is not a synopsis of the study and does not require review or approval because it is simply extracted from the protocol. Attached signatures indicate approval of the statistical analysis sections of the SAP, as well as accompanying TFL templates. These sections must be agreed upon prior to database lock. When the SAP and TFL templates are agreed upon and finalized, they will serve as the template for a portion of this study's CSR.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified in the appropriate section of the CSR. Any substantial deviations from this SAP will be agreed upon between the sponsor and QDS. Deviations from this SAP, both substantial and non-substantial, will be documented in the CSR. Any updates to their respective analyses, study designs, and TFL presentations after this SAP is finalized and approved will be documented in a running Note to the SAP document.

3. STUDY OBJECTIVES

3.1. Primary Objective

The primary objective of this study is to assess the safety of nivolumab (Cohort 1) and combination of nivolumab/lirilumab (Cohort 2).

3.2. Secondary Objectives

The secondary objectives of this study are:

- To assess the change in CD8+ TIL density from pre-treatment Transurethral Resection of Bladder Tumor (TURBT) to post-treatment Radical Cystectomy (RC) tissues separately in patients treated with nivolumab or combination of nivolumab/lirilumab.

- To assess percentage (%) change in CD8+ TIL density from pre-treatment TURBT to post-treatment RC tissues separately in patients treated with nivolumab and combination of nivolumab/lirilumab.

- To describe the rate of patients in each cohort who do not get RC within 6 weeks after completion of neoadjuvant treatment specifically and directly related to treatment-related adverse events (AEs).

- To assess the antitumor efficacy of nivolumab and combination of nivolumab/lirilumab as measured by pathologic complete (pT0N0) and partial (<pT2N0) response rate in the two cohorts.

- To assess the rate of recurrence-free survival (RFS) at the two-year time point from the time of registration in patients treated with nivolumab and combination of nivolumab/lirilumab.

- To assess the prognostic and predictive value of the expression of baseline immunohistochemistry (IHC) markers of interest (e.g. PD-1, PD-L1, PD-L2, NKG2D, KIR2DL1/2/3), and change in expression, for pathologic partial and complete tumor response (defined by cystectomy pathologic staging <pT2N0 and pT0N0, respectively), in patients treated with nivolumab and combination of nivolumab/lirilumab.

- To assess the prognostic and predictive value of peripheral blood mononuclear cell (PBMC) T-cell subset status (%CD4+ T-cells, %CD8+ T-cells, %Treg T-cells, %Myeloid Derived Suppressor Cells, %Natural Killer cells, etc.) and change in status, as assessed by flow cytometry analysis, for pathologic partial and complete tumor response (defined by cystectomy pathologic staging < pT2N0 and pT0N0, respectively), in patients treated with nivolumab and combination of nivolumab/lirilumab.

3.3. Exploratory Objectives

- To compare CD8+ TIL density in post-treatment RC tissues in patients treated with nivolumab and combination of nivolumab/lirilumab.

- To assess the prognostic and predictive relationship between pre- and post- treatment TIL and NK-cell level and activation and pathologic partial and complete response (defined by cystectomy pathologic staging <pT2N0 and pT0N0, respectively) as well as two-year RFS, in patients treated with nivolumab and combination of nivolumab/lirilumab.

- To assess impact of prior BCG exposure on rates of pathologic partial and complete response (defined by cystectomy pathologic staging <pT2N0 and pT0N0, respectively) as well as two-year RFS, in patients treated with nivolumab and combination of nivolumab/lirilumab.

- To assess the prognostic and predictive relationship of tumor mutational load, neo-epitope burden, intrinsic molecular subtypes (basal vs. luminal), and T-cell clonality with pathologic partial and complete response (defined by cystectomy pathologic staging <pT2N0 and pT0N0, respectively) as well as two-year RFS, in patients treated with nivolumab and combination of nivolumab/lirilumab.

- To assess the prognostic and predictive relationship of pre- and post-treatment peripheral blood T-cell subsets, CD4+/CD8+ and CD4+/FOXP3+ ratios and plasma cytokine multiplex panels with pathologic partial and complete response (defined by cystectomy pathologic staging <pT2N0 and pT0N0, respectively) as well as two-year RFS, in patients treated with nivolumab and combination of nivolumab/lirilumab.

- To assess the prognostic and predictive relationship between pre- and post-neoadjuvant treatment levels in plasma cytokine biomarkers of interest (e.g. IFN-α, TGF-β, IL-10, IL-4, IL-5, IL-13, IFN-γ, etc.) and pathologic partial and complete response (defined by cystectomy pathologic staging <pT2N0 and pT0N0, respectively) as well as two-year RFS, in patients treated with nivolumab and combination of nivolumab/lirilumab.

- To assess prognostic and predictive associations between baseline tumor and/or tumor infiltrating lymphocyte tissue and ctDNA genomic alterations, gene expression, and methylation signatures for pathologic partial and complete response (defined by cystectomy pathologic staging <pT2N0 and pT0N0, respectively) as well as two-year RFS, in patients treated with nivolumab and combination of nivolumab/lirilumab.

- To assess prognostic and predictive value of serum circulating antibody profiles on pathologic partial and complete response (defined by cystectomy pathologic staging <pT2N0 and pT0N0, respectively) as well as two-year RFS, in patients treated with nivolumab and combination of nivolumab/lirilumab.

- To assess CD8+ TIL density by central pathology review using image analysis in both cohorts.

4. STUDY DESIGN

4.1. General Study Design and Plan

This is a Phase Ib open-label clinical trial for patients with cisplatin-ineligible MIBC (T2-T4a, N0-N1, M0). Patients will be sequentially enrolled first into Cohort 1 treated with nivolumab alone (N=12). In the absence of the occurrence of high rate of treatment related AEs as defined in protocol Section 5.4 and 13.1.1 with neoadjuvant nivolumab treatment, the study will proceed with enrollment into Cohort 2 of neoadjuvant treatment with combination nivolumab/lirilumab. (In both cohorts, neoadjuvant treatment must start within 8 weeks of transurethral resection of the first TURBT that showed muscularis propria invasion). Each group will receive a total of 4 weeks (week 0 and 4) of neoadjuvant therapy followed by radical cystectomy (RC) with bilateral (standard or extended) pelvic lymph node dissection (PLND).

