Official Title of Study:

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

(CheckMate 9UT: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 9UT)

Protocol: CA209-9UT

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Clinical Protocol CA2099UT

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

(CheckMate 9UT: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 9UT)

Protocol Amendment Number: 04

Incorporates Administrative Letters 01 and 04

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DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Protocol Amendment 04	22-Sep-2021	• Details of closure of the study, with provision for participants currently on treatment to continue. • Removal of pharmacokinetic (except for immunogenicity), biomarker, healthcare resource utilization, and patient-reported outcome (PRO) assessments. • Removal of study-related efficacy assessment and Pathology Review Committee. Sites should continue efficacy assessment as per the local standard of care. • Updates were made to Appendices 1, 2, 4, 5, and 11 • Administrative Letters 01 and 04 were incorporated.
Administrative Letter 04	16-Apr-2021	Updated study personnel information.
Administrative Letter 03	21-Oct-2020	Updated study personnel information.
Administrative Letter 02	17-Jun-2020	Updated study personnel information.
Administrative Letter 01	16-Dec-2019	To include GI Adverse Event Algorithm to Appendix 5, which had been inadvertently left out of the protocol.
Revised Protocol 03	01-Nov-2019	This revision incorporates the following: • Removed eligibility for non-CIS participants • Only 1 BCG-containing arm (Arm B) will be expanded after safety lead-in instead of 2 (Arm B and Arm D) • Updated the randomization schema to address BCG strains and availability • Updated sample size, CR estimates, and decision-making criteria • Updated appendices • Made minor typographical and grammar corrections
Revised Protocol 02	10-May-2019	[redacted] make random bladder biopsies at screening optional, allow for urine cytology to be tested on a voided specimen, and increase the window for repeat TURBT for participants with stage T1 disease from 4 to 8 weeks to be consistent with professional society guidelines. Yearly upper tract imaging is added to be consistent with NCCN guidelines, and histologic confirmation of tumor progression identified on imaging and/or clinical examination is added. Clarification is provided regarding the exclusion criterion for prior systemic chemotherapy and immunotherapy, which applies only if these therapies were administered for the treatment of urothelial carcinoma. A subsection was added to the protocol describing the adverse events of special interest of Hemophagocytic lymphohistiocytosis (HLH) and Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome. Language was added to clarify condom requirements for males who are sexually active with WOCBP. Secondary items incorporated into this revised protocol include clarifications regarding timing and need for some laboratory testing and some protocol-specific activities,

		excluding participants who have received a live/attenuated vaccine within 30 days of first treatment, prohibiting live/attenuated vaccines during treatment and until 100 days post last dose, and making minor clarifications and edits throughout the protocol to ensure consistency between sections.
Revised Protocol 01	23-Mar-2018	Revises language and stratification factors in alignment with final FDA guidance for BCG Unresponsive NMIBC [redacted] Adds language to provide plan for evaluation of suspicious urine cytology Allows randomization of participants with PD-L1 not evaluable tumor tissue Clarifies exclusion criteria Adds details regarding prohibited and restricted treatments and serotonin syndrome Minor clarifications throughout document for consistency across sections
Original Protocol	20-Dec-2017	Not applicable

OVERALL RATIONALE FOR THE PROTOCOL AMENDMENT 04

As of early April 2021, Study CA2099UT enrollment was significantly behind the projected target enrollment, at 28.1% (number of participants enrolled 135; target enrollment 480). Since the study would be unable to meet the scientific objectives within a projected timeline, a decision was made in May to close the study. Importantly, there is no change to the understanding of the safety profile of nivolumab or nivolumab/BMS-986205, with or without intravesical Bacillus Calmette-Guerin (BCG) in participants with BCG-unresponsive, high-risk, NMIBC.

Protocol Amendment 04 describes the modification to study procedures. All participants must be re-consented upon approval and implementation of Protocol Amendment 04. These changes affect all participants and should be implemented when Protocol Amendment 04 is implemented at the site.

Key changes in Protocol Amendment 04 include:

- Details of closure of the study, with provision for participants currently on treatment to continue
- Removal of pharmacokinetic (except for immunogenicity), biomarker, healthcare resource utilization, and patient-reported outcome (PRO) assessments
- Removal of study-related efficacy assessment and Pathology Review Committee (PRC). Sites should continue efficacy assessment as per local standard of care

Other clarifications and editorial updates were made throughout the protocol to improve clarity and readability and to keep consistency throughout the document.

Changes instituted in Protocol Amendment 04 should override any existing protocol requirements in the event of any apparent discrepancies.

This amendment incorporates the changes from the approved Administrative Letters 01 and 04, which are detailed in the Document History but not listed in the Summary of Key Changes below.

SUMMARY OF KEY CHANGES OF PROTOCOL AMENDMENT 04

Section Number & Title	Description of Change	Brief Rationale
Synopsis, Rationale	Added that no formal hypotheses or efficacy objectives would be done for this study. Only safety and immunogenicity assessments will be conducted.	Only safety and immunogenicity will be assessed.
Synopsis, Objectives and Endpoints	Only safety objectives and endpoints were retained in the table.	Only safety and immunogenicity will be assessed.
Synopsis, Overall Design; Section 5.1: Overall Design	Removed language pertaining to the first 34 CIS participants, and the criteria to move to full enrollment.	The decision points are no longer planned due to the study closure.
Synopsis, Number of Participants; Section 5.2: Number of Participants	Text was deleted and number of participants enrolled was added.	As of 02-Jun-2021, enrollment for new participants was closed.

SUMMARY OF KEY CHANGES OF PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Synopsis, Study Schematic; Figure 5.1-1: Overall Design	Schema was updated to remove the decision points and follow-up.	The decision points and efficacy follow-up are no longer planned due to the study closure.
Synopsis, Treatment Arms and Duration	Removed language that the Data Monitoring Committee (DMC) will provide independent oversight over risk-benefit of study treatment.	DMC will review only safety and study conduct.
Synopsis, Duration; Section 5.3: End of Study Definition	Definition of study completion and full enrollment was removed.	The primary analysis and full enrollment are no longer planned.
Synopsis, Reference List	List was updated.	The efficacy follow-up is no longer planned due to the study closure.
Table 2-2: On-treatment Procedural Outline for Arms A and C (CA2099UT) and Table 2-3: On-treatment Procedural Outline for Arms B and D (CA2099UT)	Added adverse event reporting requirements specified in Section 9.2.	Added to highlight requirements specified in Section 9.2.
	Clarified that the pregnancy test requires serum or urine within 24 hours prior to first dose and then every 4 weeks (± 1 week) regardless of dosing schedule.	Updated to reflect the latest program level requirement.
	Removed row for imaging assessments.	Efficacy assessments will be performed as per the local standard of care.
	Deleted rows for individual efficacy tests and noted that efficacy assessments will be conducted per the local standard of care.	Efficacy assessments will be performed as per the local standard of care.
	Deleted health outcomes and biomarker assessments.	Health outcomes and biomarker assessments are no longer collected.
	Deleted PK (except immunogenicity) assessments.	PK (except immunogenicity) samples are no longer collected.
	Footnote on handling of lab samples was deleted.	Samples are no longer submitted to PRC.
Table 2-4: Follow-up Procedural Outline (CA2099UT)	The column for efficacy follow-up was removed and all “Notes” associated with efficacy were removed. As a result, the associated footnote was also removed.	Efficacy assessment will be performed as per the local standard of care.

SUMMARY OF KEY CHANGES OF PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
	Added adverse event reporting requirements specified in Section 9.2.	Added to highlight requirements specified in Section 9.2.
	Imaging and efficacy assessment rows were removed.	Efficacy assessment will be performed as per the local standard of care.
	Deleted health outcome and PK (except immunogenicity) assessments.	Health outcome and PK (except immunogenicity) samples are no longer collected.
Section 3.1: Study Rationale	Deleted the paragraph regarding aim of the study.	No formal hypotheses or efficacy objectives are planned due to the study closure.
Section 3.1.1: Research Hypothesis	This section is no longer applicable as per this protocol amendment.	No formal research hypothesis due to the study closure.
Section 3.1.2: Changes Per Protocol Amendment 04	New section added to provide the changes that were made as per this protocol amendment.	This section is added to provide key changes and rationale.
Section 4: Objectives and Endpoints, Table 4-1 (Objectives and Endpoints)	The objectives and endpoints for efficacy, quality of life/patient-reported outcomes, pharmacokinetics, and healthcare resource utilization were removed.	These assessments are no longer being done as per this protocol amendment.
Section 5.1: Overall Design	Added language that efficacy follow-up along with other study procedures and risk-benefit assessment by DMC and PRC will not be done.	Efficacy follow-up and other procedures are no longer planned.
Section 5.1.2: Randomization Phase	Removed Randomization Phase Part 3 and Total Randomization.	Risk-benefit assessment by DMC and central efficacy review by PRC are no longer planned.
Section 5.1.3: Data Monitoring Committee and Other External Committees	Updated the text to remove risk-benefit assessment by DMC and independent review by PRC.	No risk-benefit assessment by DMC and independent review by PRC are planned.
Section 5.4.6: Rationale for Complete Response Rate in Participants with Carcinoma in Situ as a Primary Endpoint	Section was deleted as not applicable as per this protocol amendment.	Efficacy assessment will be conducted per the local standard of care.
Section 5.4.7: Rationale for Evaluation of Predictive Biomarkers	Section was deleted as not applicable as per this protocol amendment.	Biomarker samples will not be collected.
Section 6.1: Inclusion Criteria	Added text that enrollment to the study was closed and male participants should	As of 02-Jun-2021, enrollment for new participants was closed.

SUMMARY OF KEY CHANGES OF PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
	follow the updated contraceptive guidance. Criteria 4)e) and 4)f) were updated.	Contraceptive language is updated to reflect the latest program level requirement.
Section 7.1: Treatments Administered	Removed requirements of when PK samples are obtained.	PK (except for immunogenicity) will not be collected.
Section 7.2: Method of Treatment Assignment	Clarified that there will be no centralized randomization.	Removed for clarification and consistency.
Section 7.3: Blinding	Clarified that this is a randomized open-label study, so blinding procedures are not applicable and access to treatment assignment information is unrestricted.	Added to clarify expectation of the blinding procedures.
Section 7.4.4.1: Nivolumab	Added that in case of confirmed or suspected severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, nivolumab administration should be delayed.	Included language to clarify expectations for delaying treatment in participants with suspected or confirmed SARS-CoV-2 infection.
Section 7.4.4.2: Nivolumab Plus BMS-986205	Added that in case of confirmed or suspected SARS-CoV-2 infection, nivolumab plus BMS-986205 administration should be delayed.	Included language to clarify expectations for delaying treatment in participants with suspected or confirmed SARS-CoV-2 infection.
Section 7.4.5.1: Nivolumab; Section 7.4.5.2: Nivolumab Plus BMS-986205	Added the criteria to resume treatment in case of confirmed or suspected SARS-CoV-2 infection.	Included language to clarify expectations for resuming treatment in participants with suspected or confirmed SARS-CoV-2 infection.
Section 7.7: Concomitant Therapy	Added that Coronavirus disease 2019 (COVID-19) vaccines are allowed concomitant therapy.	Added clarification on COVID-19 vaccines, and risk benefit statement of non-live vaccines.
Section 7.7.1.1: Prohibited Treatments	Updates were made to the bullet points regarding herbal supplements and prophylactic antimicrobial therapy.	Updated to reflect the latest program level standard for complementary medication and added clarification on prophylactic antimicrobial therapy.
Section 7.7.1.2: Restricted Treatments	Removed the bullet point about participants avoiding proton pump inhibitors.	Results from Study CA017089 showed that coadministration with a proton pump inhibitor (omeprazole) did not meaningfully change the total exposure for BMS-986205 or total active moiety.

SUMMARY OF KEY CHANGES OF PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 8.1: Discontinuation from Study Treatment	In the bullet point for disease progression or recurrence, removed language pertaining to PRC confirmation of progression or recurrence.	Efficacy assessment is performed as per the local standard of care.
Section 8.1.4: Post Study Treatment Study Follow-up	Clarified that as per this protocol amendment, efficacy follow-up is not required, and participants will be followed for assessment of safety through 100 days post last dose of study treatment.	Efficacy follow-up is no longer required.
Section 9: Study Assessments and Procedures (Follow-up Phase)	Clarified when the follow-up phase ends.	Added clarification as to when follow-up phase ends.
Section 9.1: Efficacy Assessments	Noted that efficacy assessments will be conducted as per local standard of care. Definitions of Complete Response, Recurrence, and Progression were updated accordingly.	Efficacy assessment will be conducted as per the local standard of care.
Section 9.1.1: Imaging Assessment for the Study; Section 9.1.2: Cystoscopy; Section 9.1.3: Urine Cytology; Section 9.1.4: Bladder Biopsy	Noted that efficacy assessments will be conducted as per local standard of care.	Efficacy assessment will be conducted as per the local standard of care.
Section 9.2.1: Time Period and Frequency for Collecting AE and SAE Information	Added time period of collection of AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection.	To allow for the evaluation of the impact of SARS-CoV-2 infection on participant safety.
Section 9.2.3: Follow-up of AEs and SAEs	Updated description of timing of AE/SAE collection to include the collection of SARS-CoV-2 infection-related AEs/SAEs.	To allow for the evaluation of the impact of SARS-CoV-2 infection on participant safety.
Section 9.4.1: Clinical Safety Laboratory Assessments	In Table 9.4.1-1, added sensitivity for Pregnancy Tests.	Added to reflect the latest program level requirement.
Section 9.5.2: Pharmacokinetics and Immunogenicity Assessments	Removed “Pharmacokinetics” from Section heading and added that only immunogenicity assessments will be collected. As a result, the section and Table 9.5.2-1 was updated to remove PK assessments/timepoints.	PK (except for immunogenicity) will not be collected.
Section 9.6: Pharmacodynamics	Added that “Per Protocol Amendment 04, pharmacodynamics will not be collected.”	Pharmacodynamics will not be collected.
Section 9.8: Biomarkers	Added that “Per Protocol Amendment 04, biomarkers will not be collected.” As a result, Table 9.8-1 was deleted.	Biomarkers will not be collected.

SUMMARY OF KEY CHANGES OF PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 9.9: Health Economics OR Medical Resource Utilization and Health Economics	Added that "Per Protocol Amendment 04, health economics/medical resource utilization and health economics parameters will not be evaluated."	Health economics/medical resource utilization and health economics parameters will not be evaluated.
Section 9.10: Immunogenicity Assessments	Removed mention of efficacy and PK assessments.	Only the effect of immunogenicity on safety may be explored
Section 9.11.1: Patient-reported Outcomes	Added that "Per Protocol Amendment 04, patient-reported outcomes will not be evaluated."	Patient-reported outcomes will not be evaluated.
Section 10: Statistical Considerations; Section 10.2: Populations for Analyses	Added that "Per Protocol Amendment 04, only safety and immunogenicity analyses will be conducted."	Only safety and immunogenicity analyses will be conducted.
Section 10.1: Sample Size Determination	Added that "Per Protocol Amendment 04, sample size will be limited to the participants enrolled as of 02-Jun-2021.	As of 02-Jun-2021, enrollment for new participants was closed.

SUMMARY OF KEY CHANGES OF PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
	The following sample size considerations refer to the original study design."	
Section 10.2: Populations for Analyses	Only Enrolled, Treated, and Immunogenicity populations were defined.	Only safety and immunogenicity analyses will be conducted.
Section 10.3: Statistical Analyses	Removed language regarding planned statistical analyses of primary and secondary endpoints.	Only safety and immunogenicity analyses will be conducted.
Section 10.3.1: Efficacy Analyses	Added that formal efficacy analyses will not be conducted, and descriptive summary statistics may be provided for internal dissemination only. The tabular summary of the planned statistical analyses of primary and secondary endpoints was deleted.	Only safety and immunogenicity analyses will be conducted.
Section 10.3.2: Safety Analyses	Removed "secondary" and "exploratory".	To align with other sections.
Section 10.3.3: Other Analyses	Removed entire language and added language on immunogenicity analysis.	Only safety and immunogenicity analyses will be conducted.
Section 10.3.4: Initial Evaluation of Efficacy and Safety	This section was no longer applicable as per Protocol Amendment 04.	Only safety and immunogenicity analyses will be conducted. The decision points are no longer planned.
Section 11: References	List was updated.	Updated based on changes per Protocol Amendment 04.
Appendix 1: Abbreviations and Trademarks	List was updated.	Updated based on changes per Protocol Amendment 04.
Appendix 2: Study Governance Considerations	Monitoring section was updated.	Update allows for alternative monitoring in circumstances where on-site monitoring is not advised.
Appendix 4: Women of Childbearing Potential Definitions and Methods of Contraception (Contraception Guidance for Male Participants with Partner(s) of Childbearing Potential)	Appendix was updated. Specified that it is applied to Arms C and D of the study. The definition of end of relevant systemic exposure was updated to 1 month (approximately 4 weeks).	Updated to reflect the latest program level requirement.
Appendix 5: Management Algorithms for Immuno-oncology Agents	Algorithms were updated.	Updated to reflect the latest program level requirement.
Appendix 11: Country Specific Requirements	Italy was removed from the list of countries where exclusion of HIV positive participants is locally mandated.	Updated as per the latest country level requirement.

SUMMARY OF KEY CHANGES OF PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
	The numbering for exclusion criteria pertaining HIV test was corrected.	The numbering was corrected to align with exclusion criteria.

