Official Title of Study:

A Phase 3, Randomized, Double-blind Trial of Nivolumab in Combination with Intravesical BCG Versus Standard of Care BCG Alone in Participants with High-risk Non-muscle Invasive Bladder Cancer That is Persistent or Recurrent After Treatment with BCG

NCT Number: NCT04149574

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Protocol Number: CA2097G8
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Date: 16-Aug-2019
Revised Date: 11-Oct-2021

CLINICAL PROTOCOL CA2097G8

A Phase 3, Randomized, Double-blind Trial of Nivolumab in Combination with Intravesical BCG versus Standard of Care BCG Alone in Participants with High-risk Non-muscle Invasive Bladder Cancer That Is Persistent or Recurrent After Treatment with BCG

(CheckMate 7G8: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 7G8)

Short Title: A Study Comparing Nivolumab and Intravesical BCG to BCG Alone in High-risk Non-muscle Invasive Bladder Cancer

Protocol Amendment No.: 01

Incorporates Administrative Letters 01 and 02

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DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Protocol Amendment 01	11-Oct-2021	Key updates to the protocol include: • Details of closure of the study, with provision for participants currently on treatment to continue. • Clarification that all pharmacokinetic, biomarker, patient-reported outcomes, and healthcare resource utilization assessments are no longer applicable per Protocol Amendment 01. • Clarification that study-related efficacy assessment and Pathology Review Committee are no longer applicable per Protocol Amendment 01. Sites should continue efficacy assessment as per local standards of care. Additionally, dose modification criteria and immuno-oncology agent management algorithms were updated per the current National Cancer Institute Common Terminology Criteria for Adverse Events version (v5).
Administrative Letter 02	18-Feb-2021	The purpose of this letter is notification of study personnel change.
Administrative Letter 01	27-Nov-2019	The purpose of this letter is to correct typographical errors and to update the information in the study protocol Appendix 7. In Spain, Italy, Peru, and France HIV laboratory testing is not a country-specific requirement
Original Protocol	16-Aug-2019	Not applicable

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 01:

As of May 2021, the CA2097G8 study enrollment was significantly behind the projected target enrollment, at 5% since first patient first visit; therefore, the study will be unable to meet its scientific objectives. As such, the primary reason for this protocol amendment is to implement the decision to close participant enrollment to the study as of 02-Jun-2021.

Key updates to the protocol include:

- Details of closure of the study, with provision for participants currently on treatment to continue.
- Clarification that all pharmacokinetic (PK), biomarker, patient-reported outcomes, and health care resource utilization assessments are no longer applicable per Protocol Amendment 01.
- Clarification that study-related efficacy assessment and Pathology Review Committee are no longer applicable per Protocol Amendment 01. Sites should continue efficacy assessment as per local standards of care.

Additionally, dose modification criteria and immuno-oncology (I-O) agent management algorithms were updated per the current National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version (v5).

Relevant components of Administrative Letters 01 and 02 are also incorporated. Additional updates, including to sections of the Synopsis, have been made to align the protocol with respect to these changes. This protocol amendment applies to all participants and should override any existing protocol requirements in the event of any apparent contraindications.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	Updated Clinical Trial Physician and included Clinical Scientist.	Provided current study contact information.
Synopsis	Modified to align with changes in body of protocol.	Aligned with protocol body.
Section 2: Schedule of Activities	Added “Not applicable per Protocol Amendment 01” to the title of Table 2-1.	Aligned with study closure as of Protocol Amendment 01.
Table 2-1: Screening Procedural Outline (CA2097G8)	Updated Table 2-2 to include “per local standards of care” for the q52 week body imaging assessment.	Clarify that the imaging assessment schedule included in the protocol is per local standards of care.
Table 2-2: On-treatment Procedural Outline for Arms A and B (CA2097G8)	Updated Table 2-1, Table 2-2, and Table 2-3 to indicate that tumor sample submission, biomarker sampling, efficacy assessments, health outcomes, PK and immunogenicity, and survival and efficacy follow-ups are no longer applicable per Protocol Amendment 01.	Aligned with study closure as of Protocol Amendment 01.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-3: Follow-up Procedural Outline (CA2097G8)	Added text under "notes" for "Adverse Event (AE) Assessment (Including SAE)" in Tables 2-2 and 2-3 for the continuous collection of information and follow-up requirements for AEs associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.	Included timing for the collection of AEs associated with SARS-CoV-2 infection and follow-up requirements.
Section 3.1.1: Changes per Protocol Amendment 01	New sub-section added to describe the reason for study closure, procedures put into effect, and key changes to the protocol.	Provided rationale for study closure.
Section 3.1.2: Study Hypothesis	Indicated that study hypothesis is no longer applicable per Protocol Amendment 01.	Aligned with study closure as of Protocol Amendment 01.
Section 4: Objectives and Endpoints	Added language to clarify that only safety assessments will be conducted as of Protocol Amendment 01.	Aligned with study closure as of Protocol Amendment 01.
Section 5: Study Design	Added language describing closure of the study as of 02-Jun-2021 and resulting removal of the initial benefit/risk assessment by the Data Monitoring Committee.	Aligned with study closure as of Protocol Amendment 01.
Figure 5.1-1: CA2097G8 Study Design Schematic	Updated the figure to indicate that efficacy assessments will be conducted per local standards of care, and participants will be for safety assessments through 100 days following last dose of study treatment.	Aligned with study closure as of Protocol Amendment 01.
Section 5.1.1: Screening Phase	The following modifications were made: • Added language describing closure of the study as of 02-Jun-2021 and clarified that the screening phase is no longer applicable per Protocol Amendment 01. •	Aligned with study closure as of Protocol Amendment 01.
Section 5.1.2: Treatment Phase	Deleted text that described: • Timing of on-study cytoscopy and urine cytology, and bladder biopsies in participants with carcinoma in situ • Clinical decision-making would be based on investigator assessment of recurrence/progression. • End of treatment period Added the following text: "For all participants, follow local standards of care for efficacy assessments"	Removed treatment procedures that were not applicable per Protocol Amendment 01 and clarified that local standards of care should be followed for efficacy assessments instead.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 5.1.3: Follow-up Phase	Indicated that survival and efficacy follow-ups after Visit 2 are no longer applicable per Protocol Amendment 01.	Aligned with study closure as of Protocol Amendment 01.
Section 5.1.4: Data Monitoring Committee and Other External Committees	Indicated that the Data Monitoring Committee and Pathology Review Committee are not applicable per Protocol Amendment 01.	Aligned with study closure as of Protocol Amendment 01.
Section 5.2: Number of Participants	Indicated what was planned prior to study closure and what is no longer applicable as of Protocol Amendment 01.	Aligned with study closure as of Protocol Amendment 01.
Section 5.3: End of Study Definition	Clarified that with study closure, study completion will occur when all participants complete study procedures described in Section 2.	Clarified expectations for study completion with study closure per Protocol Amendment 01.
Section 5.4.2: Rationale for Event-free Survival as Primary Endpoint	Indicated that rationale is not applicable per Protocol Amendment 01.	Aligned with study closure as of Protocol Amendment 01.
Section 6: Study Population	Added sentence to clarify that enrollment into the study was closed and that male participants continuing treatment should follow the updated contraceptive guidance in the eligibility criteria and in Appendix 4.	Clarified expectations for male contraceptive guidance with study closure per Protocol Amendment 01.
Section 7.1.1: Nivolumab Dosing	Updated first paragraph to include that flushing the intravenous line with diluent is permitted to ensure that the complete dose of nivolumab is administered over approximately 30 minutes.	Clarified expectations for nivolumab administration.
Section 7.3: Blinding	Added language at the beginning of the section to clarify that blinding is not required to meet study objectives per Protocol Amendment 01, and for the requirement of following Interactive Response Technology instruction and alerting the Medical Monitor if the blind is broken.	Provided guidance on how to proceed if the blind was broken by investigators due to it being in the best interest of the participant per Protocol Amendment 01 or in the case of accidental unblinding.
Section 7.4: Dosage Modification	Added Table 7.4-1 for AE criteria for delay, resume, and discontinuation of study treatment.	Reorganized dose delay, resume, and discontinuation criteria for improved readability and to align with the current NCI CTCAE v5.
Section 7.4.3: Dose Delay Criteria	Added language for SARS-CoV-2 infection.	Updated dose delay criteria to include expectations in cases of confirmed or suspected SARS-CoV-2 infection.
Section 7.4.3.1: Nivolumab/ Nivolumab-placebo Dose Delay Criteria	Modified text to align criteria for dose delay, resume, and discontinuation with Table 7.4-1.	Updated dose delay, resume, and discontinuation criteria to align with the current NCI CTCAE v5.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 7.4.4.1: Nivolumab/Nivolumab-placebo Criteria to Resume Treatment Section 8.1.1: Nivolumab/ Nivolumab-placebo Dose Discontinuation		
Section 7.4.4.1: Nivolumab/ Nivolumab-placebo Criteria to Resume Treatment Section 7.4.4.2: BCG Criteria to Resume Treatment	Added language for SARS-CoV-2 infection.	Updated criteria to resume treatment to include expectations in cases of confirmed or suspected SARS-CoV-2 infection.
Section 7.7: Concomitant Therapy	Added language for coronavirus disease 2019 (COVID-19) vaccines.	Provided expectations for concomitant use of COVID-19 vaccines.
Section 7.7.1: Prohibited and/or Restricted Treatments	Removed language describing use of marijuana and its derivatives.	Use of marijuana and its derivatives is permitted with BMS Medical Monitor (or designee) approval.
Section 8.1: Discontinuation From Study Treatment	Updated bullet for disease progression and recurrence to “locally diagnosed.”	Aligned with study closure as of Protocol Amendment 01.
Section 8.1.3: Post Study Treatment Study Follow-up	Added text to clarify that efficacy follow-up is no longer required as of Protocol Amendment 01 and that participants will be followed for safety only.	Aligned with study closure as of Protocol Amendment 01.
Section 9: Study Assessments and Procedures	Updated second paragraph following bullets to include participant evaluation for cardiac toxicity.	Clarified expectations for participant evaluation for cardiac toxicities.
Section 9.1: Efficacy Assessments (and all related sub-sections)	Added text to clarify that efficacy assessments will be conducted per local standards of care per Protocol Amendment 01 and that previously planned efficacy assessments are no longer applicable per Protocol Amendment 01.	Clarified expectations for efficacy assessments with study closure per Protocol Amendment 01.
Section 9.2.1: Time Period and Frequency	Added text related to SARS-CoV-2 infection.	Included timing for the collection of AEs associated SARS-CoV-2 infection.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
for Collecting AE and SAE Information		
Section 9.2.3: Follow-up of AEs and SAEs	Added text related to SARS-CoV-2 infection.	Included follow-up requirements for AEs associated SARS-CoV-2 infection.
Section 9.5: Pharmacokinetics Section 9.6: Pharmacodynamics Section 9.8: Biomarkers Section 9.8.2: Immunogenicity Assessments Section 9.8.3: Other Assessments (and all related sub-sections) Section 9.9: Health Care Resource Utilization and Health Economics	Updated to clarify that previously planned PK, pharmacodynamics, immunogenicity, and biomarkers assessments as well as health care resource utilization and health economics parameters will not be evaluated, since these are no longer applicable as of Protocol Amendment 01.	Clarified expectations for previously planned assessments/evaluations with study closure per Protocol Amendment 01.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 10: Statistical Considerations Section 10.1: Sample Size Determination Section 10.2: Populations for Analyses Section 10.3.1: Efficacy Analyses Section 10.3.2: Safety Analyses Section 10.3.3: Other Analyses (and all related sub-sections) Section 10.3.4: Interim Analyses	Added language to clarify that, per Protocol Amendment 01: • Descriptive analyses of investigator-assessed efficacy data will be conducted. • Sample size will be limited to the participants enrolled as of 02-Jun-2021. • Populations for analysis will be limited to enrolled, randomized, and treated populations. • Efficacy, outcomes research, PK, pharmacodynamics, immunogenicity, biomarker, and interim analyses are no longer applicable. • Only limited safety analyses will be conducted.	Clarified expectations for statistical considerations with study closure per Protocol Amendment 01.
Appendix 2: Study Governance Considerations	The following modifications were made: • Updated first paragraph for Monitoring section to further describe that details on monitoring can be found in the monitoring plan. • Added section for Dissemination of Clinical Study Data.	These changes were made to: • Clarify expectations for monitoring. • Provide details on how clinical study information will be made available.
Appendix 4: Women of Childbearing Potential Definitions and Methods of Contraception	"Contraception Guidance for Male Participants with Partner(s) of Childbearing Potential" was updated to the following: "Given that nivolumab is not a genotoxic agent, and that relevant systemic concentrations sufficient to produce a risk of fetal toxicity are not expected in WOCBP partners from exposure to a male participant's seminal fluid, male study participants will not be required to use contraceptive measures and/or a latex or other synthetic condom during sexual activity with a WOCBP partner."	The use of contraception for male participants treated with nivolumab is no longer needed.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Appendix 5: Management Algorithms	Replaced I-O agent management algorithms with those aligned with NCI CTCAE v5.	Updated management algorithms for immune-mediated AEs to align with current NCI CTCAE v5 and nivolumab Investigator's Brochure.
Appendix 7: Country Specific Requirements	Updated list of countries to which exclusion criteria related to human immunodeficiency virus (HIV) apply.	Clarified country-specific differences for HIV-positive participants.
All	Minor formatting and typographical corrections.	These changes are minor and therefore have not been summarized.

TABLE OF CONTENTS

1 SYNOPSIS

Protocol Title: A Phase 3, Randomized, Double-blind Trial of Nivolumab in Combination with Intravesical BCG versus Standard of Care BCG Alone in Participants with High-risk Non-muscle Invasive Bladder Cancer That Is Persistent or Recurrent After Treatment with BCG

Short Title: A Study Comparing Nivolumab and Intravesical BCG to BCG Alone in High-risk Non-muscle Invasive Bladder Cancer

Study Phase: 3

Rationale:

High-risk non-muscle invasive bladder cancer (NMIBC) is treated with transurethral resection of bladder tumor (TURBT) followed intravesical bacillus Calumette-Guerin (BCG). Patients may have persistent or recurrent disease after this treatment. In patients that have persistent or recurrent disease that is not classified as BCG unresponsive,[1] standard of care is repeat TURBT and intravesical induction and maintenance BCG. Available evidence suggests the rate of recurrence for these patients is approximately 40% at 24 months, which is significantly worse than the rate of recurrence in BCG-naïve patients treated with BCG.[2]

Intravesical BCG results in tumor inflammation and nivolumab enhances T-cell activity within the tumor; combining BCG with nivolumab therefore offers the potential for improved response of the tumor to immunotherapy. This study aims to demonstrate that treatment with nivolumab in combination with intravesical BCG will improve event-free survival (EFS) vs intravesical BCG alone. Additional clinical endpoints include worsening-free survival (WFS), complete response rate (CRR) in patients with carcinoma in situ (CIS), and overall survival (OS). Additional objectives of the study include characterization of safety and tolerability, pharmacokinetics, potential predictive biomarkers, and changes in patient-reported outcomes for quality of life assessment.

Changes per Protocol Amendment 01

As of May 2021, the CA2097G8 study was behind its enrollment target. Bristol-Myers Squibb undertook several mitigation actions to improve participant recruitment. Unfortunately, despite all efforts, the study was less than 5% of target enrollment since first patient first visit. Based on current timelines, the study would be unable to meet its scientific objectives within a projected timeline. As a result, a decision was made to close the study. It is important to note that there is no change to the understanding of the safety profile of nivolumab in combination with BCG for the participants with bladder cancer.

As of 02-Jun-2021 (Dear Investigator Letter; Approved v1.0 930170267), the following measures were put into effect:

- Enrollment for new participants was closed effective immediately.
- Participants who signed study consent prior to this notification and were undergoing screening were permitted to be randomized to study treatment.
- Participants currently on treatment were allowed to continue study treatment.
- For participants currently on efficacy follow-up, it is at the discretion of the investigator and participant whether to continue the efficacy follow-up, until Protocol Amendment 01 is approved by the relevant Health Authorities and Ethics Committees/Institutional Review Boards at the site.

Protocol Amendment 01 describes the modification to study procedures. All participants must be re-consented upon approval and implementation of Protocol Amendment 01. These changes affect all participants and should be implemented when this Protocol Amendment 01 is implemented at the site.

Key changes in Protocol Amendment 01 include:

- Details of closure of the study, with provision for participants currently on treatment to continue.
- Clarification that all pharmacokinetic, biomarker, patient-reported outcomes, and health care resource utilization assessments are no longer applicable per Protocol Amendment 01.
- Clarification that study-related efficacy assessment and Pathology Review Committee are no longer applicable per Protocol Amendment 01. Sites should continue efficacy assessment as per local standards of care.

The changes instituted in Protocol Amendment 01 should override any existing protocol requirements in the event of any apparent contraindications.

Study Hypothesis:

Not applicable per Protocol Amendment 01:

Treatment of high-risk persistent or recurrent NMIBC that is not classified as BCG unresponsive with systemically administered nivolumab in combination with intravesical BCG will result in improvement in EFS when compared with intravesical BCG alone.

Study Population:

This study will enroll eligible adult participants (male and female, ages 18 years or age of majority, and older) with high-risk NMIBC that is persistent or recurrent after treatment with BCG and does not qualify as BCG unresponsive.

Key Inclusion Criteria:

- Histologically confirmed persistent or recurrent high-risk non-muscle-invasive urothelial carcinoma (UC) (high-grade [HG] Ta [TaHG] and/or T1 and/or CIS)
- Predominant histologic component (> 50%) must be urothelial (transitional cell) carcinoma
- Persistent or recurrent disease ≤ 24 months of last BCG dose, but not classified as BCG unresponsive
- Eastern Cooperative Oncology Group (ECOG) performance status 0-2
- Participants with multiple prior diagnoses of NMIBC which may have been treated with BCG or other intravesical therapy, that preceded the qualifying episode and associated recurrence are permitted
- Must have undergone each of the following procedures within 90 days of randomization. If these procedures are performed as part of the participant's routine care, they do not need to be repeated provided that they were performed within the required time period:
    - Complete excision of all papillary disease (T1/TaHG)
    - Resection or fulguration of all detectable CIS, if feasible
    - The presence of any suspicious lesions must be recorded and these lesions will be biopsied.
    - Urine cytology must be obtained from a voided specimen (except from the first morning urination) or by bladder wash.
    - Computed Tomography (CT) scan of the chest and CT or MRI of the abdomen, pelvis, and all other areas of suspected disease < 90 days prior to randomization
    - Pelvic examination, preferably under anesthesia to exclude locally advanced disease

Patients who have received less than adequate BCG as defined here (ie, only 1 course of induction BCG ± 1 additional BCG dose) cannot be considered BCG unresponsive (except patients with disease within 6 months of induction BCG therapy). T1 patients are eligible for the study if they have recurrence 6-24 months after the last BCG dose.

Key Exclusion Criteria:

- UC in the upper genitourinary tract (kidneys, renal collecting systems, ureters) within 24 months of enrollment
- UC and/or CIS in the prostatic urethra within 12 months of enrollment
- Previous or concurrent muscle invasive, locally advanced, or disseminated/metastatic UC
- Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-cytotoxic T-lymphocyte-associated protein 4 antibody, or any other antibody or drug specifically targeting T-cell costimulation or checkpoint pathways
- Recurrent high-risk NMIBC that is classified as BCG unresponsive:
    - Persistent or recurrent CIS alone or with recurrent Ta/T1 (noninvasive papillary disease/tumor invades the subepithelial connective tissue) disease within 12 months of completion of adequate BCG therapy**

- Recurrent TaHG/any T1 disease within 6 months of completion of adequate BCG therapy**
- T1HG disease < 6 months following an induction BCG course (at least 5 of 6 induction doses)
  - *** Adequate BCG treatment is defined as at least 2 courses of BCG. This can include 2 induction courses (at least 5 of 6 doses of an initial induction course plus at least 2 of 6 doses of a second induction course) or 1 induction course (at least 5 of 6 induction doses) and at least 2 of 3 doses of a maintenance cycle ("5+2").*

- Prior systemic chemotherapy or immunotherapy for UC. Intravesical chemotherapy and/or interferon administered prior to the current recurrence or as a single dose at the time of TURBT is permitted.
- Prior radiation therapy for bladder cancer
- Prior surgery for bladder cancer other than TURBT and/or bladder biopsies

Objectives and Endpoints:

Objectives and endpoints are no longer applicable per Protocol Amendment 01.

As of Protocol Amendment 01, only descriptive safety and investigator-assessed efficacy analyses will be conducted. No other analyses of efficacy, quality of life/patient-reported outcomes, pharmacokinetics, or health care resource utilization are planned. Previously collected biomarker samples may be analyzed, but no further collections are planned with Protocol Amendment 01.

Objectives	Endpoints
Primary	
• To compare the **EFS** per PRC of nivolumab plus BCG vs BCG alone in all randomized participants	• **EFS**, defined as the time from randomization until any of the following events: recurrence (TaHG, T1 or CIS) or progression of disease, or death from any cause. For participants with CIS (+/- papillary disease) at study entry, a lack of complete response of the CIS component at the 13-week assessment will be considered an event.
Secondary	
• To compare the **WFS** of nivolumab plus BCG vs BCG alone in all randomized participants	• **WFS,** defined as the time from randomization to progression to muscle invasive disease, cystectomy, systemic chemotherapy, radiotherapy, or death from any cause.
• To compare the **OS** of nivolumab plus BCG vs BCG alone in all randomized participants	• **OS**, defined as the time from randomization to death from any cause.
• To evaluate the **CRR** at first disease assessment (week 13) in all randomized participants with CIS (+/- papillary disease) at study entry by treatment arm (nivolumab plus BCG and BCG alone)	• **CRR**, defined as the proportion of participants with CIS (+/- papillary disease) at study entry who are disease free at the first disease assessment.
• To evaluate the duration of response (**DoR**) in all randomized participants with CIS (+/- papillary disease) at study entry who achieved CRR at first disease assessment by treatment arm (nivolumab plus BCG and BCG alone)	• **DoR** is restricted to participants with CIS (+/- papillary disease) at study entry who are disease free at the first disease assessment and is defined as the time between the date of the first CR to the date of

Objectives	Endpoints
	first documented recurrence, progression, or death due to any cause.
• To describe the safety and tolerability of nivolumab plus BCG and BCG alone in all treated participants	• Overall safety and tolerability will be measured by the incidence of AEs, SAEs, AEs leading to discontinuation, IMAEs, deaths, and laboratory abnormalities and changes from baseline.

Overall Design:

- This is a Phase 3, randomized, double-blind, international, multicenter study of nivolumab in combination with BCG vs nivolumab-placebo with BCG in adult patients with high-risk NMIBC that is persistent or recurrent after treatment with BCG and does not qualify as BCG unresponsive.
- Participants are assigned 1 of 2 treatment groups (Arm A and Arm B). Treatment assignment is based on 3 stratification factors used in randomization:
  1. Disease status per PRC:
     i) CIS (+/- papillary disease)*
     ii) T1 (+/- TaHG)*
     iii) TaHG only
  2. Time from last dose of BCG until NMIBC high risk recurrence per investigator:
     i) early recurrence* (for participants enrolled with CIS, early recurrence is defined as any recurrence within 12 months after last BCG dose; for participants enrolled without CIS, early recurrence is defined as any recurrence within 6 months after last BCG dose)
     ii) late recurrence (for participants enrolled with CIS, late recurrence is defined as any recurrence occurring more than 12 months after last BCG dose; for participants enrolled without CIS, late recurrence is defined as any recurrence occurring more than 6 months after last BCG dose)
  3. Intended BCG strain:
     i) TICE
     ii) Other

* Participants enrolled with T1 recurrence within 6 months of last BCG dose will be excluded from the randomization, per eligibility criteria, as they are considered as BCG unresponsive.

Number of Participants:

Prior to Protocol Amendment 01, it was expected that approximately 700 participants would be randomized in a 1:1 ratio to 1 of 2 treatment arms.

As of 02-Jun-2021, enrollment into this study was closed.

Not applicable per Protocol Amendment 01:

Assuming a 20% screen failure rate, it is estimated that approximately 875 participants with persistent or recurrent high-risk NMIBC after prior BCG treatment will be enrolled. It will take approximately 20.5 months to randomize 700 participants in the study.

The sample size is based on a comparison of the EFS distribution between participants randomized to receive nivolumab plus BCG and participants randomized to receive nivolumab-placebo plus BCG.

Treatment Arms and Duration:

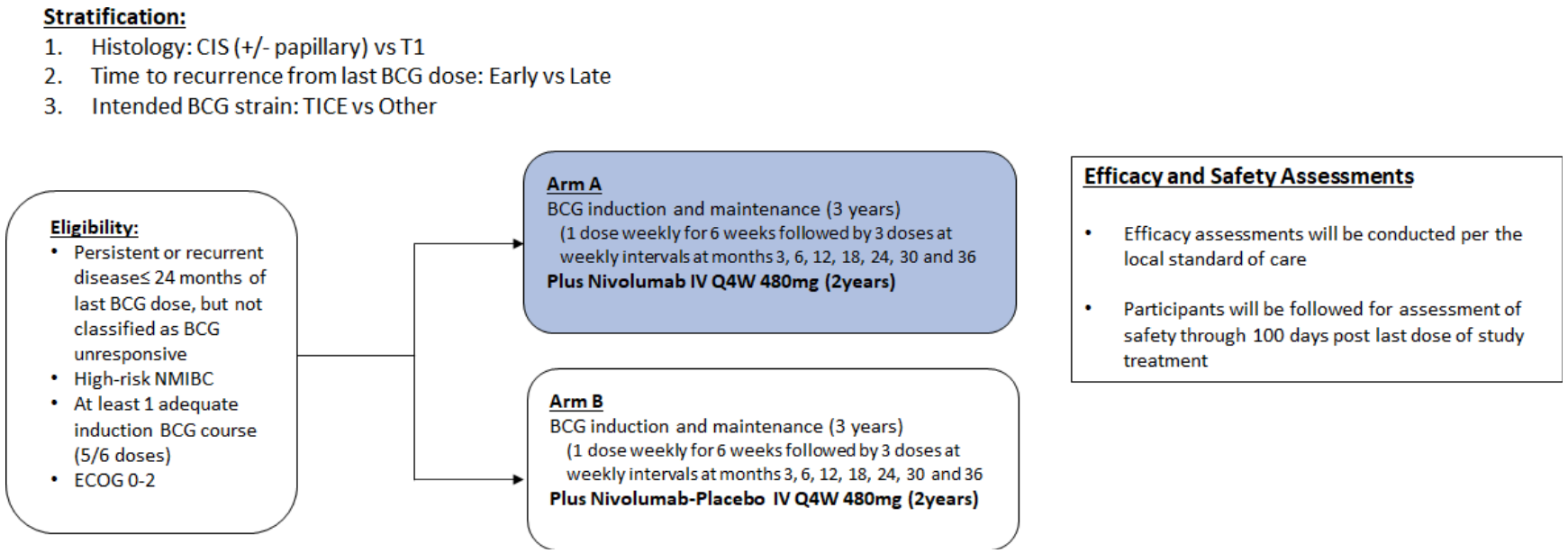
Study Treatments for CA2097G8		
Medication	**Potency**	**IP/Non-IP**
BMS-936558 (Nivolumab) Solution for Injection	10 mg/mL	IP
BCG[a]	Various per BCG strain	IP
0.9% Sodium Chloride for Injection	n/a	IP
5% Dextrose for Injection	n/a	IP

n/a=not applicable

[a] This product may be obtained by the investigational sites as local commercial product in certain countries as allowed by local regulations. These products should be prepared/stored/administered in accordance with the package insert or the Summary of Product Characteristics.

The study schematic is presented in **Figure 1.**

Figure 1: **CA2097G8 Study Design Schematic**



During the **treatment phase**:

- Participants will receive:
    - Arm A: **Nivolumab 480 mg intravenous (IV)** every 4 weeks (Q4W) for up to 24 months (104 weeks) and intravesical BCG (induction) weekly for 6 weeks followed by maintenance intravesical BCG weekly for 3 weeks at 3, 6, 12, 18, 24, 30, and 36 months
    - Arm B: **Nivolumab-placebo IV** Q4W for up to 24 months (104 weeks) and intravesical BCG (induction) weekly for 6 weeks followed by maintenance intravesical BCG weekly for 3 weeks at 3, 6, 12, 18, 24, 30, and 36 months

- The dose of BCG used for each weekly intravesical treatment will be based on current prescribing information for the particular BCG strain and preparation administered. This may vary as BCG strain and/or preparation administered may vary based on geographic region. BCG will be given at full dose.
- For each arm, 1 treatment cycle equals 4 weeks.

Per Protocol Amendment 01, participants are permitted to continue on study treatment. The treatment period will end when the participant is discontinued from the last dose of study treatment (nivolumab/nivolumab-placebo or BCG) or completes 3 years of study treatment.

Nivolumab/nivolumab-placebo may be delayed (withhold dose) or permanently discontinued. Participants who require delay should be re-evaluated weekly or more frequently if clinically indicated and resume dosing when re-treatment criteria are met. There will be no dose escalations or reductions of nivolumab/nivolumab-placebo allowed. Administration of nivolumab/nivolumab-placebo should not be delayed if BCG treatment is delayed.

BCG can be delayed, modified, or discontinued for BCG-related toxicity. Administration of BCG should not be delayed if nivolumab/nivolumab-placebo treatment is delayed.

The **follow-up phase** will begin when the decision to discontinue a participant from the last study treatment is made or when 3 years of study treatment has been completed. There will be a standard safety follow-up for a minimum of 100 days after last dose of last study treatment.

Not applicable per Protocol Amendment 01:

Survival follow-up begins after safety follow-up, with visits every 3 months until the end of the study. Efficacy assessments will occur until disease recurrence (other than low-grade Ta) or progression per PRC (based on a positive urinary cytology, bladder biopsy, or imaging) or treatment discontinuation, whichever is later.

Data Monitoring Committee: Yes; however, no longer applicable per Protocol Amendment 01

References:

[1] US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research. BCG-unresponsive non-muscle invasive bladder cancer: Developing drugs and biologics for treatment guidance for industry. February 2018 (Accessed June 18, 2019).

[2] Steinberg RL, Thomas LJ1, Mott SL, O'Donnell MA. Bacillus Calmette-Guérin (BCG) treatment failures with non-muscle invasive bladder cancer: A data-driven definition for BCG unresponsive disease. Bladder Cancer 2016;2(2):215-24.

2 SCHEDULE OF ACTIVITIES

Table 2-1: Screening Procedural Outline (CA2097G8)–*Not Applicable per Protocol Amendment 01*

Procedure	Screening Visit	Notes[a] (All windows are based on calendar days)
Eligibility Assessments		
Informed Consent	X	Register in Interactive Response Technology (IRT) system to obtain participant number. Informed consent must be obtained prior to any study procedure, except for those done as part of routine clinical practice including, but not limited to, cystoscopy, urine cytology, transurethral resection of the bladder tumor (TURBT), or cross-sectional imaging. Study allows for re-enrollment of a participant who has discontinued participation as a pretreatment failure. If re-enrolled, the participant must be re-consented and assigned a new participant number from IRT.
Inclusion/Exclusion Criteria	X	Must be confirmed prior to randomization.
Medical History	X	All medical history relevant to the disease under study, which includes concomitant medications, prior cancer therapy, and American Joint Committee on Cancer stage. Also include smoking history (including electronic cigarettes) and alcohol history.
Tumor Sample Submission (Bladder Biopsy)[b]	X	Participants with CIS should have bladder mapping at baseline (see Section 9.1.5) by random biopsy or by fluorescence cystoscopy with biopsy of all areas of abnormality. If bladder mapping is not performed at baseline, this must be performed at Week 26 (± 5 week). For participants with clinical stage T1 disease, a repeat TURBT is required within approximately 8 weeks after the initial TURBT to confirm complete resection of disease and to ensure that no tumor has invaded the muscularis propria of the bladder prior to randomization.
Cystoscopy	X	See Section 9.1.3.
Urine Cytology[b]	X	Sample will be reviewed by PRC prior to randomization. See Section 9.1.4.
Body Imaging	X	Contrast enhanced computed tomography (CT) of the chest, contrast-enhanced CT/magnetic resonance imaging (MRI) of the abdomen and pelvis (including excretory imaging) and all other known/suspected sites of disease should be performed during screening within 90 days prior to randomization. Options for participants with contraindications to intravenous (IV) contrast are delineated in the protocol. See Section 9.1.7.