The RC with bilateral (standard or extended) PLND will occur as soon as possible but within 6 weeks after the last neoadjuvant dose in either cohort.

Off treatment visit will occur approximately 30 days following cystectomy (cystectomy is not performed, Off Treatment visit should be performed at next scheduled appointment or treating physician discretion, as clinically indicated) and patients will be followed for 100 days after neoadjuvant treatment for AEs. Adverse events may be reviewed at the next visit ≥ 100 days after last dose of neoadjuvant therapy or phone follow-up may be done to review adverse events.

Patients will be followed clinically and radiographically for at least 2 years post-cystectomy or when study-wide follow-up ends per standard of care. Date of diagnosis for recurrence, first subsequent therapy and survival shall be reported. Phone follow-up may also be done for patients unable or unwilling to return for follow-up evaluations.

4.2. Study Population

The study will aim to screen 43 eligible patients in order to enroll 36 patients in the trial (assuming about 20% tumor tissue assessment screen failure rate). Estimate at least 2-3 patients per month at approximately 8 sites. The estimated time for accrual completion will be approximately 18 months.

4.3. Treatment Administration

Neoadjuvant treatment must start within 8 weeks of transurethral resection of the first bladder tumor (TURBT) that showed muscularis propria invasion.

4.3.1. Study treatment

Patients enrolled in the trial will be administered one of two of the following treatment regimens:

Cohort 1: Nivolumab 480 mg IV every 4 weeks for 2 neo-adjuvant doses (week 0 and 4).

Cohort 2: Nivolumab 480 mg IV + lirilumab 240 mg IV every 4 weeks for 2 neo-adjuvant doses (week 0 and 4).

4.3.2. Dose Delays

A +/-3 day window is allowed for scheduled therapy. Dose delays are permitted. NO dose modifications will be allowed.

4.3.3. Discontinue treatment

If the Grade 3 toxicity does not resolve to ≤ Grade 1 within 21 days, all study therapy will be permanently discontinued.

If the patient experiences Grade 4 treatment related hematologic toxicity in either study cohort, all study therapy must be permanently discontinued regardless of the time to resolution ≤ Grade 1.

5. EFFICACY MEASUREMENTS

Patients should be evaluated for pathologic tumor response at post-treatment radical cystectomy time point. Tumor recurrence will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline Version 1.1 (Protocol Appendix V).

Efficacy measurements listed below:

5.1. Tumor Response

Only those patients who have received at least one dose of therapy, and undergo radical cystectomy will be considered evaluable for tumor response. RECIST response assessments will be performed locally for the trial.

5.2. CD8+ T-Cell Density

The CD8+ T-cell density is defined as the number of CD8+ tumor-infiltrating T-cells per 100 tumor cells within a 400x high power field (HPF).

The CD8+ T-cell density will be calculated as:

Tumor Infiltrating CD8+ T-cell density (CD8+ T-cells per 100 tumor cells) = (Total # of CD8+ TILS)/ (Total # of tumor cells per HPF) x 100

Five representative tumor fields with the greatest gross tumor infiltrating lymphocyte fields (minimum 100 tumor cells per representative field) will be chosen for measurement by microscope analysis by the pathologist with the final CD8+ T-cell density determined as the mean of the CD8+ T-cell density across the five fields.

5.3. %CD8+ Tumor-Infiltrating T-Cells

The %CD8+ tumor-infiltrating T-cells will be quantified by immunohistochemistry (IHC) analysis of tissue. Using semi-automated image analysis, a staining percentage determined by dividing the area of brown 3,3'-Diaminobenzidine (DAB) staining by the area of epithelial cells will be obtained.

Five representative tumor fields with the greatest gross tumor infiltrating lymphocyte fields will be chosen for measurement by the pathologist with the final %CD8+ tumor-infiltrating T-cells determined as the mean of the %CD8+ tumor-infiltrating T-cells across the five fields

5.4. Pathologic Tumor Response Definitions

Pathologic response (<ypT2N0M0) is defined by post-treatment radical cystectomy tumor stages with N0 and M0 status with the following T-stages: T0, Ta, Tis, T1.

Pathologic tumor stage reported according to American Joint Commission on Cancer (AJCC) Staging system T, N, M categories for bladder cancer (SAP Appendix II).

5.4.1 Pathologic Complete Response

Pathologic response (ypCR) is defined by post-treatment radical cystectomy tumor stages with N0 and M0 status with the following T-stages: T0.

5.4.2 Pathologic Non-Response

Pathologic non-response (ypNR) is defined by post-treatment radical cystectomy tumor stages with any node-positive (N1, N2, N3) or metastases-positive (M1) status. In addition, patients with N0 and M0 status with the following T-stages are also classified as pathologic non-responders: T2, T2a, T2b, T3, T3a, T3b, T4, T4a, T4b.

5.5. Tumor IHC Staining Intensity Definitions

For validated IHC targets, standardized IHC staining intensity cutoffs will be utilized. For all other IHC targets, IHC staining will be categorized as:

Grade	Stain
0	<1% cells stained
1+	1 to <5% cells stained
2+	5 to 10% cells stained
3+	≥ 10% cells stained

5.6. Recurrence-Free Survival (RFS) as per RECIST 1.1

Recurrence is defined as the Progressive Disease (PD) in Overall Response assessed by ERECIST 1.1 or death after radical cystectomy. RFS time is defined as the duration of time from start of treatment to time of first documented recurrence (after radical cystectomy) or death, whichever occurs first.

5.7. Overall Survival (OS)

OS is defined as the duration of time from start of treatment to time of death.

5.8. Other Efficacy Measurements

ECOG performance status will be assessed at screening, TURBT, day 1 at each infusion, surgery and at the off treatment visits.