TABLE OF CONTENTS

1 SYNOPSIS

Protocol Title: 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 (CheckMate 9UT: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 9UT)

Study Phase: Phase 2b

Rationale:

Targeting the immunosuppressive properties of the cancer cells themselves, such as by inhibiting the immunosuppressive enzyme indoleamine-1,2-dioxygenase 1 (IDO1) and the immune checkpoint receptor programmed cell death protein-1 (PD-1), is a promising approach in cancer immunotherapy. Preliminary data in participants with advanced urothelial carcinoma (UC) evaluating an IDO1 inhibitor in combination with anti-PD-1 therapy have shown that this combination may improve the efficacy of anti-PD-1 therapy alone, with potentially similar toxicity. BMS-986205 is an optimized IDO1 inhibitor characterized by once-daily dosing and deeper inhibition of IDO1 activity, as measured by peripheral blood kynurenine suppression, than other inhibitors. BMS-986205 has also demonstrated preliminary evidence of clinical activity in combination with immune checkpoint inhibitor nivolumab in multiple tumor types, including UC.

As of 02-Jun-2021, enrollment for new participants was closed. As a result of Protocol Amendment 04, there are no formal hypotheses or efficacy objectives for this study. Only safety and immunogenicity assessments will be conducted.

Study Population:

Adult participants (18 years of age and older, or age of majority) with pathologically proven carcinoma in situ (CIS)-containing bacillus Calmette-Guerin (BCG) unresponsive high-risk non-muscle-invasive bladder cancer (NMIBC).[1,2,3] Patients must have CIS to participate. Participants should be considered medically unfit for radical cystectomy or should have refused radical cystectomy after consultation with their oncologist/urologist. Participants must not have evidence of UC in the upper urinary tracts (kidneys, renal pelves, ureters) or in the prostatic urethra. Previous or concurrent muscle invasive or disseminated bladder cancer is not permitted. Prior systemic treatment, radiation therapy, or surgery for bladder cancer other than transurethral bladder tumor resection (TURBT) or bladder biopsies is also not permitted.

Key Inclusion Criteria:

- Pathologically demonstrated BCG-unresponsive*, CIS-containing high-risk NMIBC defined as CIS with or without papillary component diagnosis required within **10 weeks (70 days)** prior to randomization and must be confirmed by the Pathology Review Committee (PRC).

  * BCG-unresponsive disease is defined as being at least one of the following[2,3]:

  – 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 high-grade Ta/any T1 disease within 6 months of completion of adequate BCG therapy** [per revised protocol 03, participants must also have CIS to be eligible]
  - • T1 high-grade disease at the first evaluation following an induction BCG course (at least 5 of 6 induction doses) [per revised protocol 03, participants must also have CIS to be eligible]

  ** Adequate BCG treatment is defined as at least 2 courses of BCG. This can include 2 induction courses (at least five of six doses of an initial induction course plus at least two of six 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").

- Predominant histologic component (> 50%) must be urothelial (transitional cell) carcinoma
- Must have undergone each of the following procedures within 10 weeks (70 days) of randomization (except 90 days for CT or MRI). If these procedures are performed as part of the participant's routine care, they do not need to be repeated provided they were performed within the required time period:
  - Complete excision of all papillary disease (T1/TaHG). For participants with T1 lesions, a re-staging TURBT must be performed within 8 weeks after the initial TURBT to ensure that the pathology specimen contains muscularis propria that is free of invasive tumor per PRC.
  - 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.
  - The presence of any suspicious lesions must be recorded and these lesions will be biopsied. Random sampling of bladder mucosa for detection of occult CIS during the screening period is optional, but should be performed at the time of screening transurethral resection/biopsy of bladder tumor and/or CIS within 10 weeks (70 days) of randomization, if possible. The bladder should be mapped by visual inspection and random biopsies taken from the trigone, right and left lateral walls, posterior wall, dome and prostatic urethra (in male participants).
  - 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.
  - Computed tomography (CT) scan of the chest and CT or magnetic resonance imaging (MRI) of the abdomen and 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
  - Participants should either be deemed medically unfit for radical cystectomy, or should have refused radical cystectomy after consultation with their urologist or oncologist.

Key Exclusion Criteria:

- Women who are pregnant or breastfeeding

- Participants with a personal or family (ie, in a first-degree relative) history of cytochrome b5 reductase deficiency (previously called methemoglobin reductase deficiency) or other diseases that put them at risk of methemoglobinemia. All participants will be screened for methemoglobin levels prior to randomization.
- Participants with a history of glucose-6-phosphate dehydrogenase (G6PD) deficiency or other congenital or autoimmune hemolytic disorders. All participants will be screened for G6PD deficiency prior to randomization.
- Evidence of locally advanced or metastatic bladder cancer as seen in cross-sectional imaging of the chest, abdomen, and pelvis
- 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
- Locally advanced disease demonstrated by pelvic examination preferably performed under anesthesia
- Previous or concurrent muscle invasive or disseminated/metastatic bladder cancer
- Prior treatment with an anti-PD-1, anti-programmed death ligand 1 (PD-L1), anti-PD-L2, or anti-cytotoxic T-lymphocyte-associated protein 4 (anti-CTLA-4) antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways
- Prior treatment with BMS-986205 or any other IDO1 inhibitors
- Prior systemic chemotherapy or immunotherapy for UC. Intravesical chemotherapy and/or interferon administered prior to the date of tumor sample submission is permitted.
- Prior radiation therapy for bladder cancer
- Prior surgery for bladder cancer other than TURBT and/or bladder biopsies
- Participants who have received a live /attenuated vaccine within 30 days of first treatment

Objectives and Endpoints:

Only safety and immunogenicity assessments will be conducted. No analyses of efficacy, quality of life/patient-reported outcomes, pharmacokinetics, or healthcare resource utilization are planned. Previously collected biomarker samples may be analyzed, but no further collections are planned with this amended protocol.

Objectives	Endpoints
• To describe the safety and tolerability of nivolumab and nivolumab + BMS-986205, alone or in combination with intravesical BCG.	• Overall safety and tolerability will be measured by the incidence of AEs, SAEs, AEs leading to discontinuation, immune-mediated AEs, deaths, and laboratory abnormalities and changes from baseline.

Overall Design:

This is a Phase 2b, randomized, open-label study of nivolumab or nivolumab plus BMS-986205, with or without intravesical BCG, in adult (18 years of age and older, or age of majority) participants with BCG-unresponsive, high-risk NMIBC.

- After a safety-lead in the BCG-containing arms, participants will be randomized to one of 4 parallel treatment arms as follows: Arm A (nivolumab monotherapy), Arm B (nivolumab and BCG), Arm C (nivolumab and BMS-986205), and Arm D (nivolumab and BMS-986205 and BCG).
  - Per revised protocol 03, due to a global shortage of intravesical BCG, after the approximately 8 participants in Arm D complete the safety lead-in phase, further enrollment in Arm D will be paused. Enrollment in Arms A, B, and C will continue per protocol.
- Sufficient, recent tumor tissue obtained within 10 weeks (70 days) prior to randomization from the tumor obtained at TURBT must be submitted (1) for review by the PRC to confirm the diagnosis of high-risk NMIBC and exclude tumor invasion of the muscularis propria and (2) to the analytical testing laboratory for PD-L1 expression. If sufficient tissue is not available, either additional tissue will be requested from the site or a repeat TURBT will be required.
- A 6-week safety lead-in will be conducted in participants randomized to receive BCG and nivolumab with or without BMS-986205 (Arms B and D) to determine safe dose levels to be administered during the treatment phase. Enrollment in the safety lead-in will be staggered so that the safety lead-in phase for Arm B is adequately assessed prior to the enrollment of Arm D.
- Following the safety lead-in, participants with CIS, with or without papillary disease, will be randomized into study Arms A, B, and C.

Number of Participants:

As of 02-Jun-2021, enrollment for new participants was closed. Number of participants enrolled was 135, as of early April 2021.

Treatment Arms and Duration:

Study treatment:

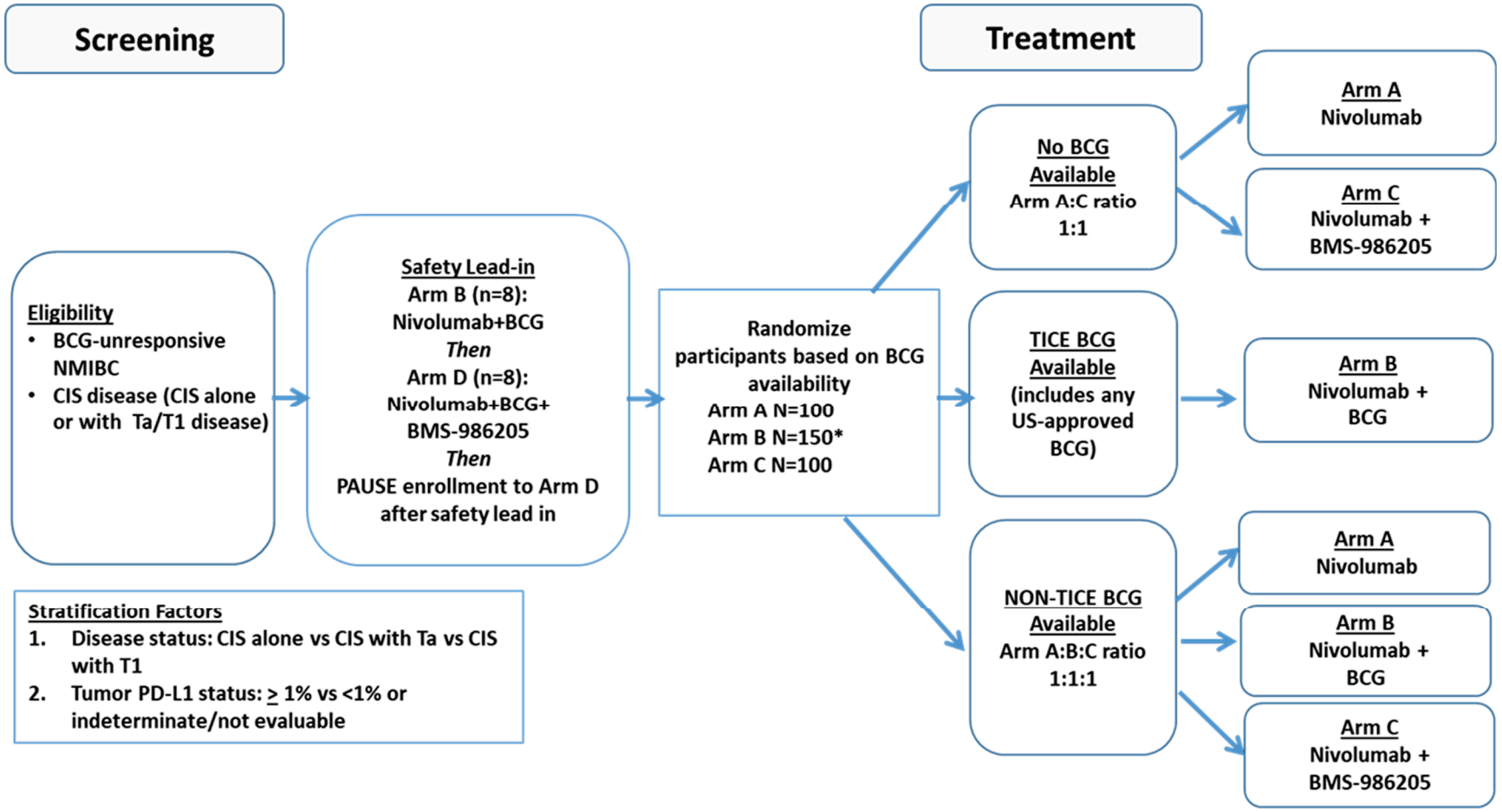
Study Drugs for CA2099UT		
Medication	**Potency**	**IP/Non-IP**
BMS-936558-01 (Nivolumab) Solution for Injection	10 mg/mL	IP
BMS-986205-04	100 mg	IP
BMS-986205-04	50 mg	IP

Study Drugs for CA2099UT		
Medication	**Potency**	**IP/Non-IP**
BCG	Dose according to prescribing information for BCG strain and preparation administered	IP

Abbreviations: IP = investigational product

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

Figure 1: Study Schematic



During the treatment phase, participants will receive:

- Arm A: Nivolumab 480 mg IV Q4W for up to 52 weeks (12 months)
- Arm B: Nivolumab 480 mg IV Q4W for up to 52 weeks (12 months) and intravesical BCG (induction) weekly for 6 weeks followed by maintenance intravesical BCG weekly for 3 weeks at 3 months, 6 months and 12 months following the first intravesical dose. The dose 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. Every effort should be made to continue a participant on the same strain of BCG for the duration of study participation.
- Arm C: Nivolumab 480 mg IV Q4W and BMS-986205 100 mg PO QD for up to 52 weeks (12 months)
- Arm D: Nivolumab 480 mg IV Q4W and BMS-986205 100 mg PO QD for up to 52 weeks (12 months), and intravesical BCG (induction) weekly for 6 weeks followed by maintenance intravesical BCG weekly for 3 weeks at 3 months, 6 months, and 12 months following the first intravesical dose. The dose 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. Arm D enrollment will be paused after the safety lead-in.

For each arm, 1 treatment cycle equals 4 weeks.

Dose reductions are not permitted for nivolumab or for BCG after the safe-dose level has been determined in the safety lead-in. One dose reduction is permitted for BMS-986205, from 100 mg QD to 50 mg QD. No re-escalation is permitted after dose reduction.

Doses of nivolumab, BMS-986205 and BCG should be delayed due to treatment-related AEs described in Section 7.4 of the protocol. Treatment-related AEs resulting in permanent discontinuation of study treatment are described in Section 8 of the protocol. Treatment may be discontinued due to unacceptable toxicity, withdrawal of consent, disease recurrence or progression, or completion of treatment cycles and follow-up, whichever occurs first. An external Data Monitoring Committee (DMC) will provide independent oversight of safety and study conduct.

Duration:

The start of the trial is defined as the first visit for the first participant screened. End of the trial and end of the study are defined as the final date when all participants have completed study procedures described in the protocol, including follow-up visits.

[1] 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.

[2] 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.

[3] Steinberg RL, Thomas LJ, Mott SL, O'Donnell MA. Bacillus Calmette-Guerin (BCG) Treatment Failures with Non-Muscle Invasive Bladder Cancer: A Data-Driven Definition for BCG Unresponsive Disease. Bladder Cancer 2016: 2: 215-224

2 SCHEDULE OF ACTIVITIES

Procedures to be performed during screening for all participants are listed in Table 2-1, during treatment for Arms A and C in Table 2-2, during treatment for Arms B and D in Table 2-3, and during follow-up for all participants in Table 2-4. Abbreviations are defined in Appendix 1.

Table 2-1: Screening Procedural Outline (CA2099UT)

Procedure[a]	Screening Visit	Notes (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, 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, American Joint Committee on Cancer (AJCC) stage, glucose-6-phosphate dehydrogenase (G6PD) deficiency history, and personal and/or family (first-degree relative) history of cytochrome b5 reductase deficiency. Also include smoking history (including electronic cigarettes) and alcohol history.
Tumor Sample Submission (Bladder Biopsy)[b]	X	All participants must have tumor tissue available, obtained within 10 weeks (70 days) prior to randomization. • [redacted] • For diagnosis (Section 9.1.4): Tumor tissue samples (1-10 hematoxylin and eosin (H&E) stained slides, with at least 1 slide /disease site) representing the diagnosis of high-risk NMIBC (CIS, CIS with TaHG, or CIS with T1) and excluding tumor invasion into the muscularis propria will be collected and sent to independent Pathology Review Committee (PRC). At least one slide must contain muscularis propria, preferably taken from the most significant area of disease. If the diagnosis cannot be confirmed, then additional slides will be requested from the site. For participants with T1 lesions, a re-staging TURBT must be performed within 8 weeks after the initial TURBT to ensure that the pathology specimen contains muscularis propria that is free of invasive tumor and the H&E stained samples must be sent to PRC.

Table 2-1: Screening Procedural Outline (CA2099UT)

Procedure[a]	Screening Visit	Notes (All windows are based on calendar days)
		If tumor tissue was obtained > 70 days prior to randomization, participants must have a repeat cystoscopy ≤ 70 days prior to randomization. If the repeat cystoscopy shows papillary tumor, repeat TURBT is required (see Section 9.1.4).
Cystoscopy	X	See Section 9.1.2.
Urine Cytology[b]	X	Sample will be reviewed by PRC prior to randomization. See Section 9.1.3.
Body Imaging	X	See Section 9.1.1. Must be performed within 90 days prior to randomization.
Safety Assessments		
Full Physical Examination, Measurements, Vital Signs and Performance Status	X	Height, weight, ECOG Performance Status (Appendix 6), blood pressure, heart rate, and temperature must be collected within 14 days prior to randomization.
Oxygen Saturation	X	Oxygen saturation by pulse oximetry or co-oximetry at rest within 14 days prior to randomization.
ECG	X	At rest.
Assessment of Signs and Symptoms	X	Must be collected 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
Laboratory Tests		
Complete Blood Count (CBC) with differential, Chemistry, Endocrine, Viral, methemoglobin levels, G6PD levels, C-reactive protein, Urinalysis	X	All testing, except viral, CRP, and G6PD below, must be performed within 14 days prior to randomization. Methemoglobin levels to be assessed on arterial or venous blood sample or by co-oximetry. Viral testing, C-reactive protein, and G6PD must be within 28 days prior to randomization. For HIV: testing at sites where locally mandated; see Appendix 11. For full list of assessments, see Section 9.4.1.
Pregnancy Test (WOCBP only)	X	Serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) to be done at screening visit and within 24 hours of first dose of study therapy.