Table 2-1: Screening Procedural Outline (CA2097G8)–*Not Applicable per Protocol Amendment 01*

Procedure	Screening Visit	Notes[a] (All windows are based on calendar days)
Other Imaging	X	As clinically indicated (see Section 9.1.7).
Biomarker Sampling		
Not applicable per Protocol Amendment 01.		
Safety Assessments		
Targeted Physical Examination, Measurements, Vital Signs and Performance Status	X	Height, weight, Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) (Appendix 6), blood pressure, heart rate, and temperature must be collected within 14 days prior to randomization.
Electrocardiogram (ECG)	X	ECGs should be recorded after the participant has been supine for at least 5 minutes.
Assessment of Signs and Symptoms	X	Must be performed within 14 days prior to randomization.
Concomitant Medication Use	X	Must be collected within 14 days prior to randomization. Record vaccine use within 30 days prior to randomization.
Serious Adverse Event (SAE) Assessment	X	SAE collection from time of consent. All AEs (SAEs or non-serious AEs) associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection collected from time of consent.
Laboratory Tests		
Complete Blood Count (CBC) with Differential, Chemistry, Endocrine, Viral, Urinalysis	X	All testing, except viral, must be performed within 14 days prior to randomization. Viral testing must be within 28 days prior to randomization. For human immunodeficiency virus (HIV): testing at sites where locally mandated; see Appendix 7. Refer to Section 9.4.4 for list of laboratory tests to conduct.
Pregnancy Test (WOCBP Only)	X	Serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [HCG]) to be done at screening visit and within 24 hours of first dose of study treatment.

[a] Some of the assessments referred to in this section may not be captured as data in the case report form (CRF). They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

[b] Complete instructions on collecting, processing, handling, and shipment of samples will be provided in a separate lab manual.

Table 2-2: On-treatment Procedural Outline for Arms A and B (CA2097G8)

Procedure[a]	Arm A: Nivolumab 480 mg IV Q4W Plus Intravesical BCG Arm B: Nivolumab-placebo IV Q4W Plus Intravesical BCG		
	Nivolumab/Nivolumab-placebo Visits[b] **Cycle 1 – Cycle 26** **(Day 1 ± 3 days)** **(1 Cycle = 4 Weeks)**	**BCG Visits[b,c]** **(± 3 days)**	**Notes[d]**
Study Treatment			
Randomize	X	X	Participant will be randomized via IRT to Arm A or Arm B.
Dispense Study Drug	X	X	First dose should be administered within 3 calendar days following randomization, but no earlier than ≥ 14 days following last TURBT/bladder biopsy. Nivolumab/nivolumab-placebo will be administered at Day 1 of each cycle. Bacillus Calumette-Guerin (BCG) will be administered as described in footnote "c."
Safety Assessments			
Targeted Physical Examination, Measurements, Vital Signs, Performance Status	X		For each cycle, weight, ECOG PS, blood pressure, heart rate, and temperature within 3 calendar days prior to dosing. For Cycle 1 Day 1 and beyond, targeted physical examination to be performed only as clinically indicated.
Adverse Event (AE) Assessment (Including SAE)	Continuously		Record at each visit. Collect continuously throughout the treatment period and for a minimum of 100 days following the last dose of study treatment. All AEs (SAEs or non-serious AEs), including those associated with SARS-CoV-2 infection, must be collected continuously during the treatment period. Participants will be followed for all SAEs and non-serious AEs of special interest (as defined in Section 9.2). All AEs (SAEs and non-serious AEs)

Table 2-2: On-treatment Procedural Outline for Arms A and B (CA2097G8)

Procedure[a]	Arm A: Nivolumab 480 mg IV Q4W Plus Intravesical BCG Arm B: Nivolumab-placebo IV Q4W Plus Intravesical BCG		
	Nivolumab/Nivolumab-placebo Visits[b] **Cycle 1 – Cycle 26** **(Day 1 ± 3 days)** **(1 Cycle = 4 Weeks)**	**BCG Visits[b,c]** **(± 3 days)**	**Notes[d]**
			associated with confirmed or suspected SARS-CoV-2 infection will be followed until: • Resolution • Condition stabilizes • Event is otherwise explained • Event is deemed irreversible • Participant is lost to follow-up (as defined in Section 8.3) • For suspected cases, until SARS-CoV-2 infection is ruled out See Section 9.2 for additional information on collection of AEs and SAEs.
Concomitant Medication Use	Continuously		Record at each visit.
Laboratory Tests			
CBC with Differential, Chemistry Panel Thyroid Testing	X		Must be performed within 72 hours prior to nivolumab dosing. Refer to Section 9.4.4 for list of laboratory tests. Thyroid testing to be performed every 8 weeks (2 cycles).
Urinalysis		X	Performed prior to dosing at visits BCG is administered. Microscopic analysis required for abnormal dipstick urinalysis or clinical symptoms suggestive of urinary tract infection. A urine culture should be sent if there is suspicion of a urinary tract infection.
Pregnancy Test (WOCBP Only)	X		Serum or urine within 24 hours prior to first dose and then every 4 weeks (± 1 week) regardless of dosing schedule.

Table 2-2: On-treatment Procedural Outline for Arms A and B (CA2097G8)

Procedure[a]	Arm A: Nivolumab 480 mg IV Q4W Plus Intravesical BCG Arm B: Nivolumab-placebo IV Q4W Plus Intravesical BCG		
	Nivolumab/Nivolumab-placebo Visits[b] **Cycle 1 – Cycle 26** **(Day 1 ± 3 days)** **(1 Cycle = 4 Weeks)**	**BCG Visits[b,c]** **(± 3 days)**	**Notes[d]**
Efficacy Assessments			
Not applicable per Protocol Amendment 01. Sites should continue efficacy assessments as per local standards of care.			
Imaging Assessments			
Body Imaging	See Notes		Contrast-enhanced CT of the chest, contrast-enhanced CT/MRI of the abdomen and pelvis (including excretory imaging) and all other known/suspected sites of disease. Imaging will be performed, per local standards of care,every 52 weeks (± 4 weeks) from randomization, as described in Section 9.1.7, or at the discretion of the investigator due to symptoms, to exclude disease progression, or to exclude UC in the upper urinary tracts.
Other Imaging			As clinically indicated (see Section 9.1.7).
Health Outcomes			
Not applicable per Protocol Amendment 01.			
Biomarker Sampling			
Not applicable per Protocol Amendment 01.			
Pharmacokinetic (PK) and Immunogenicity			
Not applicable per Protocol Amendment 01.			

[a] If a dose is delayed, the procedures scheduled for that same time point (except efficacy assessments) should also be delayed to coincide with when that time point's dosing actually occurs.

[b] Where possible, BCG can be administered on the same visits as nivolumab/nivolumab-placebo and assessments for both study treatments can be combined.

[c] Participants in the study will receive one induction course of BCG (6 doses - 1 dose weekly for 6 weeks) followed by maintenance BCG for a total of 3 years treatment. Maintenance dosing includes 3 doses of BCG at weekly intervals at months 3, 6, 12, 18, 24, 30, and 36 (see Table 7.1.2-1 for dosing detail by week). BCG dose will be administered ± 3 days of nivolumab/nivolumab-placebo dosing (with a minimum of 5 days between BCG doses). BCG treatment should not be given within 14 days after TURBT/bladder biopsy. Fourteen days is the minimum requirement; BCG can be delayed greater than 14 days after TURBT/bladder biopsy based on routine clinical practice. BCG administration is independent of nivolumab/nivolumab-placebo cycles and study visits, however, where possible, BCG can be administered on the same visits as nivolumab/nivolumab-placebo, in which case assessments for both study treatments can be combined.

[d] Some of the assessments referred to in this section may not be captured as data in the CRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

Table 2-3: Follow-up Procedural Outline (CA2097G8)

Procedure	Follow-up[a] (FU) Visits 1 and 2	***Not applicable per Protocol Amendment 01*** **Survival Follow-up**[b]	***Not applicable per Protocol Amendment 01*** **Efficacy Follow-up**	Notes[c]
Safety Assessments				
Targeted Physical Examination, Measurements, Vital Signs, and Performance Status	See note			Weight, ECOG PS, blood pressure, heart rate, and temperature, to be performed only as clinically indicated.
Adverse Events Assessment (Including Serious Adverse Events)	X	See Notes	See Notes	Record at each visit. All SAEs and non-serious AEs should be collected continuously during the treatment period and for a minimum of 100 days following discontinuation of study treatment. Participants will be followed for all SAEs, non-serious AEs of special interest (as defined in Section9.2), and all AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection until: • Resolution • Condition stabilizes • Event is otherwise explained • Event is deemed irreversible

Table 2-3: Follow-up Procedural Outline (CA2097G8)

Procedure	Follow-up[a] (FU) Visits 1 and 2	***Not applicable per Protocol Amendment 01*** **Survival Follow-up**[b]	***Not applicable per Protocol Amendment 01*** **Efficacy Follow-up**	Notes[c]
				• Participant is lost to follow-up (as defined in Section 8.3) • For suspected cases, until SARS-CoV-2 infection is ruled-out See Section 9.2 for additional information on collection of AEs and SAEs.
Concomitant Medication Assessment	X			Record at each visit.
Subsequent Bladder Cancer Treatment and Disease Assessment	X	X		To include cystectomy, radiotherapy, systemic chemotherapy, and progression.
Survival Status	X	X		Every 3 months after FU visit 2; may be accomplished by site visit or phone contact.
Laboratory Tests				
CBC with Differential, Chemistry Panel, Thyroid Testing	FU visit 1 - yes FU visit 2 - only if toxicities are present			Refer to Section 9.4.4 for full list of laboratory tests.

Table 2-3: Follow-up Procedural Outline (CA2097G8)

Procedure	Follow-up[a] (FU) Visits 1 and 2	***Not applicable per Protocol Amendment 01*** Survival Follow-up[b]	***Not applicable per Protocol Amendment 01*** Efficacy Follow-up	Notes[c]
Pregnancy (WOCBP Only)	X	See Notes	See Notes	Serum or urine pregnancy testing is only required at FU visit 1 and 2, unless increased frequency and duration is required per local regulations.
Imaging Assessments				
Not applicable per Protocol Amendment 01. Sites should continue imaging assessments as per local standards of care.				
Efficacy Assessments				
Not applicable per Protocol Amendment 01. Sites should continue efficacy assessments as per local standards of care.				
Health Outcomes				
Not applicable per Protocol Amendment 01.				
PK and Immunogenicity Assessments				
Not applicable per Protocol Amendment 01.				

[a] FU visit 1 should occur 30 days from the last dose (± 7 days) of the last dose of study treatment or can be performed on the date of discontinuation if that date is greater than 42 days from the last dose. FU visit 2 occurs approximately 100 days (± 7 days) from last dose of study treatment. See Section 5.1.3. Both follow-up visits should be conducted in person.

[b] ***Not applicable per Protocol Amendment 01.*** Survival follow-up visits to occur every 3 months (± 14 days) from FU visit 2. Survival visit may be conducted in person or by telephone. Survival follow-up visits may coincide with efficacy follow-up visits (see below). BMS may request that survival data be collected on all treated participants outside of the 3-month specified window. At the time of such request, each participant will be contacted to determine their survival status unless the participant has withdrawn consent for all contact.

[c] Some of the assessments referred to in this section may not be captured as data in the CRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

3 INTRODUCTION

CA2097G8 is a randomized, double-blind, Phase 3 trial of nivolumab or nivolumab-placebo in combination with intravesical bacillus Calumette-Guerin (BCG) in participants with recurrent or persistent high-risk non-muscle-invasive bladder cancer (NMIBC) after treatment with BCG who are not BCG unresponsive. Nivolumab is an immuno-oncologic checkpoint inhibitor that enhances T-cell anti-tumor activity. BCG treatment results in tumor inflammation, with the potential result of improved response to the combination of BCG and nivolumab.

The study aims to demonstrate that treatment with nivolumab in combination with intravesical BCG will improve event-free survival (EFS) vs intravesical BCG alone. Additional clinical endpoints include worsening-free survival (WFS), complete response rate (CRR) in participants with carcinoma in situ (CIS), and overall survival (OS). Additional objectives of the study include characterization of safety and tolerability, pharmacokinetics (PK), potential predictive biomarkers, and changes in patient-reported outcomes (PROs) for quality of life (QoL) assessment.

3.1 Study Rationale

Individually targeting immune checkpoint receptors such as programmed cell death protein-1 (PD-1) has demonstrated clinical activity across multiple tumor types, including advanced urothelial carcinoma (UC), for which several studies to date have demonstrated activity of therapeutic compounds aimed at the PD-1 receptor and its ligand, programmed cell death-ligand 1 (PD-L1).[1,2,3]

In high-risk NMIBC, the standard of care (SOC) is transurethral resection of the tumor followed by intravesical BCG treatment. As BCG results in tumor inflammation and nivolumab enhances T-cell activity within the tumor, combining BCG with nivolumab may result in the potential for improved response of the tumor to immunotherapy.

3.1.1 Changes per Protocol Amendment 01

As of May-2021, the CA2097G8 study was behind its enrollment target. Bristol-Myers Squibb (BMS) undertook several mitigation actions to improve participant recruitment. Unfortunately, despite all efforts, the study was less than 5% of target enrollment since first patient first visit. Based on current timelines, the study would be unable to meet its scientific objectives in this evolving therapeutic landscape. As a result, a decision was made to close the study. It is important to note that there is no change to the understanding of the safety profile of nivolumab in combination with BCG for the participants with bladder cancer.

As of 02-Jun-2021 (Dear Investigator Letter; Approved v1.0 930170267), the following measures were put into effect:

- Enrollment for new participants was closed effective immediately.
- Participants who signed study consent prior to this notification and were undergoing screening were permitted to be randomized to study treatment.
- Participants on treatment were allowed to continue study treatment.

- For participants currently on efficacy follow-up, it is at the discretion of the investigator and participant whether to continue the efficacy follow-up, until Protocol Amendment 01 is approved by the relevant Health Authorities and Ethics Committees/Institutional Review Boards (EC/IRBs) at the site.

Protocol Amendment 01 describes the modification to study procedures. All participants must be re-consented upon approval and implementation of Protocol Amendment 01. These changes affect all participants and should be implemented when this Protocol Amendment 01is implemented at the site.

Key changes in Protocol Amendment 01 include:

- Details of closure of the study, with provision for participants currently on treatment to continue.
- Clarification that all pharmacokinetic (PK), biomarker, patient-reported outcomes, and health care resource utilization assessments are no longer applicable per Protocol Amendment 01.
- Clarification that study-related efficacy assessment and Pathology Review Committee (PRC) are no longer applicable per Protocol Amendment 01. Sites should continue efficacy assessment as per local standards of care.

Additionally, dose modification criteria and immuno-oncology (I-O) agent management algorithms were updated per the current National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version (v5).

The changes instituted in Protocol Amendment 01 should override any existing protocol requirements in the event of any apparent contraindications.

3.1.2 Study Hypothesis

Not applicable per Protocol Amendment 01:

Treatment of high-risk persistent or recurrent NMIBC that is not classified as BCG unresponsive with systemically administered nivolumab in combination with intravesical BCG will result in improvement in EFS when compared with intravesical BCG alone.

3.2 Background

3.2.1 Indication Background

Bladder cancer is the ninth most common cancer worldwide, with nearly 430,000 new cases diagnosed in 2012.[4,5] Bladder cancer ranks as the fifth most commonly diagnosed noncutaneous solid malignancy in the US, estimated to account for 79,000 new cases and almost 17,000 deaths in 2017.[6] Bladder cancer is more common in men than in women, with a ratio of approximately 3:1.[6,7] The majority of cases are UC, with mixed or variant histologies (such as squamous cell carcinoma, adenocarcinoma, micropapillary carcinoma, or neuroendocrine carcinoma) comprising a smaller subset.[8]

Approximately 75% to 80% of all bladder cancers present as superficial, non-muscle-invasive disease, while the remaining 20% to 25% are muscle invasive or metastatic at the time of presentation.[9] NMIBCs are confined to either the mucosal lining or lamina propria of the bladder, not yet having penetrated into the muscular bladder wall (muscularis propria).[7] Initial treatment for patients with NMIBC includes transurethral resection of the bladder tumor (TURBT). This procedure is therapeutic in that the entire tumor is removed if feasible, and it is also prognostic in that it allows for accurate clinical staging and grading of the tumor. The need for subsequent therapy after TURBT is based on several well-described clinical and pathological risk factors for disease recurrence and progression that can be determined based on endoscopic examination of the bladder and pathologic evaluation of the tumor specimen. These risks factors include tumor grade, stage, size, multiplicity, recurrence rate, and the presence or absence of CIS.[7] These risk factors have been used to create 3 clinical risk groupings (ie, low, intermediate, and high), which may assist clinicians and patients in determining prognosis and the need for additional therapy after TURBT. High-risk NMIBC includes any high-grade (HG) papillary Ta tumor (TaHG), any grade T1 tumor, and/or the presence of CIS.[7]

Following the initial report of its successful use in bladder cancer patients,[10] intravesical BCG became the SOC as adjuvant treatment for patients with high-risk NMIBC after TURBT. Multiple studies and meta-analyses have demonstrated that a 6-week induction course of intravesical BCG followed by maintenance treatment for 3 years of BCG treatment significantly decreases the risk of bladder tumor recurrence and progression in patients with high-risk NMIBC when compared with no additional treatment or treatment with intravesical chemotherapy.[7,11,12,13,14,15] Despite the recognized benefit of BCG treatment in this patient population, tumor recurrence and progression within 5 years following BCG induction and maintenance is common, occurring in 40% to 80% (recurrence) and 25% to 45% (progression) of patients.[16,17,18,19] While some patients will respond to a second induction course, for patients with persistent NMIBC, treatment with BCG beyond 2 induction courses does not have any additional clinical benefit.[20]

Treatment options for patients with recurrence after initial treatment for high-risk NMIBC with BCG therapy depend on a variety of factors, including timing of recurrence, amount of previous BCG exposure, and stage of disease. Recurrent NMIBC may be suitable for further treatment with BCG, or may be considered BCG unresponsive.

A consensus definition of BCG unresponsive NMIBC has been developed to specifically define the population of patients who will no longer benefit from further BCG treatment (see Section 6.2.1).[21,22] Treatment for patients with high-risk NMIBC that is BCG unresponsive remains a challenge. Therapeutic options include radical cystectomy or single/combination agent chemotherapy. The prognosis of this group of patients remains poor, and ongoing studies[23,24] are addressing this unmet need.

The SOC for patients with high-risk NMIBC who have persistent or recurrent disease after BCG (either induction treatment alone or induction and maintenance treatment with BCG) that is not BCG unresponsive is TURBT followed by retreatment with BCG induction and maintenance.

Patients with recurrence of high-risk NMIBC have a worse prognosis than those with a new diagnosis. [25] Outcomes of patients with persistent or recurrent disease that is not BCG unresponsive have not been studied specifically given the recent standardization of this diagnostic categorization. However, available evidence suggests the rate of recurrence in this group of patients may be estimated at approximately 40% at 24 months.[26]

The natural history of NMIBC is that patients may have repeated episodes of disease recurrence and treatment with resection with or without intravesical treatment, dependent on the risk category. Repeated episodes of disease require tumor resection and intravesical therapy. Patients may become BCG unresponsive and require more aggressive surgery (radical cystectomy), or may progress to un-resectable/metastatic disease and require chemotherapy.

The morbidity and mortality from radical cystectomy is significant, including a 31% perioperative complication rate, a 21% readmission rate, and a 1%-3% mortality rate following the procedure.[27] Despite this procedure's potentially curative intent, radical cystectomy is not performed in approximately 50% of indicated patients due to reasons that include advanced age, comorbid conditions, or patient refusal[28] and in those patients, treatment options are limited with significant unmet medical need.

For patients who do progress to metastatic disease, the prognosis is poor, and responses to standard platinum based chemotherapy regimens generally are short-lived; the median survival of patients with metastatic disease is approximately 14 - 15 months.[29]

Patients with persistent/recurrent high-risk NIMIBC after treatment with BCG are at higher risk of further recurrence/progression, and are therefore more frequently require radical cystectomy or progress to un-resectable/metastatic disease. New treatment options for persistent/recurrent high-risk NMIBC should reduce or delay subsequent recurrence or progression and therefore the requirement for cystectomy and the occurrence of metastatic disease. The addition of nivolumab with BCG may augment the immunological effect of BCG and provide additional clinical benefit vs BCG alone address this unmet need.

3.2.2 Nivolumab Mechanism of Action

Nivolumab (also referred to as BMS-936558, MDX1106, or ONO-4538) 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.[30] 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.

OPDIVO™ (nivolumab) is approved for the treatment of several types of cancer in multiple regions including the United States (US, Dec-2014), the European Union (EU, Jun-2015), and Japan (Jul-2014).

3.2.3 BCG Mechanism of Action

Although the exact mechanism of action is unknown, the anti-tumor effects of BCG appear to be T-lymphocyte dependent. When administered intravesically to treat bladder cancer, BCG produces a local acute inflammatory reaction and a subacute granulomatous reaction that involves macrophage and lymphocyte infiltration in the mucosal bladder lining (urothelium) and lamina propria of the bladder.

Evidence to date suggests that cells of the immune system, as well as bladder cancer cells themselves, have important roles in the anti-tumor effect of intravesical BCG.[31] Requirements for effective BCG therapy include an intact immune system, live BCG, and close contact between cancer cells and BCG. BCG's anti-tumor activity appears to be mediated through activation of the immune system and induction of an inflammatory response that includes an influx of immune cells into the bladder wall and release of a wide range of cytokines and chemokines that appear in the urine of BCG-treated patients. CD4+ cells predominate in the urine and bladder mucosa after BCG treatment. However, CD8+ cells are required for effective treatment and natural killer cells, granulocytes, and macrophages are also important constituents of the cellular response to BCG. BCG treatment results in a massive release of cytokines into the urine, including IL-1, IL-2, IL-5, IL-6, IL-8, IL-10, IL-12, IL-18, tumor necrosis factor (TNF), IFN-γ, granulocyte-macrophage colony-stimulating factor (GM-CSF) and TNF-related apoptosis-inducing ligand. Studies also support a role of BCG in the maturation of dendritic cells by signaling through toll-like receptors and secretion of inflammatory cytokines such as IL-12, IFN-γ, and TNF-α.[32]

Both bladder cancer cells and benign urothelial cells appear to play a role in the initial recognition and processing of BCG.[31] Bladder cancer cell attachment to BCG is mediated through fibronectin, leading to BCG internalization and subsequent secretion of immune-activating effectors by cancer cells including IL-6, IL-8, GM-CSF, and TNF. Bladder cancer cells also may function as antigen-presenting cells for BCG, and BCG may have direct cytotoxic effects on bladder cancer cells.

For additional information on the mechanism of action of live BCG (intravesical), see the current prescribing information (Summary of Product Characteristics [SmPC], United States [US] Prescribing Information [USPI], or country-specific label).

3.3 Benefit/Risk Assessment

There is significant unmet need in patients who have persistence or recurrence of high-risk NMIBC that is not BCG unresponsive. New therapies are required to reduce the rate of recurrence, cystectomy, and progression to metastatic disease.

There is evidence for the efficacy of nivolumab in UC and proof of concept for PD-1 inhibition in NMIBC:

- In metastatic UC, nivolumab as monotherapy has received accelerated approval in the US for the treatment of patients with locally advanced or metastatic UC who have had disease progression during or following platinum-containing chemotherapy or who have had disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. It has received approval in the EU for the treatment of locally advanced unresectable or metastatic UC in adults after failure of prior platinum-containing therapy. See the current prescribing information for nivolumab (Opdivo®) for more information.
- In NMIBC, preliminary evidence of clinical activity of PD-1 inhibition comes from study Keynote-057, a single-arm study of pembrolizumab in BCG-unresponsive NMIBC.[26] In the interim analysis of this study, the response rate of CIS participants treated with pembrolizumab monotherapy was 39% at Month 3, with 80.2% of participants having a CR duration of ≥ 6 month.[33] The safety profile was consistent with the profile of pembrolizumab across tumor types. These data are clinically significant in a group of participants for whom there are no effective intravesical or systemic treatment options, and cystectomy is the SOC.

In addition, the safety profile of both nivolumab and BCG are both well characterized.

Extensive details on the safety profile of nivolumab are available in the Investigator's Brochure (IB) and will not be repeated herein.

Overall, the safety profile of nivolumab monotherapy is manageable and generally consistent across completed and ongoing clinical trials with no maximum tolerated dose (MTD) reached at any dose tested up to 10 mg/kg. Most adverse events (AEs) were low grade (Grade 1 to 2) with relatively few related high-grade (Grade 3 to 4) AEs. There was no pattern in the incidence, severity, or causality of AEs with respect to nivolumab dose level.

A pattern of immune-mediated AEs (IMAEs) has been defined, for which management algorithms have been developed; these are provided in Appendix 5. Most high-grade events were manageable with the use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in these algorithms.

Additional details on the safety profile of nivolumab, including results from other clinical studies, are also available in the nivolumab IB.

The incidence and pattern of BCG-related adverse effects are well characterized and are presented in the current prescribing information.

The safety and tolerability of nivolumab in combination with intravesical BCG is currently unknown. BMS study CA2099UT[23] is examining the combination of nivolumab with BCG in participants with BCG unresponsive high-risk NMIBC. At the time of protocol writing, the first 8 participants treated with nivolumab plus BCG in study CA2099UT have passed the dose-limiting toxicity evaluation period and been reviewed by the Data Monitoring Committee (DMC) (data on file, May 2019). The study is continuing unchanged.

To ensure an ongoing favorable benefit/risk assessment for participants enrolled into the present study, the following safety measures will be employed throughout the conduct of the study:

- Institution of an external DMC to provide independent oversight of safety, study conduct, and benefit/risk assessment of nivolumab in combination with BCG
- Rigorous safety monitoring by BMS to ensure participants' safety, including regular and systematic review of safety data, close follow-up of reported AEs, and intensive site and study investigator training/education on the implementation of the nivolumab and BCG toxicity management strategies

4 OBJECTIVES AND ENDPOINTS

Objectives and endpoints are no longer applicable per Protocol Amendment 01.

As of Protocol Amendment 01, only descriptive safety and investigator-assessed efficacy analyses will be conducted. No other analyses of efficacy, quality of life/patient-reported outcomes, PK, or health care resource utilization are planned. Previously collected biomarker samples may be analyzed, but no further collections are planned with Protocol Amendment 01.

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Primary	
• To compare the **EFS** per PRC of nivolumab plus BCG vs BCG alone in all randomized participants	• **EFS**, defined as the time from randomization until any of the following events: recurrence (TaHG, T1 or CIS) or progression of disease, or death from any cause. For participants with CIS (+/- papillary disease) at study entry, a lack of complete response of the CIS component at the 13-week assessment will be considered an event.
Secondary	
• To compare the **WFS** of nivolumab plus BCG vs BCG alone in all randomized participants	• **WFS,** defined as the time from randomization to progression to muscle invasive disease, cystectomy, systemic chemotherapy, radiotherapy, or death from any cause.
• To compare the **OS** of nivolumab plus BCG vs BCG alone in all randomized participants	• **OS**, defined as the time from randomization to death from any cause.
• To evaluate the **CRR** at first disease assessment (Week 13) in all randomized participants with CIS (+/- papillary disease) at study entry by treatment arm (nivolumab plus BCG and BCG alone)	• **CRR**, defined as the proportion of participants with CIS (+/- papillary disease) at study entry who are disease free at the first disease assessment.
• To evaluate the duration of response (**DoR**) in all randomized participants with CIS (+/- papillary disease) at study entry who achieved CRR at first disease assessment by treatment arm (nivolumab plus BCG and BCG alone)	• **DoR** is restricted to participants with CIS (+/- papillary disease) at study entry who are disease free at the first disease assessment and is defined as the time between the date of the first CR to the date of first documented recurrence, progression, or death due to any cause.
• To describe the safety and tolerability of nivolumab plus BCG and BCG alone in all treated participants	• Overall safety and tolerability will be measured by the incidence of AEs, SAEs, AEs leading to discontinuation, IMAEs, deaths, and laboratory abnormalities and changes from baseline.