6. SAFETY MEASUREMENTS

Safety will be evaluated by

- Adverse events
- Concomitant medications and procedures
- Clinical laboratory tests,
- Physical examination findings,
- Vital signs measurements, and

6.1. Adverse Events

Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient administered a medicinal product in a clinical investigation and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (e.g., including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a product (investigational or marketed), whether or not considered related to the product (investigational or marketed).

After informed consent, but prior to initiation of study treatment (nivolumab and lirilumab), only AEs/SAEs caused by a protocol-mandated intervention will be collected (e.g., SAEs related to invasive procedures such as biopsies). After the initiation of study treatment, all identified AEs and SAEs must be recorded and described on the appropriate page of the electronic Case Report Form (eCRF). If known, the diagnosis of the underlying illness or disorder should be recorded, rather than individual symptoms. The following information should be documented for all AEs: date of onset and resolution, severity of the event; the investigator's opinion of the relationship to investigational product (see definitions below); treatment required for the AE treatment required for the AE; cause of the event (if known); and information regarding resolution/outcome.

Only clinically significant laboratory abnormalities that require active management will be recorded as AEs or SAEs on the eCRF (e.g., abnormalities that require study drug dose delay, discontinuation of study treatment, more-frequent follow-up assessments, further diagnostic investigation, etc.).

The categories and definitions of severity used for clinical trials AEs are defined in the NCI's Common Terminology Criteria (CTCAE) V5.0 (http://www.ctep.cancer.gov).

The categories of causal relationship or attribution to study drug are presented as Definite, Probable, Possible, Unlikely, Unrelated. Categories 'Definite', 'Probable' and 'Possible' are considered study drug related. Categories 'Unlikely' and 'Unrelated' are considered not study drug-related.

AEs related to nivolumab and lirilumab should be followed for 100 days after last dose of study therapy until ≤ grade 1 or stabilization, and reported as SAEs if they become serious. Any AE's (serious or not) that occur more than 100 days after the last dose of study therapy but that are deemed to be at least possibly related to study therapy shall be reported.

6.2. Concomitant Medications and Procedures

Concomitant medications and procedures will be collected during the trial and recorded in the CRF page.

6.3. Clinical Laboratory Assessments

Clinical laboratory tests will be collected at screening, day 1 of cycles 1 through 4, end of cycle 4, day 1 of each additional cycle and day 1 of cycle 9 or end of treatment.

6.4. Physical Examination and Medical History

Physical examination findings will be collected at screening, day 1 of each infusions, surgery and end of treatment. Medical and surgical history will also be collected during screening.

Physical examination and medical history data will not be analyzed and displayed in this SAP. The weight and height will be summarized in baseline characteristics table.

6.5. Electrocardiogram

ECG will be obtained during screening. ECG data will not be analyzed and reported in this SAP.

7. GENERAL STATISTICAL CONSIDERATIONS

This section will go into detail about the statistical approaches and methodology for this study analysis. Statistical analysis and programming of tables and listings will be conducted by QDS, using SAS® Release 9.4 (SAS Institute Inc., Cary, North Carolina, USA).

7.1. Study Design and Sample Size Considerations

This is a Phase Ib study evaluating whether the addition of lirilumab to nivolumab is feasible and safe in patients with cisplatin-ineligible muscle-invasive urothelial carcinoma of the bladder in the neoadjuvant therapy setting. Eligible patients will be assigned sequentially to either nivolumab monotherapy in Cohort 1, and if there is no negative safety signal (assessed by interim safety analyses) after the first 12 patients, subsequent patients will be assigned to Cohort 2 treated with nivolumab/lirilumab.

There will be 12 patients in cohort 1 treated with nivolumab and 24 patients in cohort 2 treated with nivolumab+ lirilumab for the final analysis.

7.2. Methodology

Continuous data will be summarized with the following descriptive statistics: number of observations (n), mean, standard deviation (SD), median, minimum (min), and maximum (max). Categorical data will be summarized with frequencies and percentages. Hypothesis testing for categorical data will use nonparametric methods.

In general, listings will be presented by patient. Tables will be summarized and presented by cohort in specific analysis populations.

7.3. Handling of Dropouts or Missing Data

All attempts will be made to prevent any missing values. Missing or invalid data will be treated as missing, not imputed.

No data imputation will be done for safety parameters except for the adverse events (AEs) with missing starting date. If the AE onset date is unknown, then the date of first study treatment will be used for classification of AEs that were experienced following administration of study drug. If the relationship between AE and study medication (nivolumab or lirilumab) is missing, then the "related" is assigned in the AE analysis.

7.4. Endpoints

7.4.1. Primary Endpoint

The primary endpoint of this study is the rate of Grade 3 or higher adverse events during neoadjuvant treatment.

Analytic Plan for Primary Objective: The rates of Grade 3 or higher treatment-related AE during neoadjuvant treatment will be reported along with 90% exact binomial confidence intervals. In Cohort 1 the maximum width of the confidence interval is 0.51 while in Cohort 2 it is 0.36.

7.4.2. Secondary Endpoints

The secondary objective endpoints for this study are listed below:

7.4.2.1. The key secondary endpoint is the change in tumor-infiltrating CD8+ T-cell density from TURBT to radical cystectomy in each cohort

Analytic Plan for This Key Secondary Objective:

In each cohort, a one-sample Wilcoxon signed-rank test will be used to test whether the mean change in TIL density differs significantly from zero. Our hypothesis is that the change in TIL density between TURBT and radical cystectomy will be approximately 3.0 CD8+ TILs per 100 tumor cells within HPF.

Additionally, the TIL density at radical cystectomy will be compared between the two cohorts using a Wilcoxon rank sum test.

7.4.2.2. The average percentage (%) change in the CD8+ TIL density from TURBT to RC in each of the two cohorts. Each individual patient's percent change will be defined as [(Cystectomy TIL Density) – (TURBT TIL Density)] / (TURBT TIL Density).

Analytic Plan for this secondary endpoint: The mean percent change of CD8+ TIL density from pre-treatment (TURBT) to post-treatment (Radical Cystectomy, RC) samples in all 12 patients in Cohort 1 and all 24 patients in Cohort 2 will be calculated and compared between the two cohorts using a Wilcoxon rank sum test.