[a] Some of the assessments referred to in this section may not be captured as data in the eCRF. 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 C (CA2099UT)

Procedure[a]	Arm A: Nivolumab 480 mg IV Q4W Arm C: Nivolumab 480 mg IV Q4W plus BMS-986205 100 mg PO QD			
	Cycle 1 Day 1 (C1D1) (1 Cycle = 4 Weeks)	Cycle 2 (Day 1 ± 3 days)	Cycle 3-13 (Day 1 ± 3 days)	Notes[b]
Study Drug				
Randomize	X			
Dispense Study Drug	X	X	X	First dose to be administered within 3 calendar days following randomization. Nivolumab will be administered at Day 1 of each cycle. For Arm C, BMS-986205 will be administered once a day during each cycle.
Dispense Pill Diary (Arm C only)	X	X	X	Review pill diary during each visit for compliance of daily administration of BMS-986205. Collect pill diary at the completion of each cycle.
Safety Assessments				
Targeted Physical Examination, measurements, Vital Signs, Performance Status	X also on C1D15 ± 3 days for Arm C	X	X	For each cycle, weight, vital signs, and ECOG Performance Status within 3 calendar days prior to dosing. For Cycle 1 Day 1 and beyond, targeted physical examination to be performed only as clinically indicated.
Oxygen Saturation (Arm C only)	X also on C1D15 ± 3 days	X	X	Oxygen saturation by pulse oximetry or co-oximetry at rest prior to dosing
ECG (12-lead)	X also on C1D15 ± 3 days for Arm C	See note	See note	At rest, pre-dose. For C2 and beyond: Pre-dose, as clinically indicated, including if concomitant medications which may prolong the QTc interval are added (Appendix 8).

Table 2-2: On-treatment Procedural Outline for Arms A and C (CA2099UT)

Procedure[a]	Arm A: Nivolumab 480 mg IV Q4W Arm C: Nivolumab 480 mg IV Q4W plus BMS-986205 100 mg PO QD			
	Cycle 1 Day 1 (C1D1) (1 Cycle = 4 Weeks)	**Cycle 2 (Day 1 ± 3 days)**	**Cycle 3-13 (Day 1 ± 3 days)**	**Notes[b]**
Adverse Event (AE) Assessment (including SAEs)	Continuously			Record at each visit. All AEs and SAEs must be collected continuously during the treatment period and for a minimum of 100 days following last dose. Participants will be followed for all AEs and SAEs of special interest (as defined in Section 9.2.9), and all AEs and SAEs associated with confirmed or suspected SARS-CoV-2 infection until resolution, the condition stabilizes, the event is otherwise explained, the event is deemed irreversible, 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. 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 CBC with differential also on C1D15 ± 3 days for Arm C	X	X	Must be performed within 72 hours prior to Nivolumab dosing Refer to Section 9.4.1 for list of laboratory tests. Thyroid testing to be performed every 8 weeks (2 cycles). Methemoglobin must be assessed for Arm C on arterial or venous blood sample or by co-oximetry at every treatment visit or more frequently as clinically indicated based on symptoms (see Section 7.4.7). Participants may continue BMS-986205 dosing until methemoglobin result is available unless clinical signs

Table 2-2: On-treatment Procedural Outline for Arms A and C (CA2099UT)

Procedure[a]	Arm A: Nivolumab 480 mg IV Q4W Arm C: Nivolumab 480 mg IV Q4W plus BMS-986205 100 mg PO QD			
	Cycle 1 Day 1 (C1D1) (1 Cycle = 4 Weeks)	Cycle 2 (Day 1 ± 3 days)	Cycle 3-13 (Day 1 ± 3 days)	Notes[b]
				or symptoms of methemoglobinemia are present based on the clinical judgment of the investigator. Methemoglobin testing can be stopped if BMS-986205 is discontinued and the prior methemoglobin level is ≤ the ULN.
Pregnancy Test (WOCBP only)	X	X	X	Serum or urine within 24 hours prior to first dose and then every 4 weeks (± 1 week) regardless of dosing schedule.
Efficacy Assessments	See note			Efficacy assessments will be conducted per the local standard of care
Immunogenicity				
Blood Samples for Immunogenicity for Nivolumab	See note			Refer to Table 9.5.2-1.

[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] Some of the assessments referred to in this section may not be captured as data in the eCRF. 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: On-treatment Procedural Outline for Arms B and D (CA2099UT)

Procedure[a]	Arm B: Nivolumab 480 mg IV Q4W plus intravesical BCG Arm D: Nivolumab 480 mg IV Q4W plus intravesical BCG plus BMS-986205 100 mg QD			
	Cycle 1 Day 1 (C1D1) (1 Cycle = 4 Weeks)	Cycle 2 - 13[b] (Day 1 ± 3 days)	BCG only visits[b] (± 3 days)	Notes[c]
Study Drug				
Randomize	X			
Dispense Study Drug	X	X	X	First dose to be administered within 3 calendar days following randomization or 14 days following last TURBT/bladder biopsy, whichever is later. Nivolumab will be administered at Day 1 of each cycle. For Arm D, BMS-986205 will be administered once a day during each cycle. BCG will be administered as described in footnote "b."
Dispense Pill Diary (Arm D only)	X	X		Review pill diary during each visit for compliance of daily administration of BMS-986205. Collect pill diary at the completion of each cycle.
Safety Assessments				
Targeted Physical Examination, measurements, Vital Signs, Performance Status	X Also on C1D15 ± 3 days for Arm D	X		For each cycle, weight, blood pressure, heart rate, temperature, and ECOG Performance Status within 3 calendar days prior to dosing. For Cycle 1 Day 1 and beyond, targeted physical examination to be performed only as clinically indicated.
Oxygen Saturation (Arm D only)	X Also on C1D15 ± 3 days	X		Oxygen saturation by pulse oximetry or co-oximetry at rest prior to dosing

Table 2-3: On-treatment Procedural Outline for Arms B and D (CA2099UT)

Procedure[a]	Arm B: Nivolumab 480 mg IV Q4W plus intravesical BCG Arm D: Nivolumab 480 mg IV Q4W plus intravesical BCG plus BMS-986205 100 mg QD			
	Cycle 1 Day 1 (C1D1) (1 Cycle = 4 Weeks)	Cycle 2 - 13[b] (Day 1 ± 3 days)	BCG only visits[b] (± 3 days)	Notes[c]
ECG	X Also on C1D15 ± 3 days for Arm D	See note		At rest, pre-dose. For cycle 2 and beyond, pre-dose, as clinically indicated, including if concomitant medications which may prolong the QTc interval are added (Appendix 8).
Adverse Event (AE) Assessment (including SAEs)	Continuously			Record at each visit. All AEs and SAEs must be collected continuously during the treatment period and for a minimum of 100 days following last dose. Participants will be followed for all AEs and SAEs of special interest (as defined in Section 9.2.9), and all AEs and SAEs associated with confirmed or suspected SARS-CoV-2 infection until resolution, the condition stabilizes, the event is otherwise explained, the event is deemed irreversible, 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. 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	X CBC with differential also on C1D15 ± 3 days for Arm D	X		Must be performed within 72 hours prior to Nivolumab dosing Refer to Section 9.4.1 for list of laboratory tests.

Table 2-3: On-treatment Procedural Outline for Arms B and D (CA2099UT)

Procedure[a]	Arm B: Nivolumab 480 mg IV Q4W plus intravesical BCG Arm D: Nivolumab 480 mg IV Q4W plus intravesical BCG plus BMS-986205 100 mg QD			
	Cycle 1 Day 1 (C1D1) (1 Cycle = 4 Weeks)	Cycle 2 - 13[b] (Day 1 ± 3 days)	BCG only visits[b] (± 3 days)	Notes[c]
Thyroid Testing				Thyroid testing to be performed every 8 weeks (2 cycles). Methemoglobin must be assessed for Arm D on arterial or venous blood sample or by co-oximetry at every treatment visit except BCG-only visits or more frequently as clinically indicated based on symptoms (See Section 7.4.7). Participants may continue BMS-986205 dosing until methemoglobin result is available unless clinical signs or symptoms of methemoglobinemia are present based on the clinical judgment of the investigator. Methemoglobin testing can be stopped if BMS-986205 is discontinued and the prior methemoglobin level is ≤ the ULN.
Urinalysis	X	See note	X	Must be performed on the day of BCG dosing 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	X		Serum or urine within 24 hours prior to first dose and then every 4 weeks (± 1 week) regardless of dosing schedule.

Table 2-3: On-treatment Procedural Outline for Arms B and D (CA2099UT)

Procedure[a]	Arm B: Nivolumab 480 mg IV Q4W plus intravesical BCG Arm D: Nivolumab 480 mg IV Q4W plus intravesical BCG plus BMS-986205 100 mg QD			
	Cycle 1 Day 1 (C1D1) (1 Cycle = 4 Weeks)	Cycle 2 - 13[b] (Day 1 ± 3 days)	BCG only visits[b] (± 3 days)	Notes[c]
Efficacy Assessments	See note			Efficacy assessments will be conducted per the local standard of care
Immunogenicity				
Blood Samples for Immunogenicity for Nivolumab	See note			Refer to Table 9.5.2-1.

[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] BCG will be administered at C1D1, C1D8, C1D15, C1D22, C2D1, C2D8, C4D1, C4D8, C4D15, C7D1, C7D8, C7D15, C13D1, C13D8, and C13D15. The first BCG dose will be administered at C1D1 (Nivolumab dosing) ± 3 days. Thereafter, BCG will be administered 7 days (± 3 days) from the last BCG dose, except for C4D1, C7D1 and C13D1. For C4D1, C7D1 and C13D1, BCG dose will be administered ± 3 days of nivolumab dosing, unless nivolumab dosing is delayed. Also 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.

[c] Some of the assessments referred to in this section may not be captured as data in the eCRF. 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 2-4: Follow-up Procedural Outline (CA2099UT)

Procedure	Follow-up[a] Visits 1 and 2	Notes[b]
Safety Assessments		
Targeted Physical Examination, Measurements, Vital Signs, and Performance Status	See note	Weight, blood pressure, heart rate, temperature and ECOG Performance Status, to be performed only as clinically indicated.
Adverse Events Assessment (including Serious Adverse Events)	See note	Record at each visit. SAEs should be approved in RAVE within 5 days from entry. All AEs and SAEs must be collected for a minimum of 100 days following the last dose of study treatment. Participants will be followed for all SAEs, non-serious AEs of special interest (as defined in Section 9.2.9), and all AEs and SAEs associated with confirmed or suspected SARS-CoV-2 infection until resolution, the condition stabilizes, the event is otherwise explained, the event is deemed irreversible, 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. 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	X	
Laboratory Tests		
CBC with Differential, Chemistry Panel, Thyroid Testing	Visit 1-yes Visit 2 - only if toxicities are present	For full list of assessments, see Section 9.4.1.
Pregnancy (WOCBP only)	X	Serum or urine pregnancy testing.
Blood Samples for Immunogenicity for Nivolumab	See notes	Refer to Table 9.5.2-1.

[a] Participants must be followed for at least 100 days after last dose of study treatment. Follow-up 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 30 days from the last dose. Follow-up visit #2 occurs approximately 100 days (± 7 days) from last dose of study treatment. Both follow-up visits should be conducted in person.

[b] Some of the assessments referred to in this section may not be captured as data in the eCRF. 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

CA2099UT is an open-label, randomized Phase 2b trial of nivolumab or nivolumab combined with the indoleamine-1,2-dioxygenase 1 (IDO1) inhibitor BMS-986205 (linrodostat mesylate), either alone or in combination with intravesical bacillus Calmette-Guerin (BCG), in participants with BCG-unresponsive non-muscle-invasive bladder cancer (NMIBC). Nivolumab is an immuno-oncologic checkpoint inhibitor that enhances T-cell migration to the tumor. BCG treatment results in tumor inflammation, with the potential result of improved response of the tumor to immunotherapy. BMS-986205 is an inhibitor of IDO1, an enzyme that participates in the immunosuppressive environment within tumors by converting tryptophan to kynurenine and other immunosuppressive metabolites. BMS-986205 is being developed for use in patients with multiple solid tumors, including bladder cancer.

This is the first Phase 2 study evaluating nivolumab with or without BMS-986205 in participants with NMIBC. The study will assess the efficacy and safety of nivolumab alone (Arm A), nivolumab combined with BCG (Arm B), nivolumab combined with BMS-986205 (Arm C), and nivolumab combined with BMS-986205 and BCG (Arm D preliminary safety, as per revised protocol 03). Efficacy will be measured by the primary endpoint of complete response (CR) rate in the subgroup of participants with carcinoma in situ (CIS). This and other clinical endpoints will be evaluated in the treatment of pathologically proven high-risk, BCG-unresponsive NMIBC in participants who are either medically unfit for or have refused radical cystectomy.

3.1 Study Rationale

Individually targeting immune checkpoint receptors such as programmed cell death protein-1 (PD-1) and cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) 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] Targeting the immunosuppressive properties of the cancer cells themselves, such as by inhibiting IDO1, is a promising approach in cancer immunotherapy. Preliminary data in participants with advanced UC evaluating an IDO1 inhibitor in combination with anti-PD-1 therapy have shown that this combination may improve the efficacy of anti-PD-1 therapy alone, with potentially similar toxicity.[4] BMS-986205 is an optimized IDO1 inhibitor characterized by once-daily dosing and deeper inhibition of IDO1 activity than other inhibitors, as measured by peripheral blood kynurenine suppression. BMS-986205 has also demonstrated preliminary evidence of clinical activity in combination with nivolumab in multiple tumor types, including UC, in the first-in-human Study CA017003.[5,6]

3.1.1 Research Hypothesis

This section is not applicable as per Protocol Amendment 04.

3.1.2 Changes Per Protocol Amendment 04

As of early April 2021, Study CA2099UT enrollment was significantly behind the projected target enrollment, at 28.1% (number of subjects enrolled 135; target enrollment 480). Since the study

would be unable to meet the scientific objectives within a projected timeline, a decision was made in May 2021 to close the study. Importantly, there is no change to the understanding of the safety profile of nivolumab or nivolumab/BMS-986205, with or without intravesical BCG in participants with BCG-unresponsive, high-risk, NMIBC.

As of 02-Jun-2021, the following were put into effect:

- Enrollment for new participants was closed effective immediately
- Participants, who signed study consent prior to this notification and are undergoing screening, can be permitted to be randomized to study treatment
- Participants currently on treatment can be 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 04 is approved by the relevant Health Authorities and Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) at the site

Protocol Amendment 04 describes the modification to study procedures. All participants must be re-consented upon approval and implementation of Protocol Amendment 04. These changes affect all participants and should be implemented when Protocol Amendment 04 is implemented at the site.

Key changes in Protocol Amendment 04 will include:

- Details of closure of the study, with provision for participants currently on treatment to continue
- Removal of pharmacokinetic (except for immunogenicity), biomarker, healthcare resource utilization, and patient-reported outcome (PRO) assessments
- Removal of study-related efficacy assessment and Pathology Review Committee (PRC). Sites should continue efficacy assessment as per local standard of care

The changes instituted in Protocol Amendment 04 should override any existing protocol requirements in the event of any apparent discrepancies.

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.[7,8] Bladder cancer ranks as the fifth most commonly diagnosed non-cutaneous solid malignancy in the US, estimated to account for 79,000 new cases and almost 17,000 deaths in 2017.[9] Bladder cancer is more common in men than in women, with a ratio of approximately 3:1.[9,10] The majority of cases are UCs, with mixed or variant histologies (such as squamous cell carcinoma, adenocarcinoma, micropapillary carcinoma, or neuroendocrine carcinoma) comprising a smaller subset.[11]

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.[12] NMIBCs are confined to either the mucosal lining or lamina propria of the bladder, not yet having penetrated into the muscular bladder wall.[10] 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.[10] 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 stage T1 tumor, and/or the presence of CIS.[10,11]

Soon following the initial report of its successful use in bladder cancer patients[13], intravesical BCG became the standard of care (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 3 years of maintenance treatment significantly decreases the risk of bladder tumor recurrence and progression in patients with high-risk NMIBC when compared to no additional treatment or treatment with intravesical chemotherapy.[10,14,15,16,17,18] Despite the recognized benefit of BCG treatment in this patient population, tumor recurrence and progression within 5 years following BCG induction and maintenance is not uncommon, occurring in 40% to 80% (recurrence) and 25% to 45% (progression) of patients.[19,20,21,22] While some patients will respond to a second induction course, treatment with BCG beyond 2 induction courses does not have any additional clinical benefit.[23]

Treatment for patients with high-risk NMIBC who do not respond to intravesical BCG treatment remains a challenge. A variety of single agents and treatment combinations, administered either intravesically or systemically, have been studied in the BCG-unresponsive population.[24,25,26] Since the initial approval of BCG in 1990, no therapy to-date has proven sufficiently efficacious with a clinically meaningful durable response rate in BCG-unresponsive patients, resulting in only one treatment (valrubicin), with little long-term benefit, receiving approval by health authorities for the treatment of BCG-unresponsive NMIBC.[25] As a result, the only remaining therapeutic option for patients with residual or recurrent high-risk NMIBC following unsuccessful BCG treatment is radical cystectomy.[27] However, radical cystectomy is not performed in more than 50% of eligible patients due to reasons that include advanced age, comorbid conditions, or patient refusal.[28] In those patients who undergo radical cystectomy, morbidity is significant, including a 31% perioperative complication rate, a 21% readmission rate and a 1%-3% mortality rate following the procedure.[29]

The lack of effective new treatments has led to an important unmet therapeutic need in patients with high-risk NMIBC who will no longer benefit from BCG therapy, and who are not candidates for or refuse radical cystectomy. This unmet therapeutic need has been recognized by organizations including the US Food and Drug Administration (FDA), the International Bladder Cancer Consensus Group, and the American Urological Association[24,30], and it formed the basis for a recent FDA guidance titled "BCG-Unresponsive Nonmuscle Invasive Bladder Cancer: Developing Drugs and Biologics for Treatment Guidance for Industry, February, 2018."[27] This communication provides guidance for the pharmaceutical industry with respect to the development of drugs and biologics for this patient population, and it is in alignment with recommendations from the International Bladder Cancer Group with respect to acceptable designs, durations, and endpoints for clinical studies.