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Tertiary/Exploratory	
• To evaluate the cystectomy-free survival (**CFS**) in all randomized participants by treatment arm (nivolumab plus BCG and BCG alone)	• **CFS**, defined as the time from randomization to cystectomy or death from any cause
• To evaluate the progression-free survival (**PFS**) per PRC in all randomized participants by treatment arm (nivolumab plus BCG and BCG alone)	• **PFS**, defined as the time from randomization to progression to muscle invasive or metastatic disease (T2+) of disease or death from any cause
• To evaluate disease specific survival (**DSS**) in all randomized participants by treatment arm (nivolumab plus BCG and BCG alone)	• **DSS,** defined as the time from randomization to death from UC
• To evaluate **best overall CRR**, as well as **CRR at Week 26, at Week 52, and at Week 104** in all randomized participants with CIS (+/- papillary disease) at study entry by treatment arm (nivolumab plus BCG and BCG alone)	• **Best overall CRR**, defined as the proportion of participants with CIS (+/- papillary disease) at study entry who achieve disease free at any disease assessment during study treatment. • **CRR at different time points**, defined as the proportion of participants with CIS (+/- papillary disease1) at study entry who are disease free at each of the specified disease assessment time points (ie, Week 26, Week 52, and Week 104).
• To assess the participant's cancer-related symptoms and quality of life	• Change in subscales of the EORTC QLQ-C30 • Change in subscales of the EORTC QLQ-NMIBC24
• To evaluate the participant's overall health status and utility for health	• Change in scores in both the EQ-5D-5L visual analog scale and the utility index
• To identify biomarkers that predict clinical efficacy	• Correlation of selected biomarkers with (EFS and PFS) and safety (incidence of AEs) endpoints
• To characterize nivolumab PK and immunogenicity in combination with BCG	• PK parameters, immunogenicity, exposure-response (E-R) relationships between select PK measures of exposure and safety and efficacy endpoints, if applicable

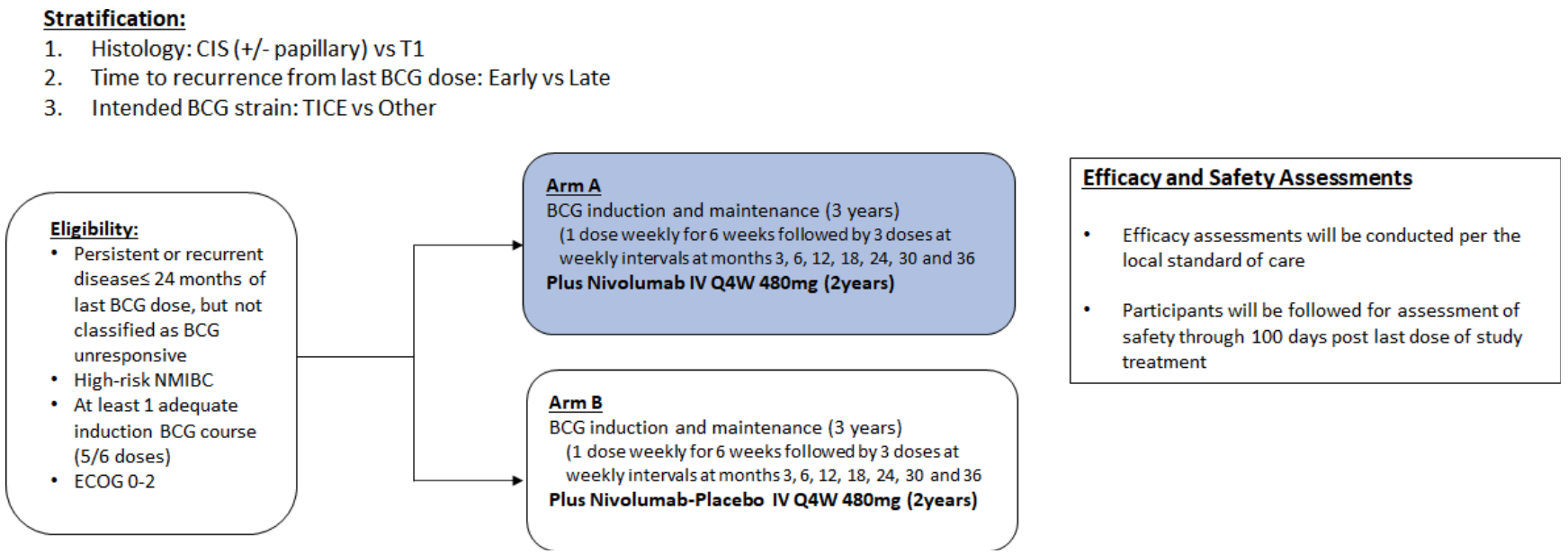
5 STUDY DESIGN

5.1 Overall Design

This is a Phase 3, randomized, double-blind, international, multicenter study of nivolumab in combination with BCG vs nivolumab-placebo with BCG in adult participants with high-risk NMIBC that is persistent or recurrent after treatment with BCG and does not qualify as BCG unresponsive.[21]

The study design schematic is presented in Figure 5.1-1.

Figure 5.1-1: CA2097G8 Study Design Schematic



The study will proceed through 3 phases: screening, treatment, and follow-up.

As of 02-Jun-2021, enrollment into this study was closed. Protocol Amendment 01 removes the decision points and the efficacy follow-up along with other study procedures. As a result, initial benefit/risk assessment by the Data Monitoring Committee (DMC) and PRC will be removed.

5.1.1 Screening Phase

As of 02-Jun-2021, enrollment into this study was closed. Therefore, the screening phase is no longer applicable per Protocol Amendment 01.

Not applicable per Protocol Amendment 01:

Screening begins by establishing the participant's initial eligibility and signing of the informed consent form (ICF). All screening tests must be completed as per the inclusion criteria (Section 6.1) and the time and events table (Section 2 Table 2-1). This includes complete excision of all papillary disease or CIS (if feasible) and biopsy of all suspicious lesions, urine cytology, and appropriate imaging of the chest, abdomen and pelvis. Screening tests that were performed as part of SOC do not need to be repeated.

Representative diagnostic pathology slides, obtained at TURBT within 90 days prior to randomization, which can be used to confirm the diagnosis of high-risk NMIBC and exclude the presence of tumor invasion into the muscularis propria, must be available. Tumor tissue samples (1-10 hematoxylin and eosin [H&E] stained slides), with at least one slide containing muscularis propria, preferably from the area of the bladder with the greatest disease burden, must be sent to independent Pathology Review Committee (PRC) for review. Confirmation of diagnosis by the PRC is required for randomization.

Sufficient, recent tumor tissue obtained within 90 days prior to randomization from the bladder tumor tissue obtained at TURBT (formalin-fixed paraffin-embedded block or 20 slides) will be submitted to the analytical laboratory for determination of PD-L1 expression and for biomarker studies. If less than 15 slides are available, please contact the Medical Monitor for discussion. Confirmation of receipt of acceptable tumor tissue by the analytical laboratory is required prior to randomization.

If sufficient tissue is not available within 90 days prior to randomization, then the site will be asked for additional tissue or a repeat TURBT will be required.

If tissue for diagnosis or biomarker assessment was obtained > 70 days prior to randomization, a repeat cystoscopy is required ≤ 70 days prior to randomization to ensure there is no recurrent disease. See Section 9.1.5 for further details.

Participants may not have received any systemic or intravesical anticancer therapy after the date that the submitted tumor tissue was obtained, with the exception of a single dose of intravesical chemotherapy at the time of TURBT. For participants with CIS, bladder mapping must be performed with random biopsy or with florescence cystoscopy with biopsy of all areas suspicious for disease.

Participants will be assessed for complete study eligibility prior to randomization as specified in Table 2-1.

The screening phase ends with either confirmation of full eligibility and randomization of the participant or with the confirmation that the patient is a screen failure. This study permits reenrollment of a participant who discontinued the study as a pretreatment failure prior to randomization. If reenrolled, the participant must be reconsented. A new participant identification number will be assigned by the Interactive Response Technology (IRT) at the time of reenrollment.

5.1.2 Treatment Phase

The treatment phase begins with the randomization of the participant in the IRT system. The participant is randomly assigned to 1 of the 2 treatment arms as noted in the study schematic.

Stratification factors for randomization will include: disease status per PRC; time from last dose of BCG to recurrence per investigator; and intended BCG strain. Full details can be found in Section 5.2.

During the treatment phase, participants will receive:

- Arm A: **Nivolumab 480 mg intravenous (IV)** every 4 weeks (Q4W) for up to 24 months (104 weeks) and intravesical BCG (induction) weekly for 6 weeks followed by maintenance intravesical BCG weekly for 3 weeks at 3, 6, 12, 18, 24, 30, and 36 months (see Table 7.1.2-1)
- Arm B: **Nivolumab-placebo IV** Q4W for up to 24 months (104 weeks) and intravesical BCG (induction) weekly for 6 weeks followed by maintenance intravesical BCG weekly for 3 weeks at 3, 6, 12, 18, 24, 30, and 36 months (see Table 7.1.2-1)

For each arm, 1 treatment cycle equals 4 weeks. Day 1 of Cycle 1 will be the first dose of either study treatment.

The dose of BCG used for each weekly intravesical treatment will be based on current prescribing information for the particular BCG strain and preparation administered. This may vary as BCG strain and/or preparation administered may vary based on geographic region in which the participant is receiving treatment. Sites are required to declare which BCG strain they intend to use during the screening period for the purposes of stratification. BCG will be given at full dose, unless the dose is reduced due to lower urinary tract symptoms whilst on study (see Section 7.4.2).

For all participants, follow local standards of care for efficacy assessments.

5.1.3 Follow-up Phase

The follow-up phase will begin when the decision to discontinue a participant from the last study treatment is made (no further study treatment) or when 3 years of study treatment has been completed (eg, a participant may be discontinued from nivolumab/nivolumab-placebo study treatment on or before 24 months but remains on maintenance BCG study treatment for 36 months [see Sections 5.4.4 and 5.4.5]).

Participants must be followed for at least 100 days after last dose of last study treatment.

- Follow-up (FU) visit 1 should occur 30 days from the last dose (± 7) days or can be performed on the date of discontinuation if that date is greater than 42 days from the last dose.
- FU visit 2 occurs approximately 100 days (± 7 days) from last dose of study treatment.
- Both visits should be conducted in person.

Not applicable per Protocol Amendment 01:

Survival follow-up begins after FU visit 2.

- Survival follow-up visits occur every 3 months (± 14 days) until the end of the study.

Not applicable per Protocol Amendment 01:

Efficacy follow-up:

- Efficacy assessments occur until disease recurrence (other than low-grade Ta) or progression, per PRC (based on a positive urinary cytology, bladder biopsy, or imaging), or treatment discontinuation, whichever is later.
- For participants who have not had PRC confirmed progression or recurrence during the on-treatment period, efficacy assessments will continue as per Table 2-3 and Section 9.1.8.
- Where scheduling allows, efficacy follow up and survival follow up can coincide.

Treatment beyond disease recurrence/progression is not permitted except in the case of a low-grade papillary Ta tumor (TaLG) UC recurrence only, or for participants with CIS and/or Ta at Week 13 (see Section 8.1.4).

5.1.4 Data Monitoring Committee and Other External Committees

Not applicable per Protocol Amendment 01:

An independent, external DMC will be established to provide oversight of safety and efficacy considerations in this protocol and to provide advice to the Sponsor regarding actions the committee deems necessary for the continued protection of participants enrolled in the study. The DMC will be charged with assessing such actions in light of an acceptable benefit/risk profile for nivolumab and nivolumab-placebo plus BCG. The DMC will act in an advisory capacity to BMS and will monitor participant safety and evaluate the available efficacy data for the study. Data and summaries will be made available to the DMC. The BMS Oncology Clinical Development Department has primary responsibility for design and conduct of the study.

Additional details concerning DMC oversight are provided in the DMC charter.

Pathology Review Committee

Not applicable per Protocol Amendment 01:

An independent PRC will review cystoscopy reports, imaging reports, participant biopsy slides, and urinary cytology obtained prior to randomization to confirm the diagnosis of high-risk

NMIBC. Similarly, on-study cystoscopy and imaging reports, biopsies, and urine cytology will be submitted to the PRC to exclude or confirm recurrence or progression.

Additional details concerning PRC responsibilities are provided in the PRC charter and in Section 9.1.8.

5.2 Number of Participants

Prior to Protocol Amendment 01, it was expected that approximately 700 participants would be randomized in a 1:1 ratio to receive nivolumab with BCG vs nivolumab-placebo with BCG and stratified by the following 3 factors:

1. Disease status per PRC:
   a) CIS (+/- papillary disease)[a]
   b) T1 (+/- TaHG)[a]
   c) TaHG only
2. Time from last dose of BCG until NMIBC high risk recurrence per investigator:
   a) early recurrence [a] (for participants enrolled with CIS, early recurrence is defined as any recurrence within 12 months after last BCG dose; for participants enrolled without CIS, early recurrence is defined as any recurrence within 6 months after last BCG dose)
   b) late recurrence (for participants enrolled with CIS, late recurrence is defined as any recurrence occurring more than 12 months after last BCG dose; for participants enrolled without CIS, late recurrence is defined as any recurrence occurring more than 6 months after last BCG dose)
3. Intended BCG strain:
   a) TICE
   b) Other

[a] Participants enrolled with T1 recurrence within 6 months of last BCG dose will be excluded from the randomization, per eligibility criteria 2d Section 6.1, as they are considered as BCG unresponsive (defined in Section 6.2.1).

As of 02-Jun-2021, enrollment into this study was closed.

Not applicable per Protocol Amendment 01:

Assuming a 20% screen failure rate, it is estimated that approximately 875 participants with persistent or recurrent high-risk NMIBC after prior BCG treatment will be enrolled using the following enrollment assumptions: up to 3 randomized participants for the first 2 months, 9 randomized participants per month for Month 3 and 4, 19 randomized participants per month for Month 5 and 6, 24 randomized participants per month for Month 7 and 8, 38 randomized participants per month for Month 9 and 10, 43 randomized participants per month for Month 11 and 12, 48.5 randomized participants per month from Month 13 to 16, and 53 randomized participants per month thereafter.

Based on the above information, it will take approximately 20.5 months to randomize 700 participants in the study.

Details regarding sample size calculation are found in Section 10.1.

5.3 End of Study Definition

As of 02-Jun-2021, enrollment into this study was closed; therefore, study completion will be when all participants complete study procedures described in Section 2, including safety visits.

The start of the trial is defined as the first participant's first visit. End of trial is defined as the last participant's last study visit or scheduled procedure shown in the Schedule of Activities. Primary completion is defined as the final date on which data for the primary endpoint was or is expected to be collected, if this is not the same. (Primary completion date is detailed in Section 10.1.) Study completion is defined as the final date on which data for the last efficacy analysis, as per hierarchical procedure defined in Sections 10.1 and 10.3.1, was or is expected to be collected, if this is not the same.

5.4 Scientific Rationale for Study Design

5.4.1 Rationale for the Combination of Nivolumab with BCG in NMIBC

Immune checkpoint inhibitors such as nivolumab target pathways used by cancer cells to evade immune system attack. Such pathways may be important in recurrent NMIBC as evidenced by the association between PD-L1 expression and higher bladder cancer stage, and by the high levels of PD-L1 expression in the BCG granulomata of those failing prior BCG treatment.[34] Thus, elevated PD-L1 expression may be one possible mechanism by which bladder cancer cells evade treatment.

Previous studies in participants with advanced UC suggest that tumors with an immune-inflamed (associated with high CD8+ infiltration) or immune-suppressed phenotype may have better response to immunotherapies, including checkpoint inhibitors, than tumors with an immune-desert phenotype.[35] BCG appears to have a role in the recruitment of CD4+ and CD8+ lymphocytes into the bladder wall,[31] augmenting the inflamed phenotype of a particular bladder tumor and potentially making it more susceptible to treatment with a checkpoint inhibitor such as nivolumab.

These findings suggest that the balance between CD8+ cytotoxic T-cells and negative immune regulatory elements in the microenvironment of a bladder tumor may be critical in determining the host's overall immune response and ultimate clinical outcome. An avid local immune response within the bladder that results from BCG treatment may improve response to anti-PD1 therapy, while anti-PD1 therapy with nivolumab may help to overcome tumor-associated immunosuppression that mitigates the effectiveness of BCG treatment in BCG-unresponsive tumors. This provides a strong rationale for combining nivolumab with BCG in patients with NMIBC.

5.4.2 Rationale for Event-free Survival as Primary Endpoint

Not applicable per Protocol Amendment 01:

EFS is the primary endpoint for this study, defined as the time from randomization until any of the following events: recurrence (TaHG, T1, or CIS) or progression of disease or death from any cause. For participants with CIS (with or without papillary disease) at baseline, a lack of complete response of the CIS component at the 13-week assessment will be considered an event.

This endpoint has been selected in order that all participants in the study can be evaluated by 1 single primary endpoint. Because of the frequent co-existence of CIS and papillary disease, a single primary endpoint ensures that the papillary component can be evaluated consistently in all study participants. As such, most clinical trials have evaluated high-risk participants with and without CIS together, and clinical practice treats high-risk recurrences similarly whether CIS or non-CIS.[12,23] Given the demonstrated benefit of PD-1 inhibition in CIS NMIBC and in non-CIS metastatic UC[26,33] it is reasonable to assume that benefit would be similar across histological subtypes. Evaluating the CIS and non-CIS population with 1 single endpoint is therefore appropriate.

Although CIS can be removed in some participants by TURBT prior to study entry, it is not possible in all participants with CIS, unlike participants with papillary disease only where disease is expected to be completely removed by TURBT. Participants with CIS therefore pose a challenge with respect to a time-to-event endpoint in which the event is defined solely as recurrence of disease.

Food and Drug Administration (FDA) guidance supports the use of EFS as an endpoint to support registration.[36] In addition, a report from an FDA/American Urological Association (AUA) public workshop provides insight into trial design (including assessment of appropriate clinical endpoints) for the development of new therapies for patients with high-risk NMIBC. [37] This workshop supports the approach of including a mix of patients with CIS and non-CIS in the study population, and using a time-to-event endpoint including failure to achieve complete response (CR) in patients with CIS and recurrence in patients with CIS or papillary disease[37] as events. These guidances support the definition of EFS and its use as a single primary endpoint in this study.

5.4.3 Rationale for Stratification Factors

Patients with high-risk NMIBC have CIS, T1, or TaHG disease, or a combination of these. Although the high-risk category defines patients who are generally considered to be at higher risk for recurrence, the risk is not uniform within the group, and T stage is a key determinant of prognosis with CIS and T1 both having a significantly higher risk than TaHG.[7,18] For this reason, tumor stage is included as a stratification factor. This approach also facilitates the analysis of CR in CIS patients as a secondary endpoint.

The time from the initial diagnosis of high-risk NMIBC to recurrence is also an important predictor of future recurrence. Retrospective analysis of clinical trial data[26] demonstrate that patients with a

shorter interval to recurrence have a higher risk for subsequent recurrence. The time limit which dichotomizes the population into lower and higher risk groups is tumor stage dependent, and defined as < 6 months or ≥ 6 months in patients with papillary disease only, and < 12 months or ≥ 12 months in patients with CIS (with or without papillary disease). This classification aligns with the definition for BCG unresponsive disease (see Section 6.2.1), which is a central clinical concept on which this study is based.

Different strains of BCG are used as SOC in varying regions, with some countries having more than one strain approved. There are no conclusive data showing a difference in efficacy or safety between available strains, although there is an ongoing non-inferiority trial comparing the TICE and Tokyo-172 strains in BCG-naive patients.[38] As the TICE strain is widely used globally and is the only strain approved in many countries, stratification by BCG strain (TICE vs other) will be used to ensure balance between the arms.

5.4.4 Rationale for 2-year Duration of Treatment

The optimal duration of immunotherapy in NMIBC is currently unknown. Because immunotherapy engages the immune system to control the tumor, continuous treatment as is required with targeted agents or cytotoxic therapy may not be necessary.

In the adjuvant setting, the standard approach across the nivolumab development program is to treat with 1 year of nivolumab. This approach has demonstrated efficacy in the setting of advanced melanoma,[39] where 1 year of treatment with adjuvant nivolumab following resection was superior to ipilimumab treatment.

In this study, nivolumab is utilized to augment the immune response in the bladder of participants who have recurrence following BCG treatment. Participants are treated with up to 3 additional years of BCG (see Section 5.4.5) in accordance with evidence-based SOC. In order to increase the potential for synergy with BCG, nivolumab will therefore be given for 2 years with BCG. This will ensure that the susceptibility of the BCG inflamed phenotype to PD-1 inhibition is harnessed through a sufficient duration of the BCG course to optimize clinical benefit.

5.4.5 Rationale for Duration of BCG Treatment

The SOC globally for high-risk NMIBC patients with recurrence of disease who are not bacillus Calumette-Guerin (BCG) unresponsive globally is induction and maintenance BCG therapy, given according to the SWOG 8507 protocol.[12] This protocol forms the basis of guidance from the AUA[7] and European Association of Urology (EAU).[18]

Participants in the study will receive 1 induction course of BCG (6 doses = 1 dose weekly for 6 weeks) followed by maintenance BCG according to this schedule for a total of 3 years treatment. Maintenance dosing includes 3 doses of BCG at weekly intervals at Month 3, 6, 12, 18, 24, 30, and 36. This equals a total of 27 doses of BCG over 3 years. (See Section 7.1.2 and Table 7.1.2-1 for dosing details.)

5.4.6 Rationale for Double-blind Study Design

The study will be double-blind and placebo controlled. This approach will minimize bias in evaluation of study endpoints, including the primary study endpoint of EFS, which is dependent on investigator-assessed findings at cystoscopy in addition to central PRC of urine cytology and histologic analysis of biopsy/excision specimens. Additionally, blinding is particularly important for accurately assessing quality of life with PROs, which is a key exploratory objective of the study.

Participants in the control arm will be administered a placebo dose of nivolumab every 4 weeks. This will ensure that follow-up visits occur with equal frequency in the experimental and control arms, and hence minimize bias in the evaluation of AE frequency between arms.

Individual participant unblinding is permitted upon documentation of recurrence or progression in order to make informed decisions about future treatment (see Section 7.3).

5.5 Justification for Dose

5.5.1 Justification for Nivolumab Dose

A nivolumab dose of 480 mg given Q4W was selected for this study based on available PK, safety, and efficacy data.

Nivolumab PK has been extensively studied in multiple tumor types, including melanoma, non-small-cell lung cancer (NSCLC), renal cell carcinoma (RCC), classical Hodgkin lymphoma, SCCHN, colorectal cancer, and UC, and has been safely administered at doses up to 10 mg/kg every 2 weeks (Q2W). Nivolumab monotherapy was originally approved as a body-weight based dose of 3 mg/kg Q2W and was recently updated to 240 mg Q2W or 480 mg Q4W in multiple indications.[40,41] Less frequent 480 mg Q4W dosing regimens can reduce the burden to patients of frequent, lengthy IV treatments and allow combination of nivolumab with other agents using alternative dosing regimens.

The benefit/risk profiles of nivolumab 240 mg Q2W and 480 mg Q4W are predicted to be comparable to 3 mg/kg Q2W. This assessment is based on a comprehensive characterization of nivolumab PK, safety, efficacy, and exposure-response (E-R) relationships across indications. Population PK (PPK) analyses have shown that the PK of nivolumab is linear with proportional exposures over a dose range of 0.1 to 10 mg/kg; no clinically meaningful differences in PK across ethnicities and tumor types were observed. Using the PPK model, the exposures following administration of several dosing regimens of nivolumab administered as a flat dose were simulated, including 240 mg Q2W and 480 mg Q4W. The simulated average serum concentration at steady state following administration of nivolumab 480 mg Q4W are predicted to be similar to those following administration of nivolumab 240 mg Q2W and nivolumab 3 mg/kg Q2W administered to participants over a wide body weight range (34 to 180 kg) across tumor types.

Extensive E-R analyses of multiple PK measures (maximum serum concentration at Day 1, average serum concentration at Day 28 [Cavg28], and trough serum concentration at Day 28 [Cmin28]) and efficacy and safety endpoints indicated that the efficacy of the flat-dose 480 mg IV regimen are similar to that of 3 mg/kg Q2W IV regimen. In E-R efficacy analyses for OS and

objective response rate (ORR) conducted in melanoma, RCC, and NSCLC using Cavg28 as the exposure measure, probabilities of achieving a response and survival probabilities at 1 year and 2 years for IV 480 mg Q4W were similar to that of IV 3 mg/kg Q2W. In E-R safety analyses, it was demonstrated that the exposure margins for safety are maintained following nivolumab 480 mg Q4W, and the predicted risks of discontinuations due to AEs or death, AE Grade 3+, and IMAEs. Grade 2+ are similar following nivolumab 480 mg Q4W relative to nivolumab 3 mg/kg Q2W across tumor types. In addition, nivolumab exposures with 240 mg Q2W and 480 mg Q4W flat-dose IV regimens across tumor types are maintained well below the corresponding exposures observed with the well-tolerated 10 mg/kg IV nivolumab Q2W dose regimen.

Additional details on nivolumab posologies and benefit/risk can be found in the IB.

5.5.2 Justification for BCG Dose

The appropriate dose and dosing schedule of BCG in combination with systemic immuno-oncology (I-O) agents in BCG relapse is unknown. In this study, BCG is being administered to augment the local immune response in the bladder and to work synergistically with nivolumab in order to overcome potential immune inhibitory mechanisms used by bladder cancer cells to evade the local immune response induced by BCG.

BCG strains used in routine clinical practice vary by geographic location, with different strains currently being utilized in the United States, Europe, and Japan. [42] The dose used for each weekly intravesical BCG treatment will be based on current prescribing information for the particular BCG strain.

6 STUDY POPULATION

As of 02-Jun-2021, enrollment into this study was closed. Male participants continuing treatment should follow the updated contraceptive guidance in Appendix 4.

For entry into the study, the following criteria MUST be met.

6.1 Inclusion Criteria

1) Signed Written Informed Consent

a) Prior to study participation, written informed consent from participants, guardians, or legally acceptable representatives must be obtained according to local laws and regulations (Appendix 2).

b) Participants must be willing and able to comply with scheduled visits, treatment schedule, laboratory testing, and other requirements of the study.

2) Type of Participant and Target Disease Characteristics

a) Histologically confirmed persistent or recurrent high-risk non-muscle-invasive UC (TaHG and/or T1 and/or CIS)

b) Predominant histologic component (> 50%) must be urothelial (transitional cell) carcinoma

c) Treated with at least 1 adequate course of induction BCG therapy (at least 5 out of 6 doses)

d) Persistent or recurrent disease ≤ 24 months of last BCG dose, but not classified as BCG unresponsive (definition in Section 6.2.1)

e) Sufficient tissue for both biomarker analysis and central PRC confirmation of diagnosis (Section 5.1.1)

f) Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-2 (Appendix 6)

g) Participants with multiple prior diagnoses of NMIBC which may have been treated with BCG or other intravesical therapy, that preceded the qualifying episode and associated recurrence, are permitted

h) Must have undergone each of the following procedures within 90 days of randomization. If these procedures are performed as part of the participant's routine care, they do not need to be repeated provided that they were performed within the required time period:

i) Complete excision of all papillary disease (T1/TaHG). For participants with T1 lesions, a restaging TURBT must be performed within 8 weeks after the initial TURBT to ensure papillary disease is fully resected, and the pathology specimen must contain muscularis propria that is free of invasive tumor per PRC.

ii) Resection or fulguration of all detectable CIS, if feasible. Fluorescence-guided cystoscopy is encouraged but not mandated. It is understood that due to the nature of this disease, complete resection of CIS cannot be assured.

iii) The presence of any suspicious lesions must be recorded and these lesions will be biopsied.

iv) Urine cytology must be obtained from a voided specimen (except from the first morning urination) or by bladder wash. Recognizing the possibility of occult CIS, cytology at screening does not need to be negative for study participation.

v) Computed tomography (CT) scan of the chest and CT or MRI of the abdomen, pelvis, and all other areas of suspected disease to exclude locally advanced or metastatic bladder cancer or synchronous UC in the upper urinary tracts within 90 days prior to randomization.

vi) Pelvic examination, preferably under anesthesia to exclude locally advanced disease.

3) Age and Reproductive Status

a) Males and females, ages 18 or age of majority, and older

b) Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [HCG]) within 24 hours prior to the start of study treatment.

c) WOCBP must agree to follow instructions for method(s) of contraception (see Appendix 4) for the duration of treatment with study treatment(s) and for 5 months after the last dose of study treatment (ie, 30 days [duration of ovulatory cycle] plus the time required for nivolumab to undergo approximately 5 half-lives).

d) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception and fetal protection (see Appendix 4) for the duration of treatment with study treatment(s) and 7 months after the last dose of study treatment (ie, 90 days [duration of sperm turnover] plus the time required for nivolumab to undergo approximately 5 half-lives). In addition, male participants must be willing to refrain from sperm donation during this time.

e) WOCBP who are continuously not heterosexually active are also exempt from contraceptive requirements, and still must undergo pregnancy testing as described in this section.

Investigators shall counsel WOCBP, and male participants who are sexually active with WOCBP, on the importance of pregnancy prevention and the implications of an unexpected pregnancy and the potential of fetal toxicity occurring due to transmission of study drug, present in seminal fluid, to a developing fetus, even if the participant has undergone a successful vasectomy or if the partner is pregnant. Investigators shall advise on the use of highly effective methods of contraception (Appendix 4) which have a failure rate of < 1% when used consistently and correctly.

6.2 Exclusion Criteria

1) Medical Conditions

a) Woman who are breastfeeding

b) Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured or not requiring treatment, such as basal or squamous cell skin cancer, prostate cancer with evidence of undetectable prostate specific antigen, low-risk prostate cancer or renal cell cancer < 3 cm under surveillance, or carcinoma in situ of the cervix or breast

c) Patients with serious or uncontrolled medical disorders

d) Participants with an active, known, or suspected autoimmune disease

e) Participants with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

f) Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of start of study treatment. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

g) UC in the upper genitourinary tract (kidneys, renal collecting systems, ureters) within 24 months of enrollment

h) UC and/or CIS in the prostatic urethra within 12 months of enrollment

i) Previous or concurrent muscle invasive, locally advanced, or disseminated/metastatic UC

j) Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-cytotoxic T-lymphocyte-associated protein 4 antibody, or any other antibody or drug specifically targeting T-cell costimulation or checkpoint pathways

k) Recurrent high-risk NMIBC that is classified as BCG unresponsive:

- Persistent or recurrent CIS alone or with recurrent Ta/T1 (noninvasive papillary disease/tumor invades the subepithelial connective tissue) disease within 12 months of completion of adequate BCG therapy**
- Recurrent TaHG/any T1 disease within 6 months of completion of adequate BCG therapy**

- T1HG disease < 6 months following an induction BCG course (at least 5 of 6 induction doses)
  *** Adequate BCG treatment is defined as at least 2 courses of BCG. This can include 2 induction courses (at least 5 of 6 doses of an initial induction course plus at least 2 of 6 doses of a second induction course) or 1 induction course (at least 5 of 6 induction doses) and at least 2 of 3 doses of a maintenance cycle ("5+2").*

l) New York Heart Association (NYHA) functional Classification of Heart Failure: Class III or Class IV

m) Has any contraindication to intravesical BCG therapy, including evidence of active tuberculosis

2) Prior/Concomitant Therapy

a) Prior systemic chemotherapy or immunotherapy for UC. Intravesical chemotherapy and/or interferon administered prior to the current recurrence or as a single dose at the time of TURBT is permitted.

b) Prior radiation therapy for bladder cancer

c) Prior surgery for bladder cancer other than TURBT and/or bladder biopsies

d) Use of an investigational agent within 4 weeks of randomization

e) Participants who have received a live /attenuated vaccine within 30 days of first treatment

f) Treatment with botanical preparations (eg, herbal supplements or traditional Chinese medicines) intended for general health support or to treat the disease under study within 2 weeks prior to randomization/treatment. Refer to Section 7.7.1 for prohibited therapies.

3) Physical and Laboratory Test Findings

a) White blood cells (WBC) < 2000/µL

b) Neutrophils < 1500/µL

c) Platelets < $100*10^3$/µL

d) Hemoglobin < 9.0 g/dL

e) Serum creatinine > 1.5x upper limit of normal (ULN), unless creatinine clearance ≥ 40 mL/min (measured or calculated using the Cockroft-Gault formula)

f) Aspartate aminotransferase (AST)/ alanine aminotransferase (ALT): > 3.0x ULN

g) Total bilirubin > 1.5x ULN (except participants with Gilbert syndrome who must have a total bilirubin level of < 3.0x ULN)

h) Any positive test result for hepatitis B virus or hepatitis C virus indicating presence of virus, eg, Hepatitis B surface antigen (HBsAg, Australia antigen) positive, or hepatitis C antibody (anti-HCV) positive (except if HCV-RNA negative).

i) Known history of positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). NOTE: Testing for HIV must be performed at sites where mandated locally (Appendix 7).

4) Allergies and Adverse Drug Reaction

a) History of allergy or hypersensitivity to study drug components

5) Other Exclusion Criteria

a) Prisoners or participants who are involuntarily incarcerated. (Note: under certain specific circumstances and only in countries where local regulations permit, a person who has been imprisoned may be included or permitted to continue as a participant. Strict conditions apply and BMS approval is required.)

b) Participants who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness

Eligibility criteria for this study have been carefully considered to ensure the safety of the study participants and that the results of the study can be used. It is imperative that participants fully meet all eligibility criteria.

6.2.1 BCG Unresponsive Definition and Patient Eligibility

Patients are eligible for this study if they have persistent or recurrent high-risk NMIBC after treatment with at least 1 induction course of BCG (Section 6.1 [2c]). The recurrence must be ≤ 24 months after the last dose of BCG and not meet the criteria to be classified as BCG unresponsive (Section 6.1 [2d]).