7.4.2.3. Proportion of patients in each cohort who do not get a radical cystectomy specifically and directly related to treatment related AEs within 6 weeks of the last dose of neoadjuvant treatment.

Analytic Plan for this secondary endpoint: The proportion of patients in each treatment cohort who do not get radical cystectomy specifically and directly related to treatment related AEs within 6 weeks of the completion of neoadjuvant treatment, will be reported along with exact binomial 90% confidence intervals for each cohort and compared between the two cohorts using Fisher's exact test.

7.4.2.4. Proportion of patients with pathologic complete (pT0N0) and partial (<pT2N0) response in the two cohorts.

Analytic Plan for this secondary endpoint: The proportion of patients in each treatment cohort with pathologic complete response (CR) and pathologic partial response (PR) will be reported along with exact binomial 90% confidence intervals for each cohort

7.4.2.5. Proportion of patients who are alive and free of disease in each cohort at 2 years from registration.

Analytic Plan for this secondary endpoint: Recurrence-free survival (defined as patients who are alive and without evidence of disease recurrence) from the time of registration will be estimated using Kaplan-Meier method for each treatment cohort and compared between the two cohorts using a log-rank test. The two-year disease-free survival estimates and confidence intervals will be provided for each cohort.

7.4.2.6. The relationship between the expression of baseline IHC markers of interest (e.g. PD-1, PD-L1, PD-L2, NKG2D, KIR2DL1/2/3), and change in expression, for pathologic partial and complete tumor response (defined by cystectomy pathologic staging <pT2N0 and pT0N0, respectively), in patients treated with nivolumab and combination of nivolumab/lirilumab. To also compare the association of study cohort and pathologic response stratified by levels of expression of these biomarkers of interest.

Analytic Plan for this secondary endpoint: As a general strategy, IHC marker levels in responders vs. non-responders will be compared by a t-test or Wilcoxon rank sum test as appropriate. In addition to evaluating expression on a continuous scale we will explore quantile values for each marker as potential thresholds to discretize the marker levels. The two-year RFS will then be compared between marker groups with a Fisher's exact test as well as via time-to-even analyses using standard methods for survival analysis. Changes in biomarker levels will be computed and compared between groups using a Wilcoxon rank sum test.

7.4.2.7. The relationship between peripheral blood mononuclear cell (PBMC) T-cell subset status (%CD4+ T-cells, %CD8+ T-cells, %Treg T-cells, %Myeloid Derived Suppressor Cells, %Natural Killer cells, etc.) and change in status, as assessed by flow cytometry analysis, for pathologic partial and complete tumor response (defined by cystectomy pathologic staging < pT2N0 and pT0N0, respectively), in patients treated with nivolumab and combination of nivolumab/lirilumab.

Analytic Plan for this secondary endpoint: The PBMC T-cell subset status in responders vs. non-responders will be compared by a t-test or Wilcoxon rank sum test as appropriate.

7.4.3. Exploratory Objective Endpoints

7.4.3.1. To compare the CD8+ TIL density at radical cystectomy between the patients treated with nivolumab and combination of nivolumab/lirilumab.

7.4.3.2. The prognostic and predictive relationship between pre- and post- treatment TIL and NK-cell level and activation and pathologic partial and complete response (defined by cystectomy pathologic staging <pT2N0 and pT0N0, respectively) as well as two-year RFS, in patients treated with nivolumab and combination of nivolumab/lirilumab.

7.4.3.3. To assess impact of prior BCG exposure on rates of pathologic partial and complete response (defined by cystectomy pathologic staging <pT2N0 and pT0N0, respectively) as well as two-year RFS, in patients treated with nivolumab and combination of nivolumab/lirilumab.

7.4.3.4. To assess the prognostic and predictive relationship of tumor mutational load, neo-epitope burden, intrinsic molecular subtypes (basal vs. luminal), and T-cell clonality with pathologic partial and complete response (defined by cystectomy pathologic staging <pT2N0 and pT0N0, respectively) as well as two-year RFS, in patients treated with nivolumab and combination of nivolumab/lirilumab

7.4.3.5. To assess the prognostic and predictive relationship of pre- and post-treatment T-cell subsets, CD4+/CD8+ and CD4+/FOXP3+ ratios and plasma cytokine multiplex panels with pathologic partial and complete response (defined by cystectomy pathologic staging <pT2N0 and pT0N0, respectively) as well as two-year RFS, in patients treated with nivolumab and combination of nivolumab/lirilumab.

7.4.3.6. To assess the prognostic and predictive relationship between pre- and post-neoadjuvant treatment levels in plasma cytokine biomarkers of interest (e.g. IFN-α, TGF-β, IL-10, IL-4, IL-5, IL-13, IFN-γ, etc.) and pathologic partial and complete response (defined by cystectomy pathologic staging <pT2N0 and pT0N0, respectively) as well as two-year RFS, in patients treated with nivolumab and combination of nivolumab/lirilumab.

7.4.3.7. To assess prognostic and predictive associations between baseline tumor and/or tumor infiltrating lymphocyte tissue and ctDNA genomic alterations, gene expression, and methylation signatures for pathologic partial and complete response (defined by cystectomy

pathologic staging <pT2N0 and pT0N0, respectively) as well as two-year RFS, in patients treated with nivolumab and combination of nivolumab/lirilumab.

7.4.3.8. To assess prognostic and predictive value of serum circulating antibody profiles on pathologic partial and complete response (defined by cystectomy pathologic staging <pT2N0 and pT0N0, respectively) as well as two-year RFS, in patients treated with nivolumab and combination of nivolumab/lirilumab.

7.4.3.9. To assess CD8+ TIL density by central pathology review using image analysis in TURBT and radical cystectomy in each arm

7.5. Analysis Populations

The study will aim to screen 43 eligible patients in order to enroll 36 patients in the trial. There will be 12 patients in cohort 1 and 24 patients in cohort 2. There will be a safety population for safety analysis and an efficacy population for efficacy analysis.