To facilitate trial design, disease states following treatment with BCG have been specified, and 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.[26,31] Patients meeting this definition will have received adequate BCG treatment, defined as at least 2 courses of BCG (either 2 induction courses or 1 induction and 1 maintenance course) but have either not responded to treatment or have developed a high-risk recurrence within 6 months (for patients with papillary disease) or 12 months (for patients with CIS) of their last exposure to BCG.[24,26,27,31] Endpoints for single-arm, registrational studies in the BCG-unresponsive NMIBC population have been clearly addressed in the FDA Guidance for developing drugs and biologics in this population.[27] For BCG-unresponsive patients, the focus of registrational studies is placed on CIS. The FDA recognizes that the natural history of CIS is to persist despite surgical treatment, and that participants entering any study with a diagnosis of CIS will likely have residual CIS post-TURBT. For such patients, the CR rate can provide primary evidence of efficacy of a therapeutic intervention, thereby supporting a regulatory submission. Some published literature suggests a 50% CR rate at 6 months for CIS participants would be clinically meaningful;[24] however, there are no regulatory guidelines specifying a minimum efficacy threshold, and durable CR rates (eg, 30% at 12 months) would also be considered clinically meaningful.

3.2.2 Nivolumab Mechanism of Action

Cancer immunotherapy rests on the premise that tumors can be recognized as foreign rather than as self and can be effectively attacked by an activated immune system. An effective immune response in this setting is thought to rely on immune surveillance of tumor antigens expressed on cancer cells that ultimately results in an adaptive immune response and cancer cell death. Meanwhile, tumor progression may depend upon acquisition of traits that allow cancer cells to evade immunosurveillance and escape effective innate and adaptive immune responses.[32,33,34] Current immunotherapy efforts attempt to break the apparent tolerance of the immune system to tumor cells and antigens by mechanisms such as introducing cancer antigens by therapeutic vaccination or by modulating regulatory checkpoints of the immune system. T-cell stimulation is a complex process involving the integration of numerous positive as well as negative co-

stimulatory signals in addition to antigen recognition by the T-cell receptor (TCR).[35] Collectively, these signals govern the balance between T-cell activation and tolerance.

PD-1 is a member of the CD28 family of T-cell co-stimulatory receptors that also includes CD28, CTLA 4, ICOS, and BTLA.[36] PD-1 signaling has been shown to inhibit CD28-mediated upregulation of interleukin (IL)-2, IL-10, IL-13, interferon-gamma (IFN-γ) and Bcl-xL. PD-1 expression has also been noted to inhibit T-cell activation, and expansion of previously activated cells. Evidence for a negative regulatory role of PD-1 comes from studies of PD-1 deficient mice, which develop a variety of autoimmune phenotypes.[37] These results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self-antigens.

In vitro, nivolumab (BMS-936558) binds to PD-1 with high affinity (EC50 = 0.39-2.62 nM), and inhibits the binding of PD-1 to its ligands PD-L1 and PD-L2 (IC50 = ± 1 nM). Nivolumab binds specifically to PD-1 and not to related members of the CD28 family such as CD28, ICOS, CTLA 4 and BTLA. Blockade of the PD-1 pathway by nivolumab results in a reproducible enhancement of both proliferation and IFN-γ release in the mixed lymphocyte reaction (MLR). Using a cytomegalovirus (CMV) re-stimulation assay with human peripheral blood mononuclear cells (PBMC), the effect of nivolumab on antigen specific recall response indicates that nivolumab augmented IFN-γ secretion from CMV specific memory T-cells in a dose-dependent manner vs isotype-matched control. In vivo blockade of PD-1 by a murine analog of nivolumab enhances the anti-tumor immune response and result in tumor rejection in several immunocompetent mouse tumor models (MC38, SA1/N, and PAN02).[38]

See also the Investigator Brochure (IB) for nivolumab Section 4.1 (nonclinical pharmacology studies) and Section 4.2 (nonclinical PK) for more information on the mechanism of action.

3.2.3 BMS-986205 Mechanism of Action

IDO1 catalyzes the degradation of tryptophan to N-formyl-kynurenine, which is the first and rate limiting step leading to the production of kynurenine and downstream metabolites. The activity of IDO1 causes immune tolerance by inhibiting T-cell function through local depletion of the essential amino acid tryptophan and through generation of inhibitory kynurenine pathway metabolites.[39] In healthy humans, IDO1 is expressed in the placenta, the mucosa of the female genital tract, the lungs, and the lymphoid organs.[40] IDO1 expression in the placenta is believed to play a role in maternal tolerance to allogeneic fetuses[41]. However, functional roles of IDO1 in the lungs and female genital tract are not as clear but may be involved in combating infections or play a role in immune tolerance. In the immune system, IDO1 is expressed in dendritic cells and macrophages. IDO1 is strongly induced by pro-inflammatory mediators such as IFN-γ and endotoxins during the late phase of inflammatory reactions, in which its immunosuppressive role contributes to the physiologic feedback control of the immune response.[42]

IDO1 is highly expressed in several types of human malignancies. High levels or frequencies of IDO1 expression are detected in multiple tumor types.[43,44] IDO1 expression in tumors is believed to induce immune tolerance as evident by a decrease in tumor infiltration of immune cells and an increase in the proportion of regulatory T-cells (Treg) in tumor infiltrating lymphocytic populations. Increased IDO1 is also correlated with diverse tumor progression parameters and shorter patient-survival times in many cancer indications. IDO1 has been shown to be significantly up-regulated together with the programmed death receptor ligand 1 (PD-L1).[45] The enzyme is also reported to provide a critical resistance mechanism in anti-tumor T-cell immunotherapy targeting CTLA 4.[46] Furthermore, tumor IDO1 transcript is increased in patients with advanced melanoma and metastatic renal cell carcinoma (RCC) after treatment with the anti-PD-1 antibody nivolumab.[47,48] These findings suggest that IDO1 is an important regulator of the immunosuppressive mechanisms responsible for tumor escape from host immune surveillance. Inhibition of IDO1 using pharmaceutical agents such as BMS-986205 may alleviate the immunosuppressive properties of the tumor microenvironment and achieve more durable responses and greater patient survival benefits, particularly when used in combination with other cancer immunotherapy agents, such as nivolumab.

See also the Investigator Brochure (IB) for BMS-986205 Section 4.1 (nonclinical pharmacology studies) and Section 4.2 (nonclinical PK) for more information on the mechanism of action of BMS-986205.

3.2.4 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.[49] 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 (TRAIL). 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.[50]

Both bladder cancer cells and benign urothelial cells appear to play a role in the initial recognition and processing of BCG.[49] 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], US Prescribing Information [USPI], or country-specific label).

3.3 Benefit/Risk Assessment

There continues to be a significant unmet therapeutic need for patients with BCG-unresponsive, high-risk NMIBC that has been recognized by consensus groups, professional organizations, and health regulatory agencies.[24,30] Radical cystectomy is the only treatment option for these patients, and for those who are either unable or unwilling to undergo this procedure, there is no remaining treatment option. Nivolumab, with or without BMS-986205, either alone or in combination with intravesical BCG, has the potential for clinically meaningful benefit in this BCG-unresponsive population. 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 urothelial carcinoma in adults after failure of prior platinum-containing therapy. See the current prescribing information for nivolumab (Opdivo®) for more information.

Nivolumab has been shown to have an acceptable safety profile; this safety profile, based on extensive clinical experience, is described in detail in the current IB for nivolumab. Details concerning nonclinical toxicology and safety pharmacology of BMS-986205 are provided in the IB. Clinical experience regarding BMS-986205 is limited. The safety, tolerability, and efficacy of BMS-986205 administered alone and in combination with nivolumab is currently being assessed in Study CA017003, the first-in-human, Phase 1/2a dose escalation and cohort expansion study in advanced malignant tumors.[6] Preliminary analysis of safety results from this study have revealed a favorable safety profile, with the most commonly reported drug-related adverse events (AEs) (occurring in > 5% of 286 participants as of 14-Sept-2017) being fatigue, nausea, decreased appetite, and aspartate transaminase/alanine transaminase (AST/ALT) elevations. Furthermore, the 100 mg once daily (QD) dose of BMS-986205 in combination with nivolumab appears to have a safety profile similar to that reported for nivolumab monotherapy, except for infrequent, manageable and reversible anemia and limited instances of clinically insignificant methemoglobin elevation, which may be related to p-chloroaniline production. Metabolism of BMS-986205 produces a p-chloroaniline metabolite, which is associated with the formation of methemoglobin as well as with hemolytic anemia. In Study CA017003, as of 14-Sept-2017, 12% of participants (33 of 283 participants with reported values) had methemoglobin values above their institutional upper limit of normal (ULN). None of the participants with elevations in methemoglobin, nor any

other participants on study, had symptoms attributable to methemoglobin, nor were there any dose reductions, interruptions, or discontinuations due to elevations of methemoglobin. The highest methemoglobin level reported was 6%, below the commonly accepted thresholds for the development of cyanosis (10%) and the development of more severe symptoms (20%).[51] Drug-related Grade 3 anemia was reported in approximately 1.4% of participants. Based on these findings, entry criteria and monitoring parameters were developed in an attempt to reduce the risk of their occurrence and impact. Participants with cytochrome b5 reductase and glucose-6-phosphate dehydrogenase (G6PD) deficiencies are excluded due to the increased risk of methemoglobinemia and hemolysis, respectively. Guidance for detection and management of methemoglobinemia as well as guidelines for dose interruptions, reductions, and discontinuation are provided in Section 7.4.7 (detection), Section 7.7.4 (management), Section 7.4.2 (dose modification), Section 7.4.4.2 (dose delay), and Section 8.1.2 (discontinuation).

This study assesses investigational (BMS-986205) and marketed (nivolumab) drugs whose effects on pregnancy are not yet known or fully defined. Contraception is therefore required for participants who are women of child-bearing potential (WOCBP) or male, and for female partners of male participants who are WOCBP. Contraception guidelines presented in Appendix 4 were initially developed for the nivolumab development program and apply to all female participants and partners of male participants who could be exposed to the drug and who could become pregnant both during treatment and during a defined period after study treatment. In these nivolumab program contraceptive guidelines, hormone-based contraception (eg, pill or hormone-releasing intrauterine device [IUD]) is considered to be a highly effective method for WOCBP who are participants in a nivolumab program study. However, in this study, hormone-based contraceptives are not considered highly effective methods of contraception for WOCBP participants in treatment Arms C and D or partners of male participants in Arms C and D, due to a lack of data regarding potential drug-drug interactions (DDI) between BMS-986205 and hormone-based contraception that could reduce the efficacy of these contraceptives.

A pattern of immune-mediated adverse events (IMAEs) has been defined for treatment with nivolumab monotherapy and nivolumab in combination with other immune-targeting agents such as BMS-986205. Overall, the incidence, severity, and response to dose interruption and steroid treatment with BMS-986205 at 100 mg combined with nivolumab appears similar to that of nivolumab monotherapy. Management algorithms have been developed for these events and are provided in Appendix 5. Most high-grade events are manageable with the use of corticosteroids or hormone replacement therapy (for endocrinopathies) as instructed in these algorithms.

Additional details on the safety profiles of BMS-986205 and nivolumab, including results from other clinical studies, are also available in the respective IBs.

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, with or without BMS-986205, in combination with intravesical BCG is currently unknown. A safety lead-in for the 2 BCG-containing treatment arms will be performed in order to determine any dose-limiting toxicity (DLT) as well as the safety profiles of these treatment combinations. See Section 5.1.1 for details.

To ensure an ongoing favorable risk/benefit 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 Data Monitoring Committee (DMC) to provide independent oversight of safety, study conduct and benefit risk of BMS-986205 in combination with nivolumab, with and without BCG
- Rigorous safety monitoring by BMS to ensure participants' safety including regular and systematic review of safety data, close follow-up of reported adverse events, and intensive site and study investigator training/education on the implementation of the BMS-986205, nivolumab, and BCG toxicity management strategies.

Preliminary evidence of clinical activity of nivolumab in combination with BMS-986205 has been observed in the advanced bladder cancer cohort in Study CA017003, with 8 partial responses (PRs) out of 25 (32%; 95% CI: 15, 54) evaluable participants.[6] ORR in participants with only one line of prior therapy has been 40% (95% CI 16, 68), and response has been associated with PD-L1 expression with an ORR of 46% (95% CI 19, 75) in PD-L1 positive and 22% (95% CI 3, 60) in PD-L1 negative participants, respectively. These data are based on the first imaging assessment, and it is anticipated that responses for some participants will deepen with extended time on therapy as has been observed with immunotherapy treatments. Potential benefit of combining IDO1-targeting therapies with anti-PD-1 therapies in patients with bladder cancer has also been reported for another IDO1 inhibitor that is currently in development.[4]

Evaluating the combination of nivolumab and BMS-986205, with or without intravesical BCG, will provide clinical data allowing clinicians to select the appropriate treatment for each patient based on the individual risk-benefit ratio. The promising clinical activity of BMS-986205 combined with nivolumab in participants with advanced bladder cancer, together with the manageable safety profile and the ongoing need for recurrence-free and survival-prolonging agents for a large segment of the previously treated NMIBC population, supports further development of this combination and initiation of this Phase 2b study.

More detailed information about the known and expected benefits and risks and reasonably anticipated AEs of nivolumab and BMS-986205 may be found in their respective IBs. The benefits/risks for live BCG can be determined by consulting the current Patient Information Leaflet, USPI, Development Safety Update Report or SmPC.

4 OBJECTIVES AND ENDPOINTS

Not applicable per Protocol Amendment 04. Only safety and immunogenicity assessments will be conducted. No analyses of efficacy, quality of life/patient-reported outcomes, pharmacokinetics, or healthcare resource utilization, are planned. Previously collected biomarker samples may be analyzed, but no further collections are planned with this amended protocol.

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
• To describe the safety and tolerability of nivolumab and nivolumab + BMS-986205, alone or in combination with intravesical BCG.	• Incidence of adverse events (AEs), serious AEs, deaths and laboratory abnormalities in all treated participants. • Overall safety and tolerability will be measured by the incidence of AEs, SAEs, AEs leading to discontinuation, immune-mediated AEs, deaths, and laboratory abnormalities and changes from baseline.
• To characterize the immunogenicity of nivolumab.	• Incidence of anti-nivolumab antibodies and their potential relationship with safety.

5 STUDY DESIGN

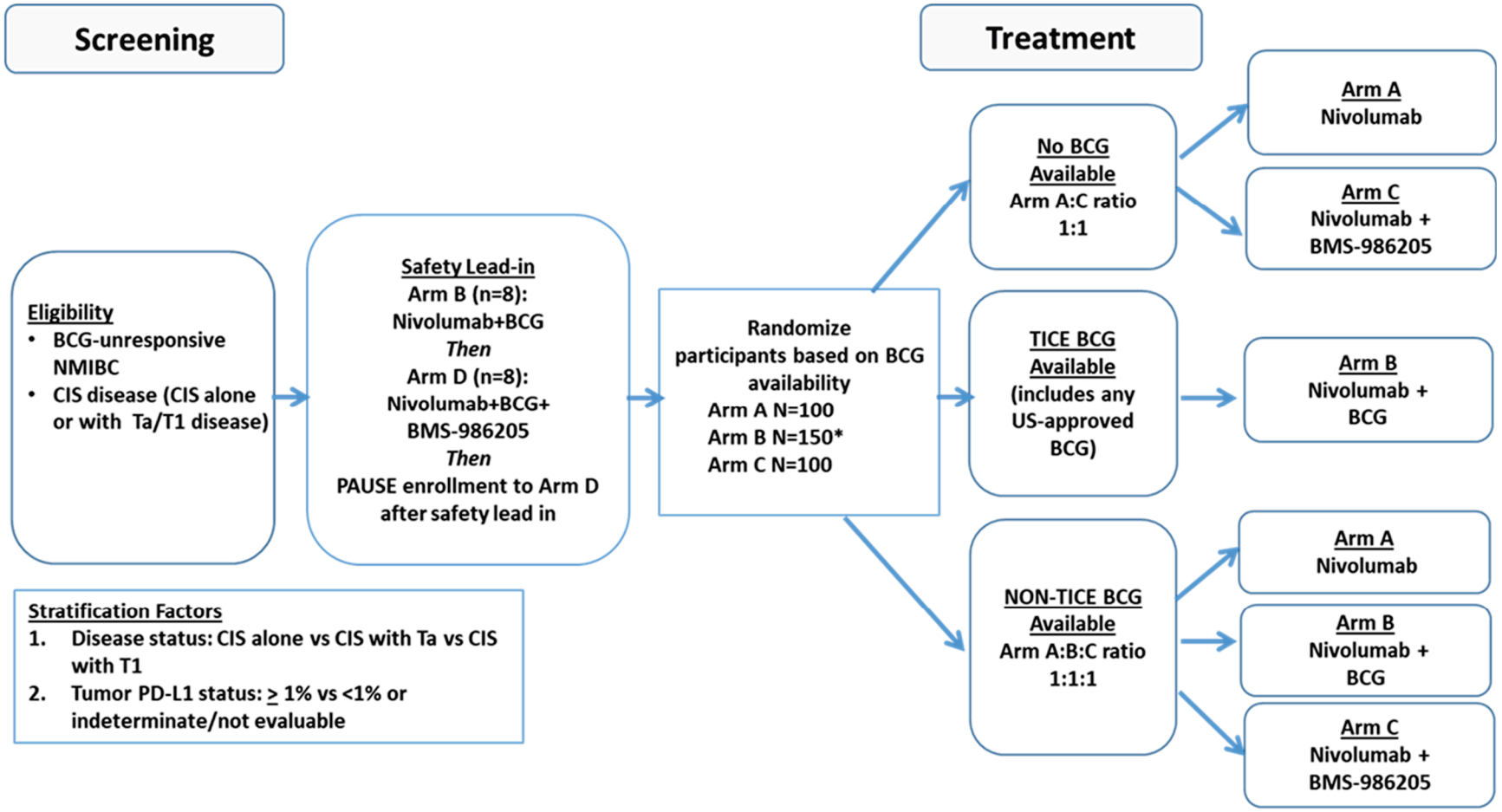
5.1 Overall Design

This is a Phase 2b, randomized, open-label study of nivolumab or nivolumab plus BMS-986205, with or without intravesical BCG, in adult (18 years of age and older, or age of majority) participants with pathologically proven BCG-unresponsive, high-risk NMIBC.[27,31] UC must be the predominant histologic sub-type of the recurrent tumor. Participants should be considered medically unfit for radical cystectomy, or they should have refused radical cystectomy after consultation with their oncologist/urologist. Participants must not have evidence of UC in the upper urinary tracts (kidneys, renal pelvis, ureters) or in the prostatic urethra. Previous or concurrent muscle invasive or disseminated bladder cancer is not permitted. Prior systemic treatment, radiation therapy, or surgery for bladder cancer other than TURBT or bladder biopsies is also not permitted.