In order to assess a participant's eligibility for the study, the NMIBC recurrence must not meet the Food and Drug Administration (FDA) definition for BCG-unresponsive disease below:[21]

- Persistent or recurrent CIS alone or with recurrent Ta/T1 (noninvasive papillary disease/tumor invades the subepithelial connective tissue) disease within 12 months of completion of adequate BCG therapy**
- Recurrent TaHG/any T1 disease within 6 months of completion of adequate BCG therapy**
- T1HG disease at the first evaluation following an induction BCG course (at least 5 of 6 induction doses)

**Adequate BCG treatment is defined as at least 2 courses of BCG. This can include 2 induction courses (at least 5 of 6 doses of an initial induction course plus at least 2 of 6 doses of a second induction course) or 1 induction course (at least 5 of 6 induction doses) and at least 2 of 3 doses of a maintenance cycle ("5+2").

This definition includes patients who have T1 disease at the first evaluation following induction BCG. The timing of the first disease evaluation following induction BCG may vary due to differences in local clinical practice and individual patient factors. To ensure a consistent approach in this study, the eligibility criteria exclude all patients with T1 disease within 6 months following induction BCG (see Section 6.2).

Patients who have received less than adequate BCG as defined here (ie, only 1 course of induction BCG ± 1 additional BCG dose) cannot be considered BCG unresponsive (except patients with disease within 6 months of induction BCG therapy). T1 patients are eligible for the study if they have recurrence 6-24 months after the last BCG dose.

6.3 Lifestyle Restrictions

Not applicable. No restrictions are required.

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but who are not subsequently randomized in the study/included in the analysis population. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, as applicable, and to respond to queries from regulatory authorities. Minimal information includes date of consent, demography, screen failure details, eligibility criteria, and any serious AEs (SAEs).

6.4.1 Retesting During Screening or Lead-In Period

Participant reenrollment: This study permits the reenrollment of a participant who has discontinued the study as a pretreatment failure (ie, has not been treated). If reenrolled, the participant must be reconsented.

Retesting of laboratory parameters and/or other assessments within any single screening or lead-in period will be permitted (in addition to any parameters that require a confirmatory value).

The most current result prior to Randomization is the value by which study inclusion will be assessed, as it represents the participant's most current, clinical state.

Laboratory parameters and/or assessments that are included in Table 2-1, Screening Procedural Outline, may be repeated in an effort to find all possible well-qualified participants. Consultation with the Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

7 TREATMENT

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo or medical device intended to be administered to a study participant according to the study randomization or treatment allocation.

Study treatment includes both Investigational [Medicinal] Product (IP/IMP) and Noninvestigational [Medicinal] Product (Non-IP/Non-IMP) and can consist of the following:

- Nivolumab
- Nivolumab-placebo, and
- BCG.

An investigational product, also known as investigational medicinal product in some regions, is defined a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as non-investigational products.

Table 7-1: Study Treatments for CA2097G8

Product Description/ Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open Label	Packaging/ Appearance	Storage Conditions (per label)
BMS-936558 (Nivolumab) Solution for Injection	10 mg/mL	IP	Open Label[a]	Vials	Refer to the label on container and/or Pharmacy Manual
BCG[b]	Various per BCG strain	IP	Open Label[a]	Various per BCG strain	As per package insert
0.9% Sodium Chloride for Injection	n/a	IP	Open Label[a]	Various (local commercial product)	As per package insert
5% Dextrose for Injection	n/a	IP	Open Label[a]	Various (local commercial product)	As per package insert

[a] The term "open label" refers to the medication as it is upon receipt at the pharmacy. The trial will be conducted in a double-blinded fashion with respect to the nivolumab/nivolumab-placebo.

b This product may be obtained by the investigational sites as local commercial product in certain countries as allowed by local regulations. These products should be prepared/stored/administered in accordance with the package insert or SmPC.

7.1 Treatments Administered

The selection and timing of dose for each participant is as follows:

Table 7.1-1: Selection and Timing of Dose

Study Treatment	Unit Dose Strength(s)/ Dosage Level(s)	Dosage Formulation Frequency of Administration	Route of Administration
Nivolumab/ Nivolumab-placebo	480 mg (n/a for placebo)	Solution for injection administered every 4 weeks, max treatment duration is 2 years	IV
BCG	Dose according to prescribing information for BCG strain	Refer to Table 2-2	Intravesical

7.1.1 Nivolumab Dosing

Participants should receive nivolumab at a dose of 480 mg as an approximately 30-minute infusion on Day 1 of each treatment cycle until recurrence or progression, unacceptable toxicity, withdrawal of consent, completion of 24 months of treatment, or the study ends, whichever occurs first. If needed, flush the intravenous line with an appropriate amount of diluent (eg, 0.9% Sodium Chloride or 5% Dextrose in water) to ensure that the complete dose is administered over approximately 30 minutes. For participants with CIS and/or TaHG at Week 13 assessment, see Section 8.1.4.

Participants should begin study treatment within 3 calendar days of randomization but no earlier than ≥ 14 days following last TURBT/bladder biopsy. Nivolumab/nivolumab-placebo and BCG should begin concurrently or within 3 days of each other. Cycle 1 will begin at the time of the first dose of study treatment.

There should be a minimum of 26 days between nivolumab/nivolumab-placebo doses. There will be no dose escalations or reductions of nivolumab/nivolumab-placebo allowed. For Q4W dosing cycles, participants may be dosed within a ± 3 day window. Premedications are not recommended for the first dose of nivolumab/nivolumab-placebo.

Participants should be carefully monitored for infusion reactions during nivolumab administration. If an acute infusion reaction is noted, participants should be managed according to Section 7.7.4.

Doses of nivolumab/ nivolumab-placebo may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment. Dosing visits are not skipped, only delayed.

Please refer to the current Investigator Brochure and/or Pharmacy Manual for further details regarding storage, preparation, and administration of nivolumab.

Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

7.1.2 BCG Dosing

Participants should begin study treatment within 3 calendar days of randomization but no earlier than ≥ 14 days following last TURBT/bladder biopsy. BCG and nivolumab/nivolumab-placebo should begin concurrently or within 3 days of each other. Cycle 1 will begin at the time of the first dose of study treatment.

Participants should receive an intravesical instillation of BCG weekly for 6 weeks starting on Day 1 of BCG treatment (induction period) and then weekly for 3 weeks at 3, 6, 12, 18, 24, 30 and 36 months after the first BCG dose (maintenance period) (see Table 7.1.2-1).

Table 7.1.2-1: Timing of Intravesical BCG Maintenance Dose

Time		Weekly BCG Dose (Days)[a] for 3 Weeks
Months	**Week (Wk)**	**Days to Dose**
3	13	Wk 14 (D1), Wk 15 (D1), Wk 16 (D1)
6	26	Wk 27 (D1), Wk 28 (D1), Wk 29 (D1)
12	52	Wk 53 (D1), Wk 54 (D1), Wk 55 (D1)
18	78	Wk 79 (D1), Wk 80 (D1), Wk 81 (D1)
24	104	Wk 105 (D1), Wk 106 (D1), Wk 107 (D1)
30	130	Wk 131 (D1), Wk 132 (D1), Wk 133 (D1)
36	156	Wk 157 (D1), Wk 158 (D1), Wk 159 (D1)[b]

[a] Must be a minimum of 5 days between BCG doses.

[b] Treatment will complete after 3 years and 15 days (± 3 days).

The BCG dose should be prepared and administered according to the package insert. **BCG may be obtained by the investigational sites, where possible/allowed by local regulations**, **as local commercial product in certain countries. These products should be prepared/stored/ administered in accordance with the package insert or SmPC and local practice.**

Typical procedure is as follows:

- A urethral catheter will be inserted into the bladder by a qualified medical professional under aseptic conditions. The bladder will then be drained, after which the BCG suspension will be instilled slowly, under gravity. The catheter will then be withdrawn. BCG should not be given if the urethra is traumatized during catheter insertion or if there is gross hematuria.
- The participant should retain the BCG suspension for as long as possible for up to 2 hours. The participant should lie prone during the first 15 minutes following instillation, after which the participant is allowed to be in the upright position. At the end of 2 hours, the participant should void in the seated position. The participant will be instructed to maintain adequate fluid intake in the hours following BCG treatment to flush the bladder.

Participants should receive BCG until recurrence, progression, unacceptable toxicity, withdrawal of consent by the participant, or completion of 3 years of treatment, whichever occurs first. For participants with CIS and/or TaHG at Week 13 assessment, see Section 8.1.4.

Participants should begin study treatment within 3 calendar days of randomization and at least 14 days after the last bladder tumor resection or bladder biopsy, whichever occurs later (if local standard clinical practice requires longer than 14 days between biopsy and initiation of BCG, this is acceptable). If BCG treatment after the first dose is delayed for any reason, nivolumab/nivolumab-placebo should continue as scheduled, unless the participant has study drug toxicity meeting nivolumab dose delay criteria. If nivolumab is delayed for any reason, BCG treatment should continue as scheduled, unless the participant meets BCG dose delay criteria (eg, study drug toxicity or other reasons including traumatic catheterization/gross hematuria).

For details on prepared drug storage, preparation, and administration, please see the BCG package insert.

7.2 Method of Treatment Assignment

All participants will be centrally randomized using an IRT. Before the study is initiated, each user will receive log-in information and directions on how to access the IRT. After the participant's initial eligibility is established and informed consent has been obtained, the participant must be enrolled into the study by accessing an IRT to obtain the participant number. Every participant who signs the informed consent form must be assigned a participant number in IRT. The investigator or designee will register the participant for enrollment by following the enrollment procedures established by BMS. The following information is required for enrollment:

- Whether informed consent was obtained
- Year of birth
- Gender at birth

Once enrolled in IRT, enrolled participants who have met all eligibility criteria will be ready to be randomized through the IRT. Disease status data will be transferred directly from the PRC. Confirmation of receipt of acceptable tumor tissue for biomarker analysis will be provided by the analytical laboratory. The following information is required for participant randomization:

- Participant number
- Year of birth
- Disease status based on PRC assessment:
    - Presence of CIS[a] (Yes vs No)
    - Presence of T1[a,b] (Yes vs No)
    - Presence of TaHG[a,b,c] (Yes vs No)
- Time from last received BCG dose until high-risk NMIBC recurrence[a,b,c] (≤ 6 months after last BCG dose vs between 6 and ≤ 12 months after last BCG dose vs > 12 months after last BCG dose)
- Intended BCG strain for study treatment (TICE vs other)
- Confirmation of receipt of acceptable tumor tissue by the analytical laboratory

[a] Participants enrolled with CIS (+/- TaHG) will be considered as early recurrence if they have recurrence ≤ 6 months or between 6 and ≤ 12 months after last BCG dose, and will be considered as late recurrence if they have recurrence > 12 months after last BCG dose. Participants enrolled with CIS + T1 will be considered as early recurrence if they have recurrence between 6 and ≤ 12 months after last BCG dose, late recurrence if they have recurrence > 12 months after last BCG dose, and are not eligible if they have recurrence ≤ 6 months after last BCG dose (see also note b).

[b] Participants enrolled with T1 (+/- TaHG) recurrence occurring ≤ 6 months after last BCG dose received will be excluded from the randomization, per eligibility criteria 2d Section 6.1, as they are considered as BCG unresponsive (defined in Section 6.2.1), and will be considered as late recurrence if they have recurrence between 6 and ≤ 12 months or > 12 months after last BCG dose.

[c] Participants enrolled with TaHG only will be considered as early recurrence if they have recurrence ≤ 6 months after last BCG dose, and will be considered as late recurrence if they have a recurrence between 6 and ≤ 12 months or > 12 months after last BCG dose.

Study treatment will be dispensed at the study visits as listed in Schedule of Activities (Section 2).

See Sections 5.1 and 5.1.2 for a description of treatment assignment during the treatment phase of the study.

The exact details for using the IRT will be detailed in the IRT manual.

7.3 Blinding

As of Protocol Amendment 01, it has been determined that blinding is not required. In both scenarios where the investigators may break the blind in the best interest of the participant or in case of accidental unblinding, IRT instructions should be followed along with a notification to the Medical Monitor.

This is a randomized, double-blind study. Access to treatment codes will be restricted from all participants and site and BMS personnel prior to final database lock, with exceptions as specified below. Each investigative site must assign an unblinded pharmacist/designee, and an unblinded site monitor will be assigned to provide oversight of drug supply and other unblinded study documentation.

To further minimize bias, the investigative clinical site staff is masked to results from PD-L1 analysis.

Blinding of treatment assignment is critical to the integrity of this clinical study. However, in the event of a medical emergency or pregnancy in an individual participant in which knowledge of the investigational product is critical to the participant's management, the blind for that participant may be broken by the investigator. The participant's safety takes priority over any other considerations in determining if a treatment assignment should be unblinded.

Before breaking the blind of an individual participant's treatment, the investigator should determine that the unblinded information is necessary, ie, that it will alter the participant's immediate management. In many cases, particularly when the emergency is clearly not related to the investigational product, the problem may be properly managed by assuming that the participant is receiving active product. It is highly desirable that the decision to unblind treatment assignment

be discussed with the Medical Monitor, but the investigator always has ultimate authority for the decision to unblind. The actual TASK of unblinding can be delegated by the investigator to a designee assigned the task on the Delegation of Authority. The Principal Investigator or appointed designee should only call in for emergency unblinding AFTER the decision to unblind the participant has been documented.

For this study, the method of unblinding for emergency purposes is through the IRT. For information on how to unblind in an emergency, consult the IRT manual.

In case of an emergency, the investigator(s) has unrestricted access to randomization information via the IRT and is capable of breaking the blind through the IRT system without prior approval from sponsor. Following the unblinding, the Investigator shall notify the Medical Monitor and/or designee.

In cases of accidental unblinding, contact the Medical Monitor and ensure every attempt is made to preserve the blind.

Any request to unblind a participant for nonemergency purposes should be discussed with the Medical Monitor.

Designated staff of BMS Research & Development (R&D) may be unblinded (obtain the randomization codes) prior to database lock to facilitate the bioanalytical analysis of PK samples and immunogenicity. A bioanalytical scientist in the Bioanalytical Sciences department of BMS R&D (or a designee in the external central bioanalytical laboratory) will be unblinded to (may obtain) the randomized treatment assignments in order to minimize unnecessary bioanalytical analysis of samples.

7.4 Dosage Modification

AE criteria for delaying, resuming, and discontinuing study treatment is provided in Table 7.4-1.

Table 7.4-1: Adverse Event Criteria for Delay, Resume, and Discontinuation of Nivolumab

Drug-related AE per NCI CTCAE v5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Gastrointestinal			
Colitis or Diarrhea	Grade 2	Delay dose	Dosing may resume when AE resolves to baseline
	Grade 3	Nivolumab monotherapy: Delay dose	Dosing may resume when AE resolves to baseline
	Grade 4	Permanently discontinue	
Renal			
Serum Creatinine Increased	Grade 2 or 3	Delay dose	Dosing may resume when AE resolves to Grade ≤ 1 or baseline value
	Grade 4	Permanently discontinue	
Pulmonary			
Pneumonitis	Grade 2	Delay dose	Dosing may resume after pneumonitis has resolved to ≤ Grade 1
	Grade 3 or 4	Permanently discontinue	
Hepatic			
AST, ALT, or TBili increased	AST or ALT > 3× and ≤ 5× ULN or TBili > 1.5× and ≤ 3× ULN, regardless of baseline value	Delay dose	Dosing may resume when laboratory values return to baseline after discussion with the Medical Monitor
	AST or ALT > 5× ULN or TBili > 3× ULN, regardless of baseline value	Delay dose or permanently discontinue	In most cases of AST or ALT > 5× ULN, study treatment will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, a discussion between the investigator and the Medical Monitor/designee must occur and approval must be obtained from Medical Monitor prior to resuming therapy
	Concurrent AST or ALT > 3× ULN and TBili > 2×	Permanently discontinue	

Table 7.4-1: Adverse Event Criteria for Delay, Resume, and Discontinuation of Nivolumab

Drug-related AE per NCI CTCAE v5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
	ULN, regardless of baseline value		
Endocrinopathy			
Adrenal Insufficiency	Grade 2 adrenal insufficiency	Delay dose	Dosing may resume after adequately controlled with hormone replacement
	Grade 3 or 4 adrenal insufficiency or adrenal crisis	Delay dose or permanently discontinue	Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If adrenal insufficiency resolves or is adequately controlled with physiologic hormone replacement, participant may not require discontinuation of study drug
Hyperglycemia	Hyperglycemia requiring initiation or change in daily management (Grade 2 or 3)	Delay dose	Dosing may resume if hyperglycemia resolves to Grade ≤ 1 or baseline value or is adequately controlled with glucose-controlling agents
	Grade 4	Delay dose or permanently discontinue	Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If hyperglycemia resolves or is adequately controlled with glucose-controlling agents, participant may not require discontinuation of study drug
Hypophysitis/Hypopituitarism	Symptomatic Grade 1-3 that is also associated with corresponding abnormal laboratory value and/or pituitary scan	Delay dose	Dosing may resume if endocrinopathy resolves to be asymptomatic or is adequately controlled with only physiologic hormone replacement
	Grade 4	Delay dose or permanently discontinue	Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If endocrinopathy resolves or is adequately controlled with physiologic hormone replacement, participant may not require discontinuation of study drug

Table 7.4-1: Adverse Event Criteria for Delay, Resume, and Discontinuation of Nivolumab

Drug-related AE per NCI CTCAE v5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Hyperthyroidism or Hypothyroidism	Grade 2 or 3	Delay dose	Dosing may resume if endocrinopathy resolves to be asymptomatic or is adequately controlled with only physiologic hormone replacement or other medical management
	Grade 4	Delay dose or permanently discontinue	Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If endocrinopathy resolves or is adequately controlled with physiologic hormone replacement or other medical management, participant may not require discontinuation of study drug
Skin			
Rash	Grade 2 rash covering > 30% body surface area or Grade 3 rash	Delay dose	Dosing may resume when rash reduces to ≤ 10% body surface area
	Suspected Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), or drug reaction with eosinophilia and systemic symptoms (DRESS)	Delay dose	Dosing may resume if SJS, TEN, or DRESS is ruled out and rash reduces to ≤ 10% body surface area
	Grade 4 rash or confirmed SJS, TEN, or DRESS	Permanently discontinue	
Neurological			
Guillain-Barre Syndrome (GBS)	Any Grade	Permanently discontinue	
Myasthenia Gravis (MG)	Any Grade	Permanently discontinue	

Table 7.4-1: Adverse Event Criteria for Delay, Resume, and Discontinuation of Nivolumab

Drug-related AE per NCI CTCAE v5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Encephalitis	Any Grade encephalitis	Delay dose	After workup for differential diagnosis (ie, infection, tumor related), if encephalitis is not drug related, then dosing may resume when AE resolves
	Any Grade drug-related encephalitis	Permanently discontinue	
Myelitis	Any Grade myelitis	Delay dose	After workup for differential diagnosis (ie, infection, tumor related), if myelitis is not drug related, then dosing may resume when AE resolves
	Any Grade drug-related myelitis	Permanently discontinue	
Neurological (other than GBS, MG, encephalitis, or myelitis)	Grade 2	Delay dose	Dosing may resume when AE resolves to baseline
	Grade 3 or 4	Permanently discontinue	
Myocarditis			
Myocarditis	Symptoms induced from mild to moderate activity or exertion	Delay dose	Dosing may resume after myocarditis has resolved
	Severe or life-threatening, with symptoms at rest or with minimal activity or exertion and/or where intervention indicated	Permanently discontinue	
Other Clinical AEs			
Pancreatitis: Amylase or Lipase Increased	Grade 3 with symptoms	Delay dose	Note: Grade 3 increased amylase or lipase without signs or symptoms of pancreatitis does not require dose delay Dosing may resume when participant becomes asymptomatic
	Grade 4	Permanently discontinue	

Table 7.4-1: Adverse Event Criteria for Delay, Resume, and Discontinuation of Nivolumab

Drug-related AE per NCI CTCAE v5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Uveitis	Grade 2 uveitis	Delay dose	Dosing may resume if uveitis responds to topical therapy (eye drops) and after uveitis resolves to Grade ≤ 1 or baseline. If participant requires oral steroids for uveitis, then permanently discontinue study drug
	Grade 3 or 4 uveitis	Permanently discontinue	
Other Drug-related AE (**not listed above**)	Grade 2 non-skin AE, except fatigue	Delay dose	Dosing may resume when AE resolves to Grade ≤ 1 or baseline value
	Grade 3 AE - First occurrence lasting ≤ 7 days	Delay dose	Dosing may resume when AE resolves to Grade ≤ 1 or baseline value
	Grade 3 AE - First occurrence lasting > 7 days	Permanently discontinue	
	Recurrence of Grade 3 AE of any duration	Permanently discontinue	
	Grade 4 or life-threatening adverse reaction	Permanently discontinue	
Other Laboratory Abnormalities			
Other Drug-related Laboratory Abnormality (**not listed above**)	Grade 3	Delay dose	Exceptions: No delay required for: Grade 3 lymphopenia Permanent discontinuation for: Grade 3 thrombocytopenia > 7 days or associated with bleeding
	Grade 4	Permanently discontinue	Exceptions: The following events do not require discontinuation of study drug: • Grade 4 neutropenia ≤ 7 days • Grade 4 lymphopenia or leukopenia • Grade 4 isolated electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are responding to

Table 7.4-1: Adverse Event Criteria for Delay, Resume, and Discontinuation of Nivolumab

Drug-related AE per NCI CTCAE v5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
			supplementation/appropriate management within 72 hours of their onset
Infusion Reactions (Manifested by fever, chills, rigors, headache, rash, pruritus, arthralgia, hypotension, hypertension, bronchospasm, or other allergic-like reactions)			
Hypersensitivity Reaction or Infusion Reaction	Grade 3 or 4	Permanently discontinue	See Section 7.7.4 (Treatment of Infusion-related Reactions)

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DRESS, drug reaction with eosinophilia and systemic symptoms; GBS, Guillain-Barre syndrome; MG, myasthenia gravis; NCI CTCAE v5, National Cancer Institute Common Terminology Criteria for Adverse Events version 5; SJS, Stevens-Johnson syndrome; TBili, total bilirubin; TEN, toxic epidermal necrolysis; ULN, upper limit of normal.

7.4.1 Nivolumab/Nivolumab-placebo Dose Modifications

No dose modifications are permitted for nivolumab/nivolumab-placebo.

7.4.2 BCG Dose Modifications

BCG dose modification due to BCG toxicity (such as dysuria, urinary frequency, urinary urgency, cystitis, and hematuria) is allowed according to local guidelines and standard clinical practice.[43,44,45,46] The reason for dose reduction, and the change of dose, must be clearly documented in the case report form (CRF).

7.4.3 Dose Delay Criteria

7.4.3.1 Nivolumab/Nivolumab-placebo Dose Delay Criteria

Dose delay criteria apply for all drug-related AEs, regardless of whether the event is attributed to nivolumab, placebo, or both. Delay administration of both nivolumab and placebo if any of the delay criteria in Table 7.4-1 are met. Delay nivolumab and placebo dosing for any AE, laboratory abnormality, or intercurrent illness which, in the judgement of the investigator, warrants delaying the dose of study medication.

Delay administration of both nivolumab and placebo in case of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, either confirmed or suspected.

For participants who require delay of nivolumab/nivolumab-placebo, re-evaluate weekly, or more frequently, if clinically indicated and resume dosing when criteria to resume treatment are met (see Section 7.4.4). Continue tumor assessments per protocol even if dosing is delayed.

Administration of BCG should not be delayed if nivolumab/nivolumab-placebo treatment is delayed.

7.4.3.2 BCG Dose Delay Criteria

Administration of BCG should be delayed if the participant develops a concurrent febrile illness, a urinary tract infection (UTI), or gross hematuria during the treatment period and for 14 days after traumatic urinary catheterization or bladder biopsy. In addition, investigators may delay BCG in accordance with clinical judgment and standard local practice. The reason for dose delay must be clearly documented.

Administration of nivolumab/nivolumab-placebo should not be delayed if BCG treatment is delayed.

7.4.4 Criteria to Resume Treatment

7.4.4.1 Nivolumab/Nivolumab-placebo Criteria to Resume Treatment

Participants may resume study treatment if they have completed AE management (ie, corticosteroid taper) or are on ≤ 10 mg prednisone or equivalent and meet the requirements per Table 7.4-1.

- Prior to re-initiating treatment in a participant with a dosing delay lasting > 10 weeks, the Medical Monitor (or designee) must be consulted. Continue tumor assessments per protocol

even if dosing is delayed. Continue periodic study visits to assess safety and laboratory studies every 4 weeks or more frequently if clinically indicated during such dosing delays.

- Participants with SARS-CoV-2 infection (either confirmed or suspected) may resume treatment if all of the following are met:
  - At least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared or positive test result (eg, RT-PCR or viral antigen); and
  - Resolution of acute symptoms (including at least 24 hours has passed since last fever without fever reducing medications); and
  - Evaluation by the Investigator with confirmation that there are no sequelae that would place the participant at a higher risk of receiving investigational treatment; and
  - Consultation with the Medical Monitor or designee. For suspected cases, treatment may also resume if SARS-CoV-2 infection is ruled out and other criteria to resume treatment are met.

7.4.4.2 BCG Criteria to Resume Treatment

BCG administration can resume when the concurrent febrile illness, UTI, or gross hematuria resolve and antibiotic treatment has ended. For other dose delay reasons, BCG can resume in accordance with clinical judgment and standard local practice.

- Participants with SARS-CoV-2 infection (either confirmed or suspected) may resume treatment if all of the following are met:
  - At least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared or positive test result (eg, RT-PCR or viral antigen); and
  - Resolution of acute symptoms (including at least 24 hours has passed since last fever without fever reducing medications); and
  - Evaluation by the Investigator with confirmation that there are no sequelae that would place the participant at a higher risk of receiving investigational treatment; and
  - Consultation with the Medical Monitor or designee. For suspected cases, treatment may also resume if SARS-CoV-2 infection is ruled out and other criteria to resume treatment are met.

7.4.5 Management Algorithms for Immuno-oncology Agents

I-O agents are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. Nivolumab is considered as the I-O agent in this protocol. Early recognition and management of AEs associated with I-O agents may mitigate severe toxicity. Management algorithms have been developed to assist investigators in assessing and managing the following groups of AEs:

- Gastrointestinal
- Renal
- Pulmonary (For participants with dyspnea, complete blood count (CBC) and methemoglobin should be measured.)
- Hepatic

- Endocrinopathy
- Skin
- Neurological (For participants with confusion, methemoglobin should be measured.)
- Myocarditis

The above algorithms are found in the Appendix 5 of this protocol.

7.5 Preparation/Handling/Storage/Accountability

For nivolumab, refer to the current version of the IB and/or Pharmacy Manual for complete storage, handling, dispensing, and infusion information.

For BCG, refer to the current prescribing information for complete storage, handling, and dispensing information.

The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study Participants. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

The product storage manager should ensure that the study treatment is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS. If concerns regarding the quality or appearance of the study treatment arise, the study treatment should not be dispensed and contact BMS immediately.

Study treatment not supplied by BMS will be stored in accordance with the package insert.

Investigational product documentation (whether supplied by BMS or not) must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

Further guidance and information for final disposition of unused study treatment are provided in Appendix 2.

7.5.1 Retained Samples for Bioavailability/Bioequivalence/Biocomparability

Not applicable.

7.6 Treatment Compliance

Study treatment compliance will be periodically monitored by drug accountability, as well as the participant's medical record and electronic case report form. Drug accountability should be reviewed by the site study staff at each visit to confirm treatment compliance. Sites should discuss discrepancies with the participant at each on-treatment study visit.

7.7 Concomitant Therapy

Concomitant medications are recorded at baseline and throughout the treatment phase of the study 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 treatment must be documented in the concomitant therapy section of the CRF.

Coronavirus disease 2019 (COVID-19) vaccines that are NOT live are allowed and should be handled in the same manner as other vaccines. Administration may occur during the study, including during the administration of the BMS study treatment and after the last administration of the BMS study treatment. Non-live COVID-19 vaccination is considered a simple concomitant medication within the study. However, the efficacy and safety of non-live vaccines (including non-live COVID-19 vaccines) in participants receiving nivolumab, with or without intravesical BCG, is unknown.

7.7.1 Prohibited and/or Restricted Treatments

The following medications are prohibited during the study until recurrence or progression (unless utilized to treat a drug-related AE):

- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids (except as stated in Section 7.7.3)
- Any concurrent antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive, nonpalliative radiation therapy, or standard or investigational agents for treatment of NMIBC)
- Any complementary medications (eg, herbal supplements, traditional Chinese medicines, marijuana and its derivatives) intended to treat the disease under study. Such medications are permitted if they are used as supportive care. Approval from BMS-Medical Monitor (or designee) is required prior to concurrent use.
- Any live/attenuated vaccine (eg, varicella; zoster; yellow fever; rotavirus; oral polio; and measles, mumps, rubella) during treatment and until 100 days post last dose.

7.7.2 Other Restrictions and Precautions

Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization are excluded. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

7.7.2.1 Imaging Restriction and Precautions

It is the local imaging facility's responsibility to determine, based on participant attributes (eg, allergy history, diabetic history, and renal status), the appropriate imaging modality and contrast regimen for each participant. Imaging contraindications and contrast risks should be considered in this assessment. Participants 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. Specific to MRI, participants with severe renal insufficiency (ie, estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m2) are at increased risk of nephrogenic systemic fibrosis. MRI contrast should not be given to this participant population. In addition, participants may be excluded from MRI if they have tattoos, metallic implants, pacemakers, etc.

Gentle hydration before and after IV contrast should follow local SOC. The ultimate decision to perform MRI in an individual participant in this study rests with the site radiologist, the investigator, and the standards set by the local Ethics Committee.

7.7.3 Permitted Therapy

Participants are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Adrenal replacement steroid doses > 10 mg daily prednisone are permitted. A brief (less than 3 weeks) course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of nonautoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.

7.7.4 Treatment of Infusion-related Reactions

If an infusion-related reaction should occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the study Medical Monitor/designee and reported as an SAE if it meets the criteria. Infusion reactions should be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE; Version 5.0) guidelines.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines, as appropriate:

For Grade 1 symptoms (mild reaction; infusion interruption not indicated; intervention not indicated):

- Remain at bedside and monitor participant until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg at least 30 minutes before additional nivolumab administrations.

For Grade 2 symptoms (moderate reaction required therapy or infusion interruption but responds promptly to symptomatic treatment [eg, antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]); prophylactic medications indicated for ≤ 24 hours):

- Stop the study treatment infusion, begin an IV infusion of normal saline, and treat the participant with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor participant until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor participant closely. If symptoms recur, then no further study treatment will be administered at that visit.
- For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg

should be administered at least 30 minutes before nivolumab infusion. If necessary, corticosteroids (up to 25 mg of hydrocortisone or equivalent) may be used.

For Grade 3 or 4 symptoms (severe reaction, Grade 3: prolonged [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [eg, renal impairment, pulmonary infiltrates]). Grade 4: Life-threatening; pressor or ventilatory support indicated):

- Immediately discontinue infusion of study treatment. Begin an IV infusion of normal saline and treat the participant as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Participant should be monitored until the investigator is comfortable that the symptoms will not recur. Study treatment will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor participant until recovery of the symptoms.

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

7.8 Treatment After the End of the Study

At the end of the treatment period as defined in Section 7.1, BMS will not continue to provide BMS-supplied study treatment to participants/investigators unless BMS chooses to extend the study. The investigator should ensure that the participant receives appropriate SOC to treat the condition under study.