7.5.1. Safety Population

The safety population is defined as all patients treated with at least one dose of nivolumab and/or lirilumab. It is the same as "Evaluable for Toxicity" population that used in protocol. All safety data collected up to the end of the study (i.e., through the last follow-up evaluation) are included in the safety analysis.

7.5.2. Efficacy Population

The efficacy population is defined as all patients who received at least one dose of trial therapy, undergo radical cystectomy and have at least one of the following tumor evaluations listed below. Patients who exhibited objective disease recurrence prior to the end of treatment will also be considered as part of the efficacy population.

Below is the list of tumor evaluations:

1. CD8+ T-Cell Density

2. %CD8+ Tumor-Infiltrating T-Cells
3. Pathologic Tumor Response
4. Tumor IHC Staining Intensity Definitions

7.6. Safety Analysis

The safety evaluations include AEs, concomitant medication, clinical laboratory assessments, vital signs, and physical examination. Safety analysis will be assessed for the safety population.

The results of this study will be reported using summary tables, figures, and data listings. Continuous variables will be summarized using mean, SD, median, minimum, and maximum. Categorical variables will be summarized by presenting the number (frequency) and percentage in each cohort.

If any screening safety data is repeated, the measurement taken closest to dosing will be used in the analysis as pre-study baseline. If any post-dose safety data is repeated, the measurement taken first at the particular visit in question will be used in the analysis.

7.6.1. Disposition

Disposition data (e.g. informed consent, treated patients, surgery, etc.) will be summaries descriptive by cohort and overall patients for the patients who enrolled into the study. Patients who signed informed consent and registered are considered as enrolled into the study.

7.6.2. Demographics and Baseline Characteristics

Demographic data (e.g. age, gender, race, height, screening body weight, cancer pathology, etc.) will be summarized descriptively (number of patients (frequency), mean, SD, median, minimum, and maximum) by cohort and overall in the safety population.

7.6.3. Medical and surgical History

Medical and surgical history data (e.g. surgical procedure, prior cancer therapy signs and symptoms, etc.) that collected during screening will be summaries by cohort and overall.

7.6.4. Concomitant Medications and Procedure

The use of concomitant medications and procedure will be recorded on the CRFs. The concomitant medications will be coded to a World Health Organization Drug Dictionary (WHO-DD) term.

The use of concomitant medications and procedures will be summarized by cohort and overall group for the safety population. In each of these summary tables, the number and percentage of patients taking each medication will be presented by ATC Classification.

7.6.5. Study treatment and Surgery

The count and percentage of Nivolumab and Lirilumab administration completion and dose delay by cohort will be displayed. The number of patients who receive radical cystectomy will be summarized as well,

7.6.6. Adverse Events

7.6.6.1. Primary Endpoint, Grade 3 or Higher Treatment-related AE

The rates of Grade 3 or higher treatment-related AE during neoadjuvant treatment will be reported along with 90% exact binomial confidence intervals.

7.6.6.2. Secondary Endpoint, Patient who Did not Get Radical Cystectomy Due to AE

The proportion of patients in each treatment cohort who do not get radical cystectomy specifically and directly related to treatment related AEs within 6 weeks of the completion of neoadjuvant treatment, will be reported along with exact binomial 90% confidence intervals for each cohort and compared between the two cohorts using Fisher's exact test. This is one of secondary objective endpoints.

The Identification of the AEs that cause patients do not get radical cystectomy by selecting "Caused Study Discontinuation" in AE CRF page, and with related to Nivolumab/Lirilumab, and patients do not have radical cystectomy surgery.

7.6.6.3. AE Summary Analysis by System Organ Class and Preferred Term

Treatment-emergent AEs (TEAEs) are those that occur after administration of the first study dose until 100 days after last dose of study medication. In the case where the start date of the AE is unknown, it will be assumed to be treatment-emergent. TEAEs will be summarized by System Organ Class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA®). The latest version of MedDRA (V 20.0) will be used. The frequency of patients who experience TEAEs will be summarized by cohort and overall. Patients, having the same AE more than once per group, will be counted once for each PT and once within each SOC.

All AEs, TEAEs, treatment-related AEs, Grade 3 or higher treatment-related AEs, SAEs, TEAEs caused stopping study medications, TEAEs leading to early termination, fatal TEAEs will be summarized by cohort and overall group. Also, above AE categories will be summarized by SOC and PT as well.

Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0) will be used to manifest AE grade.

7.6.7. Clinical Laboratory Data

Numeric clinical laboratory data will be summarized at each visit (clinical data collection point) using descriptive statistics. Non-numeric laboratory tests will be summarized separately using frequency counts on unique responses. Individual change from baseline in lab values will be calculated and summarized descriptively. The Lab shift table will be displayed at each visit for each laboratory test.

7.6.8. Vital Signs Data

Vital sign collected value and change from baseline will be summarized by visit and displayed by cohort and overall treatment group.

7.7. Efficacy Analysis

All Efficacy analyses are performed for efficacy population except Recurrent-Free Survival and Overall Survival analyses. The RFS and OS analyses are performed for safety population.

7.7.1. The mean change of CD8+ TIL density in each cohort

There are 2 CD8+ TIL density readings for each patient. One is prior and another one is after study treatment. Patients obtained prior treatment CD8+ TIL density from TURBT. Patents obtained post treatment CD8+ TIL density from radical cystectomy. The mean change in CD8+ TIL density of each cohort will be calculated by averaging the change in TIL densities of all patients in the cohort.

In each cohort a one-sample Wilcoxon signed-rank test will be used to test whether the mean change in TIL density differs significantly from zero. This is key secondary objective (SAP section 7.4.2.1).

Additionally, the TIL density at radical cystectomy (post study treatment) will be compared between the two cohorts using a Wilcoxon rank sum test. This is the first exploratory objective (SAP section 7.4.3.1).

7.7.2. The average percent (%) change of CD8+ TIL density in each cohort

Each individual patient's percent change is defined as:

100* [(Cystectomy TIL Density) – (TURBT TIL Density)] / (TURBT TIL Density).