Representative diagnostic pathology slides, obtained at TURBT within 10 weeks (70 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 submitted to the PRC for confirmation of diagnosis. Sufficient, recent tumor tissue obtained within 10 weeks (70 days) prior to randomization from the bladder tumor tissue obtained at TURBT (formalin-fixed paraffin-embedded block or 20 slides [minimum 15]) will be submitted to the analytical laboratory for determination of PD-L1 expression and for biomarker studies. If sufficient tissue is not available within 10 weeks (70 days) prior to randomization, then the site will be asked for additional tissue or a repeat TURBT will be required. The PRC and the analytical lab must provide IRT with confirmation of diagnosis and PD-L1 expression (≥ 1%, < 1%, indeterminate, not evaluable) prior to randomization. Participants should not have received any systemic or intravesical anticancer therapy after the date that the submitted tumor tissue was obtained.

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

Figure 5.1-1: CA2099UT Study Schematic



During the treatment phase, participants will receive:

- Arm A: Nivolumab 480 mg IV every 4 weeks (Q4W) for up to 52 weeks (12 months)
- Arm B: Nivolumab 480 mg IV Q4W for up to 52 weeks (12 months) and intravesical BCG (induction) weekly for 6 weeks followed by maintenance intravesical BCG weekly for 3 weeks at 3 months, 6 months and 12 months following the first intravesical dose. The dose 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. Every effort should be made to continue a participant on the same strain of BCG for the duration of study participation.
- Arm C: Nivolumab 480 mg IV Q4W and BMS-986205 100 mg PO QD for up to 52 weeks (12 months)
- Arm D: Nivolumab 480 mg IV Q4W and BMS-986205 100 mg PO QD for up to 52 weeks (12 months), and intravesical BCG (induction) weekly for 6 weeks followed by maintenance intravesical BCG weekly for 3 weeks at 3 months, 6 months, and 12 months following the first intravesical dose. The dose 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. Arm D will be held to enrollment after the safety lead-in.

For each arm, 1 treatment cycle equals 4 weeks.

Dose reductions will not be allowed for nivolumab or for BCG after the safe-dose level has been determined in the safety lead-in. One (1) dose reduction from 100 mg QD to 50 mg PO QD will be permitted for BMS-986205 (Section 7.4.2).

On-study cystoscopy and urinary cytology in all participants will begin 13 weeks following the first dose of nivolumab and will continue every 13 weeks thereafter. Bladder biopsies will be obtained at 26 weeks and 52 weeks after the first dose of nivolumab in CIS participants. Efficacy assessments must occur until disease recurrence or progression per PRC, or until treatment discontinuation, whichever occurs later. Treatment beyond disease recurrence is not permitted except in the case of a low-grade Ta UC recurrence only.

A safety lead-in will be conducted in participants randomized to receive BCG and nivolumab without or with BMS-986205 (Arms B and D, respectively) to determine safe-dose levels to be administered during the treatment phase. Enrollment in the safety lead-in will be staggered so that the safety lead-in phase for Arm B is adequately assessed prior to the enrollment of Arm D. After the safety lead-in (see Section 5.1.1), participants with CIS, with or without papillary disease, will be randomized in a 1:1:1 ratio into study Arms A through C.

Revised protocol 03 study design modifications include limiting enrollment only to participants with CIS and increasing the sample size for each arm, in order that this randomized study design will be able to demonstrate a CR rate and duration of response in CIS participants. A second key modification is that due to global shortages of BCG, only 1 BCG-containing arm (Arm B) will

move forward with randomization instead of 2 (Arms B and D). Thus, after the safety lead-in to Arm D, enrollment will be paused. Modified randomization, based on the availability of BCG at the site, allows sites facing BCG shortage at the time of participant enrollment to enroll participants in the study (Section 5.4.9). Once 150 total participants have been randomized to Arm B, the BCG-containing arm, Arm B will stop enrollment. At that point, new participants would be randomized via the "No BCG available" category to either Arm A or C, if open for enrollment (see Figure 5.1-1). Lastly, the number of non-TICE BCG treated participants was limited to 70 to ensure at least 80 participants are treated with TICE BCG in Arm B, the only strain approved in the US and many other countries.

As of 02-Jun-2021, enrollment into this study was closed. Protocol Amendment 04 removes the decision points and the efficacy follow-up along with other study procedures. As a result, randomization Phase Part 3, initial risk/benefit assessment by the Data Monitoring Committee, and Independent Pathology Review Committee (PRC) will be removed.

5.1.1 Safety Lead-in Phase

The safety lead-in will be conducted to evaluate the safe dose level of combination intravesical BCG and systemic IO therapy. Enrollment in the safety lead-in will be staggered so that the safety lead-in phase for Arm B is adequately assessed prior to the enrollment of Arm D. Approximately 8 participants will be enrolled in Arm B, and these participants will receive BCG induction, consisting of 6 weekly treatments, plus nivolumab. The dose of nivolumab is 480 mg IV every 4 weeks. BCG will be administered at full strength according to the prescribing information for the particular strain and preparation administered.

Safety data from these first 8 participants in Arm B who have been treated and followed for at least 6 weeks on study (after completing BCG induction and nivolumab) will be evaluated, and a decision will be made as to whether or not to continue enrollment into Arm B with the starting dose or to de-escalate to a lower dose. The decision regarding de-escalation, including which study treatment to de-escalate, will be made based on the number and type of dose-limiting toxicities (DLTs). Particular attention will be given to the well-characterized, local bladder-related toxicity of intravesical BCG and whether the severity of these symptoms during treatment with full-dose BCG and systemic I-O therapy warrants dose modification or discontinuation in this patient population.

After the safety lead-in phase for Arm B is fully evaluated and a safe dose is established, enrollment in Arm D will begin. Approximately 8 participants will be enrolled in Arm D, and these participants will receive BCG induction, consisting of 6 weekly treatments, plus nivolumab and BMS-986205. The dose of nivolumab is 480 mg IV every 4 weeks and BMS-986205 is 100 mg administered orally daily. BCG will be administered at full strength according to the prescribing information for the particular strain and preparation administered. Safety data for these first 8 participants in Arm D will be evaluated in a similar fashion to that described above for Arm B.

Per revised protocol 03, due to a global shortage of intravesical BCG, after the approximately 8 participants in Arm D complete the safety lead-in phase, further enrollment in Arm D will be paused. Enrollment in Arms A, B, and C will continue per protocol.

A safe dose will be established if ≤ 25% of the evaluable participants in a given treatment arm experience DLTs, at which point that treatment arm will be re-opened to randomization of CIS participants. If > 25% of the first 8 evaluable participants experience DLTs, and following DMC review and agreement, up to an additional 8 participants may be treated at the starting dose to better define safety and tolerability. Agreement will also be reached as to whether any additional treatment guidelines should be administered. If > 25% of DLT-evaluable participants in a given treatment arm exhibit DLTs after an additional 8 participants are treated and followed for at least 6 weeks on study, the protocol may be amended to evaluate different dose levels of nivolumab, BMS-986205, and/or BCG, depending on the toxicities observed.

Definition of DLTs in Safety Lead-in Phase (Arms B and D): Dose limiting toxicities are defined as any of the items listed below which occur during the first 6 weeks for which no alternative cause, other than study treatment, can be identified.

- Any ≥ Grade 2 uveitis or eye pain that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Any ≥ Grade 2 pneumonitis or interstitial lung disease that does not resolve with dose delay and treatment with systemic steroids in 14 days (radiologic changes may take longer to resolve). The management algorithm for pneumonitis or pulmonary toxicity can be found in Appendix 5
- Any ≥ Grade 3 non-skin AE, with the exception of laboratory abnormalities, fatigue and nausea, that cannot be attenuated (defined as returning to Grade 1, radiologic changes may take longer to resolve) or controlled by appropriate care within 14 days (appropriate care being defined as treatment outlined in AE management algorithms in Appendix 5).
- Any ≥ Grade 3 irritative bladder symptoms
- Any ≥ Grade 3 gross hematuria
- Any fever >38.5°C that is attributed by the investigator to treatment with BCG
- Any evidence of disseminated BCG infection including BCG sepsis, granulomatous prostatitis, or granulomatous orchitis
- Any Grade 4 AE including laboratory abnormalities except Grade 4 leukopenia or neutropenia lasting < 14 days and asymptomatic amylase/lipase elevation
- Any of the following hepatic function laboratory abnormalities:
  - AST or ALT > 5 to 8x ULN for > 2 weeks
  - AST or ALT >8x ULN
  - Total Bilirubin > 3 to 5x ULN for > 2 weeks
  - Total Bilirubin >5x ULN
  - Concurrent AST or ALT > 3x ULN and total bilirubin > 2x ULN for which no alternative cause, other than study treatment, can be identified
- ≥ Grade 3 thrombocytopenia associated with bleeding
- Methemoglobin levels ≥ 15 % (Arm D only)
- Grade ≥ 3 hemolysis requiring transfusion or medical intervention such as steroids (Arm D only)

Safety lead-in participants should discontinue treatment if they experience any AE, laboratory abnormality or intercurrent illness (regardless of causality) which, in the opinion of the investigator, presents a substantial clinical risk to the participant with continued BCG, nivolumab and/or BMS-986205 dosing. Such discontinuation, however, will not be considered a DLT unless it meets at least one of the DLT criteria defined above. Treatment delay, modification and discontinuation criteria are to be followed for management of safety lead-in participants.

5.1.2 Randomization Phase

Participants are to have tumor tissue samples submitted for PD-L1 testing performed by the analytical laboratory during the screening period. PD-L1 testing together with tumor CIS and disease status per PRC (CIS alone vs CIS with Ta vs CIS with T1) will be used as stratification factors for randomization. Since this is an open-label study, randomization is for administrative purposes and balancing of treatment arms (see below).

Investigators will classify participants as BCG refractory or BCG early relapsing for the purpose of analysis and not for stratification. Per revised protocol 03, participants must have CIS to be eligible, but will be stratified based on the CIS as well as any Ta/T1 disease. BCG refractory will be defined as recurrent T1 or high-grade Ta disease within 6 months of completion of adequate BCG without a disease-free interval or persistent CIS (alone or with recurrent T1, high grade Ta) within 12 months of completion of adequate BCG without a disease-free interval. BCG refractory will also include high-grade T1 disease or any stage or grade progression (stage T1 after initial Ta or CIS, any-grade progression to high grade) at the first evaluation following BCG induction alone (at least 5 of 6 induction doses). BCG early relapsing will be defined as recurrent T1 or high grade Ta, after achieving a disease-free state, within 6 months of completion of adequate BCG therapy, or recurrent CIS (alone or with recurrent T1, high grade Ta) after achieving a disease-free state within 12 months of adequate BCG therapy.

Safety Lead-In Phase: The Safety Lead-In phase will run from initiation of the study until approximately 16 participants are enrolled in the safety lead-in for Arms B and D.

- The study will begin with enrollment of 8 CIS participants into Arm B.
- Enrollment will then be held until the safety lead-in for Arm B is adequately assessed and a safe dose is established.
- After the safety lead-in for Arm B is complete, approximately 8 CIS participants will be enrolled in Arm D. There will be a hold on enrollment into Arm D following completion of the safety lead-in.
- If indicated, and upon DMC review, an additional 8 participants may subsequently be enrolled into Arm B and/or Arm D after evaluation of the initial 8 safety lead-in participants in that arm to better define safety and tolerability.

Randomization: Randomization will be modified based on the availability of BCG and BCG strains (see Figure 5.1-1 and Section 5.4.9).

- Sites will be classified based on their BCG availability at the time of participant randomization:
  1) "No BCG available" (6 induction and the first 3 maintenance doses not being available at the time of consent)
  2) "TICE BCG available" (for the purposes of randomization, any BCG strain that becomes approved in the US during the conduct of the study [regardless of site geographic location] will be included in the category of TICE BCG)
  3) "Non-TICE BCG available"

- The 3 arms (treatment details in Section 5.1) are:
  1) Arm A with nivolumab, N = 100 participants
  2) Arm B with nivolumab + intravesical BCG, N = 150 participants
     a) Non-TICE participants capped at ≤ 70 to ensure at least 80 TICE participants; after reaching the non-TICE cap, non-TICE participants will be randomized into either Arm A or Arm C.
     b) Once 150 total participants are randomized to Arm B, enrollment will be stopped. Arm B is the only BCG-containing arm so once enrollment stops, future participants will be randomized into either Arm A or C, if open for enrollment, via the "No BCG available" category.
  3) Arm C with nivolumab + BMS-986205, N = 100 participants
- Based on BCG availability at the site, randomization will lead to participants' enrollment in the following arms:
  - No BCG available: Arm A and C (1:1)
  - TICE BCG available: Arm B; if Arm B is closed to enrollment, then Arm A or C (1:1)
  - Non-TICE BCG available: Arm A, B, and C (1:1:1) until Arm B is closed to non-TICE participants, then Arm A or C (1:1)
- If TICE BCG shortage resolves by assessment of the sponsor, randomization of TICE BCG participants may switch to Arms A, B, or C in a 1:1:1 ratio at the sponsor's discretion.

Randomization Phase Part 1: The Part 1 randomization will begin after treatment initiation of approximately 8 participants in the safety lead-in for Arm D, and it will run through the end of the Arm D safety lead-in.

- After approximately 8 participants initiate treatment in the safety lead-in Arm D, randomization of participants will begin into Arms A, B, and C.

Randomization Phase Part 2: The Part 2 randomization will begin at the conclusion of the safety lead-in for Arm D and run until the 6-month decision point is reached for each treatment arm.

- Randomization of CIS participants will continue in all treatment arms (A, B, C).

5.1.3 Data Monitoring Committee and Other External Committees

An independent, external Data Monitoring Committee (DMC) will be established to provide oversight of safety 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 act in an advisory capacity to Bristol-Myers Squibb (BMS) and will monitor participant safety for the study. Data and summaries will be made available to the DMC, and the committee will provide advice regarding toxicity during the safety lead-in period. The BMS Oncology Development Department has primary responsibility for design and conduct of the study. Details concerning governance are provided in Appendix 2.

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

5.2 Number of Participants

As of 02-Jun-2021, enrollment into this study was closed. Number of participants enrolled was 135, as of early April 2021.

5.3 End of Study Definition

The start of the trial is defined as the first visit for the first participant screened. End of the trial and end of the study are defined as the final date when all participants completed study procedures described in Section 2 including follow-up visits.

5.4 Scientific Rationale for Study Design

Bladder cancer is an immunologic malignancy, and multiple studies have shown that bladder cancer specimens harbor tumor infiltrating lymphocytes.[52,53] Immunohistochemical (IHC) staining for intratumoral CD8+ T-cells in tissue samples from 69 participants with bladder cancer (pT2, pT3, or pT4) demonstrated that participants with higher numbers of CD8+ tumor-infiltrating lymphocytes (TILs) within the tumor (8 or more) had better disease-free survival ($p < 0.001$) and overall survival ($p = 0.018$) than did participants with similar-staged bladder cancer and fewer intratumoral CD8+ TILs.[53]

Immunotherapy has played a major role in the treatment of superficial bladder cancer since the introduction of intravesical BCG.[13] Randomized trials have repeatedly demonstrated that treatment with intravesical BCG results in significantly lower rates of tumor recurrence and progression.[54] While the mechanism of action of BCG remains poorly defined, studies support an immunological mechanism including a role of BCG in the recruitment of CD4+ and CD8+ T-lymphocytes, the maturation of dendritic cells by signaling through Toll-like receptors, and in the secretion of inflammatory cytokines such as IL- 12, IFN-γ, and TNF-α.[49,49]

Despite the immunogenicity of bladder cancer, patients with bladder cancer also exhibit tumor-associated immunologic suppression, particularly evident as an impaired T-cell response, which may worsen with advanced tumor stage.[55,56,57] Bladder cancer specimens have been shown to be infiltrated by regulatory T-cells, and to express high levels of inhibitory cytokines.[56] In addition, aberrant expression of T-cell coregulatory molecules, known to inhibit the immune response, have been demonstrated on bladder cancer cells and TILs and have correlated with clinical outcomes.[58] These findings suggest that the balance between CD8+ cytotoxic T-cells and negative immune regulatory elements in the tumor microenvironment may be critical in determining the host's overall immune response and ultimate clinical outcome.