8 DISCONTINUATION CRITERIA

8.1 Discontinuation From Study Treatment

Participants MUST discontinue investigational product (and non-investigational product at the discretion of the investigator) for any of the following reasons:

- Participant's request to stop study treatment. Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant
- Termination of the study by BMS
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness. (Note: Under

specific circumstances and only in countries where local regulations permit, a participant who has been imprisoned may be permitted to continue as a participant. Strict conditions apply and BMS approval is required.)
- Additional protocol-specified reasons for discontinuation (Sections 8.1.1 and 8.1.2)
- Disease progression or recurrence locally diagnosed.

Refer to the Schedule of Activities, Section 2, for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that can be completed.

In the case of pregnancy, the investigator must immediately, within 24 hours of awareness of the pregnancy, notify the BMS Medical Monitor/designee of this event. In most cases, the study treatment will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety). Refer to Section 9.2.5.

All participants who discontinue study treatment should comply with protocol specified follow-up procedures as outlined in Section 2. The only exception to this requirement is when a participant withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study treatment is discontinued prior to the participant's completion of the study, the reason for the discontinuation must be documented in the participant's medical records and entered on the appropriate CRF page.

8.1.1 Nivolumab/Nivolumab-placebo Dose Discontinuation

Nivolumab/nivolumab-placebo treatment must be permanently discontinued per criteria in Table 7.4-1 in Section 7.4. Discontinue nivolumab for any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the participant with continued nivolumab dosing.

- Any event that leads to delay in dosing lasting > 10 weeks from the previous dose requires discontinuation, with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related adverse events are allowed.
  - Dosing delays lasting > 6 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the BMS Medical Monitor (or designee).

Prior to re-initiating treatment in a participant with a dosing delay lasting > 10 weeks, the BMS Medical Monitor (or designee) must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.

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

8.1.2 Discontinuation of BCG

BCG treatment should be permanently discontinued for the following:

- Any event requiring discontinuation of nivolumab/nivolumab-placebo as in Section 8.1.1
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the participant with continued BCG dosing
- Systemic BCG reaction (see current BCG prescribing information for description)
- BCG infection (see current BCG prescribing information for description)

Participant may continue nivolumab/nivolumab-placebo treatment if BCG is discontinued.

The duration of treatment with BCG is based on global standard evidence-based guidelines (Section 5.4.5). Every effort should be made to treat participants with the full course of BCG as defined in the protocol, although if the participant and investigator agree that it is in the participant's best interests to discontinue BCG treatment, the participant should be counselled appropriately and the reason for discontinuation should be documented in the CRF.

8.1.3 Post Study Treatment Study Follow-up

Per Protocol Amendment 01, efficacy follow-up is not required. Participants on efficacy follow-up at the time of Protocol Amendment 01 implementation at each site will conclude efficacy follow-up. Local standard of care assessments should be followed.

Participants will be followed for assessment of safety through 100 days post last dose of study treatment.

Not applicable per Protocol Amendment 01:

In this study, EFS is a key endpoint of the study. Post study follow-up is of critical importance and is essential to preserving participant safety and the integrity of the study. Participants who discontinue study treatment must continue to be followed (in this study or a rollover study) for collection of outcome and/or survival follow-up data as required and in line with Section 5 until death or the conclusion of the study.

BMS may request that survival data be collected on all treated/randomized participants outside of the protocol-defined window (Section 2, Table 2-3). At the time of this request, each participant will be contacted to determine his/her survival status unless the participant has withdrawn consent for all contacts or is lost to follow-up.

8.1.4 CIS and/or TaHG at Week 13: Continued Treatment

Participants should continue treatment with nivolumab/nivolumab-placebo and BCG until disease recurrence, progression, unacceptable toxicity, treatment discontinuation, or until the end of the defined treatment periods.

In participants with CIS (with or without papillary disease) at baseline, the presence of CIS and/or a positive cytology at the first disease assessment (Week 13) is defined as an EFS event and is

considered equivalent to recurrence. The presence of TaHG is considered recurrence and also defined as an EFS event (see Section 9.1.1).

Evidence from the BCG-naïve setting suggests[47] that with continued BCG exposure, many participants with CIS at the first disease assessment respond to continued BCG treatment after the first disease assessment (Week 13) and by the second disease assessment (Week 26). For this reason, study participants who have CIS at Week 13 (either positive cytology, cystoscopy and biopsy findings, or both) may continue treatment until Week 26. Similarly, participants with TaHG at Week 13 may also derive delayed benefit from continued treatment, and may also continue on study treatment until Week 26. TaHG at Week 13 should be treated with TURBT as appropriate in line with SOC.

Participants with CIS and/or TaHG at Week 13 must have no other evidence of recurrence or progression to continue treatment. It is at the investigator's discretion to continue treating such participants based on their clinical assessment of the best interests of the participant and appropriate patient counselling and documented consent, including consideration of alternative treatment options such as cystectomy.

In participants who have CIS and/or TaHG disease at Week 13 and who are treated beyond Week 13, subsequent CIS or recurrent TaHG a will require permanent discontinuation.

8.2 Discontinuation from the Study

Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information.

- Participants should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible.
- The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study treatment only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page.
- In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

8.3 Lost to Follow-up

- All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with persons authorized by the participant.
- Lost to follow-up is defined by the inability to reach the participant after a minimum of three documented phone calls, faxes, or emails as well as lack of response by participant to one registered mail letter. All attempts should be documented in the participant's medical records.

- If it is determined that the participant has died, the site will use permissible local methods to obtain date and cause of death.
- If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the participant's informed consent, then the investigator may use a Sponsor retained third-party representative to assist site staff with obtaining participant's contact information or other public vital status data necessary to complete the follow-up portion of the study.
- The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information.
- If after all attempts, the participant remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the participant's medical records.

9 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in the Schedule of Activities.
- Protocol waivers or exemptions are not allowed.
- All immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue treatment.
- Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Schedule of Activities.

Additional measures, including non-study required laboratory tests, should be performed as clinically indicated or to comply with local regulations. Laboratory toxicities (eg, suspected drug induced liver enzyme evaluations) will be monitored during the follow-up phase via on-site/local labs until all study drug-related toxicities resolve, return to baseline, or are deemed irreversible.

Evaluate participant immediately to rule out cardiac or pulmonary toxicity if participant shows cardiac or pulmonary-related signs (hypoxia, abnormal heart rate, or changes from baseline) or symptoms (eg, dyspnea, cough, chest pain, fatigue, palpitations).

Some of the assessments referred to in this section may not be captured as data in the CRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

9.1 Efficacy Assessments

Per Protocol Amendment 01, efficacy assessments will be conducted per the local standards of care.

Not applicable per Protocol Amendment 01:

Efficacy assessments occur until disease recurrence (other than TaLG) or progression, per PRC (based on a positive urinary cytology, bladder biopsy, or imaging), or until treatment discontinuation, whichever occurs later (Table 2-2 and Table 2-3).

9.1.1 Event-free Survival Evaluation

Not applicable per Protocol Amendment 01:

The following events, included in the EFS definition, will be assessed by the PRC per its charter and by the investigator throughout the duration of the study (see below):

- CR in CIS participants
- Persistent CIS (Week 13) in CIS participants
- Recurrence
- Progression

If the PRC is no longer active during the follow-up phase, events will be assessed by the investigator.

9.1.2 Complete Response Assessment in CIS Participants

Not applicable per Protocol Amendment 01:

Determination of CR in CIS participants will be based on results of:

- Cystoscopy and urinary cytology (Sections 9.1.3 and 9.1.4) at all time points
- Bladder biopsy (Section 9.1.5) at the Week 26 time point and at any time point where biopsy is done for cause
- Imaging assessments (Section 9.1.7)

CIS participants are those with CIS +/- papillary disease prior to study entry.

9.1.2.1 Complete Response at First On-study Assessment (Week 13)

Not applicable per Protocol Amendment 01:

A CIS participant will be classified as having a CR at the first on-study assessment (Week 13) if the participant has a normal cystoscopy with a negative (including atypical) urinary cytology.

In case of abnormal cystoscopy, a biopsy of the abnormal area(s) in the bladder (Section 9.1.5) is required. Participants will be classified as having a CR at the first on-study assessment if biopsies are free of TaHG or ≥ T1 UC or CIS. The biopsy may show TaLG UC only.

In the case of suspicious cytology and no abnormalities or TaLG UC only on biopsy, see Section 9.1.4.2. For details on positive/suspicious cytology with a normal biopsy and the assessment of CR, see Sections 9.1.4.1 and 9.1.4.2.

9.1.2.2 Persistent CIS at First On-study Assessment (Week 13)

Not applicable per Protocol Amendment 01:

CIS participants with persistent CIS at Week 13 who develop a concurrent TaHG or T1 papillary tumor at the first on-study evaluation, or biopsy-confirmed stage ≥ T1 will be classified as disease recurrence and/or progression as appropriate (see Table 9.1.2.4-1).

CIS participants with persistent CIS at Week 13 who do not develop a concurrent TaHG or T1 papillary tumor, or biopsy-confirmed stage ≥ T1 will be classified as **persistent CIS**. This will be classified as an EFS event.

For details on positive/suspicious cytology with a normal biopsy and the assessment of CR, see Sections 9.1.4.1 and 9.1.4.2.

9.1.2.3 Complete Response After First On-study Assessment in Participants with Persistent CIS at First Assessment

Not applicable per Protocol Amendment 01:

Participants with CIS at the first disease assessment will be permitted to continue on study treatment until Week 26 (see Section 8.1.4), based on the clinical judgment of the investigator. Such participants may have a CR at the Week 26 assessment.

CIS participants with persistent CIS only at the first on-study evaluation can be classified as having a CR at the Week 26 assessment if the following criteria are met: cystoscopic examination of the bladder must either be normal based on investigator report or, if any abnormality is seen, biopsy of the abnormal area(s) must not demonstrate TaHG UC, any ≥ T1 UC, or CIS. Participants with only TaLG UC will be classified as having CR.

For details on positive/suspicious cytology with a normal biopsy and the assessment of CR, see Sections 9.1.4.1 and 9.1.4.2.

The primary endpoint of EFS and the secondary endpoint of CR rate will be based on the Week 13 CR assessment only. DoR will include the Week 13 assessment and subsequent assessments. Exploratory endpoints will examine CR at additional time points (see Section 4).

9.1.2.4 Disease Recurrence/Progression

Per Protocol Amendment 01, disease recurrence and progression will be determined in all participants throughout the duration of the study by the investigator according to local standards of care.

Not applicable per Protocol Amendment 01:

This determination of recurrence or progression will be based on evaluation of urinary cytology and tissue obtained at bladder biopsy, whether the biopsy is performed for cause or as required by

the protocol. Any abnormality in any participant (CIS or non-CIS) discovered on cystoscopic examination of the bladder that is suspicious for recurrent papillary tumor or CIS must be biopsied and evaluated. This biopsy is in addition to the required biopsies in screening and at Week 26 in CIS participants. Protocol-defined or off-schedule imaging may also inform a diagnosis of progression.

Recurrence is defined as the presence of high-risk bladder lesions, including TaHG or T1 UC or CIS in the bladder biopsy specimen. Participants with only TaLG UC on bladder biopsy will not be classified as having a recurrence, per PRC.

Recurrence is also defined as a positive (malignant) urinary cytology, per PRC. A positive urinary cytology should be investigated as detailed in Section 9.1.4.1.

A suspicious urine cytology must be evaluated as described in Sections 9.1.4.1 and 9.1.4.2. A suspicious cytology alone does not define recurrence. Participants with an initial suspicious cytology who are found to have a positive (malignant) cytology on repeat testing, high-risk disease on for-cause or random biopsies from the bladder or prostatic urethra (CIS, TaHG, ≥ T1), or an upper tract lesion on imaging will be classified as having recurrence/progression on the date of the original suspicious cytology result.

CIS participants with CIS only +/- positive cytology at Week 13 will be classified as having persistent disease. This is considered equivalent to recurrence.

Participants with CIS and/or Ta at Week 13 may continue treatment, irrespective of disease stage at screening. Participants with Ta who continue treatment must have resection (TURBT) of disease in accordance with SOC (see Section 8.1.4).

Progression is defined as any tumor invasion into the muscularis propria of the bladder (ie, progression of any high-risk NMIBC to MIBC [Stage T2 or greater]) or the development of extravesical or disseminated disease based on cross-sectional imaging and/or clinical examination, whichever occurs first. Although not required, progression detected by imaging and/or clinical examination should be confirmed histologically, if feasible.

The classification of recurrence and progression is summarized in Table 9.1.2.4-1.

Table 9.1.2.4-1: Determination of Recurrent/Progression of High-risk NIMBC

Baseline[a]	**On-treatment (All visits)**					
	TaLG[b]	TaHG[c]	T1	CIS[d]	Positive Cytology Only[d]	Muscle-invasive (>=T2)/Locoregional (Extra Vesical)/Regional Node/ Metastasis/Upper Urinary Tract Tumor
(1) Non-CIS TaHG (2) CIS Alone (3) CIS with TaLG (4) CIS with TaHG (5) Non-CIS T1 (6) CIS with T1	No event	Recurrence	Recurrence	Recurrence	Recurrence	Progression

[a] Arranged from lowest to highest severity.

[b] Participants with TaLG alone at baseline are not eligible for the study.

[c] Participants with TaHG at Week 13 may continue treatment after TURBT. Please see Section 8.1.4.

[d] Participants with CIS and/or positive cytology only at Week 13 may continue treatment, and may be considered to have persistent disease rather than recurrence. (see Section 8.1.4).

9.1.3 Cystoscopy

Per Protocol Amendment 01, efficacy assessments will be conducted per the local standards of care.

Not applicable per Protocol Amendment 01:

Cystoscopic examination of the urinary bladder and urethra will be performed within 90 days of randomization (Table 2-2). Fluorescence-guided cystoscopy may also be used but is not required. However, the same method of assessment used at baseline (prior to randomization) should be employed throughout the entire study period where possible.

The entire urethra and bladder mucosa should be visualized during each cystoscopic examination. Investigators are required to completely document all findings on the study CRF, including presence/absence of papillary tumors, number and size of tumors, and abnormal areas of erythema or other abnormalities possibly consistent with CIS. The location of tumors or abnormalities should be clearly documented on the CRF. Other bladder pathology, including, but not limited to, bladder diverticula, stones, and trabeculation, should also be documented. This documentation will be submitted to PRC to aid in their evaluation of urinary cytology and bladder biopsies.

Cystoscopy examination will continue per AUA[7] and EAU[18] guidelines for 5 years following randomization, regardless of early discontinuation of study treatment, until documented PRC assessed recurrence or progression. Cystoscopy examinations will take place at Week 13 (± 1 week) and at 6, 9, 12, 15, 18, 21, 24, 30, 36, 42, 48, and 60 months (± 4 weeks) (3 months = 13 weeks); see Table 9.1.4-1. After 5 years, cystoscopy will be every year (± 1 month).

9.1.4 Urine Cytology

Not applicable per Protocol Amendment 01:

A voided (except from the first morning urination) or bladder wash specimen for urinary cytology will be obtained, reviewed by the investigator, and sent to the PRC for review within 90 days prior to randomization. Urine cytology will be performed with cystoscopy at the following time points: Week 13 (± 1 week) and 6, 9, 12, 15, 18, 21, 24, 30, 36, 42, 48, and 60 months (± 4 weeks) (3 months = 13 weeks) (see Table 9.1.4-1) until PRC assessed recurrence or progression.

Urine cytology may be repeated if read by the PRC as suspicious (see Sections 9.1.4.2 and 9.1.4.3).

If a bladder wash specimen is obtained, the bladder will be emptied, and the bladder wash sample will be obtained by rinsing the bladder at least twice with 50 cc of normal saline, either through the cystoscope or through a urinary catheter. The material will be placed in a urine collection specimen cup.

Urine cytology tests will continue per AUA[7] and EAU[18] guidelines for 5 years following randomization, regardless of early discontinuation of study treatment, until documented PRC assessed recurrence or progression. After 5 years, urine cytology will be every year (± 1 month).

Table 9.1.4-1: Timing of Cystoscopy and Urine Cytology

Months	Week	Assessment Day[a] (± 4 weeks)
3	13	Week 14, Day 1[b]
6	26	Week 27, Day 1
9	39	Week 40, Day 1
12	52	Week 53, Day 1
15	65	Week 66, Day 1
18	78	Week 79, Day 1
21	91	Week 92, Day 1
24	104	Week 105, Day 1
30	130	Week 131, Day 1
36	156	Week 157, Day 1
42	182	Week 183, Day 1
48	208	Week 209, Day 1
60[c]	260	Week 261, Day 1

[a] Should not occur < 6 weeks after most recent dose of BCG.

[b] Window is ± 1 week at Week 13.

[c] After 5 years, cystoscopy and urine cytology will be every year (± 1 month).

9.1.4.1 Positive Cytology with Normal Cystoscopy

Not applicable per Protocol Amendment 01:

If the cytology is positive (defined by the presence of malignant cells), the source of the positive cytology should be investigated with:

1) Cystoscopic examination of the bladder
2) Biopsies targeted to any visually abnormal areas of the bladder,
3) Random bladder biopsies and a biopsy of the prostatic urethra (in male participants) if no visually abnormal areas are seen on cystoscopy, and
4) Contrast studies of the upper urinary tracts if the source of the positive cytology cannot be localized to the lower urinary tract.

Split urinary cytology specimens from the upper and lower urinary tracts are encouraged, but not required, to isolate the source of the positive cytology from the upper tracts.

Complete response requires a negative (including atypical) urinary cytology per PRC.

9.1.4.2 Suspicious Cytology with Normal Cystoscopy

Not applicable per Protocol Amendment 01:

A suspicious urine cytology with a negative cystoscopy poses a particular challenge as there are currently no guidelines available to assist clinicians with decisions including whether to perform additional testing, what type of additional testing to perform, or whether to change surveillance strategies.[48] A suspicious cytology in combination with a negative cystoscopy at any efficacy evaluation requires a repeat urine cytology 4 weeks after the initial suspicious cytology result. If the repeat cytology is negative (including atypical), the participant will be classified as having a CR on the date of the original suspicious cytology. If the repeat cytology is positive (malignant), the participant will be classified as having recurrence/progression on the date of the original suspicious cytology and the source of the positive cytology should be evaluated as described in Section 9.1.4.1.

If the repeat cytology is again suspicious, random bladder biopsies (left bladder wall, right bladder wall, posterior bladder wall, bladder dome, trigone) and biopsy of the prostatic urethra (in male participants) must be performed. Such random biopsies can be done in combination with required biopsies from areas of prior papillary tumor/CIS based on prior examination and bladder mapping if the suspicious cytology result was obtained during the 26 week evaluation in CIS participants. Alternatively, random biopsies should be done as a separate procedure at any other evaluation. Contrast studies of the upper urinary tracts must also be performed if the repeat cytology is suspicious, with the study being performed (CT, MRI, retrograde pyelograms) left to the discretion of the investigator.

If high-risk disease is identified in the random biopsies from the bladder or in the prostatic urethra (CIS, TaHG, any ≥ T1), or if an upper tract lesion is identified on imaging, the participant will be classified as having recurrence/progression on the date of the original suspicious cytology. If no cause for the suspicious cytology is found, or if the participant is found to have TaLG disease in the bladder or prostatic urethra, the participant will be classified as having a CR on the date of the original suspicious cytology and treatment/evaluations will proceed as per protocol.

9.1.4.3 Suspicious Cytology, Abnormal Cystoscopy

Not applicable per Protocol Amendment 01:

A participant (CIS or non-CIS) with a suspicious cytology and an abnormal cystoscopy must be evaluated with bladder biopsy as specified in Section 9.1.5. If biopsies obtained from the cystoscopically abnormal area(s) demonstrate TaHG, ≥ T1 UC, or CIS, the participant will be classified as having recurrence/progression. If biopsies obtained from the cystoscopically abnormal areas demonstrate only benign tissue or TaLG UC, the participant will be considered free of recurrence/progression and, in the case of a CIS participant, as CR. The need for upper tract imaging, in addition to bladder biopsy, will be left to the judgment of the investigator but will not be required for classification as no recurrence/progression or CR.

Bladder biopsy, whether for cause or as required at the Week 26 time point, must be free of high-risk disease (CIS, TaHG, any ≥ T1) per PRC for the participant to be classified as having a CR. Participants with only TaLG UC on bladder biopsy will be classified as having a CR.

9.1.5 Bladder Biopsy

Per Protocol Amendment 01, efficacy assessments will be conducted per the local standards of care.

Complete resection of all papillary disease (Ta/T1) is required for all participants within 90 days prior to randomization. At least one slide must contain musclaris propria, preferably from the area of most significant disease. For participants with clinical stage T1 disease, a repeat TURBT is required within 8 weeks after the initial TURBT to confirm complete resection of disease and to ensure that no tumor has invaded the muscularis propria of the bladder prior to randomization. The location, number, and size of each bladder tumor should be documented in the screening CRF.

Any areas of abnormality consistent with possible CIS (such as erythema) must be biopsied and/or resected prior to randomization. The location of the abnormality should be documented in the CRF.

If the tumor tissue was obtained > 70 days prior to the anticipated randomization date, a repeat cystoscopy is required prior to randomization to ensure the participant does not have recurrent disease. The repeat cystoscopy must be completed ≤ 70 days prior to randomization. If there is papillary NMIBC on the repeat cystoscopy, the participant's eligibility needs to be reassessed and the tissue must be submitted to the PRC for assessment. The disease stage should be updated to take account of all TURBT findings. Bladder mapping in all CIS participants to identify occult disease should be performed at baseline, using one of the following techniques:

- Random sampling of the bladder mucosa (in which case, biopsies should be obtained from the bladder dome, right and left lateral walls, posterior wall, trigone, and prostatic urethra [in male participants])
- Fluorescence cystoscopy with biopsy of all abnormal areas

In participants in whom it is not feasible to perform bladder mapping at baseline, it is acceptable to defer this procedure until Week 26 (± 5 weeks).

Not applicable per Protocol Amendment 01:

Any abnormality in any participant (CIS or non-CIS) discovered on cystoscopic examination of the bladder that is suspicious for recurrent papillary tumor or CIS must be biopsied and evaluated. All papillary lesions identified on surveillance cystoscopy must be fully resected, if feasible. The location, number, and size of these lesions should be recorded in the CRF.

In addition, on-study biopsy is required at 26 (± 5) weeks following randomization in CIS participants, even if the bladder is normal on visual inspection (see Table 2-2). In such cases, areas of prior papillary tumor and/or CIS, based on prior examination and bladder mapping must be biopsied even if these areas are normal to visual inspection. Bladder mapping is required in CIS

participants at 26 weeks if not performed prior to randomization. If any of these areas are biopsied at 26 weeks based on the presence of an abnormality on cystoscopy, or due to the presence of tumor on prior examination as described above, an additional random biopsy from the area is not required.

To the extent feasible, all papillary tumors and abnormalities consistent with possible CIS should be fully resected or biopsied during the follow-up period after the participant completes all on-study evaluations. The location, number, and size of these lesions should be documented on the CRF.

During the treatment and follow-up periods, biopsy specimens will be evaluated by the investigator and by the PRC per its charter, or by the investigator if the PRC is no longer active.

9.1.6 Patient-reported Outcomes

Not applicable per Protocol Amendment 01:

The evaluation of PROs is an increasingly important aspect of clinical efficacy in oncology trials. Such data provide an understanding of the impact of treatment from the participant's perspective and offer insights into patient experience that may not be captured through physician reporting. Additionally, generic health-related QoL measures provide data needed for calculating utility values to inform health economic models.

Participants will be asked to complete the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Cancer (EORTC QLQ-C30), the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Non-muscle-invasive Bladder Cancer (EORTC QLQ-NMIBC24), and the EuroQoL Group's 5-level version of the EQ-5D (EQ-5D-5L) in the participant's preferred language when available. Participants will complete all measures on Day 1 of every dosing cycle at the site while on treatment and during FU visits 1 and 2. In addition, the EORTC QLQ-C30 and EQ-5D-5L will be administered at some survival follow-up visits. The QLQ-C30 and EQ-5D-5L may be administered by telephone using standardized scripts. When survival visits coincide with efficacy visits, assessments can be collected at the efficacy visits.

Table 2-2 and Table 2-3 provide information regarding the timing of PRO assessments.

9.1.6.1 EORTC QLQ-C30

Not applicable per Protocol Amendment 01:

The EORTC QLQ-C30[49] is the most commonly used QoL instrument in oncology trials. The instrument's 30 items are divided among 5 functional scales (physical, role, cognitive, emotional, and social), 9 symptom scales (fatigue, pain, nausea/vomiting, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties), and a global health/QoL scale. With the exception of 2 items included in the global health/QoL scale, for which responses range from 1 (Very poor) to 7 (Excellent), item responses range from 1 (Not at all) to 4 (Very much). Raw scores for the QLQ-C30 are transformed to a 0 to 100 metric such that higher values indicate better

functioning or QoL or a higher level of symptoms. A score difference of 10 is used as an estimate of the minimally important difference (MID) for the subscales of the EORTC QLQ-C30.[50]

9.1.6.2 EORTC QLQ-NMIBC24

Not applicable per Protocol Amendment 01:

The EORTC QLQ-NMIBC24 is a bladder cancer-specific questionnaire designed to evaluate symptoms and problems associated with NMIBC.[51] The QLQ-NMIBC24 includes 9 symptom and 2 functional scales/items assessing multiple domains, including urinary symptoms, intravesical treatment issues, future worries, malaise, abdominal bloating and flatulence, and sexual functioning.

9.1.6.3 EQ-5D-5L

Not applicable per Protocol Amendment 01:

The EQ-5D-5L is a standardized instrument used to measure self-reports of general health status.[52] The instrument has 2 components: a descriptive system and a visual analog scale (VAS). The descriptive system consists of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels, reflecting no problems, slight problems, moderate problems, severe problems, and extreme problems. A dimension for which there are no problems is said to be at level 1, while a dimension for which there are extreme problems is said to be at level 5. Thus, the vectors 11111 and 55555 represent the best and the worst health state, respectively. Altogether, the instrument describes 3,125 different health states. Empirically derived weights can be applied to an individual's responses to the EQ-5D-5L descriptive system to generate a utility index measuring the value to society of his or her current health. [53]

The EQ-5D-5L VAS allows subjects to rate their own current health on a 0 to 100 point scale ranging from "the worst health you can imagine" to the "best health you can imagine," respectively. The MID for the EQ-5D-5L VAS is a 7-point change in score.[54]

The EQ-5D-5L uses a recall period of "today."

9.1.7 Imaging Assessment for the Study

Not applicable per Protocol Amendment 01:

Imaging will be performed every 52 weeks (± 4 weeks) from randomization.

At the Sponsor's discretion, scans may be submitted to an imaging core lab and may be reviewed by a Blinded Independent Central Review at a later date, or at any time during the study.

Tumor imaging is performed during screening to confirm the staging of the disease and to exclude synchronous UC in the upper urinary tracts. Imaging may also be performed at the discretion of the investigator due to symptoms, to exclude disease progression, or to exclude UC in the upper urinary tracts. Documentation of the results of imaging studies obtained during screening will be

submitted to PRC to confirm participant eligibility. Documentation of the results of imaging studies obtained during treatment will be submitted to PRC to aid in the evaluation of progression.

Contrast-enhanced CT of the chest, CT or MRI of the abdomen and pelvis, **including excretory imaging**, and all other suspected sites of disease should be performed during screening and as clinically indicated. Images should be acquired with slice thickness of 5 mm or less with no intervening gap (contiguous). Every attempt should be made to image each participant using an identical acquisition protocol on the same scanner.

Should a participant have contraindication for CT IV contrast, a noncontrast CT of the chest and a contrast-enhanced MRI of the abdomen and pelvis, including excretory imaging, and other suspected sites of disease should be obtained.

For participants in whom there is a documented contraindication to both CT and MRI IV contrasts, noncontrast enhancing CT of the chest and noncontrast enhancing CT/MRI of the abdomen and pelvis is acceptable. Imaging of the upper urinary tracts must be appropriately performed using appropriate alternative techniques per local SOC (eg, retrograde studies or endosocopy). Please consult with the medical monitor.

MRI of brain (without and with contrast) is required for participants with known or suspected brain metastases, unless participant has completed an imaging study of the brain within 28 days of study drug administration. CT of the brain (without and with contrast) can be performed if MRI is contraindicated.

9.1.8 Clinical and Pathology Review Committee Review of Efficacy Assessments

Not applicable per Protocol Amendment 01:

The primary endpoint of this study is based upon the PRC evaluation of CR, recurrence, and/or progression. Accordingly, all relevant diagnostic tests completed (per Table 2-2 and Table 2-3) at any time point must submitted to the PRC until such a time as the PRC determine recurrence/progression. This includes repeat tests such as those outlined in Sections 9.1.4.1 and 9.1.4.2.

The criteria for determining CR, recurrence, and/or progression are the same for the investigator and the PRC (see Section 9.1.1). The interpretation of individual tests may be different at the investigator's site and at the PRC, and as a consequence the determination of recurrence/progression may be different.

All clinical decisions on patient care including the discontinuation of study drug will be based on the investigator's assessment of study diagnostic tests and clinical information, and should be independent of PRC. The results of the PRC assessment will be available to sites, although investigators should make clinical decisions on the basis of their assessment of all the information available to them, including the cytology, cystoscopy, biopsy, and imaging findings locally.

If the investigator determines recurrence/progression but the PRC do not, the participant can stop study treatment in accordance with the protocol. In this situation, efficacy assessments should

continue at the protocol defined schedule and be submitted to the PRC until the PRC determine recurrence/progression or until the patient starts a subsequent line of treatment for UC (including intravesical treatment, cystectomy, or radiotherapy).

If the PRC determines recurrence/progression but the investigator does not, the participant should continue with treatment in accordance with the protocol until the investigator makes a determination of recurrence/progression. In such a situation, efficacy assessments should continue in accordance with the protocol defined schedule, including submission to PRC. Please discuss such cases with the medical monitor.

If urinary cytology findings at the site are negative and the PRC's findings of the same time point urine sample is suspicious or positive and the cystoscopy findings are negative, the site should perform additional tests to identify the source of the positive/suspicious cytology as outlined in Sections 9.1.4.1 and 9.1.4.3.

9.2 Adverse Events

The definitions of an AE or serious adverse event (SAE) can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue before completing the study.

Contacts for SAE reporting specified in Appendix 3.

IMAEs are AEs consistent with an immune-mediated mechanism or immune-mediated component for which noninflammatory etiologies (eg, infection or tumor progression) have been ruled out. IMAEs can include events with an alternate etiology that were exacerbated by the induction of autoimmunity. Information supporting the assessment will be collected on the participant's CRF.

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

Sections 5.6.1 and 5.6.2 in the IB represent the Reference Safety Information to determine expectedness of SAE for expedited reporting. All SAEs must be collected from the time of signing the consent, including those thought to be associated with protocol-specified procedures and within 100 days of discontinuation of dosing. For participants randomized/assigned to treatment and never treated with study drug, SAEs should be collected for 30 days from the date of randomization.

The investigator must report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure, (eg, a follow-up skin biopsy).

- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the appropriate section of the CRF module.
- All SAEs will be recorded and reported to Sponsor or designee within 24 hours, as indicated in Appendix 3.

- The investigator will submit any updated SAE data to the sponsor or designee within 24 hours of updated information being available.

All AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection must be collected from the date of the participant's written consent until 100 days following discontinuation of dosing.

Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify the Sponsor.

The method of evaluating and assessing causality of AEs and SAEs and the procedures for completing and reporting/transmitting SAE reports are provided in Appendix 3.