The mean percent change of CD8+ TIL density from pre-treatment (TURBT) to post-treatment (radical cystectomy) samples in all 12 patients in Cohort 1 and all 24 patients in Cohort 2 will be calculated and compared between the two cohorts using a Wilcoxon rank sum test. This is one of secondary objective endpoints.

7.7.3. Pathology response in each cohort

The proportion of patients in each treatment cohort with pathologic complete response (CR) and pathologic partial response (PR) will be reported along with exact binomial 90% confidence intervals for each cohort. This is one of secondary objective endpoints. Pathologic response (<ypT2N0M0) is defined by post-treatment radical cystectomy tumor stages with N0 and M0 status with the following T-stages: T0, Ta, Tis, T1.

The pathologic complete response (CR) is defined as: The pT0N0M0 is assigned at cystectomy tumor stage that based on bladder cancer TNM staging system. This stage indicates the patient is no evidence of primary tumor (T0) and no lymph node metastasis (N0).

The pathologic partial response (PR) is defined as: The stages that are less than T2N0M0 stage (<pT2N0M0) at cystectomy. Tumor stages with N0 and M0 status with the following T-stages: T0, Ta, Tis, and T1 are considered as partial response.

Pathologic non-response (NR) is defined by post-treatment radical cystectomy tumor stages with any node-positive (N1, N2, N3) or metastases-positive (M1) status. In addition, patients with N0 and M0 status with the following T-stages are also classified as pathologic non-responders: T2, T2a, T2b, T3, T3a, T3b, T4, T4a, T4b.

7.7.4. RFS survival analysis in each cohort

Recurrence-free survival (defined as patients who are alive and without evidence of disease recurrence) from start of treatment to first documented recurrence will be estimated using Kaplan-Meier method for each treatment cohort and compared between the two cohorts using a log-rank test. The two-year recurrence-free survival estimates and confidence intervals will be provided for each cohort. If patients do not have recurrence tumor or death event then they are censored at the last RECIST assessment date.

The proportion of patients with recurrence-free survival at the two-year time point from registration will be displayed for each cohort.

7.7.5. Overall Survival (OS)

OS is defined as the duration of time from start of treatment to time of death. Patients will be censored at the last date known alive. The Kaplan-Meier method for each treatment cohort and compared between the two cohorts using a log-rank test. The two-year OS estimates and confidence intervals will be provided for each cohort.

7.7.6. IHC markers in relationship with tumor response in each cohort

The marker levels in responders vs. non-responders will be compared by a t-test or Wilcoxon rank sum test as appropriate. In addition to evaluating expression on a continuous scale we will explore quantile values for each marker as potential thresholds to discretize the marker levels. The two-year RFS will then be compared between marker groups with a Fisher's exact test as well as via time-to-even analyses using standard methods for survival analysis. Changes in biomarker levels will be computed and compared between groups using a Wilcoxon rank sum test.

7.7.7. PBMC in relationship with tumor response in each cohort

The same strategy of above (SAP section 8.7.5) will be applied for this analysis.

7.8. Interim Analysis

There will be 3 interim safety analyses in this study. After 6 and 12 patients on Cohort 1 and 6 patients on Cohort 2 complete surgery, the study will be monitored for nivolumab or nivolumab/lirilumab treatment-related toxicities as noted below.

- Any Grade hypophysitis, meningitis, or immune-related neurologic AEs
- Grade 2 or higher myocarditis
- Persistent Grade 2 immunologic AEs (such as colitis, pneumonitis, and nephritis) that do not recover to Grade 1 or resolve within 6 weeks after the last dose of study drug (Exceptions: rash, fatigue, amylase/lipase elevations, other electrolyte abnormalities).
- Grade 3 or higher immunologic AEs such as uveitis, pericarditis, hepatitis, colitis/diarrhea, nephritis, pancreatitis, myositis, endocrine, rash, etc., except Grade 3 hypothyroidism or Grade 3 infusion reaction.
- Grade 4 non immunologic AEs, as well as Grade 4 hypothyroidism or Grade 4 infusion reaction.

The first interim safety analysis will be performed as soon as the 6th patient in cohort 1 complete radical cystectomy (RC) surgery. A treatment-related AE by toxicity grade and SOC summary tables will be provided to clinical team review to determine whether 3 or more patients meet above specified AEs. If 3 or more patients are identified, the study will be suspended for a safety review.

An AE listing will also be provided for clinical team review.

The 2nd interim safety analysis will be performed as soon as the 12th patient in cohort 1 complete RC surgery. The same AE analysis as the first interim analysis will be performed for the all 12 patients. If 6 or more patients experience above specified AEs, the study will be suspended for a safety review.

The 3rd interim safety analysis will be performed as soon as the 6th patient in cohort 2 complete RC surgery. The same AE analysis will be repeated for the all 18 patients. If 9 or more patients experience above specified AEs, the study will be suspended for a safety review.

8. SUMMARY OF CHANGES FROM PROTOCOL-SPECIFIED ANALYSES

No changes are planned.

9. REPORTING CONVENTIONS

The mean and median will be displayed to one decimal place greater than the original value and the standard deviation will be displayed to two decimal places greater than the original value. All statistical programming and analyses will be performed using SAS® Release 9.4 (SAS Institute Inc., Cary, North Carolina, USA).

The following standards will be used in the data presentation:

- Section 14 tables should be in landscape format. Output should adhere to US / International Conference on Harmonization (ICH) margins and should not require changes for European page size. For item 14 tables, a blank row will separate the header from the content of the table listing. For tables that have “n (%)”, the placement should be centered below “N=xx” in the column header. Frequency tables will be center justified. Descriptive statistics will be decimal aligned.

- Percentages presented in in-text tables should be rounded to one decimal using the SAS rounding function. If "%" is part of the column heading, do not repeat the "%" sign in the body of the table. Unless specified otherwise, "%" should reflect the total population of the treatment groups. Any deviation from that should be part of the footnote. For 0 counts, leave the corresponding percentage blank.