High levels of PD-L1 expression have been noted in UC (eg, in a recent study, 46% of participants were reported with ≥ 1% PD-L1 expression and 30% of participants with ≥ 5% PD L1 expression[2]), suggesting tumor-associated immune tolerance and escape from immune surveillance. PD-L1 expression has been reported in approximately 20% (5% cutoff) and 30% (1% cutoff) of tumor tissue samples.[3,59,60]

PD-1 and PD-L1 immune checkpoint inhibitors appear to show benefit in patients with bladder cancer progression on platinum-based therapy. Recently, atezolizumab (PD-L1 inhibitor) was approved in the US to treat metastatic UC in patients whose disease progressed during or after platinum-based chemotherapy, based on a 15% response rate in a single-arm study.[3] Likewise, nivolumab has been approved in both the US and EU for the treatment of patients with locally advanced or metastatic UC who did not respond to platinum-based chemotherapy. In an open-label, multicenter Phase 1/2 expansion cohort in participants with metastatic UC, nivolumab elicited a response rate of 24.4% with acceptable safety, regardless of tumor PD-L1 expression, in participants who had received one or more prior lines of chemotherapy (CheckMate 032 [CA209032]; NCT01928394).[59] In a larger study in unresectable or metastatic UC, CheckMate 275 (CA209275), nivolumab had clinically meaningful efficacy and a manageable safety profile.[2] In this study, at 7 months of median follow-up, 24.4% of participants remained on therapy. The confirmed objective response rate (ORR) was 19.6% (95% CI: 15.0–24.9), with Grade 3-4 treatment-related AEs occurring in 18% of participants (Grade 5, 1%), mainly fatigue and diarrhea (2% each). ORR was found to be associated with the level of tumor tissue PD-L1 expression, being 28.4% with PD-L1 expression in ≥ 5% of tumor tissue, 23.8% with PD-L1 expression in ≥ 1% of tumor tissue, and 16.1% with PD-L1 expression in < 1% of tumor tissue.

PD-L1 expression has been examined in 280 participants with clinically localized bladder cancer, including 44 participants with NMIBC.[61] PD-L1 expression in ≥ 1% of bladder tumor cells was associated with tumor stage in NMIBC, occurring in 7% of Ta, 16% of T1, and 45% of CIS tumors, respectively. All 44 NMIBC participants were treated with intravesical BCG, and 16 participants did not respond to treatment (36%). Eleven (11) of these 16 participants (69%) exhibited diffuse and intense PD-L1 expression that was present in > 90% of the cells.

IDO gene expression has also been studied in NMIBC and may potentially possess an immunosuppressive role. IDO gene expression was examined in 74 participants undergoing

surgical treatment for NMIBC and was detected significantly more frequently, and to a higher extent, in cancer tissue as compared to normal bladder mucosa. [62] IDO expression was seen more frequently, and was higher in large, high-grade or T1 tumors when compared to small, low-grade or Ta tumors. Multivariate analysis suggested a trend towards longer overall survival in patients having tumors that did not express the IDO gene.

Preliminary data suggest that oral IDO inhibitors in combination with nivolumab possess anti-tumor activity in bladder cancer. Epacadostat and BMS-986205, both oral IDO inhibitors, demonstrate a favorable safety profile and clinical activity in combination with nivolumab in multiple solid tumor types.[5,63] In a study of 40 participants with advanced UC who had failure of prior systemic therapy, the oral IDO1 inhibitor epacadostat in combination with the anti-PD-1 inhibitor pembrolizumab demonstrated an ORR of 35%, which was greater than that expected for pembrolizumab alone.[4] BMS-986205 has also demonstrated preliminary evidence of clinical activity in combination with nivolumab in the first-in-humans CA017003 study in multiple tumor types, including UC. Preliminary data from CA017003 demonstrate an ORR of 32% (95% CI: 15, 54) in 25 participants with advanced bladder cancer who had received one or more prior systemic therapies. The ORR was 40% (95% CI: 16, 68) for participants with one prior therapy and 20% (95% CI: 3, 56) for participants with 2 or more prior therapies.[6]

5.4.1 Rationale for Combination of Nivolumab with BMS-986205 in Non-Muscle-Invasive Bladder Cancer

PD-1 is a transmembrane protein primarily expressed on activated T-cells, B-cells, myeloid cells, and antigen presenting cells (APCs).[64] Binding of PD-1 to PD-L1 and PD-L2 has been shown to down-regulate T-cell activation in both murine and human systems.[36,65,66,67] PD-1/PD-L1 interactions may also indirectly modulate the response to tumor antigens through T-cell/APC interactions. Therefore, PD-1 engagement may represent one means by which tumors evade immunosurveillance and clearance.[68] Blockade of the PD-1 pathway by nivolumab has been studied in a variety of preclinical in vitro assays, and anti-tumor activity using a murine analog of nivolumab has been shown in a number of immunocompetent mouse cancer models. Nivolumab has been approved as treatment for melanoma, non-small cell lung carcinoma (NSCLC, both non-squamous and squamous histologies), head and neck cancer, RCC, hepatocellular carcinoma, colorectal cancer, bladder cancer, and Hodgkin lymphoma in the US and other countries, and is being evaluated extensively across a wide range of other solid tumors and hematological malignancies.

PD-1-blockade enhances T-cell migration to tumors by elevating IFN-γ inducible chemokines. IDO1 expression is also known to be strongly regulated by IFN-γ. In fact, in clinical trials of participants with advanced melanoma and metastatic RCC treated with nivolumab, IDO1 gene expression was increased in participants on treatment.[47,48] These increases in the expression of IDO1 are indicative of potential adaptive mechanisms of resistance to counteract the increased anti-tumor immune cell activity potentiated by PD-1/PD-L1 blockade.

In conclusion, these data support the hypothesis that combination treatment involving PD-1/PD-L1 blockade and IDO1 inhibition could result in enhanced anti-tumor activity by providing an additional mechanism of alleviating tumor-mediated immunosuppression.

5.4.2 Rationale for Combination of Nivolumab with BCG in Non-Muscle-Invasive Bladder Cancer

Immune checkpoint inhibitors such as nivolumab target pathways used by cancer cells to evade immune system attack.[69] Such pathways may be important in BCG-unresponsive 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.[61] 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.[69] BCG appears to have a role in the recruitment of CD4+ and CD8+ lymphocytes into the bladder wall,[49] 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-PD therapy, while anti-PD 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.

5.4.3 Rationale for Combination of Nivolumab/BMS-986205 with BCG in Non-Muscle-Invasive Bladder Cancer

The rationale for combining nivolumab individually with either BMS-986205 or with intravesical BCG is outlined in Section 5.4.1 and Section 5.4.2, respectively. Participants enrolled in this study are BCG unresponsive and therefore will not benefit any further from BCG treatment alone.[31] In these BCG-unresponsive patients, it is possible that the balance between the immune stimulatory effects of BCG and the immune inhibitory effects in the tumor microenvironment is tipped towards inhibition of the anti-tumor effect of the BCG-induced local inflammatory response. In addition to PD-L1 expression, IDO gene expression also appears to be positively associated with tumor stage and grade in patients with bladder cancer.[62] Higher IDO gene expression may be associated with poorer clinical outcome in patients treated for NMIBC. These findings may reflect a potential adaptive mechanism of resistance to counteract the increased anti-tumor immune cell activity potentiated by BCG treatment and PD-1/PD-L1 blockade, and they provide the rationale behind combining nivolumab, BMS-986205 and BCG in BCG-unresponsive high-risk NMIBC.

5.4.4 Rationale for Duration of Treatment

The optimal duration of immunotherapy 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.

Accumulating evidence from several clinical trials in different tumor types with nivolumab or nivolumab combined with ipilimumab, including CheckMate 275 (CA209275) in bladder cancer, indicates that most of the responses are occurring early, with a median time to response of 2 to 4 months.[2,70,71,72,73,74] A recent analysis of 1 year of adjuvant treatment with nivolumab in participants with fully resected stages IIIB, IIIC or IV melanoma demonstrated a significantly longer recurrence-free survival, and significantly less toxicity, when compared to treatment with ipilimumab, which had been previously approved in the adjuvant melanoma setting.[75] I-O treatment in the current study will be delivered as adjuvant therapy following TURBT, providing the rationale for 1 year (52 weeks) of I-O treatment.

In the current study, BCG is being utilized to augment the local immune response in the bladder of BCG-unresponsive patients. It is hypothesized that creating this inflamed phenotype will potentially improve the efficacy of I-O treatment. For this reason, duration of BCG treatment will be 12 months (52 weeks) to coincide with systemic I-O therapy. Induction and maintenance BCG will be administered according to the SWOG 8507 protocol.[15]

5.4.5 Rationale for Open-Label Study Design

This is an open label, Phase 2b study. There is no control arm or formal comparison between the treatment arms. Confirmation of CR and tumor recurrence will be made by central pathology review blinded to treatment arm, and not by the individual investigators. This obviates the need for treatment blinding and the administration of placebo, which would be unethical in the case of BCG treatment, which requires some participants to undergo multiple urethral catheterizations associated with no therapeutic benefit.

5.4.6 Rationale for Complete Response Rate in Participants with Carcinoma in Situ as a Primary Endpoint

Not applicable per Protocol Amendment 04.

5.4.7 Rationale for Evaluation of Predictive Biomarkers

Not applicable per Protocol Amendment 04.

5.4.8 Rationale for PD-L1 Expression as a Candidate Biomarker of Immuno-Oncology Therapy Efficacy

PD-L1 expression has previously been evaluated as a potential predictive marker for treatment outcome in patients receiving anti-PD-1 or anti-PD-L1 therapy for advanced UC. In a study of 315 participants with advanced UC treated with atezolizumab whose disease had progressed after prior platinum-based chemotherapy, Rosenberg and colleagues reported an ORR of 15% in all participants, with higher response rates of 26% and 18% in participants with ≥ 5% and ≥ 1% immune cells positive for PD-L1 expression, respectively.[3] A recent update from the

CheckMate 275 (CA209275) study demonstrated that the level of PD-L1 expression on tumor cells was associated with ORR in 270 participants with advanced UC receiving nivolumab monotherapy after failure of first-line platinum-based chemotherapy.[60] ORR in all 270 participants was 19.6%, with a 25% ORR in 124 participants with ≥ 1% PD-L1 expression on tumor cells and a 15.8% ORR in 146 participants with < 1% PD-L1 expression on tumor cells. Preliminary data suggest that PD-L1 expression may also be a predictive marker of outcome for advanced bladder cancer patients receiving the anti-PD-1 agent pembrolizumab in combination with an oral IDO inhibitor. With only 19 evaluable participants, Smith and colleagues reported an ORR of 64% in 11 participants with ≥ 1% PD-L1 expression on a combination of tumor and immune cells, and an ORR of 13% in 8 participants with < 1% PD-L1 expression on a combination of tumor and immune cells.[4] Inman and colleagues evaluated PD-L1 expression on tumor cells of 44 participants with NMIBC receiving intravesical BCG treatment.[61] In addition to being associated with tumor stage and grade, PD-L1 expression was present and abundant in the BCG granulomata of 11/16 participants (69%) with disease recurrence.

Taken together, the available data suggest that PD-L1 expression is a biomarker of clinical efficacy to I-O therapy. Therefore, PD-L1 will be utilized as a stratification factor in this clinical study and will be used to analyze for association with efficacy.

5.4.9 Rationale for Modified Randomization

The study design does not include formal statistical comparisons between the arms, but randomized assignment is used to ensure reasonable balance in baseline prognostic factors. Some study sites are facing intravesical BCG availability constraints due to a global BCG shortage. In light of this, randomization was modified based on BCG availability, so that sites with no BCG available continue to enroll participants. Additionally, different BCG strains are standard of care 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.[76] As the TICE strain is the only strain approved in the US and many other countries, randomization was modified to include BCG strain (categorized as TICE BCG vs non-TICE BCG). Having 3 BCG-based randomization categories (No BCG available, TICE BCG available, or Non-TICE BCG available) will maintain reasonable balance in baseline prognostic factors between the 3 treatment arms while addressing the BCG shortage (see Section 5.1.2 for randomization details).

5.5 Justification for Dose

5.5.1 Justification for Nivolumab Dose

The nivolumab dose of 480 mg Q4W was selected based on clinical data and modeling and simulation approaches using PPK and exposure-response analyses examining relationships between nivolumab exposures and efficacy (eg, overall survival, ORR) and safety responses, using data from studies in multiple tumor types (melanoma, NSCLC, and RCC) with body weight-normalized dosing (mg/kg). A flat dose is expected to reduce prescription dosing errors, shorten

pharmacy preparation time, and improve ease of administration. Extending the dosing interval to 4 weeks provides numerous benefits to patients as they would have increased flexibility between clinical visits. The PPK analyses have shown that exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks (Q2W), and no clinically meaningful differences in PK across ethnicities and tumor types were observed. Nivolumab clearance and volume of distribution were found to increase as body weight increases but less than proportionally with increasing weight, indicating that milligram-per-kilogram dosing represents an over-adjustment for the effect of body weight on nivolumab PK.

Using the PPK and exposure-response models, nivolumab exposures and probabilities of efficacy responses and risks of AEs were predicted following nivolumab 480 mg Q4W and were comparable to those following nivolumab 3 mg/kg Q2W. The overall distributions of average nivolumab steady state exposures (Cavgss) were comparable following administration with either nivolumab 3 mg/kg Q2W or nivolumab 480 mg Q4W over a wide range of body weight ranges. Nivolumab 480 mg Q4W is predicted to result in approximately 43% greater steady state peak concentrations (Cmaxss) compared to nivolumab 3 mg/kg Q2W; however, these exposures are predicted to be lower than the exposure ranges observed at doses up to nivolumab 10 mg/kg Q2W used in the nivolumab clinical program. Although the Cmaxss of nivolumab is expected to be greater following nivolumab 480 mg Q4W compared to nivolumab 3 mg/kg Q2W, the predicted Cmaxss following nivolumab 480 mg Q4W is well below the median Cmaxss achieved following administration of nivolumab 10 mg/kg Q2W, a safe and tolerable dose level.

Exposure-safety analysis demonstrated that the exposure margins for safety are maintained following nivolumab 480 mg Q4W, and the risks of discontinuations due to AEs or death, AE Grade 3+, and IMAEs Grade 2+, are predicted to be similar following nivolumab 480 mg Q4W relative to nivolumab 3 mg/kg Q2W across tumor types. Safety analyses using available data following nivolumab 3 mg/kg Q2W and 10 mg/kg Q2W administration indicated there were no differences in AE profiles across body weight groups. Finally, initial evidence demonstrates that, following administration of nivolumab 480 mg Q4W, nivolumab has been well tolerated.

Nivolumab 480 mg Q4W is predicted to have approximately 16% lower steady-state trough concentrations (Cminss) compared to nivolumab 3 mg/kg Q2W. While these exposures are predicted to be lower, they are on the flat part of the exposure-response curves and are not expected to affect efficacy, Exposure-efficacy analyses of multiple PK measures and efficacy endpoints indicated that, following administration of nivolumab 480 mg Q4W, efficacy is predicted to be similar to that following administration of nivolumab 3 mg/kg Q2W across multiple tumor types. Based on these data, nivolumab 480 mg Q4W is expected to have similar efficacy and safety profiles to nivolumab 240 mg Q2W or nivolumab 3 mg/kg Q2W.

5.5.2 Justification for BMS-986205 Dose

All participants will receive BMS-986205 100 mg PO QD in combination with nivolumab 480 mg Q4W. The selection of the dose and schedule for BMS-986205 is primarily based on available data from the ongoing Phase 1/2, first-in-human Study CA017003.

In Study CA017003, doses of BMS-986205 from 25 mg to 400 mg QD in combination with nivolumab were studied in the dose escalation part and doses of BMS-986205 100 mg and 200 mg QD were evaluated in selected expansion cohorts. The maximum tolerated dose of BMS-986205 established in this study was 200 mg QD.

At 100 mg, preliminary PK data indicated that average trough plasma levels of BMS-986205 exceeded the in vitro human whole blood IC90. Significant and sustained inhibition of serum kynurenine levels was observed at all dose levels. PK-pharmacodynamic analysis of BMS-986205 exposure and kynurenine inhibition further suggests the effects to plateau at doses starting at 100 mg QD. Maximum inhibition of serum kynurenine levels were predicted to be similar at 100 mg QD (61%) and 200 mg QD (64%). Marked but variable inhibition of intratumoral kynurenine levels was also observed at both dose levels.

Preliminary safety data (as of 11-Oct-2017) from Study CA017003 indicate that BMS-986205 is safe and tolerable at both 100 mg QD and 200 mg QD. The data suggest a more favorable tolerability profile at 100 mg, with fewer participants experiencing treatment-related ≥ Grade 3 AEs (8.5% vs 21.4%) when compared to the 200 mg AE profile.

Overall, preliminary safety data from 199 participants in Study CA017003 reveal an overall safety profile of 100 mg BMS-986205 combined with nivolumab consistent with that observed with nivolumab monotherapy, including IMAEs such as pneumonitis (2%), autoimmune hepatitis (1%), colitis (1%), and uveitis (1%). The safety profiles differ with respect to AEs potentially associated with p-chloroaniline production during metabolism of BMS-986205, including anemia and methemoglobinemia. These events were reported infrequently in participants receiving the 100 mg dose (treatment-related anemia of any grade in 3.5% of participants and Grade 3 in 1% of participants receiving 100 mg; Grade 1 methemoglobinemia in 0.5% of participants).

Available preliminary clinical activity data from Study CA017003 suggest that both doses of BMS-986205 are clinically active in participants with bladder cancer when administered in combination with nivolumab. An ORR of 32% (95% CI 15, 54) was observed in 25 previously treated bladder cancer participants.[6] This includes an ORR of 40% (95% CI 16, 68) in 15 participants with 1 prior line of therapy. ORR appeared to be associated with PD-L1 expression, being 46% (95% CI 19, 75) and 22% (95% CI 3, 60) in PD-L1 positive and PD-L1 negative participants, respectively. It is anticipated that responses for some subjects will deepen with extended time on therapy as has been observed with immunotherapy treatments.

In summary, BMS-986205 at 100 mg QD achieves trough plasma concentrations that exceed the human whole blood IC90, produces substantial serum kynurenine reductions similar to those observed at higher dose levels, demonstrates target engagement in the tumor microenvironment, appears (in combination with nivolumab) to have a more favorable tolerability profile compared to higher doses and similar to that of nivolumab monotherapy, and demonstrates clinical activity in combination with nivolumab. Based on this evidence, BMS-986205 100 mg QD will be administered in combination with nivolumab to participants in this study.