9.2.2 Method of Detecting AEs and SAEs

AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a participant. Care should be taken not to introduce bias when collecting AE and/or SAEs. Inquiry about specific AEs should be guided by clinical judgment in the context of known adverse events, when appropriate for the program or protocol.

All nonserious AEs (not only those deemed to be treatment related) should be collected continuously during the treatment period and for a minimum of 100 days following discontinuation of study treatment.

Every AE must be assessed by the investigator with regard to whether it is considered immune-mediated. For events which are potentially immune-mediated, additional information will be collected on the participant's CRF.

9.2.3 Follow-up of AEs and SAEs

- Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Appendix 3).
- Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study treatment and for those present at the end of study treatment as appropriate.
- All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic). Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and nonserious AEs of special interest (as defined in Section 9.2)

AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, the event is deemed irreversible, or until the participant is lost to follow-up (as defined in Section 8.3), or for suspected cases, until SARS-CoV-2 infection is ruled out.

Further information on follow-up procedures is given in Appendix 3.

9.2.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of SAEs is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a product under clinical investigation are met.
- An investigator who receives an investigator safety report describing SAEs or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

Sponsor or designee will be reporting adverse events to regulatory authorities and ethics committees according to local applicable laws including European Directive 2001/20/EC and FDA Code of Federal Regulations (CFR) 21 CFR Parts 312 and 320. A SUSAR (Suspected, Unexpected Serious Adverse Reaction) is a subset of SAEs and will be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

9.2.5 Pregnancy

If, following initiation of the study treatment, it is subsequently discovered that a participant is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half-lives after product administration, the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Appendix 3.

If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, or re-initiation of study treatment, a discussion between the investigator and the BMS Medical Monitor/designee must occur. If, for whatever reason, the pregnancy has ended, confirmed by negative serum pregnancy test, treatment may be resumed (at least 3 weeks and not greater than 6 weeks after the pregnancy has ended), following approvals of participant/sponsor/ IRB/EC, as applicable.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to Sponsor or designee. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

In cases where a study drug can be present in seminal fluid at exposures sufficient to potentially cause fetal toxicity, and if any sexual activity (eg, vaginal, anal, oral) has occurred between a male participant and a pregnant WOCBP partner(s), the information should be reported to the Sponsor or designee, even if the male participant has undergone a successful vasectomy. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner,

the female partner(s) must sign an ICF for disclosure of this information. Information on the pregnancy will be collected on the Pregnancy Surveillance Form.

9.2.6 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form electronic, as appropriate. Paper forms are only intended as a back-up option when the electronic system is not functioning.

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the participant to have study treatment discontinued or interrupted
- Any laboratory test result abnormality that required the participant to receive specific corrective therapy

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

9.2.7 Potential Drug-induced Liver Injury

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential drug induced liver injury (DILI) event. All occurrences of potential DILIs meeting the defined criteria must be reported as SAEs (see Section 9.2 and Appendix 3 for reporting details).

Potential drug induced liver injury is defined as:

1) Aminotransferase (AT) (ALT or AST) elevation > 3x ULN

AND

2) Total bilirubin > 2x 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.

9.2.8 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiogram, x-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

9.3 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as SAEs (see Section 9.2.1 for reporting details).

For this study, an overdose is defined as any study drug administration that is greater than 125% of the intended, protocol-defined dose

9.4 Safety

Planned time points for all safety assessments are listed in the Schedule of Activities.

9.4.1 Physical Examinations

Refer to Schedule of Activities.

9.4.2 Vital Signs

Refer to Schedule of Activities.

9.4.3 Electrocardiograms

Refer to Schedule of Activities.

9.4.4 Clinical Safety Laboratory Assessments

Investigators must document their review of each laboratory safety report.

Hematology - CBC	
Hemoglobin Hematocrit Total leukocyte count, including differential Platelet count	
Chemistry	
AST ALT Total bilirubin Alkaline phosphatase Lactate dehydrogenase Creatinine Blood urea nitrogen or serum urea Glucose	Albumin - **screening only** Sodium Potassium Chloride Calcium Phosphorus TSH, free T3 and free T4 - screening TSH, with reflexive fT3 and fT4 if TSH is abnormal - on treatment Creatine kinase Creatinine clearance - **screening only**
Urinalysis (at screening)	
Protein Glucose Blood Leukocyte esterase Specific gravity pH	

Urinalysis (performed prior to dosing at visits when BCG is administered)
Protein Glucose Blood Leukocyte esterase and/or WBC Specific gravity pH Microscopic analysis required for abnormal dipstick urinalysis or clinical symptoms suggestive of urinary tract infection. Presence of WBCs, red blood cells, or bacteria
Serology
Hepatitis B/C, (HBV sAG, HCV antibody or HCV RNA) - **screening only**
Other Analyses
Pregnancy test (WOCBP only: minimum sensitivity 25 IU/L or equivalent units of HCG) Follicle stimulating hormone (FSH) screening - only required to confirm menopause in women < age 55 (Appendix 4)

9.4.5 Imaging Safety Assessment

Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the protocol should be evaluated and handled by the study investigator as per standard medical/clinical judgment.

9.5 Pharmacokinetics

Per Protocol Amendment 01, PK will not be evaluated.

Not applicable per Protocol Amendment 01:

Samples for PK and immunogenicity (antidrug antibody [ADA]) assessment will be collected for participants at the time points indicated in Table 9.5-1 for both randomized arms. PK and ADA samples collected for the BCG arm will not be analyzed. All on-treatment PK time points are intended to align with days on which study treatment is administered. If it is known that a dose is going to be delayed, then the predose sample should be collected just prior to the delayed dose. However, if a predose sample is collected but the dose is subsequently delayed, an additional predose sample should not be collected.

Further details of sample collection, processing, and shipment will be provided in the laboratory procedures manual.

Table 9.5-1: Pharmacokinetic Sampling Schedule for All Participants

Study Day of Sample Collection[a] (1 Cycle = 4 Weeks)	Event	Time Relative to Nivolumab Dose Hour: Min	Nivolumab Pharmacokinetic Serum Sample	Nivolumab Immunogenicity Serum Sample
Cycle 1 Day 1	Predose[b]	00:00	X	X
	EOI[c]	00:30	X	
Cycle 2 Day 1	Predose[b]	00:00	X	X
Cycle 3 Day 1	Predose[b]	00:00	X	X
Cycle 4 Day 1	Predose[b]	00:00	X	X
Cycle 5 Day 1	Predose[b]	00:00	X	X
	EOI[c]	00:30	X	
Every 4 Cycles Starting at Cycle 6 Day 1 Until EOT	Predose[b]	00:00	X	X
Follow-up Period				
Follow-up 30 Day			X	X
Follow-up 100 Day			X	X

Abbreviations: EOI, end of infusion; EOT, end of treatment

[a] If a participant discontinues study drug treatment during the treatment/sampling period, they will move to sampling at the follow-up visits.

[b] Predose samples should be collected just before the administration of the drug (preferably within 30 minutes). If it is known that a dose is going to be delayed, then the predose sample should be collected just prior to the delayed dose. However, if a predose sample is collected but the dose is subsequently delayed, an additional predose sample should not be collected.

[c] End of infusion (EOI) sample should be taken immediately prior to the stopping of nivolumab infusion, preferably within 2 minutes prior to the end of infusion. If the end of infusion is delayed beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly. EOI samples may not be collected from the same IV access as the drug was administered.

9.6 Pharmacodynamics

Per Protocol Amendment 01, pharmacodynamics will not be evaluated.

9.7 Pharmacogenomics

Not applicable.

9.8 Biomarkers

Per Protocol Amendment 01, biomarkers will not be evaluated.

Not applicable per Protocol Amendment 01:

A variety of factors that could potentially predict clinical response and incidence of AEs to nivolumab combination treatments will be investigated in peripheral blood, urine, and tumor specimens taken from all participants prior to treatment. Data from these investigations will be evaluated for associations with EFS, WFS, OS, CRR and DOR data. In addition, analyses of markers between the treatment arms will provide the necessary data to identify biomarkers with predictive or prognostic value. All samples collected may also be used for future exploratory analyses (unless restricted by local requirements and/or institutional policies) to assess biomarkers associated with bladder cancer or immunotherapy treatment. Complete instructions on the collection, processing, handling and shipment of all samples described herein will be provided in a separate procedure manual.

Table 9.8-1: Biomarker Sampling Schedule: All Participants

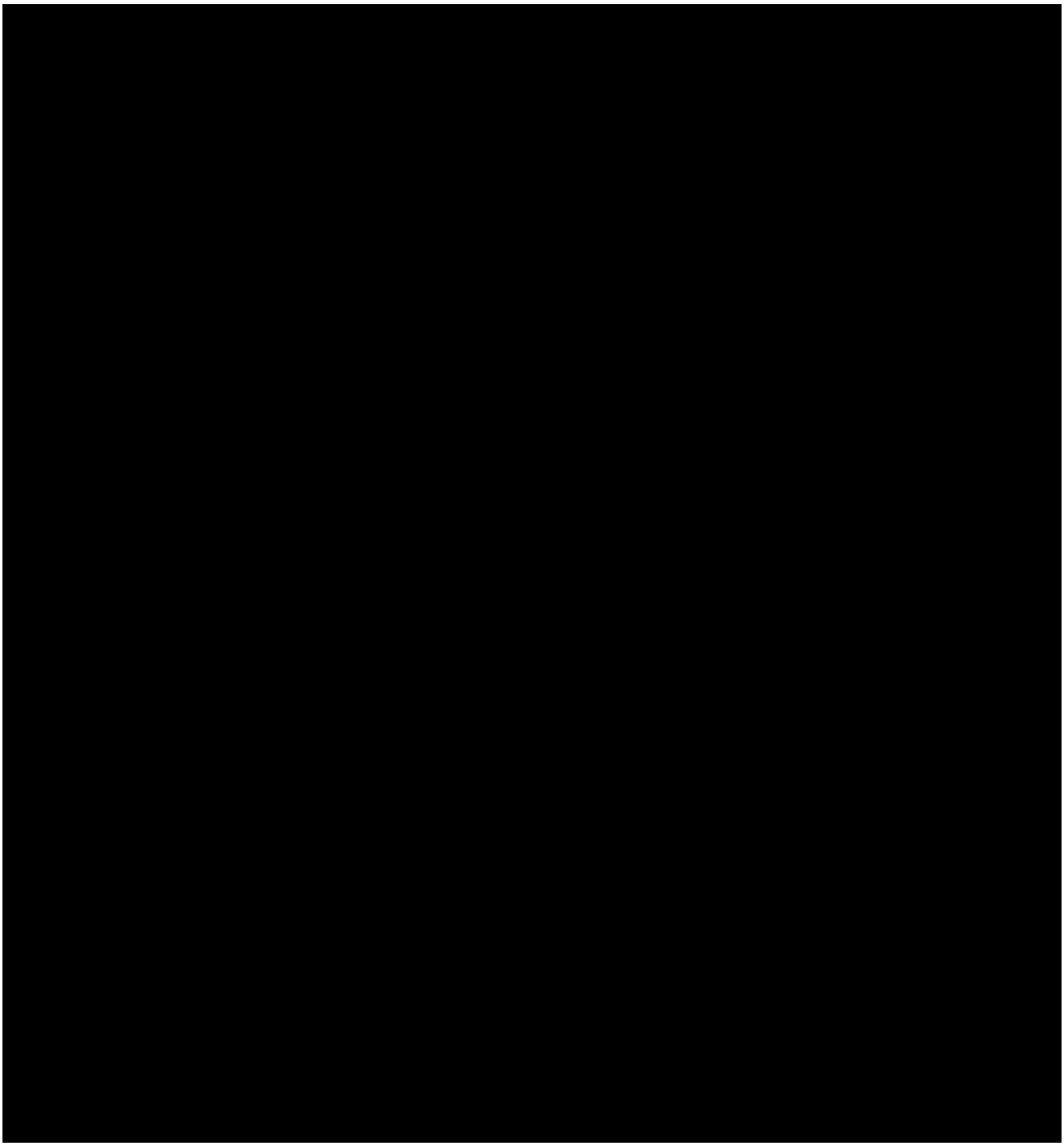
Study Day of Sample Collection[a] (1 Cycle = 4 Weeks)	Tumor Biopsy	Serum Soluble Factors	MDSCs	Whole Blood (Gene Expression)	PBMCs	Plasma ctDNA	Whole Blood DNA	Urine Markers[b]	Stool Microbiome (optional)
Screening	X					X			
Cycle 1 Day 1		X	X	X	X		X	X	X
Cycle 2 Day 1		X	X		X			X	
Cycle 3 Day 1						X			X
Cycle 4 Day 1		X			X				
Cycle 6 Day 1	X[c]		X	X		X		X	
Cycle 9 Day 1		X			X				X
Cycle 13 Day 1		X	X			X			
Cycle 18 Day 1		X			X			X	
Cycle 24 Day 1		X	X	X		X			
Upon Recurrence	X	X[d]	X[d]	X[d]	X[d]	X[d]			X

[a] Biomarker sampling occurs prior to dosing of study drug and can occur ± 5 days from the scheduled time, except for C1D1.

[b] Urine samples will be collected in the US and Canada sites only before nivolumab infusion and 1 hour after the infusion. However, do not collect after BCG administration on the same day. If BCG will be given before nivolumab on C1D1, collect the C1D1 urine markers sample before BCG administration.

[c] This is a transurethral resection of the bladder tumor (TURBT) biopsy performed at 26 weeks in CIS participants. BCG must not be given for at least 14 days after biopsy.

[d] Peripheral blood biomarker collections are optional.



[redacted]

9.8.2 Immunogenicity Assessments

Immunogenicity blood collections are discontinued with Protocol Amendment 01 and will not be evaluated.

Not applicable per Protocol Amendment 01:

Blood samples for immunogenicity analysis will be collected according to the schedule given in Section 9.5. Samples collected will be evaluated for development of ADA by a validated electrochemiluminescent immunoassay. Samples may also be analyzed for neutralizing antibodies and PK samples may be used for ADA analysis in the event of insufficient volume, to complete immunogenicity assessment, or to follow up on suspected IMAEs.

9.8.3 Other Assessments

9.8.3.1 Tumor Tissue Specimens

Per Protocol Amendment 01, tumor tissue specimens will not be collected.

Not applicable per Protocol Amendment 01:

Pretreatment tumor tissue specimens in the form of a paraffin-embedded block or 20 unstained slides will be submitted to an analytical laboratory for biomarker analysis. Confirmation of receipt of acceptable tissue for biomarker analysis is needed prior to randomization. If < 15 unstained slides are available, please discuss with the medical monitor prior to patient enrollment. Participants must provide a fresh tumor biopsy from the disease site. Archived tissue from prior biopsies or from prior surgical resection (obtained > 90 days prior to randomization) will not be accepted. If a radical cystectomy is performed post-treatment, a tissue block or at least 20 slides should be provided for biomarker analysis. For PD-L1 analysis, the PD-L1 stained tissue sections will be assessed by a pathologist and membranous PD-L1 expression will be scored in tumor cells

if a minimum of 100 evaluable tumor cells are present. Tumor samples containing less than 100 tumor cells per tissue section will be classified as not evaluable.

In addition to PD-L1 testing, the tumor samples may be used to assess other putative predictive biomarkers of nivolumab combination efficacy and/or to better characterize the tumor-immune microenvironment. Various molecular markers with potential predictive value for the treatment of bladder cancer with nivolumab and other immunotherapies are currently under investigation and may be assessed in this study. These tumor tissue biomarkers include, but are not limited to, immunohistochemistry (IHC) for PD-1, PD-L2, tumor-infiltrating lymphocytes (TILs) or subpopulations of TILs, and DNA/RNA sequencing to assess mutational data and gene expression signatures. These tumor samples may also be used to further characterize the tumor-immune microenvironment through assessment of markers that may be associated with the efficacy of nivolumab combination treatment, including, but not limited to, other T-cell checkpoint receptors and ligands (eg, Lag-3, Tim-3), and intra-tumoral immune cell subsets, including macrophages, natural killer (NK) cells, dendritic cells (DCs), and B-cells.

Collection of on-treatment biopsy samples is required in CIS participants at approximately 26 weeks following the first dose of study treatment, and 1 biopsy sample should be obtained in case of recurrence or progression in all participants (see Table 2-2 and Table 2-3). These on-treatment and recurrence biopsies are needed to understand the reasons for disease recurrence, the mechanism of action of nivolumab combinations, and how to benefit patients with optimal treatment strategies. They may be used for the assessment of markers implicated in resistance to immunotherapeutic agents, including, but not limited to, other T-cell checkpoint receptors and ligands (eg, Lag-3, Tim-3) and intratumoral immune cell subsets, including, but not limited to, T-cells, DCs, NK cells, B-cells, macrophages, and myeloid-derived suppressor cells (MDSCs). These samples may also be used to investigate the effect of nivolumab combinations on the expression of potentially relevant predictive and/or prognostic bladder cancer biomarkers. Both the pre- and on-treatment tumor samples and the sample collected upon recurrence may be retrospectively profiled for gene expression/mutation status (using whole genome/exome DNA and RNA sequencing), as well as for the expression of other immune or bladder cancer-related genes, RNAs, microRNA and proteins, or for the presence of immune cell populations using a variety of methodologies inclusive of, but not limited to, IHC, quantitative reverse transcription polymerase chain reaction (qRT-PCR), mass spectrometry, and fluorescent in-situ hybridization (FISH).

9.8.3.2 Peripheral Blood Markers

Per Protocol Amendment 01, peripheral blood markers will not be evaluated.

Not applicable per Protocol Amendment 01:

A variety of factors that may impact the immunomodulatory properties and efficacy of nivolumab combination treatments will be investigated in peripheral blood specimens taken from all participants prior to or during treatment. Data from these investigations will be evaluated for associations with response, survival, and/or safety (AE) data. Several analyses will be completed and are described briefly below.

9.8.3.2.1 Serum-soluble Factors

Per Protocol Amendment 01, serum-soluble factors will not be evaluated.

Not applicable per Protocol Amendment 01:

Blood samples for exploratory serum biomarker analyses will be drawn at specified time points. Additionally, serum samples will be collected when clinically safe and feasible, upon occurrence of drug-related SAEs of a Grade 3 or higher, and/or any laboratory abnormality regarded as a drug-related SAE. Serum samples may be assessed by enzyme-linked immunosorbent assay, seromics, microRNA profiling, circulating tumor DNA measurements, metabolomics, and/or other relevant multiplex-based protein assay methods for immune-related factors that will predict for nivolumab combination benefits or correlate with treatment-related AEs. Numerous potential serum/plasma-based biomarkers are currently under investigation for their potential to predict or correlate with safety or efficacy to nivolumab combinations or other immunotherapies, including, but not limited to, levels of soluble PD-L1, antitumor antibodies, cytokines, chemokines, inflammatory factors, NKG2D ligands (eg, soluble MICA), circulating tumor DNA (ctDNA), and microRNAs (including, but not limited to, miR-513 and miR19b).

9.8.3.2.2 Myeloid-derived Suppressor Cells

Per Protocol Amendment 01, myeloid derived suppressor cells will not be evaluated.

Not applicable per Protocol Amendment 01:

MDSCs are an immune cell population capable of suppressing T-cell activation and proliferation. Low pretreatment MDSC levels in peripheral blood may be associated with better OS in bladder cancer participants treated with nivolumab combinations. MDSCs will be measured at baseline and on-treatment to assess pharmacodynamic (PD) changes or associations with outcome.

9.8.3.2.3 Whole Blood Gene Expression

Per Protocol Amendment 01, whole blood gene expression will not be evaluated.

Not applicable per Protocol Amendment 01:

The expression level of genes related to response to nivolumab combination therapies will be quantified using molecular methods such as Affymetrix by microarray, RNA seq and qRT-PCR analysis in whole blood samples. Analysis may include, but are not necessarily limited to, genes associated with immune-related pathways, such as T-cell activation and antigen processing and presentation.

9.8.3.2.4 Peripheral Blood Mononuclear Cells

Per Protocol Amendment 01, peripheral blood mononuclear cell samples will not be collected.

Not applicable per Protocol Amendment 01:

Peripheral blood samples will be taken prior to initiation of study therapy and at designated time points on-treatment for PBMC preparation. Samples must be shipped within 48 hours to a BMS-designated analytical laboratory for processing.

These PBMC samples may be used for immunophenotyping or characterization of the immune cell subsets in the periphery, including, but not limited to, T-cells, B cells, NK cells, or subpopulations of the aforementioned immune cell types. These samples may also be used to assess immune cell function or antigen specific T-cell proliferation or activation pending emerging information from other nivolumab combination studies.

9.8.3.2.5 Plasma-circulating Tumor DNA

Per Protocol Amendment 01, plasma ctDNA will not be measured.

Not applicable per Protocol Amendment 01:

The presence of cell-free DNA in circulating blood is a well-documented phenomenon. Fragments of DNA are shed into the blood stream from dividing cells during cell proliferation or cell death. In participants with cancer, a fraction of this DNA is tumor derived and is termed ctDNA. Albeit small, fragments of DNA average between 180 to 200 base pairs and specific genomic regions can be amplified with polymerase chain reaction. Moreover, several studies have detected mutations in ctDNA that exactly correspond to mutations from the parent tumor. Using tissue and plasma, BEAMing or similar technology will be utilized to measure cell-free DNA and the presence/frequency of mutations in circulation.

9.8.3.2.6 Whole Blood DNA

Per Protocol Amendment 01, whole blood DNA will not be collected.

Not applicable per Protocol Amendment 01:

Whole blood will be collected from all participants prior to treatment to generate genomic DNA for Single Nucleotide Polymorphism (SNP) analyses. These analyses will focus on SNPs within genes associated with PD-1 and other immunoregulatory signaling pathways to determine if natural variation within those genes is associated with response to nivolumab combinations and/or with AEs during treatment. Sequencing of the blood genomic DNA will also serve as a control to determine the tumor mutational burden (TMB).

9.8.3.3 Urine Markers

Per Protocol Amendment 01, urine markers will not be evaluated.

Not applicable per Protocol Amendment 01:

A variety of immune-related factors that may predict response to treatment have been identified in the urine of bladder cancer patients treated with intravesical BCG. These factors include, but are not limited to, the urinary immune cell infiltrate and urinary cytokine profile after intravesical treatment.[55] The association between these and other urinary factors with response and/or toxicity (AEs) in BCG unresponsive patients undergoing treatment with systemic I-O therapy, with or without intravesical BCG, is currently unknown.

Voided urine specimens will be collected at baseline and during treatment for a subgroup of participants in the current study. Factors that may be associated with treatment outcome and/or

toxicity will be investigated. Data from these investigations will be evaluated for associations with CR, EFS, and safety (AE) data.

9.8.3.4 Microbiome Analysis

Per Protocol Amendment 01, microbiome analysis will not be conducted.

Not applicable per Protocol Amendment 01:

The potential influence of the gut microbiome on bladder cancer treatment outcome is not known. The microbiome is known to affect treatment of certain cancer types (ie, colorectal cancer) through several mechanisms, including promotion of disease via induction of chronic inflammation or catabolism of polyamines on other carcinogenic digestible material. In addition, the innate and adaptive immune system activation state and repertoire may be altered based on local microbiota, leading to differential activity of nivolumab in cancer participants. DNA will be extracted from fecal samples taken prior to therapy and on-treatment (Table 9.8-1). A gene sequencing approach will be utilized to survey microbial species in the gut in order to define microbiota as a function of efficacy and safety. Overall changes in the gut microbiota will also be characterized in individual participants that receive therapy.

9.9 Health Care Resource Utilization and Health Economics

Per Protocol Amendment 01, health care resource utilization and health economics parameters will not be evaluated.

Not applicable per Protocol Amendment 01:

Health care resource utilization data, associated with medical encounters, will be collected in the CRF by the investigator and study-site personnel for all participants throughout the study. Protocol-mandated procedures, tests, and encounters are excluded.

The data collected may be used to conduct exploratory economic analyses and will include:

- Number and duration of medical care encounters, including surgeries, and other selected procedures (inpatient and outpatient)
- Duration of hospitalization (total days length of stay, including duration by wards; eg, intensive care unit)
- Number and character of diagnostic and therapeutic tests and procedures
- Outpatient medical encounters and treatments (including physician or emergency room visits, tests and procedures, and medications)

10 STATISTICAL CONSIDERATIONS

Per Protocol Amendment 01, only descriptive safety and limited investigator-assessed efficacy analyses will be conducted.

10.1 Sample Size Determination

Per Protocol Amendment 01, sample size will be limited to the participants enrolled as of 02-Jun-2021.

Not applicable per Protocol Amendment 01:

The sample size for this study is based on a comparison of the EFS distribution between participants randomized to receive nivolumab plus BCG and participants randomized to receive nivolumab-placebo plus BCG ("BCG alone").

EFS distribution for the control arm ("BCG alone") has been derived from Steinberg et al data.[26] The BCG alone arm is assumed to be a 2-pieces exponential distribution with a 17 months median EFS, 80% EFS rate at first disease assessment (Week 13), and 40% EFS rate at 24 months.

The number of events and power of this primary objective were calculated assuming a proportional hazard model. Approximately 335 events (ie, recurrence, progression, death from any cause) observed among the 700 randomized participants will provides around 90% power to detect a constant hazard ratio (HR) of 0.7 with an overall type 1 error of 0.05 (2-sided), see Table 10.1-1.

The sample size takes into account a 5% drop out for EFS analysis (exponential 10% by Month 24 in each treatment arm).

An HR of 0.7 corresponds to a 52% increase in median EFS (from 17 months in BCG alone vs 26 months in nivolumab plus BCG), a 5.5% absolute EFS rate increase after first disease assessment (from 80% in BCG alone vs 85.5% in nivolumab plus BCG), and a 12.6% absolute EFS rate increase at 24 months (from 40% EFS at 24 months in the BCG alone vs 52.6% EFS at 24 months in nivolumab plus BCG).

Under the above criteria, the critical HR (cHR) would be 0.8, which corresponds to a 30% increase in median EFS (from 17 months in BCG alone vs 22 months in nivolumab plus BCG).

Table 10.1-1: Summary of EFS Assumptions (BCG Alone vs Nivolumab Plus BCG)

Periods	Hazard rates in BCG alone	Hazard rates in Nivolumab plus BCG	Hazard ratio
0 - 3 months	0.0744	0.0521	0.7
> 3 months	0.0330	0.0231	0.7

The accrual will take about 20.5 months (see Section 5.2) to randomize approximately 700 participants.

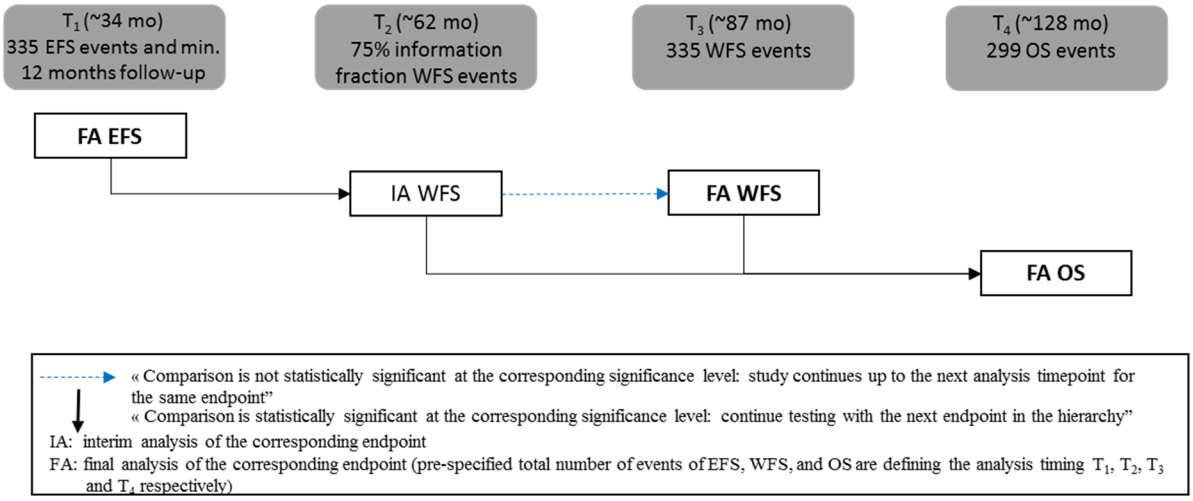
Final analysis of the primary endpoint (primary completion) will occur when at least 335 EFS events are observed, and a minimum of 12 months follow-up have been reached in all randomized participants and is projected to occur approximately 34 months after the start of the study (20.5 months of accrual and 13.5 months of follow-up).

If the required number of EFS events is not reached and all randomized participants have achieved at least 24 months follow-up, the final EFS analysis will be conducted, the statistical characteristics of the design will be recalculated according to the observed number of EFS events at the time of the analysis.

No interim analysis of EFS is planned in this study.

The key secondary endpoints of WFS and OS will be formally compared in all randomized participants using a hierarchical procedure with a fixed sequence approach as summarized in Figure 10.1-1.

Figure 10.1-1: Efficacy Analyses and Timing



WFS could be formally compared only if the primary endpoint of EFS was successful. Given the sample size, approximately 335 WFS events in all randomized subjects will provide approximately 90% power to detect an HR of 0.7 with an overall type I error of 5% (2-sided). This corresponds to a median WFS increase from 5 years to 7.1 years under exponential assumption. The calculation accounts for approximately 14% drop out for WFS analysis (exponential with 20% by 60 months).

One interim WFS analysis is planned using Lan-DeMets alpha spending function with the O'Brien-Fleming type of boundary after approximately 250 WFS events are observed (about 75% of targeted number of WFS events) and is expected to occur approximately 3.4 years after the end of accrual (about 62 months after FPFV). If the interim WFS analysis is performed exactly at 250 events, the boundary in terms of statistical significance for declaring superiority would be 0.019 (cHR = 0.74).

The boundary for declaring superiority in terms of statistical significance for the final WFS analysis after 335 events would be 0.044 (cHR = 0.80). The final analysis of WFS is projected to occur approximately 87 months after the start of the study (approximately 20.5 months accrual and 66.5 months follow-up).

OS could be formally compared only if EFS and WFS were successful. Given the sample size, approximately 299 deaths in all randomized subjects will provide approximately 70% power to detect an HR of 0.75 with an overall type I error of 5% (2-sided). This corresponds to a median OS increase from 9.7 years to 13.0 years under exponential assumption. The final analysis of OS

is projected to occur approximately 128 months after the start of the study (approximately 20.5 months accrual and 108 months follow-up). Under the above criteria, the critical HR would be 0.79.

If the required number of OS events is not reached and all randomized participants have achieved at least 10 years follow-up, the final OS analysis will be conducted, the statistical characteristics of the design will be recalculated according to the observed number of OS events at the time of the analysis.

East version 6.4 was used for sample size/power computations.

10.2 Populations for Analyses

Per Protocol Amendment 01, only safety assessments will be conducted.

For purposes of analysis per Protocol Amendment 01, the following populations are defined:

Population	Description
Enrolled	All participants who signed informed consent form and were registered into IRT
Randomized	All enrolled participants randomized via IRT
Treated	All participants who take at least 1 dose of study treatment

Unless otherwise specified, the safety analyses will be conducted in all treated participants.

Unless otherwise specified, the investigator-assessed efficacy analyses will be conducted in all randomized participants.