- The format for minimum and maximum should be "Min, Max". SD should be the default for representing scale, unless standard error has been specified. Standard deviation should be abbreviated as "SD", and presented next to the mean value, without any +/- sign. The SD should have one additional decimal place beyond that of the mean (e.g. mean has one decimal place, SD should have two).

- "N" will represent the entire treatment group for the population group being analyzed, while "n" will represent a subset of the treatment group. For tables with population designated as a row heading, "N" should be used (i.e. tables where all participant data is not available for every variable within a treatment group). As a guideline, if the number is used in a denominator it should be presented as "N". If the number is used in the numerator, it should be presented as an "n".

- The heading should consist of four lines. Line 1: Sponsor identifier. Line 2: Protocol identifier. Line 3: blank line. Line 4: Table/Appendix number Table Title – Population. The title for in-text tables should begin with the Table/Appendix number.

- All data listings will be sorted by Patient Number and time point (if applicable).

- The date format for all dates is DDMMMYYYY.

A solid line should appear both above and below the column headings of a table. A solid line should appear at the end of the table or at the bottom of each page if the table extends to more than one page. Footnotes should start after the bottom solid line.

10. REFERENCES

References are provided in the protocol.

11. TABLES, FIGURES, AND LISTINGS

See separate template document.

12. APPENDIX

12.1. Appendix I. Study procedure and Parameters

1. All pre-study assessments and scans should be done ≤ 4 weeks prior to registration with exception of first TURBT that showed muscularis propria invasion which can be done within 56 days.

Procedures	Screening	TURBT[1] (if needed)	Infusion 1	Infusion 2*	Surgery		Off Treatment[16]	Follow-Up[18]
			Day 1	Day 1				
Written Informed Consent	X							
Pathology[1]	X[1]	X[1]						
Disease Characteristics[2]	X							
Medical/Surgical History	X							
Assessment of Baseline Signs & Symptoms	X							
Height	X							
Physical Exam including Weight	X	X	X	X	X		X	
Vital Signs[3] (Temperature, Pulse, Blood Pressure)	X	X	X	X	X		X	
Performance Status	X	X	X	X	X		X	
CBC/Differential/Platelets[4]	X	X	X	X	X		X	

Procedures	Screening	TURBT[1] (if needed)	Infusion 1	Infusion 2*	Surgery		Off Treatment[16]	Follow-Up[18]
			Day 1	Day 1				
Chemistry[5]	X	X	X	X	X		X	
Hepatitis B & C Testing[6]	X							
TSH, FT3, FT4[7]	X			X[7]	X		X	
Serum Pregnancy Test[8]	X		X[8]	X[8]				
Serum Cortisol Level	X				X			
ECG	X							
Chest/Abdomen/Pelvic CT with Contrast or MRI[9]	X				X[15]			X
Research Blood Specimens[10]	X (Streck DNA tube only)		X	X	X		X	X[10]
Research Urine Specimens[10]			X	X	X		X	X[10]
Research Tissue Specimens[11]		X			X			X[11]
Treatment Administration[12]			X	X				
Oxygen Saturation by Pulse Oximetry[13]			X	X				

Procedures	Screening	TURBT[1] (if needed)	Infusion 1	Infusion 2*	Surgery		Off Treatment[16]	Follow-Up[18]
			Day 1	Day 1				
Radical Cystectomy with Pelvic Lymph Node Dissection[14]					X			
Concomitant Medication Review	X		X	X	X		X	
Adverse Events Assessment			X	X	X		X[17]	
Survival Status								X

* **Scheduled Visits:** +/-3 day window is allowed for scheduled study therapy, required tests and/or visits except as otherwise noted. Delay due to holidays, weekends, bad weather or other unforeseen circumstances will be permitted.

1 Cystoscopy with TURBT showing muscularis propria should be performed within 8 weeks (56 days) of starting study therapy. Patients must have sufficient baseline tumor tissue from either the initial or repeat TURBTs. **Tumor tissue content for CD8+ T-cell density assessment must be qualified as sufficient (≥ 20% tumor content in the specimen in initial or repeat TURBT with highest tumor content) for analysis and must be documented by the local pathologist prior to registration.** (The actual CD8+ T-analysis does not need to be done by the Central Laboratory prior to registration.) This documentation can occur at any time prior to registration. Patients will complete all other screening studies (i.e. labs, imaging, history, exam, etc.) within 28 days of starting study therapy.

2 Record date of diagnosis and stage.

3 Patients will have Temperature, Pulse and Blood Pressure taken at each visit. In addition, patients will have their blood pressure and pulse measured before, during and after the infusions at the following times:

- At the beginning of the infusion
- After nivolumab infusion and before lirilumab infusion for patients receiving lirilumab
- At the end of the infusion

4 CBC with differential and platelet count which includes WBC, ANC, Platelets, Hemoglobin, and Hematocrit required prior to each dose of study therapy. Results known prior to treatment administration.

5 Albumin, BUN/creatinine, uric acid, sodium, potassium, chloride, glucose, calcium, alkaline phosphatase, AST, ALT, total bilirubin, and total protein.

6 Hepatitis B surface antigen (HBsAg), and Hepatitis C (HCV) testing within 4 weeks of registration. These tests may be repeated during the course of the study, if clinically indicated.

7 TSH, FT3, FT4 at Screening and before Infusion 2, Day 1.

8 Required for sexually active females of child-bearing potential. Infusion 1 and Infusion 2: Must be within 24 hours prior to treatment with nivolumab.

9 CT with IV contrast is the preferred method. MRI exams of the chest/abdomen/pelvis may be performed, if CT of chest/abdomen/pelvis cannot be obtained.