5.5.3 Justification for Administration of BMS-986205 with Food

The effect of food on the PK of BMS-986205 was evaluated in healthy participants in Study CA017053. Following a single 100 mg dose, BMS‑986205 geometric mean Cmax and AUC(0-168h) were 114% (90% CI 75.4% to 161.1%) and 52.8% (37.2% to 70.3%) higher, respectively, when dosed after a high-fat meal compared to under fasting condition. BMS-986205 Cmax and AUC(0-168h) were 96.5% (71.7% to 124.8%) and 42.6% (28.0% to 58.8%) higher respectively, when dosed after a light meal compared to under fasting condition. Tmax ranged from 2 hours to 4 hours when dosing fasted and from 2 hours to 5 hours when dosed after a meal. PK variabilities were generally smaller when dosed after a meal. Similar results were also observed in cancer patients in a clinical pharmacology substudy in Study CA017003 (Data on File). Given that BMS-986205 was administered with a light meal in CA017003 where its safety profiles were evaluated and was deemed acceptable, based on these results, BMS-986205 will be administered after a meal in the current study without further restriction on the types of meal.

5.5.4 Justification for BCG Dose

The appropriate dose and dosing schedule of BCG in combination with systemic I-O agents in BCG-unresponsive patients is unknown. In the current study, BCG is being administered to augment the local immune response in the bladder and to work synergistically with nivolumab, with or without BMS-986205, in order to overcome potential immune inhibitory mechanisms used by bladder cancer cells to evade the local immune response induced by BCG. This rationale informs the duration of BCG therapy in this study, which will equal that of nivolumab and BMS-986205.

BCG strains used in routine clinical practice vary by geographic location, with different strains currently being utilized in the United States, Europe and Japan.[77] BCG will be sourced locally in some countries and will be provided by the sponsor in other countries, according to country-specific guidelines related to the use and procurement of investigational medicinal products in clinical trials. The dose used for each weekly intravesical BCG treatment will be based on current prescribing information for the particular BCG strain and preparation provided to the site for administration.

The appropriate dosing schedule for intravesical BCG administration in BCG-unresponsive patients participating in clinical trials testing novel I-O therapy combinations is unknown. SWOG 8507 defined the current SOC for BCG induction and maintenance in patients with high-risk NMIBC,[15] and this treatment schedule will be followed for the 52 weeks that clinical trial participants in the two BCG-containing treatment arms receive this intravesical therapy (Table 7.1-1).

5.5.5 Justification for Nivolumab 30-Minute Infusion

Long infusion times place a burden on participants and treatment centers. Using shorter infusion times of 30 minutes duration in participants will diminish the burden provided there is no change in safety profile. Previous clinical studies show that nivolumab has been administered safely over 60 minutes at doses ranging up to 10 mg/kg over a long treatment duration. For example, in

Study CA209010 (a Phase 2, randomized, double-blinded, dose-ranging study of nivolumab in participants with advanced/metastatic, clear cell RCC, N=167), a dose association was observed for infusion site reactions and hypersensitivity reactions (5.1% at 0.3 mg/kg, 3.7% at 2 mg/kg and 18.5% at 10 mg/kg).[78] All the events were Grade 1/2 and were manageable. Establishing that nivolumab can be safely administered using a shorter infusion time (30 minutes) is under investigation. The safety of nivolumab 3 mg/kg administered as a 30-minute infusion was assessed in Study CA209153 in participants with previously treated advanced NSCLC. Overall, there were no clinically meaningful differences in the frequency of hypersensitivity/infusion-related reactions (of any cause or treatment-related) in participants administered nivolumab over a 30-minute infusion time compared with that reported for participants with the 60-min infusion time. An infusion duration of 30 minutes for nivolumab 480 mg (~ 60% of the dose provided at 10 mg/kg) is not expected to present any safety concerns compared to the prior experience at 10 mg/kg nivolumab dose infused over a 60-minute duration. Key safety results from the interim safety population of Study CA209511 (Part 2) demonstrate that the safety profile of nivolumab 480 mg IV over 30 minutes Q4W (N=142) is consistent with the established safety profile of nivolumab (3 mg/kg Q2W administered IV over 60 minutes) across multiple indications with respect to Grade 3-4 AEs, SAEs, AEs leading to discontinuation, and IMAEs including hypersensitivity/infusion reactions IMAEs. There were no new safety concerns identified. In addition, in Study CA017003, the Phase 1/2a trial of BMS-986205 combined with nivolumab, nivolumab was administered at doses of 240 mg Q2W and 480 mg Q4W, both over 30 minutes, in combination with BMS-986205 given daily. There have been no signals of adverse tolerability with nivolumab given over 30 minutes at a dose of 480 mg Q4W in that study.

6 STUDY POPULATION

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

6.1 Inclusion Criteria

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

1) **Signed Written Informed Consent**
   a) Participants must have signed and dated an IRB/IEC approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol-related procedures that are not part of normal patient care.
   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) Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-1 (see Appendix 6)
   b) Life expectancy ≥ 6 months
3) **Pathologically demonstrated BCG-unresponsive*, carcinoma in situ (CIS)-containing high-risk NMIBC defined as CIS with or without papillary component required within**

10 weeks (70 days) prior to randomization and must be confirmed by the Pathology Review Committee (PRC).

* BCG-unresponsive disease is defined as being at least one of the following:

- 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 high-grade Ta/any T1 disease within 6 months of completion of adequate BCG therapy** [per revised protocol 03, participants must also have CIS to be eligible]
- T1 high-grade disease at the first evaluation following an induction BCG course (at least 5 of 6 induction doses) [per revised protocol 03, participants must also have CIS to be eligible]

** Adequate BCG treatment is defined as at least 2 courses of BCG. This can include 2 induction courses (at least five of six doses of an initial induction course plus at least two of six 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").

a) Predominant histologic component (> 50%) must be urothelial (transitional cell) carcinoma
b) Must have undergone each of the following procedures within 10 weeks (70 days) of randomization (except 90 days for CT or MRI). 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 re-staging TURBT must be performed within 8 weeks after the initial TURBT to ensure that the pathology specimen contains 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. Random sampling of bladder mucosa for detection of occult CIS during the screening period is optional, but should be performed at the time of screening transurethral resection/biopsy of bladder tumor and/or CIS within 10 weeks (70 days) of randomization, if possible. The bladder should be mapped by visual inspection and random biopsies taken from the trigone, right and left lateral walls, posterior wall, dome and prostatic urethra (in male participants).
   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 magnetic resonance imaging (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) Participants should either be deemed medically unfit for radical cystectomy, or should have refused radical cystectomy after consultation with their urologist or oncologist.

vii) If tumor tissue was obtained > 70 days prior to randomization, participants must have a repeat cystoscopy ≤ 70 days prior to randomization (see Section 9.1.4).

c) Pelvic examination, preferably under anesthesia, should be performed within 10 weeks (70 days) of randomization to exclude locally advanced disease.

d) Availability of a suitable formulation and mode of administration of BMS-986205 for the participant's needs, as detailed in the IB and pharmacy manual at the time of enrollment. Please contact the Medical Monitor with any queries.

4) Age and Reproductive Status

a) Males and Females, 18 years of age, 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 HCG) within 24 hours prior to the start of study treatment.

c) Women must not be breastfeeding

d) Women of childbearing potential (WOCBP) must agree to follow instructions for method(s) of contraception (see Appendix 4) for the duration of treatment with study treatment plus 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).

e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception (see Appendix 4) for the duration of treatment with study treatment plus 1 month (approximately 4 weeks) after the last dose of the study treatment. In addition, male participants must be willing to refrain from sperm donation during this time.

f) Male participants will be required to always use a latex or other synthetic condom during any sexual activity (eg, vaginal, anal, oral) with WOCBP; even if the participants have undergone a successful vasectomy or if their partner is already pregnant or breastfeeding. Males should continue to use a condom while on study plus 1 month (approximately 4 weeks) after the last dose of the study treatment. This criterion applies to azoospermic males as well.

g) WOCBP who are continuously not heterosexually active are 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. 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. **Hormonal contraceptives are not highly effective methods of contraception for participants in Arms C and D of this study who are WOCBP treated with BMS-986205, since drug interactions of BMS-986205 with hormone-based contraceptives are not yet known**.

6.2 Exclusion Criteria

1) Medical Conditions

a) Women who are pregnant or breastfeeding

b) Participants with an active, known or suspected autoimmune disease. 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.

c) Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, prostate cancer with evidence of undetectable Prostate Specific Antigen (PSA), or carcinoma in situ of the cervix or breast

d) Participants with serious or uncontrolled medical disorders

e) Participants with a personal or family (ie, in a first-degree relative) history of cytochrome b5 reductase deficiency (previously called methemoglobin reductase deficiency) or other diseases that put them at risk of methemoglobinemia. All participants will be screened for methemoglobin levels prior to randomization.

f) Participants with a history of G6PD deficiency or other congenital or autoimmune hemolytic disorders. All participants will be screened for G6PD deficiency prior to randomization.

g) Evidence of locally advanced disease or metastatic bladder cancer as seen in cross-sectional images of the chest, abdomen, and pelvis

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

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

j) Locally advanced disease demonstrated by pelvic examination preferably performed under anesthesia

k) Previous or concurrent muscle invasive or disseminated/metastatic bladder cancer

l) Participants must have recovered from the effects of major surgery requiring general anesthetic or significant traumatic injury at least 14 days before treatment assignment.

m) Uncontrolled adrenal insufficiency

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

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

p) Dementia, altered mental status, or any psychiatric condition that would prohibit the understanding or rendering of informed consent or completing quality of life questionnaire.

q) Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, unstable angina pectoris, or psychiatric illness/social situations that would limit compliance with study requirements.

r) Participants with interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity.

s) Participants with active interstitial lung disease / pneumonitis or with a history of interstitial lung disease/ pneumonitis requiring steroids

t) Prior history of serotonin syndrome

2) Prior/Concomitant Therapy

a) 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.

b) Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways

c) Prior treatment with BMS-986205 or any other IDO1 inhibitors

d) 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

e) Prior systemic chemotherapy or immunotherapy for UC. Intravesical chemotherapy and/or interferon administered prior to the date of tumor sample submission is permitted.

f) Prior radiation therapy for bladder cancer

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

h) Use of an investigational agent within 4 weeks of randomization.

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

3) Physical and Laboratory Test Findings

a) WBC < 2000/μL

b) Neutrophils < 1500/μL

c) Platelets < 100* 10^3/μL

d) Hemoglobin < 9.0 g/dL (transfusion to achieve this level is not permitted within 2 weeks of this laboratory assessment)

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

$$\text{Female CLcr} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/ dL}}$$

$$\text{Male CLcr} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg/ dL}}$$

f) AST or 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. See Appendix 11.

j) Quantitative or qualitative G6PD assay results suggesting underlying G6PD deficiency

k) Blood methemoglobin > ULN, assessed in an arterial or venous blood sample or by co-oximetry

l) Positive pregnancy test at enrollment or prior to administration of study medication

4) Allergies and Adverse Drug Reaction

a) History or presence of hypersensitivity or idiosyncratic reaction to methylene blue

b) History of allergy or hypersensitivity to study drug components

5) Other Exclusion Criteria

a) Prisoners or participants who are involuntarily incarcerated. (Note: under specific circumstances and only in countries where local regulations permit a person who has been imprisoned may be included 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.

6.3 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, may be randomized, but are not subsequently treated. 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, and to respond to queries from regulatory authorities. Minimal information includes date of consent, demography, screen failure details, eligibility criteria, and any serious AEs.

6.4.1 Retesting During Screening or Lead-In Period

Participant Re-enrollment: This study permits the re-enrollment of a participant that has discontinued the study as a pre-treatment failure (ie, participant has not been treated). If re-enrolled, the participant must be re-consented.

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.

An investigational product (IP), also known as investigational medicinal product (IMP) in some regions, is defined as 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.

Nivolumab, BMS-986205, and BCG are IPs/IMPs in this study (Table 7-1).

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

Table 7-1: Study Treatments for CA2099UT

Product Description / Class and Dosage Form	Potency	IP/Non-IP	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per label)
BMS-936558-01 (Nivolumab) Solution for Injection[a]	10 mg/mL	IP	Open Label	Vial	Refer to the label on container and/or pharmacy manual
BMS-986205-04	50 mg or 100 mg	IP	Open Label	Tablet	Refer to the label on container and/or pharmacy manual
BCG[b]	Dose according to prescribing information for BCG strain and preparation administered	IP	Open Label	Vial	Refer to the label on container and/or pharmacy manual

[a] May be labeled as "Nivolumab" or "BMS-936558-01 Solution for Injection."

[b] These products may be obtained by the investigational sites as local commercial product in certain countries if allowed by local regulations. These products should be prepared/stored/administered in accordance with the package insert or summary of product characteristics (SmPC).

7.1 Treatments Administered

The selection and timing of dose for each participant is presented in Table 7.1-1.

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

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	480 mg	Solution for injection/ every 4 weeks	IV
BMS-986205	100 mg	Tablet/once daily	PO
BMS-986205	50 mg	Tablet/once daily	PO
BCG	Dose according to prescribing information for BCG strain and preparation administered	Once weekly for 6 weeks, followed by once weekly for 3 weeks at 3 months, 6 months, and 12 months after first BCG dose	intravesical

7.1.1 Nivolumab Dosing

Participants should receive nivolumab at a dose of 480 mg as a 30-minute infusion on Day 1 of each treatment cycle (1 cycle = 4 weeks) until recurrence, progression, unacceptable toxicity, withdrawal of consent, or completion of 52 weeks of treatment, whichever occurs first. Participants randomized to Arms A or C should begin study treatment within 3 calendar days of randomization. Participants randomized to Arms B or D should begin study treatment within 3 calendar days of randomization or after 14 days from last TURBT or bladder biopsy, whichever is later.

No dose escalations or reductions are allowed for nivolumab after the safe-dose level has been determined in the safety lead-in. For Q4W dosing cycles, participants may be dosed within a ± 3 day window. Premedication is not recommended for the first dose of nivolumab.

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 7.7.5.

Doses of nivolumab may be interrupted (ie, infusion interruption), delayed, or discontinued depending on how well the participant tolerates the treatment. Dosing visits are not skipped, only delayed. BMS-986205 treatment should be continued if nivolumab dosing is interrupted or delayed. BMS-986205 treatment should be discontinued if nivolumab administration is discontinued.

7.1.2 BMS-986205 Dosing

A bottle of BMS-986205 should be dispensed to participants at each Day 1 visit within a cycle. Participants should be instructed that BMS-986205 should be administered once a day

(approximately 24 hours apart) following a meal, with approximately 240 mL (8 oz.) of water. Refer to Pharmacy Manual for additional details on dosing administration. Full details regarding BMS-986205 formulation and mode of administration at the time of enrollment are detailed in the IB and pharmacy manual, which may be updated throughout the study. Please contact the Medical Monitor with any queries.

Participants should be provided with pill diaries at each visit and instructed to record intake of BMS-986205 in the diary after each daily administration.

BMS-986205 will be administered on an out-patient basis. On days when nivolumab is administered, the dose of BMS-986205 should be given before the dose of nivolumab.

Participants should receive BMS-986205 until recurrence, progression, unacceptable toxicity, withdrawal of consent by the participant, or completion of 12 months (52 weeks) of treatment, whichever occurs first. Participants randomized to Arms A or C should begin study treatment within 3 calendar days of randomization. Participants randomized to Arms B or D should begin study treatment within 3 calendar days of randomization or after 14 days from the last TURBT or bladder biopsy, whichever is later. Doses of BMS-986205 may be modified, delayed, or discontinued depending on how well the participant tolerates the treatment (See Section 7.4.2 [modification], Section 7.4.4.2 [delay], and Section 8.1.2 [discontinuation]). If the dose of BMS-986205 is reduced, re-escalation will not be permitted. Skipped doses during dose delays should not be administered within the same cycle.

If nivolumab dosing is delayed for reasons other than study drug toxicity (eg, administrative issues, holidays, etc), BMS-986205 dosing should continue uninterrupted.

For details on prepared drug storage, preparation, and administration, please refer to the BMS-986205 IB and/or pharmacy binder. The selection and timing of dose for each participant is provided in Table 7.1-1.

7.1.3 BCG Dosing

The first BCG treatment will begin a minimum of 14 days after the bladder biopsy and/or TURBT performed prior to randomization. Participants should receive an intravesical instillation of BCG weekly for 6 weeks starting on Day 1 of treatment, and then weekly for 3 weeks at 3 months, 6 months and 12 months after the first BCG dose. See Table 2-3 for the BCG dosing schedule. BCG should not be given within 14 days after any TURBT or bladder biopsy.

No dose escalations or reductions are allowed for BCG after the safe-dose level has been determined in the safety lead-in.

The BCG dose should be prepared and administered according to the package insert. **BCG may be obtained by the investigational sites as local commercial product in certain countries if allowed by local regulations. These products should be prepared/stored/administered in accordance with the package insert or summary of product characteristics (SmPC).**

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 52 weeks of treatment, whichever occurs first. Participants should begin study treatment within 3 calendar days of randomization or 14 days after the last bladder tumor resection or bladder biopsy, whichever occurs later. If BCG treatment is delayed for any reason, nivolumab with or without BMS-986205 treatment should continue as scheduled, unless the participant has study drug toxicity meeting nivolumab and/or BMS-986205 dose delay criteria. If nivolumab and/or BMS-986205 treatment is delayed for any reason, BCG treatment should continue as scheduled, unless the participant has study drug toxicity meeting BCG dose delay criteria.

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 randomized using an Interactive Response Technology (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:

- Date that 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. Tumor PD-L1 expression data will be transferred directly from analyzing lab. The following information is required for participant randomization:

- Participant number
- Year of birth
- Disease status based on PRC assessment (CIS alone vs CIS with Ta vs CIS with T1)
  - CIS participants with both Ta and T1 disease will be classified as CIS with T1

- Tumor PD-L1 status (expressing [≥ 1%] vs non-expressing [< 1%] or indeterminate/not evaluable)

The randomization procedure will dynamically minimize the imbalance between treatment groups within the levels of the 2 stratification factors above (disease status and tumor PD-LI status) (see Section 5.1.2).