Not applicable per Protocol Amendment 01:

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign informed consent and were registered into IRT
Randomized	All enrolled participants randomized via IRT
Randomized CIS	All randomized participants with CIS (with or without papillary disease) per PRC at baseline
Randomized non-CIS	All randomized participants without CIS per PRC at baseline
Treated	All participants who take at least 1 dose of study treatment
PK	All participants with available serum time-concentration data from randomized participants dosed with nivolumab
Immunogenicity	All participants with available data from randomized participants dosed with nivolumab
Immunogenicity evaluable	All treated participants with baseline and at least 1 post-baseline immunogenicity assessment

HEOR	All treated participants who have an assessment at baseline and at least 1 subsequent assessment.
Biomarker	All randomized participants with available biomarker data (PD-L1 expression status and other assays)

Unless otherwise specified, the safety analyses will be conducted in all treated subjects.

Unless otherwise specified, the efficacy analyses will be conducted in all randomized subjects.

10.3 Statistical Analyses

The Statistical Analysis Plan (SAP) will be developed and finalized before the first database lock and will describe the selection of participants to be included in the analyses and procedures for accounting for missing, unused, and spurious data. Below is a summary of planned statistical analyses of the primary and secondary endpoints.

A description of the participant population will be included in a statistical output report, including subgroups of age, gender, and race.

10.3.1 Efficacy Analyses

Per Protocol Amendment 01, descriptive analyses of investigator-assessed efficacy will be collated as listings.

Not applicable per Protocol Amendment 01:

Endpoint	Statistical Analysis Methods
Primary	
EFS per PRC of nivolumab plus BCG vs "BCG alone" The primary definition of EFS is defined as the time between the date of randomization and the date of first documented event or death due to any cause, whichever occurs first. Events include recurrence of disease (TaHG, T1, or CIS) and progression of disease. For participants with CIS (with or without papillary disease) at study entry, lack of CR at Week 13 assessment will be considered an event. Participants who die without a reported progression/disease recurrence will be considered to have experienced an event on the date of their death. Participants who did not report progression or recurrence of disease or die will be censored on the date of their last evaluable tumor assessment. Participants who did not have any on- study tumor assessments and did not die will be censored on their date of randomization. The primary definition of EFS accounts for subsequent therapy by censoring at the last evaluable disease assessment on or prior to the date of subsequent therapy.	EFS will be analyzed in all randomized participants and will be compared between the 2 treatment arms using a stratified 2-sided log rank test with an overall 5% alpha. The HR and the corresponding 2-sided 95% confidence interval (CI) will be estimated in a stratified Cox proportional hazard model using the randomized arm as a single covariate, stratified by the stratification factors, corresponding to the comparison of EFS. The EFS curves for each randomized arm will be estimated using the Kaplan-Meier (KM) product-limit method. In addition, EFS rates at specific time points will be estimated using KM estimates on the EFS curve for each randomized arm. Associated 2-sided 95% CIs will be calculated using the Greenwood formula (using log-log transformation).

Endpoint	Statistical Analysis Methods
Further details on the censoring rules for consideration of subsequent therapies will be described in the Statistical Analysis Plan (SAP).	
Secondary	
WFS of nivolumab plus BCG vs "BCG alone" WFS is defined as the time from randomization to progression to muscle-invasive disease (ie, T2), cystectomy, systemic chemotherapy, radiotherapy, or death from any cause.	The hypothesis testing will only be performed if the higher hierarchical endpoint (eg, EFS) is met, as described in the SAP. WFS will be analyzed in all randomized participants and will be compared between the 2 treatment arms using a stratified 2-sided log rank test with an overall 5% alpha. The HR and the corresponding 2-sided (100-adjusted alpha)% confidence interval (CI) will be estimated in a stratified Cox proportional hazard model using the randomized arm as a single covariate, stratified by the stratification factors, corresponding to the comparison of WFS. The WFS curves for each randomized arm will be estimated using the KM product-limit method. In addition, WFS rates at specific time points will be estimated using KM estimates on the WFS curve for each randomized arm. Associated 2-sided 95% CIs will be calculated using the Greenwood formula.
OS of nivolumab plus BCG vs "BCG alone" OS is defined as the time between the date of randomization and the date of death due to any cause. For participants still alive, OS is censored at the last date the participant is known to be alive.	The hypothesis testing will only be performed if the higher hierarchical endpoints (EFS and WFS) are met, as described in the SAP. OS will be analyzed in all randomized participants and will be compared between the 2 treatment arms using a stratified 2-sided log rank test with an overall 5% alpha. The HR and the corresponding 2-sided 95% confidence interval (CI) will be estimated in a stratified Cox proportional hazard model using the randomized arm as a single covariate, stratified by the stratification factors, corresponding to the comparison of OS. The OS curves for each randomized arm will be estimated using the KM product-limit method. In addition, OS rates at specific time points will be estimated using KM estimates on the OS curve for each randomized arm. Associated 2-sided 95% CIs will be calculated using the Greenwood formula.
CRR at Week 13 CRR is defined as the proportion of participants with CIS (+/- TaHG/T1) per PRC at randomization who are disease free at the first disease assessment (Week 13).	CRR will be analyzed in all randomized participants with CIS (with or without papillary disease) per PRC at baseline with disease assessment at Week 13. Estimates of response rate, along with its exact 2-sided 95% CI by Clopper and Pearson,[56] will be presented by treatment group.

Endpoint	Statistical Analysis Methods
Duration of Response (DoR) DoR is defined as the time between the date of the first CR to the date of first documented recurrence, progression, or death due to any cause.	DoR will be analyzed in all randomized participants with CIS (with or without papillary disease) per PRC at baseline and achieved CR at first disease assessment (ie, Week 13). The DoR for each treatment group will be estimated using the KM product limit method and will be displayed graphically. A table will be produced presenting number of events, number of subjects involved, medians, and 95% CIs for the medians. Median values of DoR, along with 2-sided 95% CI in each treatment group will be computed based on a log-log transformation method.
Exploratory	
Exploratory efficacy endpoints definitions and analysis methods will be described in the SAP finalized before first database lock	

Additional sensitivity analyses for primary and secondary endpoints will also be performed, details will be included in the SAP.

10.3.2 Safety Analyses

Limited safety analysis will be performed in all treated participants and will be described in the SAP.

Endpoint	Statistical Analysis Methods
Secondary	
Safety	Descriptive statistics of safety will be presented using NCI CTCAE version 5.0 by treatment group. All on-study AEs, treatment-related AEs, AEs leading to discontinuation, IMAEs, SAEs, and treatment-related SAEs, and deaths will be tabulated using worst grade per NCI CTCAE version 5.0 criteria by system organ class and preferred term. On-study laboratory parameters including hematology, chemistry, liver function, and renal function will be summarized using worst grade NCI CTCAE version 5.0 criteria. Events reported from the first dose up to and including 100 days following the last dose of study treatment could be included in estimating this incidence rate.

10.3.3 Other Analyses

***Not applicable per Protocol Amendment 01*:**

Outcome research, PK, PD, immunogenicity, and biomarker exploratory analyses will be described in the SAP finalized before first database lock. The PPK and PD analyses will be presented separately from the main clinical study report.

10.3.3.1 Pharmacokinetic Analyses

***Not applicable per Protocol Amendment 01*:**

The nivolumab concentration data obtained in this study may be combined with data from other studies in the clinical development program to develop PPK models. These models may be used to evaluate the effects of intrinsic and extrinsic covariates on the PK of nivolumab and to determine measures of individual exposure (such as steady state peak, trough, and time averaged concentration). Model determined exposures may be used for E-R analyses of selected efficacy and safety endpoints. If the analyses are conducted, the results of PPK and E-R analyses will be reported separately.

10.3.3.2 Immunogenicity Analyses

***Not applicable per Protocol Amendment 01*:**

Methodology for analysis of immunogenicity will be described in the SAP.

10.3.3.3 Outcomes Research Analyses

***Not applicable per Protocol Amendment 01*:**

PRO measures include EORTC QLQ-C30, EORTC QLQ-NMIBC24, and EQ-5D-5L. Methodology for analysis of PROs will be described in the SAP.

10.3.4 Interim Analyses

***Not applicable per Protocol Amendment 01*:**

No interim analysis is planned for the primary endpoint of EFS.

One interim analysis is planned for the first secondary endpoint of WFS at 75% information fraction, as described in Section 10.1, Sample Size Determination.

11 REFERENCES

[1] Bellmunt J, de Wit R, Vaughn Dj, et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. N Engl J Med 2017;376:1015-26.

[2] Sharma P, Retz M, Siefker-Radtke A, et al. Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): A multicentre, single-arm, phase 2 trial. Lancet Oncol 2017;18:312-22.

[3] Rosenberg JE, Hoffman-Censits J, Powles, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: A single-arm, multicentre, phase 2 trial. Lancet 2016;387:1909-20.

[4] Antoni S, Ferlay J, Soerjomataram I, et al. Bladder cancer incidence and mortality: A global overview and recent trends. Eur Urol 2017;17:96-108.

[5] Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87-108.

[6] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin 2017;67:7-30.

[7] Chang SS, Boorjian SA, Chou R, et al. Diagnosis and treatment of non-muscle invasive bladder cancer: AUA/SUO guideline. J Urol 2016;196:1021-9.

[8] Kamat AM, Hahn NM, Efstathiou JA, et al. Bladder cancer. Lancet 2016;388:2796-2810.

[9] Nielsen ME, Smith AB, Meyer AM, et al. Trends in stage-specific incidence rates for urothelial carcinoma of the bladder in the United States: 1988 to 2006. Cancer 2014;120:86-95.

[10] Morales A, Eidinger D, Bruce AW. Intracavitary bacillus Calmette-Guerin in the treatment of superficial bladder tumors. J Urol 1976;116:180-3.

[11] Chou R, Buckley D, Fu R, et al. Emerging approaches to diagnosis and treatment of non-muscle-invasive bladder cancer [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US): 2015. Report No.: 15(16)-EHC017-EF. AHRQ Comparative Effectiveness Reviews.

[12] Lamm DL, Blumenstein BA, Crissman JD, et al. Maintenance bacillus Calmette-Guerin immunotherapy for recurrent TA, T1 and carcinoma in situ transitional cell carcinoma of the bladder: a randomized Southwest Oncology Group Study. J Urol 2000;163:1124-9.

[13] Sylvester RJ, van der Meijden AP, Lamm DL. Intravesical bacillus Calmette-Guerin reduces the risk of progression in patients with superficial bladder cancer: a meta-analysis of the published results of randomized clinical trials. J Urol 2002;168:1964-70.

[14] Shelley MD, Kynaston H, Court J, et al. A systematic review of intravesical bacillus Calmette-Guerin plus transurethral resection vs transurethral resection alone in Ta and T1 bladder cancer. BJU Int 2001;88:209-16.

[15] Han RF, Pan JG. Can intravesical bacillus Calmette-Guerin reduce recurrence in patients with superficial bladder cancer? A meta-analysis of randomized trials. Urology 2006;67:1216-23.

[16] Oddens J, Brausi M, Sylvester R, et al. Final results of an EORTC-GU cancers group randomized study of maintenance bacillus Calmette-Guerin in intermediate- and high-risk Ta, T1 papillary carcinoma of the urinary bladder; one-third dose versus full dose and 1 year versus 3 years of maintenance. Eur Urol 2013;63:462-72.

[17] Sylvester RJ, Brausi MA, Kirkels WJ, et al. Long-term efficacy results of EORTC genito-urinary group randomized phase 3 study 30911 comparing intraveical instillations of epirubicin, bacillus Calmette-Guerin, and bacillus Calmette-Guerin plus isoniazid in patients with intermediate- and high-risk stage Ta T1 urothelial carcinoma of the bladder. Eur Urol 2010;57:766-73.

[18] Babjuk M, Oosterlinck W, Sylvester R, et al. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder, the 2011 update. Eur Urol 2011;59:997-1008.

[19] Fernandez-Gomez J, Madero R, Solsona E, et al. Predicting nonmuscle invasive bladder cancer recurrence and progression in patients treated with bacillus Calmette-Guerin: The CUETO scoring model. J Urol 2009;182:2195-203.

[20] Catalona WJ, Hudson MA, Gillen DP, et al. Risks and benefits of repeated courses of intravesical bacillus Calmette-Guerin therapy for superficial bladder cancer. J Urol 1987;137:220-4.

[21] US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research. BCG-unresponsive non-muscle invasive bladder cancer: Developing drugs and biologics for treatment guidance for industry. February 2018.

[22] Lerner SP, Dinney C, Kamat A, et al. Clarification of bladder cancer disease states following treatment of patients with intravesical BCG. Bladder Cancer 2015;1:29-30.

[23] BMS-936558: A Phase 2, Randomized, Open-label Study of Nivolumab or Nivolumab/BMS-986205 Alone or Combined with Intravesical BCG in Participants with BCG-Unresponsive, High-Risk, Non-Muscle Invasive Bladder Cancer. (Study CA2099UT). Bristol-Myers Squibb Company; 2017. Document Control No. 930120285.

[24] Li R, Spiess PE, Kamat AM. Treatment Options for Patients with Recurrent Tumors After BCG Therapy: Are We Ignoring the Obvious? European Urology [22 Apr 2018, 74(4):405-408]

[25] Sylvester RJ, van der Meijden AP, Oosterlinck W, et al. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. Eur Urol 2006;49(3):466-5.

[26] Steinberg RL, Thomas LJ1, Mott SL, O'Donnell MA. Bacillus Calmette-Guérin (BCG) treatment failures with non-muscle invasive bladder cancer: A data-driven definition for BCG unresponsive disease. Bladder Cancer 2016;2(2):215-24.

[27] Johnson SC, Smith ZL, Golan S, et al. Temporal trends in perioperative morbidity for radical cystectomy using the National Surgical Quality Improvement Program database. Urol Oncol 2017;Aug 1. doi; 10.1016/j.urolonc.2017.07.013. [Epub ahead of print]

[28] Gore JL, Litwin MS, Lai J, et al. Use of radical cystectomy for patients with invasive bladder cancer. J Natl Cancer Inst 2010;102:802-11.

[29] von der Maase H, Hansen SW, Roberts JT, et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, Phase 3 study. J Clin Oncol 2000;18:3068-77.

[30] Pardoll D. Does the immune system see tumors as foreign or self? Annu Rev Immunol. 2003;21:807-39.

[31] Redelman-Sidi G, Glickman MS, Bochner BH. The mechanism of action of BCG therapy for bladder cancer—a current perspective. Nat Rev Urol 2014;11:153-62.

[32] Tsuji S, Matsumoto M, Takeuchi O, et al. Maturation of human dendritic cells by cell wall skeleton of Mycobacterium bovis bacillus Calmette-Guerin: Involvement of toll-like receptors. Infect Immun 2000;68:6883-90.

[33] Balar AV, Kulkarni GS, Uchio EM, et al. Keynote 057: Phase II trial of pembrolizumab (pembro) for patients (pts) with high-risk (HR) nonmuscle invasive bladder cancer (NMIBC) unresponsive to bacillus Calmette-Guérin (BCG). J Clin Oncol 2019;37(7 suppl):350.

[34] Inman BA, Sebo TJ, Frigola X, et al. PD-L1 (B7-H1) expression by urothelial carcinoma of the bladder and BCG-induced granulomata: associations with localized stage progression. Cancer 2007;109:1499-1505.

[35] Farina MS, Lundgren KT, Bellmunt J. Immunotherapy in urothelial cancer: Recent results and future perspectives. Drugs 2017;77:1077-89.

[36] Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics: Guidance for Industry. December 2018. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-trial-endpoints-approval-cancer-drugs-and-biologics (Accessed July 2, 2019)

[37] Jarow JP, Lerner SP, Kluetz PG, et al. Clinical trial design for the development of new therapies for nonmuscle-invasive bladder cancer: Report of a Food and Drug Administration and American Urological Association public workshop. Urology 2014;83(2):262-4.

[38] Svatek RS, Tangen C, Delacroix S, et al. Background and Update for S1602 “A Phase III Randomized Trial to Evaluate the Influence of BCG Strain Differences and T Cell Priming with Intradermal BCG Before Intravesical Therapy for BCG-naïve High-grade Non-muscle-invasive Bladder Cancer. Eur Urol Focus 4(2018):522-524.

[39] Weber J, Mandala M, Del Vecchio M, et al. Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. N Engl J Med 2017;377(19):1824-35.

[40] OPDIVO® (nivolumab) US Prescribing Information. Bristol-Myers Squibb, Princeton, NJ. February 2018.

[41] Opdivo. Annex I Summary of Product Characteristics. Bristol-Myers Squibb Company. 2018.

[42] Witjes JA, Dalbagni G, Karnes RJ, et al. The efficacy of BCG TICE and BCG Connaught in a cohort of 2,099 patients with T1G3 non-muscle-invasive bladder cancer. Urol Oncol 2016;34:484.

[43] Gandhi NM, Morales A, Lamm DL. Bacillus Calmette-Guérin immunotherapy for genitourinary cancer. BJU Int. 2013 Aug;112(3):288-97. doi 10.1111/j.1464-410X.2012.11754.x. Epub 2013 Mar 20.

[44] Sylvester RJ. Bacillus Calmette-Guérin treatment of non-muscle invasive bladder cancer. Int J Urol. 2011 Feb;18(2):113-20. doi: 10.1111/j.1442-2042.2010.02678.x. Epub 2010 Nov 22.

[45] Ashton A, Murthy Kusuma VR, Crew J2, Mostafid AH. BCG therapy in NMIBC: How much and for how long? Arch Esp Urol. 2018 May;71(4):342-348.

[46] Cheng CW, Ng MT, Chan SY, Sun WH. Low dose BCG as adjuvant therapy for superficial bladder cancer and literature review. ANZ J Surg. 2004 Jul;74(7):569-72.

[47] Kamat AM, Sylvester RJ, Böhle A, Palou J, Lamm DL, Brausi M, Soloway M, Persad R, Buckley R, Colombel M, Witjes JA. Definitions, End Points, and Clinical Trial Designs for Non-Muscle-Invasive Bladder Cancer: Recommendations From the International Bladder Cancer Group. J Clin Oncol. 2016 Jun 1;34(16):1935-44. doi: 10.1200/JCO.2015.64.4070. Epub 2016 Jan 25.

[48] Kim PH, Sukhu R, Cordon BH, et al. Reflex fluorescence in situ hybridization assay for suspicious urinary cytology in patients with bladder cancer with negative surveillance cystoscopy. BJU Int 2014;114(3):354-9.

[49] Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85(5):365-76.

[50] Osoba D, Rodrigues G, Myles J, et al. Interpreting the significance of changes in health-related quality of life scores. J Clin Oncol 1998;16:139-44.

[51] Blazeby JM, Hall E, Aaronson NK, et al. Validation and reliability testing of the EORTC QLQ-NMIBC24 questionnaire module to assess patient-reported outcomes in non-muscle invasive bladder cancer. Eur Urol 2014;66:1148-56.

[52] Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011;20(10):1727-36.

[53] van Hout B, Janssen MF, Feng YS, et al. Interim scoring for the EQ-5D-5L: Mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health 2012;15(5):708-15.

[54] Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. Health Qual Life Outcomes 2007;5(1):70.

[55] Kamat AM, Li R, O'Donnell MA, et al. Predicting response to intravesical bacillus Calmette-Guérin immunotherapy: Are we there yet? A systematic review. Eur Urol 2018;73(5):738-48.

[56] Clopper C, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 1934;26:404-13.

12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
ADA	anti-drug antibody
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AT	aminotransaminases
AUA	American Urological Association
BCG	bacillus Calumette-Guerin
BMS	Bristol-Myers Squibb
Cavg	average concentration
CBC	complete blood count
CFR	Code of Federal Regulations
CFS	cystectomy-free survival
cHR	critical hazard ratio
CI	confidence interval
CIS	carcinoma in situ
Cmin	minimum observed concentration
CMV	cytomegalovirus
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CR	complete response
CRF	case report form, paper or electronic
CRR	complete response rate
CT	computed tomography
CTAg	clinical trial agreement
ctDNA	circulating tumor DNA
CTLA-4	cytotoxic T-lymphocyte-associated protein-4
DC	dendritic cell

Term	Definition
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DOR	duration of response
DRESS	drug reaction with eosinophilia and systemic symptoms
DSS	disease specific survival
EAU	European Association of Urology
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
EFS	event-free survival
ELISA	enzyme-linked immunosorbent assay
EOI	end of infusion
EORTC-QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Cancer
EORTC QLQ-NMIBC24	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Non-muscle-invasive Bladder Cancer
EOT	end of treatment
EQ-5D-3L	EuroQoL 5-dimensions 3-levels (quality of life questionnaire)
EQ-5D-5L	EuroQoL 5-dimensions 5-levels (quality of life questionnaire)
E-R	exposure-response
FDA	Food and Drug Administration
FISH	fluorescent in-situ hybridization
FSH	follicle stimulating hormone
FPFV	first patient, first visit
FU	follow-up
GBS	Guillain-Barre Syndrome
GM-CSF	granulocyte-macrophage colony-stimulating factor
GFR	glomerular filtration rate
H&E	hematoxylin and eosin
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus

Term	Definition
HCG	human chorionic gonadotropin
HCV	hepatitis C virus
HG	high-grade
HIPAA	Health Insurance Portability and Accountability Act (US)
HIV	Human Immunodeficiency Virus
HR	hazard ratio
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IFN	interferon
IHC	immunohistochemistry
IMAEs	immune-mediated AEs
IMP	investigational medicinal products
I-O	immuno-oncology(ic)
IP	investigational product
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	intravenous
KM	Kaplan-Meier
MDSC	myeloid-derived suppressor cell
MG	myasthenia gravis
MID	minimal important difference
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
N/A	not applicable
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK	natural killer

Term	Definition
NMIBC	non-muscle invasive bladder cancer
Non-IMP	noninvestigational medicinal product
Non-IP	noninvestigational product
NSCLC	non-small cell lung cancers
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic
PD-1	programmed cell death protein-1
PD-LI, PD-L2	programmed cell death-ligand 1, programmed cell death-ligand 2
PFS	progression-free survival
PK	pharmacokinetic
PPK	population pharmacokinetics
PRC	Pathology Review Committee
PROs	patient-reported outcomes
PS	Performance Status
Q2W, Q3W, Q4W	quaque (every) 2 weeks, quaque (every) 3 weeks, quaque (every) 4 weeks
QoL	quality of life
qRT-PCR	quantitative reverse transcription polymerase chain reaction
R&D	Research and Development
RBC	red blood cell
RCC	renal cell carcinoma
RT-PCR	reverse transcriptase polymerase chain reaction
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCCHN	squamous cell carcinoma of the head and neck
SJS	Stevens-Johnson syndrome
SmPC	Summary of Product Characteristics
SNP	single nucleotide polymorphism

Term	Definition
SOC	standard of care
SOP	Standard Operating Procedures
SUSAR	suspected unexpected serious adverse reaction
TaHG	high-grade papillary Ta tumor
TaLG	low-grade papillary Ta tumor
TBili	total bilirubin
TEN	toxic epidermal necrolysis
TILs	tumor-infiltrating lymphocytes
TNF	tumor necrosis factor
TURBT	transurethral resection of the bladder tumor
UC	urothelial carcinoma
ULN	upper limit of normal
US	United States
USPI	US Prescribing Information
UTI	urinary tract infection
VAS	visual analog scale
WBC	white blood cell
WFS	worsening-free survival
WOCBP	women of childbearing potential

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

The term "participant" is used in the protocol to refer to a person who has consented to participate in the clinical research study. The term "subject" used in the case report form (CRF) is intended to refer to a person (participant) who has consented to participate in the clinical research study.

REGULATORY AND ETHICAL CONSIDERATIONS

GOOD CLINICAL PRACTICE

This study will be conducted in accordance with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines Good Clinical Practice (GCP),
- as defined by the International Council on Harmonisation (ICH)
- in accordance with the ethical principles underlying European Union Directive 2001/20/EC,
- United States Code of Federal Regulations, Title 21, Part 50 (21CFR50), and
- applicable local requirements.

The study will be conducted in compliance with the protocol. The protocol and any amendments and the participant informed consent will receive approval/favorable opinion by Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and regulatory authorities according to applicable local regulations prior to initiation of the study.

All potential serious breaches must be reported to the Sponsor or designee immediately. A potential serious breach is defined as a Quality Issue (eg, protocol deviation, etc) that is likely to affect, to a significant degree one or more of the following: (1) the physical, safety or mental integrity of one or more subjects/participants; (2) the scientific value of the trial (eg, reliability and robustness of generated data). Items (1) or (2) can be associated with either GCP Regulation(s) or Trial protocol(s).

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, participant recruitment materials (eg, advertisements), and any other written information to be provided to subjects/participants. The investigator or BMS should also provide the IRB/IEC with a copy of the Investigator's Brochure (IB) or product labeling information to be provided to subjects/participants and any updates.

The investigator, Sponsor or designee should provide the IRB/IEC with reports, updates and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion of an amendment from the IRB/IEC (and, if applicable, also by local health authority) except where necessary to eliminate an immediate hazard(s) to study subjects/participants.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining relevant approval/favorable opinion(s), the deviation or change will be submitted as soon as possible to:

- IRB/IEC
- Regulatory Authority(ies), if applicable by local regulations (per national requirements)

Documentation of approval/favorable opinion signed by the chairperson or designee of the IRB(s)/IEC(s) and if applicable, also by local health authority must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the participant: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects/participants currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects/participants prior to enrollment.

If the revision is done via an administrative letter, investigators must inform their IRB(s)/IEC(s).

FINANCIAL DISCLOSURE

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

INFORMED CONSENT PROCESS

Investigators must ensure that subjects/participants are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

In situations where consent cannot be given by subjects/participants, their legally acceptable representatives (as per country guidelines) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the participant volunteers to participate.

Sponsor or designee will provide the investigator with an appropriate (ie, Global or Local) sample informed consent form which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

- Provide a copy of the consent form and written information about the study in the language in which the participant is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
- Allow time necessary for participant or participant's legally acceptable representative to inquire about the details of the study.
- Obtain an informed consent signed and personally dated by the participant or the participant's legally acceptable representative and by the person who conducted the informed consent discussion.
- Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects/participants, prior to the beginning of the study, and after any revisions are completed for new information.

If informed consent is initially given by a participant's legally acceptable representative or legal guardian, and the participant subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the participant.

Revise the informed consent whenever important new information becomes available that is relevant to the participant's consent. The investigator, or a person designated by the investigator, should fully inform the participant or the participant's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the participant's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify subjects/participants must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects'/participants' signed ICF and, in the US, the subjects'/participants' signed HIPAA Authorization.

The consent form must also include a statement that BMS and regulatory authorities have direct access to participant records.

The rights, safety, and well-being of the study subjects/participants are the most important considerations and should prevail over interests of science and society.

SOURCE DOCUMENTS

The Investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original and attributable, whether the data are hand-written on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic

devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records (EMRs/EHRs), adverse event tracking/reporting, protocol required assessments, and/or drug accountability records).

When paper records from such systems are used in place of electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

STUDY TREATMENT RECORDS

Records for study treatments, including investigational and no-investigational products (whether supplied by BMS, its vendors, or the site) must substantiate study treatment integrity and traceability from receipt, preparation, administration, and through destruction or return. Records must be made available for review at the request of BMS/designee or a Health Authority.

If	Then
Supplied by BMS (or its vendors):	Records or logs must comply with applicable regulations and guidelines and should include: • amount received and placed in storage area • amount currently in storage area • label identification number or batch number • amount dispensed to and returned by each participant, including unique participant identifiers • amount transferred to another area/site for dispensing or storage • nonstudy disposition (eg, lost, wasted) • amount destroyed at study site, if applicable • amount returned to BMS • retain samples for bioavailability/bioequivalence/biocomparability, if applicable • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.
Sourced by site, and not supplied by BMS or its vendors (examples include IP sourced from the sites stock or	The investigator or designee accepts responsibility for documenting traceability and study treatment integrity in accordance with requirements applicable

If	Then
commercial supply, or a specialty pharmacy)	under law and the SOPs/standards of the sourcing pharmacy.

BMS or designee will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

CASE REPORT FORMS

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

For sites using the Sponsor or designee electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the electronic SAE form and Pregnancy Surveillance form, respectively. If electronic SAE form is not available, a paper SAE form can be used.

The confidentiality of records that could identify subjects/participants must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form. Subinvestigators in Japan may not be delegated the CRF approval task. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet Sponsor or designee training requirements and must only access the BMS electronic data capture tool using the unique user account provided by Sponsor or designee. User accounts are not to be shared or reassigned to other individuals.

MONITORING

Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable.

In addition, the study may be evaluated by Sponsor or designee internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential. The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to Sponsor or designee.

RECORDS RETENTION

The investigator (or head of the study site in Japan) must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS or designee, whichever is longer. The investigator (or head of the study site in Japan) must contact BMS prior to destroying any records associated with the study.

BMS or designee will notify the investigator (or head of the study site in Japan) when the study records are no longer needed.

If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another investigator, study site, IRB). Notice of such transfer will be given in writing to BMS or designee.

RETURN OF STUDY TREATMENT

For this study, study treatments, including investigational and non-investigational products (those supplied by BMS, a vendor or sourced by the investigator) such as partially used study treatment containers, vials and syringes may be destroyed on site.

If	Then
Study treatments supplied by BMS (including its vendors	Any unused study treatments supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless study treatments containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics). If study treatments will be returned, the return will be arranged by the responsible Study Monitor.
Study treatments sourced by site, not supplied by BMS (or its vendors) (examples include study treatments sourced from the sites stock	It is the investigator's or designee's responsibility to dispose of all containers

If	Then
or commercial supply, or a specialty pharmacy)	according to the institutional guidelines and procedures.

It is the investigator's or designee's responsibility to arrange for disposal, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The following minimal standards must be met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

It is the investigator's or designee's responsibility to arrange for disposal of all empty containers.

If conditions for destruction cannot be met the responsible Study Monitor will make arrangements for return of study treatments provided by BMS (or its vendors). Destruction of non- study treatments sourced by the site, not supplied by BMS, is solely the responsibility of the investigator or designee.

DISSEMINATION OF CLINICAL STUDY DATA

In order to benefit potential study participants, patients, healthcare providers and researchers, and to help BMS honor its commitments to study participants, BMS will make information about clinical research studies and a summary of their results available to the public as per regulatory and BMS requirements. BMS will post study information on local, national or regional databases in compliance with national and international standards for disclosure. BMS may also voluntarily disclose information to applicable databases.

CLINICAL STUDY REPORT

A Signatory Investigator must be selected to sign the clinical study report.

For each CSR related to this protocol, the following criteria will be used to select the signatory investigator:

- External Principal Investigator designated at protocol development

- National Coordinating Investigator
- Study Steering Committee chair or their designee
- Participant recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design
- Regional representation (eg, among top quartile of enrollers from a specified region or country)
- Other criteria (as determined by the study team)

SCIENTIFIC PUBLICATIONS

The data collected during this study are confidential and proprietary to Sponsor or designee. Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the clinical trial agreement (CTAg) governing [Study site or Investigator] participation in the study. These requirements include, but are not limited to, submitting proposed publications to Sponsor or designee at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTAg.

Scientific Publications (such as abstracts, congress podium presentations and posters, and manuscripts) of the study results will be a collaborative effort between the study Sponsor and the external authors. No public presentation or publication of any interim results may be made by any principal investigator, sub-investigator or any other member of the study staff without the prior written consent of the Sponsor.