10 Research blood and urine samples shall be obtained at time points noted below. Refer to Section 14 for details. **NOTE: Blood draw order is specified in the PrE0807 Lab Manual.**

Screening

One 10 mL Streck DNA tube (for germline)

Before First and Second Neoadjuvant Dose
Peripheral Blood: One 10 mL red top tube, two 10 mL green top tubes, one 10 mL Streck DNA tube and one 10 mL Streck RNA
Urine: At least 30 mL in standard urine cup

Pre-Radical Cystectomy
Peripheral Blood: One 10 mL red top tube, two 10 mL green top tubes, one 10 mL Streck DNA tube and one 10 mL Streck RNA
Urine: At least 30 mL in standard urine cup

Off Treatment Visit (approximately 30 days after Cystectomy)
Peripheral Blood: One 10 mL red top tube and two 10 mL green top tubes, one 10 mL Streck DNA tube and one 10 mL Streck RNA
Urine: At least 30 mL in standard urine cup

At Time of Recurrence, if feasible

Peripheral Blood: One 10 mL red top tube, two 10 mL green top tubes, one 10 mL Streck DNA tube and one 10 mL Streck RNA
Urine: At least 30 mL in standard urine cup

11 Research tumor tissue samples shall be obtained at time points noted below. Refer to Section 14 for details.

Screening/Study Entry
FFPE: Up to 3 blocks preferred or 1 H&E slide plus minimum of 20 unstained slides (30 preferred)

Radical Cystectomy
FFPE: Up to 3 blocks preferred or 1 H&E slide plus minimum of 20 unstained slides (30 preferred)

At Time of Recurrence, if feasible
FFPE: Up to 3 blocks preferred or 1 H&E slide plus minimum of 20 unstained slides (30 preferred)

12 See Section 6 for Treatment Plan and Section 7 for Dose Delays.

Cohort 1: Nivolumab 480 mg IV over approximately 30 minutes every 4 weeks for 2 neo-adjuvant doses (week 0 and 4) followed by radical cystectomy with bilateral (standard or extended) pelvic lymph node dissection as soon as possible but within 6 weeks after the last neoadjuvant infusion.

Cohort 2: Nivolumab 480 mg IV over approximately 30 minutes every 4 weeks for 2 neo-adjuvant doses (week 0 and 4) with at least a 30 minute rest between infusions followed by lirilumab 240 mg IV over approximately 60 minutes every 4 weeks for 2 neo-adjuvant doses (week 0 and 4) followed by radical cystectomy with bilateral (standard or extended) pelvic lymph node dissection as soon as possible but within 6 weeks after the last neo-adjuvant infusion.

13 Record oxygen saturation by pulse oximetry at rest and after exertion at each on-study visit prior to dosing.

14 Radical cystectomy with bilateral (standard or extended) pelvic lymph node dissection to be performed as soon as possible but within 6 weeks after the last neoadjuvant infusion.

15 Obtain CTs (or MRI as noted above) after second dose of nivolumab +/- lirilumab and before surgery.

16 Thirty (30) days +/- 7 days after cystectomy. If patient is removed from treatment for reason(s) other than progression, follow with regular tumor assessments per standard of care until progression or start of new treatment. Once a patient has initiated a new therapy, no further imaging assessments for this study are required.

NOTE: If cystectomy is not performed, Off Treatment visit should be performed at next scheduled appointment or treating physician discretion, as clinically indicated.

17 Patients will be followed for adverse events for 100 days after their last dose of neoadjuvant therapy. Adverse events may be reviewed at the next visit ≥ 100 days after last dose of neoadjuvant therapy or phone follow-up may be done to review adverse events. However, an adverse event occurring at any time after discontinuation of study therapy that is felt to be at least possibly related to study therapy should be recorded.

18 Patients will be followed clinically and radiographically for at least 2 years post-cystectomy or when study-wide follow-up ends per standard of care. Date of diagnosis for progression, first subsequent therapy and survival shall be reported. Phone follow-up may also be done for patients unable or unwilling to return for follow-up evaluations.

12.2. Appendix II. Bladder Cancer TNM Staging

American Joint Committee on Cancer TNM Staging System for Bladder Cancer

Pathologic T Staging

- Tx – Primary tumor cannot be assessed
- T0 – No evidence of primary tumor
- Ta – Noninvasive papillary carcinoma which does not invade into the lamina propria
- Tis – Carcinoma in situ
- T1 – Tumor invades into the lamina propria but not into the muscularis propria
- T2 – Tumor invades into the muscularis propria
- T2a – Tumor invades into the inner half of the muscularis propria
- T2b – Tumor invades into the outer half of the muscularis propria
- T3 – Tumor invades into the perivesical tissue
- T3a – Tumor microscopically invades the perivesical tissue
- T3b – Tumor macroscopically invades the perivesical tissue
- T4 – Tumor invades into adjacent organs
- T4a – Tumor invades the prostatic stroma, uterus, or vagina

T4b – Tumor invades into the pelvic wall, or abdominal wall

Pathologic N Staging

Nx – Lymph nodes cannot be assessed

N0 – No lymph node metastasis

N1 – Single regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node)

N2 – Multiple regional lymph node metastases in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph nodes)

N3 – Lymph node metastases to the common iliac lymph nodes

Pathologic M Staging

M0 – No distant metastasis

M1 – Distant metastasis

13. DOCUMENT HISTORY

Version Date	Modified By	Summary of Changes
28Feb2019	[redacted]	First draft, version 1.0
26Mar2019	[redacted]	Second draft, version 2.0 1. Added interim safety analysis in SAP section 7.8. Accordingly identified 2 tables and 1 listing to be the 3 interim analysis deliverables. 2. Added study medication administration and summary analysis in the SAP text and updated mock table. 3. Removes one-year RFS analysis. There is only 2-year RFS. Consistently used Recurrence-free instead of progression-free
11Apr2019	[redacted]	Draft Version 2.1 1. Add specification of pathology response definition at section 7.7.3 2. Add censoring date for RFS at section 7.74
29Apr2019	[redacted]	Draft final Version 1.0 Made from draft v2.1 by removing all comments to have a clear version. Updated the dates.

16May2019	[redacted]	Final Version 1.0 1. Remove RFS and OS from Efficacy Population requirement items 5, and 6. 2. The RFS and OS analyses are performed for Safety Population.
06Feb2020	[redacted]	Final Version 1.1 Update SAP to be consistent with protocol V3.0 10Dec2019