Authorship of publications at BMS is aligned with the criteria of the International Committee of Medical Journal Editors (ICMJE, www.icmje.org). Authorship selection is based upon significant contributions to the study (ie, ICMJE criterion #1). Authors must meet all 4 ICMJE criteria for authorship:

1) Substantial intellectual contribution to the conception or design of the work; or the acquisition of data (ie, evaluable subjects with quality data), analysis, or interpretation of data for the work (eg, problem solving, advice, evaluation, insights and conclusion); AND
2) Drafting the work or revising it critically for important intellectual content; AND
3) Final approval of the version to be published; AND
4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Those who make the most significant contributions, as defined above, will be considered by BMS for authorship of the primary publication. Sub-investigators will generally not be considered for authorship in the primary publication. Geographic representation will also be considered.

Authors will be listed by order of significant contributions (highest to lowest), with the exception of the last author. Authors in first and last position have provided the most significant contributions to the work.

For secondary analyses and related publications, author list and author order may vary from primary to reflect additional contributions.

APPENDIX 3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW UP AND REPORTING

ADVERSE EVENTS

Adverse Event Definition:

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study treatment and that does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study treatment, whether or not considered related to the study treatment.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or results from other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Note that abnormal lab tests or other safety assessments should only be reported as AEs if the final diagnosis is not available. Once the final diagnosis is known, the reported term should be updated to be the diagnosis.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose, as a verbatim term (as reported by the investigator), should not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae and should specify "intentional overdose" as the verbatim term

Events NOT Meeting the AE Definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

DEFINITION OF SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

SERIOUS ADVERSE EVENTS

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
Requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below) NOTE: The following hospitalizations are not considered SAEs in BMS clinical studies: • a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event) • elective surgery, planned prior to signing consent • admissions as per protocol for a planned medical/surgical procedure • routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy) • medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases • admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason) • admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)
Results in persistent or significant disability/incapacity
Is a congenital anomaly/birth defect
Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the participant or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 9.2.7 for the definition of potential DILI.)

Pregnancy and potential drug induced liver injury (DILI) must follow the same transmission timing and processes to BMS as used for SAEs (see section 9.2.5 for reporting pregnancies).

EVALUATING AES AND SAES

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

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

If an ongoing SAE changes in its intensity or relationship to study treatment or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

- SAEs, whether related or not related to study treatment, and pregnancies must be reported to BMS (or designee) immediately within 24 hours of awareness of the event.
- SAEs must be recorded on the SAE Report Form.
  - The required method for SAE data reporting is through the eCRF.
  - The paper SAE Report Form is only intended as a back-up option when the electronic data capture (EDC) system is unavailable/not functioning for transmission of the eCRF to BMS (or designee).
    - In this case, the paper form is transmitted via email or confirmed facsimile (fax) transmission
    - When paper forms are used, the original paper forms are to remain on site
- Pregnancies must be recorded on a paper Pregnancy Surveillance Form and transmitted via email or confirmed facsimile (fax) transmission.

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

SAE Telephone Contact (required for SAE and pregnancy reporting): Refer to Contact Information list

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone (FSH) level > 40 mIU/mL to confirm menopause.

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILDBEARING POTENTIAL

One of the highly effective methods of contraception listed below is required during study duration and until the end of relevant systemic exposure, defined as 5 months after the end of study treatment.*****

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of < 1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation/or implantation (These methods of contraception cannot be used by WOCBP participants in studies where hormonal contraception is prohibited)[b] – oral (birth control pills) – intravaginal (vaginal birth control suppositories, rings, creams, gels) – transdermal

• Progestogen-only hormonal contraception associated with inhibition of ovulation[b] – oral – injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation and/or implantation (This method of contraception cannot be used by WOCBP participants in studies where hormonal contraception is prohibited)[b] • Intrauterine hormone-releasing system (IUS)(This method of contraception cannot be used by WOCBP participants in studies where hormonal contraception is prohibited)[c] • Intrauterine device (IUD)[c] • Bilateral tubal occlusion
• Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.* • It is not necessary to use any other method of contraception when complete abstinence is elected. • WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2. • Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence
NOTES: [a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. [b] Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized. [c] Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness

Unacceptable Methods of Contraception*
• Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously • Diaphragm with spermicide • Cervical cap with spermicide • Vaginal Sponge with spermicide • Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action • Periodic abstinence (calendar, symptothermal, post-ovulation methods) • Withdrawal (coitus interruptus). • Spermicide only • Lactation amenorrhea method (LAM)

*** Local laws and regulations may require use of alternative and/or additional contraception methods.**

CONTRACEPTION GUIDANCE FOR MALE PARTICIPANTS WITH PARTNER(S) OF CHILD BEARING POTENTIAL.

- Given that nivolumab is not a genotoxic agent, and that relevant systemic concentrations sufficient to produce a risk of fetal toxicity are not expected in WOCBP partners from exposure to a male participant's seminal fluid, male study participants will not be required to use contraceptive measures and/or a latex or other synthetic condom during sexual activity with a WOCBP partner.

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 9.2.5 and the Appendix for Adverse Events and Serious Adverse Events Definitions and procedures for Evaluating, Follow-up and Reporting

APPENDIX 5 MANAGEMENT ALGORITHMS

These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. The guidance applies to all immuno-oncology agents and regimens.

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

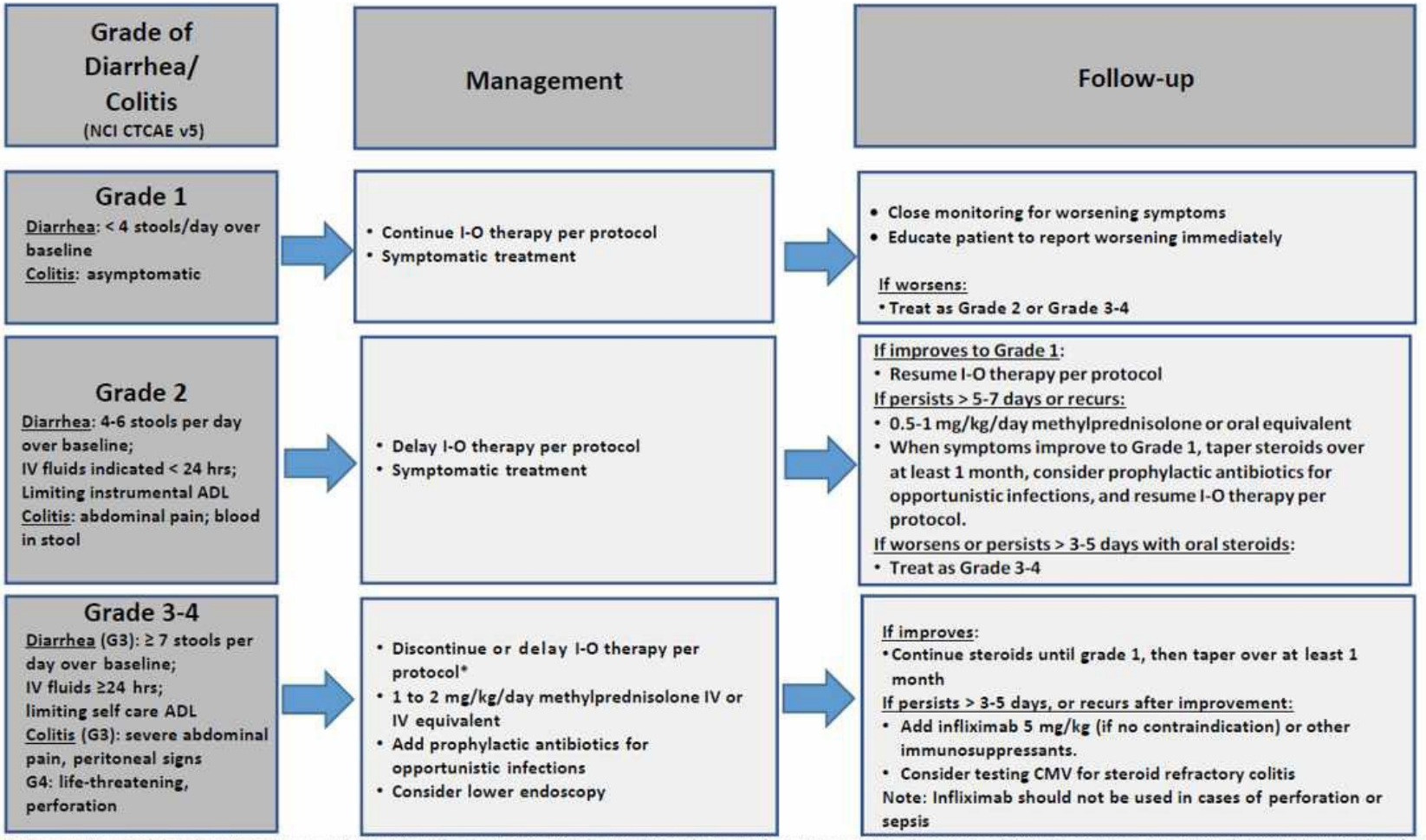
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

GI Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy.
Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

* Discontinue for Grade 4 diarrhea or colitis. For Grade 3 diarrhea or colitis, 1) Nivolumab monotherapy: Nivolumab can be delayed. 2) Nivolumab+ Ipilimumab combination: Ipilimumab should be discontinued while nivolumab can be delayed. Nivolumab monotherapy can be resumed when symptoms improve to Grade 1. Please refer to protocol for dose delay and discontinue criteria for other combinations.

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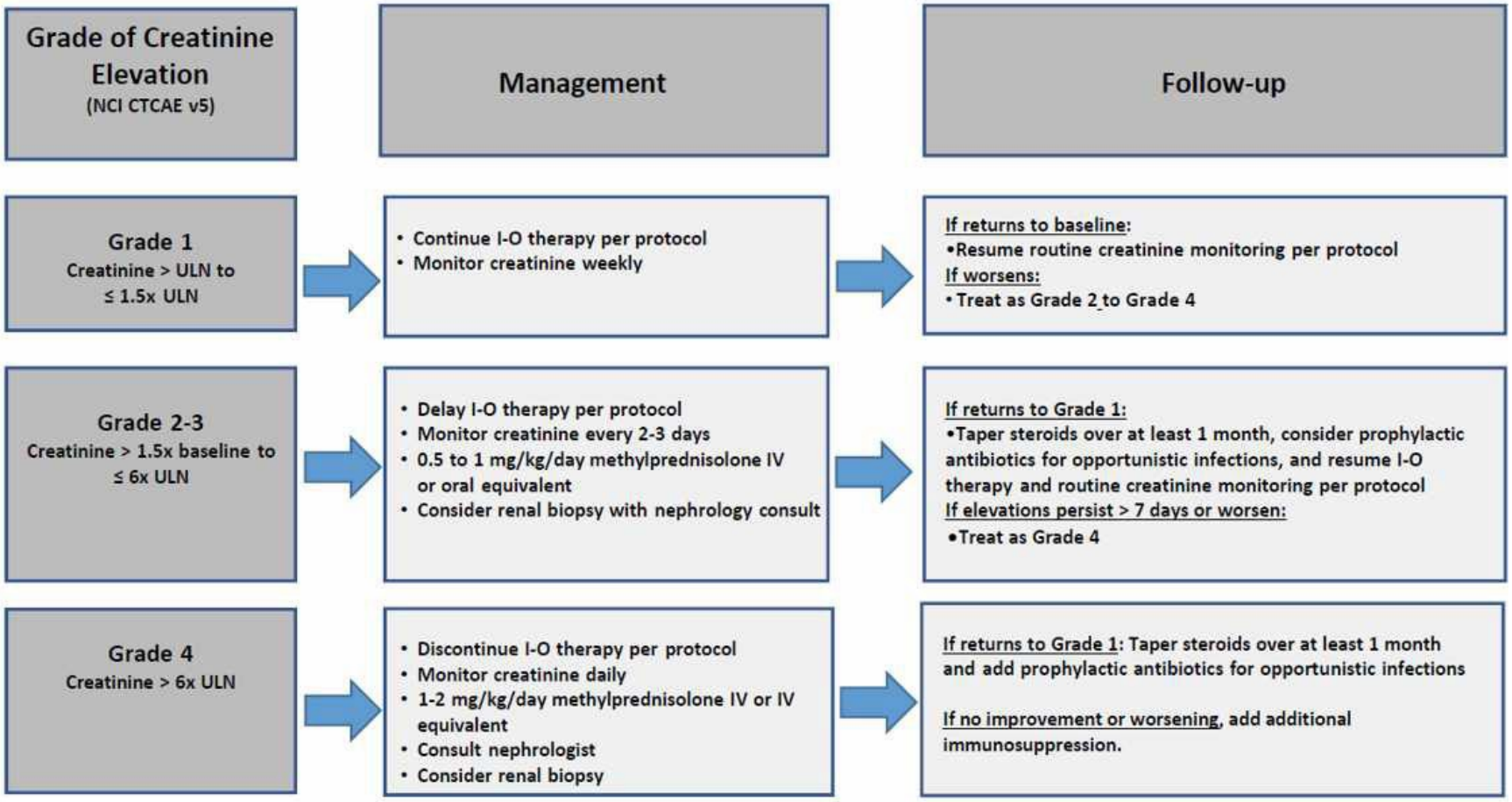
Renal Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

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Pulmonary Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.
Evaluate with imaging and pulmonary consultation.

Grade of Pneumonitis (NCI CTCAE v5)	Management	Follow-up
Grade 1 Radiographic changes only	• Consider delay of I-O therapy • Monitor for symptoms every 2-3 days • Consider Pulmonary and ID consults	• Re-image at least every 3 weeks If worsens: • Treat as Grade 2 or 3-4
Grade 2 Mild to moderate new symptoms	• Delay I-O therapy per protocol • Pulmonary and ID consults • Monitor symptoms daily, consider hospitalization • 1 mg/kg/day methyl prednisolone IV or oral equivalent • Consider bronchoscopy, lung biopsy	If improves to Grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recur: • 0.5-1 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to Grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as Grade 3-4
Grade 3-4 Severe new symptoms; New/worsening hypoxia; Life-threatening	• Discontinue I-O therapy per protocol • Hospitalize • Pulmonary and ID consults • 2-4 mg/kg/day methyl prednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider bronchoscopy, lung biopsy	If improves to baseline: • Taper steroids over at least 6 weeks If not improving after 48 hours or worsening: • Add additional immunosuppression

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

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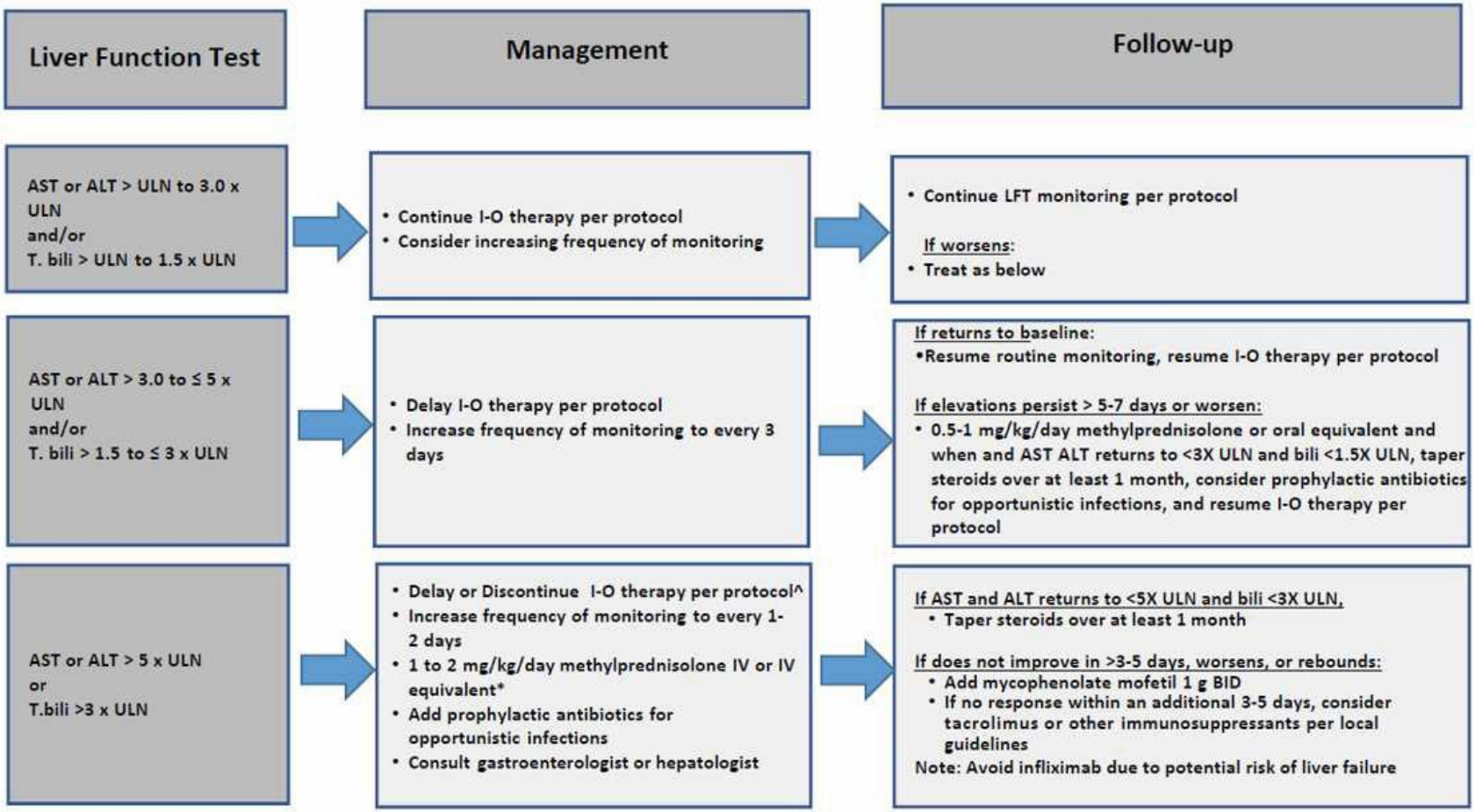
Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.
Consider imaging for obstruction.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
^ Please refer to protocol dose delay and discontinue criteria for specific details.
*The recommended starting dose for AST or ALT > 20 x ULN or bilirubin >10 x ULN is 2 mg/kg/day methylprednisolone IV.

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Endocrinopathy Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.
Consider visual field testing, endocrinology consultation, and imaging.

Endocrinopathy	Management	Follow-up
Asymptomatic TSH abnormality or Hyperglycemia requiring no medical intervention	• Continue I-O therapy per protocol • If TSH < 0.5 x LLN, or TSH > 2 x ULN, or consistently out of range in 2 subsequent measurements: o include fT4 at subsequent cycles as clinically indicated; o consider endocrinology consult	• Monitor TSH as per protocol • Monitor blood sugar • If symptomatic or blood sugar requiring initiation of treatment or change in management, manage as below
Symptomatic endocrinopathy or hyperglycemia requiring initiation of treatment or change in daily management or work up	• Evaluate endocrine function; consider endocrinology consult • Consider pituitary scan Symptomatic with abnormal lab/pituitary scan: • Delay I-O therapy per protocol • 1-2 mg/kg/day methylprednisolone IV or PO equivalent for hypophysitis • Initiate appropriate hormone/medical therapy No abnormal lab/pituitary MRI scan but symptoms persist: • Continue IO therapy. Repeat labs in 1-3 weeks /MRI in 1 month Hyperglycemia: Screen for Diabetic Ketoacidosis (DKA). If negative, continue IO and treat diabetes. If DKA hold IO, admit, manage DKA. Steroids not recommended for DKA/hyperglycemia	If improves (with or without hormone replacement): • Taper steroids over at least 1 month and consider prophylactic antibiotics for opportunistic infections • Resume I-O therapy per protocol • Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component
Suspicion of adrenal crisis (eg, severe dehydration, hypotension, shock out of proportion to current illness)	• Delay or discontinue I-O therapy per protocol • Rule out sepsis • Stress dose of IV steroids with mineralocorticoid activity • IV fluids • Consult endocrinologist	• Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component • If adrenal crisis resolves and patient is adequately controlled with physiologic hormone replacement, patient can resume IO therapy per protocol.

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

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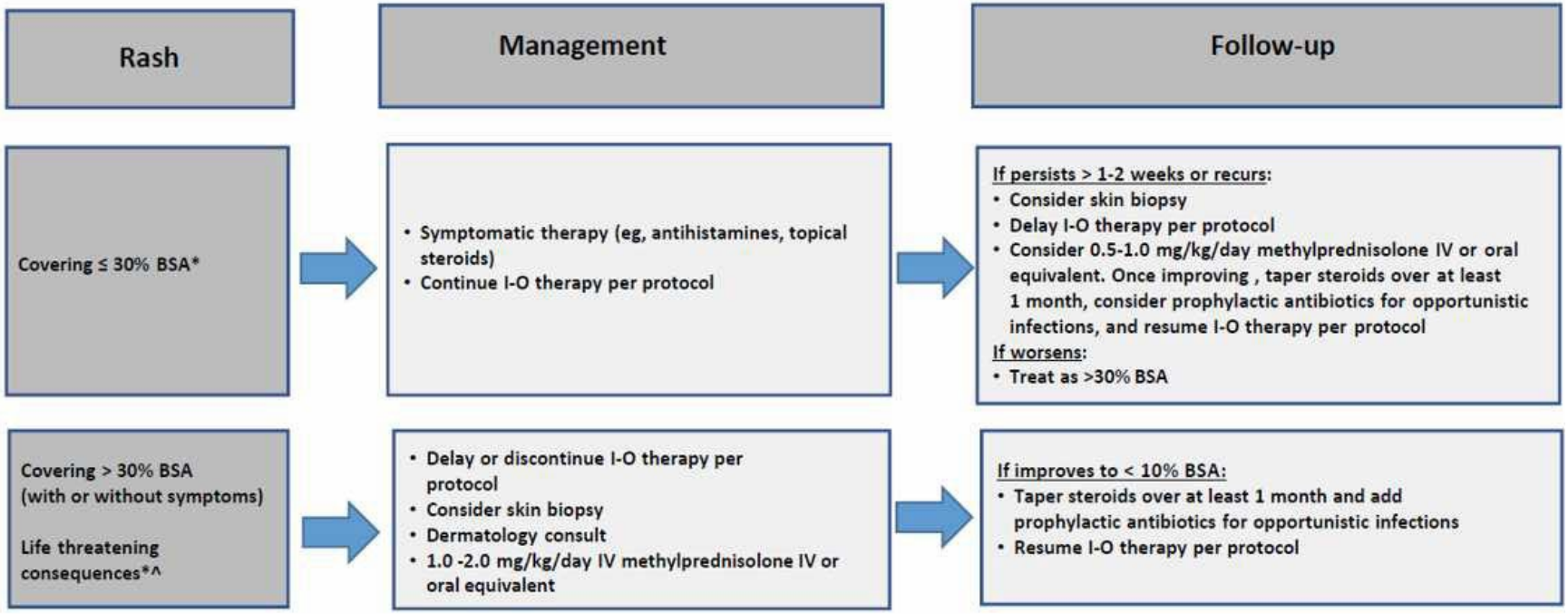
Skin Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

*Refer to NCI CTCAE v5 for term-specific grading criteria.

^If Steven-Johnson Syndrome (SJS),toxic epidermal necrosis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS, TEN, or DRESS is diagnosed, permanently discontinue I-O therapy.

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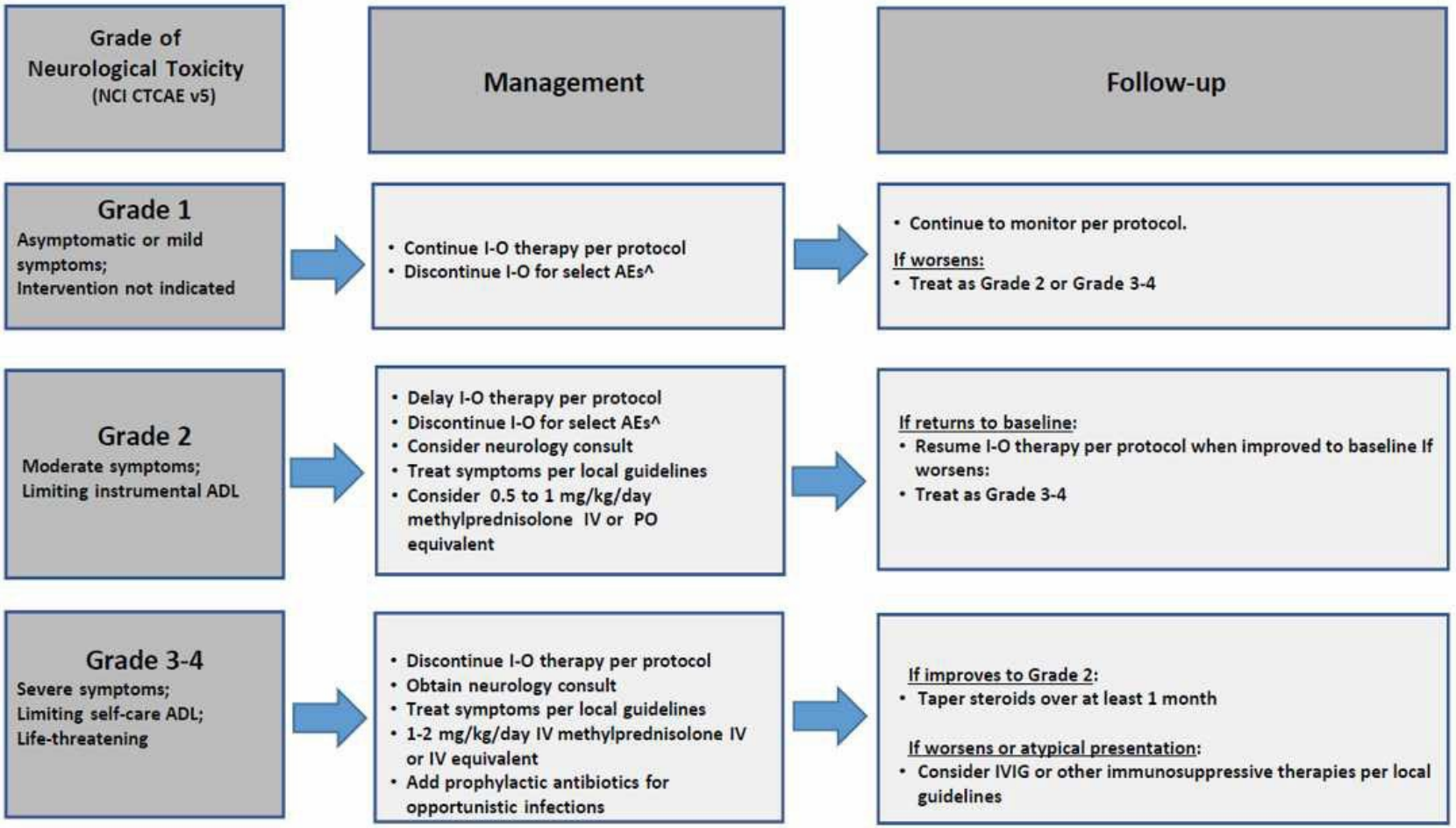
Neurological Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

^Discontinue for any grade myasthenia gravis, Guillain-Barre syndrome, treatment-related myelitis, or encephalitis.

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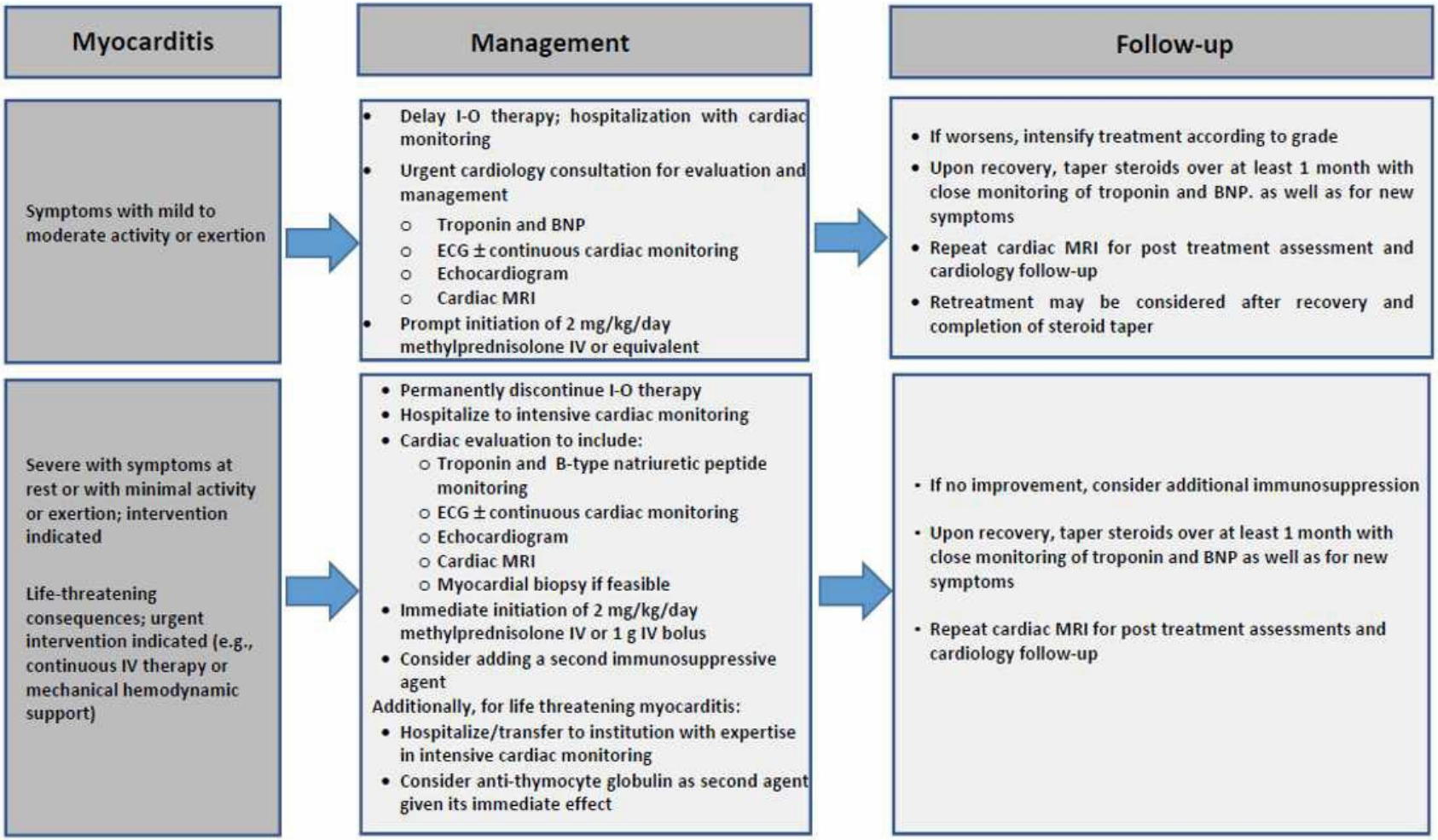
Myocarditis Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression.

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APPENDIX 6 ECOG PERFORMANCE STATUS SCALE

ECOG PERFORMANCE STATUS[a]	
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

[a] Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, and Carbone PP. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5: 649-655.

APPENDIX 7 COUNTRY SPECIFIC REQUIREMENTS

Criteria for exclusion of HIV-positive participants in Argentina, Czech Republic, Germany, and any other countries where exclusion of HIV-positive participants is locally mandated

Protocol Section	Country-specific language
Section 2 Flow Chart/Time and Events Schedule, Table 2-1: Screening Assessments-Laboratory Tests	Add "HIV" to the list of laboratory tests
Section 6.2 Exclusion Criteria, Exclusion Criterion 3 (i)	"Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)"to be replaced with "Positive test for HIV"