- Randomization will be based on the categories related to availability of BCG and BCG strains at the site at the time of participant randomization (No BCG available vs TICE BCG available vs Non-TICE BCG available)
  - For the purposes of randomization, any BCG strain that becomes approved in the US during the conduct of the study will be included in the category of TICE BCG

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

See Section 5.1.2 for a description of treatment assignment during the Randomization Phase of the study.

7.3 Blinding

This is a randomized, open-label study. It has been determined that blinding is not required to meet study objectives. Blinding procedures are not applicable and access to treatment assignment information is unrestricted. The specific treatment to be taken by a participant will be assigned using IRT. The site will contact the IRT prior to the start of study treatment administration for each participant. The site will record the treatment assignment on the applicable case report form, if required.

7.4 Dosage Modification

7.4.1 Nivolumab Dose Modifications

No dose modifications are permitted for nivolumab after a safe dose has been determined in the safety lead-in.

7.4.2 BMS-986205 Dose Modifications

A dose reduction of BMS-986205 is defined as a change from a 100 mg QD tablet to a 50 mg QD tablet.

Only one dose reduction is permitted. The participant must discontinue study treatment if a subsequent dose reduction of BMS-986205 is required (see Section 8.1.2).

Re-escalation of BMS-986205 will not be permitted once the dose of BMS-986205 has been reduced for a participant.

Doses of BMS-986205 should be reduced for the following AEs attributable to study therapy that do not otherwise meet criteria for discontinuation:

- Grade 3 fatigue, nausea, vomiting, or anemia related to study treatment
- Methemoglobin ≥ 15%

- Clinically significant elevations in methemoglobin (generally 10%, with a normal hemoglobin level) with any associated Grade 3 AE (hypoxia, dyspnea, confusion, etc.) attributable to sustained elevations of methemoglobin and not attributable to another etiology
- QTcF > 500 msec confirmed by at least 1 repeat ECG and at least 60 msec above baseline (See Appendix 8)

Dose modification and delay of BMS-986205 may occur in the setting of lower grade AEs and/or be more conservative than indicated above based on the clinical judgment of the investigator and in consultation with the BMS Medical Monitor/designee. For an AE requiring dose modification, BMS-986205 should be delayed to allow improvement of the AE, even if the AE does not otherwise meet criteria for dose delay (Section 7.4.4.2).

7.4.3 BCG Dose Modifications

No dose modifications are permitted for BCG after the safe-dose level has been determined in the safety lead-in. In the event that BCG treatment must be discontinued due to an AE, the participant may be permitted to continue treatment with nivolumab or nivolumab plus BMS-986205 where applicable.

7.4.4 Dose Delay Criteria

7.4.4.1 Nivolumab

Nivolumab administration should be delayed for the following:

- Grade 2 non-skin, drug-related AE, with the exception of fatigue
- Grade 2 drug-related creatinine, AST, ALT and/or Total Bilirubin abnormalities
- Grade 3 skin, drug-related AE
- Grade 3 drug-related laboratory abnormality, with the following exceptions:
    - Grade 3 lymphopenia or asymptomatic amylase or lipase elevations does not require dose delay
    - Grade ≥ 3 AST, ALT, or Total Bilirubin will require dose discontinuation (see Section 8.1.1)
- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, either confirmed or suspected
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

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

7.4.4.2 Nivolumab Plus BMS-986205

Nivolumab and BMS-986205 administration should be delayed for the following:

- Grade 2 non-skin, drug-related AE, with the exception of fatigue, nausea, vomiting and anemia

- Grade 2 drug-related creatinine, AST, ALT and/or Total Bilirubin abnormalities
- Grade 3 skin, drug-related AE
- Grade 3 drug-related fatigue, nausea, vomiting, and anemia
- Grade 3 drug-related laboratory abnormality, with the following exceptions:
  - Grade 3 lymphopenia or asymptomatic amylase or lipase elevations do not require dose delay
  - Grade ≥ 3 AST, ALT, or Total Bilirubin will require dose discontinuation (see Section 8.1)
- SARS-CoV-2 infection, either confirmed or suspected
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication

If nivolumab dosing is delayed for reasons other than study drug toxicity (eg, administrative issues, holidays, etc.), BMS-986205 dosing should continue uninterrupted.

In addition, **only BMS-986205** should be delayed for the following:

- Methemoglobin ≥ 15%
- Clinically significant elevations in methemoglobin (generally 10% with a normal hemoglobin level[51]) with any associated Grade 3 AE (hypoxia, dyspnea, confusion, etc.) attributable to sustained elevations of methemoglobin and not attributable to another etiology
- QTcF > 500 msec confirmed by at least 1 repeat ECG and at least 60 msec above baseline (See Appendix 8)

Participants may continue to receive nivolumab during dose delays of BMS-986205 for elevations of methemoglobin and associated events, as well as QTcF prolongations.

For participants with methemoglobin elevations with associated Grade 3 AEs, if a contribution of nivolumab to the associated AE cannot be ruled out (eg, a participant with dyspnea in whom pneumonitis has not yet been ruled out), nivolumab dosing should be delayed as well. See Section 7.7.4 for management of methemoglobinemia.

If BMS-986205 dosing is delayed, dose reduction may be necessary. See Section 7.4.2.

If dosing is resumed after a delay, BMS-986205 may be resumed as soon as the criteria to resume treatment are met (see Section 7.4.5.2). Nivolumab should be resumed as soon as possible after criteria to resume treatment are met but may be resumed later than BMS-986205 given the differences in each drug's administration.

Participants who require delay of any study treatment should be re-evaluated weekly or more frequently if clinically indicated and should resume dosing when re-treatment criteria are met.

Table 7.4.4.2-1 provides the conditions requiring dose delay or dose reduction for nivolumab and BMS-986205 in Arms C and D.

Table 7.4.4.2-1: Summary Table for Dose Delay and Reduction

Situation	Nivolumab delay	BMS-986205 delay	BMS-986205 Reduction after Delay
Grade 2 non-skin, drug-related AE, except fatigue, nausea, vomiting and anemia	Yes	Yes	No
Grade 2 drug-related creatinine, AST, ALT and/or Total Bilirubin abnormalities	Yes	Yes	No
Grade 3 skin, drug-related AE	Yes	Yes	No
Grade 3 drug-related laboratory abnormality (exceptions apply)	Yes	Yes	No
Grade 3 drug-related fatigue, nausea, vomiting, and anemia	Yes	Yes	Yes
Methemoglobin ≥ 15% or any clinically significant elevation with associated Gr 3 AE not attributable to another etiology	No	Yes	Yes
QTcF > 500 msec (and > 60 msec above baseline)	No	Yes	Yes
Other lower grade AEs (in consultation with Medical Monitor/designee)	Possibly Yes	Possibly Yes	Possibly Yes

7.4.4.3 BCG

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. Administration of nivolumab or nivolumab plus BMS-986205 should not be delayed if BCG treatment is delayed.

7.4.5 Criteria to Resume Dosing

7.4.5.1 Nivolumab

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

- Participants may resume treatment in the presence of Grade 2 fatigue
- Participants who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- For participants with Grade 2 AST, ALT and/or Total Bilirubin Abnormalities, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, is complete.
- Drug-related pulmonary toxicity, diarrhea or colitis must have resolved to baseline before treatment is resumed. Participants with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by BMS Medical Monitor (or designee).

- Participants with SARS-CoV-2 infection (either confirmed or suspected) may resume treatment if they meet all of the following:
  - At least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared or positive test result (eg, reverse transcription-polymerase chain reaction [RT-PCR] or viral antigen)
  - Resolution of acute symptoms (including at least 24 hours has passed since last fever without fever reducing medications)
  - Evaluation by the Investigator with confirmation that there are no sequelae that would place the participant at a higher risk of receiving investigational treatment
  - 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

Participants with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the BMS Medical Monitor (or designee). Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.

7.4.5.2 Nivolumab Plus BMS-986205

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

- Participants may resume treatment in the presence of Grade 2 fatigue.
- Participants who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- For participants with Grade 2 AST, ALT and/or Total Bilirubin abnormalities, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, is complete.
- Participants with combined AST/ALT AND total bilirubin values meeting discontinuation parameters (Section 8.1.1) should have treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhea or colitis must have resolved to baseline before treatment is resumed. Participants with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by BMS Medical Monitor/designee.
- Participants with SARS-CoV-2 infection (either confirmed or suspected) may resume treatment if they meet all of the following:
  - 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)
  - Resolution of acute symptoms (including at least 24 hours has passed since last fever without fever reducing medications)
  - Evaluation by the Investigator with confirmation that there are no sequelae that would place the participant at a higher risk of receiving investigational treatment

– 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

Participants with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the BMS Medical Monitor/designee. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.

For participants who have BMS-986205 held for elevations of methemoglobin, dosing may resume when the methemoglobin levels have decreased to below the institutional ULN and any associated AEs have resolved to Grade ≤ 1 or baseline value. Dose modification of BMS-986205 should be considered when resuming after a delay (see Section 7.4.2).

7.4.5.3 BCG

BCG administration can resume when the concurrent febrile illness, UTI, or gross hematuria resolve and antibiotic treatment has ended.

7.4.6 Management Algorithms

Immuno-oncology (I-O) agents are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. Nivolumab and BMS-986205 are considered as immuno-oncology agents in this protocol. Early recognition and management of AEs associated with immuno-oncology 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, 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.

7.4.7 Detection of Methemoglobinemia

BMS-986205 may produce a p-chloroaniline metabolite. P-chloroaniline has been associated with the production of methemoglobin. Symptoms of methemoglobinemia are related to the lack of oxygen delivery to tissues and are proportional to the fraction of methemoglobin, as described below for participants with normal hemoglobin levels.

Symptoms associated with elevations of methemoglobin are as follows:

- 0% to 10% - Usually asymptomatic
- 10% to 20% - Cyanosis without other symptoms
- 20% to 50% - Headache, dyspnea, lightheadedness (possibly syncope), weakness, confusion, palpitations, chest pain
- 50% to 70% - Coma, seizures, arrhythmias; acidosis
    - ➢ 70% - Usually death

Note that participants with anemia may experience symptoms at lower methemoglobin percentages than listed above, depending on the degree of anemia.

Increasing levels of methemoglobin may confound the results of standard pulse oximeters, with values of around 85% reported consistently as methemoglobin levels increase, regardless of the true oxygen saturation.

When methemoglobinemia is suspected, part of the diagnostic work-up includes evaluation for other disorders that can present with a similar clinical picture, including cardiac and pulmonary disease. A fresh peripheral blood sample (either venous or arterial) should be sent for evaluation of methemoglobin levels; methemoglobin levels may vary with storage of blood.

For management of methemoglobinemia, see Section 7.7.4. Testing is performed at screening, and as clinically indicated for all participants, and at every cycle for participants in Arms C and D.

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.

Similarly, for BMS-986205, refer to the current version of the IB and/or Pharmacy Manual for complete storage, handling, and dispensing 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

Not applicable.

7.6 Treatment Compliance

Treatment compliance of nivolumab and BCG will be monitored by drug accountability as well as the participant's medical record and electronic case report form (eCRF).

Treatment compliance of BMS-986205 will be monitored by drug accountability, as well as by recording BMS-986205 administration in the participant pill diary (as applicable), medical record, and eCRF. Participants should bring all drug containers to each study visit for drug reconciliation. The pill diary should be reviewed at each clinic visit and submitted at the end of each cycle, as applicable.

7.7 Concomitant Therapy

Concomitant medications are recorded at baseline and throughout the treatment phase of the study in the appropriate section of the eCRF. 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 eCRF.

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 or nivolumab plus BMS-986205, with or without intravesical BCG is unknown.

7.7.1 Prohibited and/or Restricted Treatments

Prohibited and/or restricted medications taken prior to and during study treatment administration in the study are described below. Medications taken within 14 weeks prior to study treatment administration must be recorded on the CRF. Vaccine use 30 days prior to randomization should be documented.

7.7.1.1 Prohibited Treatments

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

- Concomitant use of strong inhibitors of CYP3A4 and/or CYP1A2 or strong inducers of CYP3A4 and/or CYP1A2 (see Appendix 7) (Treatment Arm C and D only)
- Immunosuppressive agents

- Immunosuppressive doses of systemic corticosteroids (except as stated in Sections 7.7.2 and 7.7.3)
- Any concurrent anti-neoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents for treatment of malignancy)
- Any complementary medications (eg, herbal supplements or traditional Chinese medicines) intended to treat the disease under study. Such medications are permitted if they are used as supportive care. Please see Section 7.7.1.2 for additional restricted medications. BMS Medical Monitor (or designee) approval is required prior to concurrent use with BMS-986205
- Prophylactic antimicrobial therapy except for those administered prior to TURBT as per the institutional guidelines
- Any live/attenuated vaccine (eg, varicella, zoster, yellow fever, rotavirus, oral polio, and measles, mumps, rubella [MMR]) during treatment and until 100 days post last dose.

7.7.1.2 Restricted Treatments

Restricted therapies are not prohibited but are not recommended. Investigators should consider possible benefit risk implications of enrolling and treating participants in whom the following are clearly medically indicated:

- Grapefruit and Seville oranges and their juices can inhibit CYP3A4 (see Appendix 7) and should not be consumed while on treatment.
- Concurrent use of moderate inhibitors or inducers of CYP3A4 and/or CYP1A2 may affect the systemic exposure of BMS-986205. See Appendix 7 for a list of CYP3A4 and/or CYP1A2 modulators.
- Concurrent smoking (tobacco, marijuana, etc.) may induce CYP1A2 and decrease the systemic exposure of BMS-986205.
- Caution is warranted when consuming marijuana by means other than smoking as it may lead to increased exposure of BMS-986205 through interaction with metabolic enzymes.
- Caution is warranted when administering BMS-986205 to participants taking drugs that are highly dependent on CYP3A4 or CYP2B6 for metabolism. See Appendix 7 for a list of sensitive CYP3A4 and CYP2B6 substrates.
- Caution is warranted when administering BMS-986205 to participants taking drugs that may be associated with QT prolongation. See Appendix 8 for a list of common medications associated with QT prolongation.
- Caution is warranted when administering BMS-986205 to participants taking drugs that are subject to extensive intestinal efflux by P-gp/BCRP. See Appendix 9 for a list of common P-gp/BCRP substrates.
- Caution is warranted when using other agents known to cause methemoglobinemia (see Appendix 10). Dapsone, topical anesthetics, and antimalarial drugs are the most likely agents, and thus these medications should only be used after discussion with the Medical Monitor/designee.

- Antibacterial agents are permitted for treatment of UTIs but necessitate delay of BCG dosing until treatment with antibacterial agent(s) has ended.

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.

The development of serotonin syndrome has been associated with exposure to another investigational agent that inhibits the IDO1 enzyme. No case of serotonin syndrome has been observed with administration of BMS-986205. Given the possibility of a class effect, there is a theoretical risk that BMS-986205 could cause an increase in serotonin levels in the brain that might trigger serotonin syndrome when administered in combination with serotonergic agents or tryptophan supplements. Use caution and monitor for symptoms of serotonin syndrome in participants receiving concurrent serotonergic psychiatric medications and/or tryptophan supplements.

7.7.2.1 Imaging Restrictions 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 m^2) 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 standard of care. 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 non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.

7.7.4 Treatment of Methemoglobinemia

The following management recommendations are intended as guidelines for the investigator and may be modified based on institutional practices or local SOC, as appropriate. See Section 7.4.7 for guidance on detection of methemoglobinemia.

Initial care includes supportive measures and the administration of supplemental oxygen. In mild cases, recovery often occurs simply by delaying the administration of the offending medication. Concomitant medication lists should be reviewed for medications besides study treatment which can cause methemoglobinemia (see Appendix 10).

Further treatment is generally indicated when the methemoglobin level is above 20% or is associated with symptoms.

Intravenous methylene blue is the first-line antidotal agent and works by restoring the oxygen carrying capacity of hemoglobin by reduction of methemoglobin from its oxidized state. It is given as a 1% solution at a dose of 1 to 2 mg/kg. Most participants require only 1 dose, and symptoms should resolve within 1 hour. Methylene blue may confound the interpretation of methemoglobin levels detected by co-oximetry; alternative methods should be used after treatment with methylene blue if methemoglobin level monitoring is required. Methylene blue should be used with caution in participants with concurrent use of serotonergic psychiatric medications, as this could increase the risk of serotonin syndrome.

Exchange transfusion and hyperbaric oxygen treatment are second-line options for participants with severe methemoglobinemia whose condition does not respond to methylene blue or who cannot be treated with methylene blue. Participant transfer should occur when life-threatening methemoglobinemia that is refractory to treatment occurs in a facility that cannot provide the appropriate critical care.

7.7.5 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 NCI CTCAE (Version 4.03) 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, non-steroidal 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

Not applicable.

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 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 (Section 8.1.1)
- Disease progression or recurrence

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 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). Please call the BMS Medical Monitor within 24 hours of awareness of the pregnancy. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, a discussion between the investigator and the BMS Medical Monitor/designee must occur.

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 Discontinuation of Nivolumab

Nivolumab treatment should be permanently discontinued for the following:

- Any Grade 2 drug-related uveitis, eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the time frame permitted for dose delays OR requires systemic treatment

- Any Grade 3 non-skin, drug-related AE lasting > 7 days or recurs, with the following exceptions for laboratory abnormalities, drug-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, hypersensitivity reactions, infusion reactions, and endocrinopathies:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation.
  - Grade 3 drug-related endocrinopathies, adequately controlled with only physiologic hormone replacement do not require discontinuation. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
    - Grade ≥ 3 drug-related AST, ALT or total bilirubin requires discontinuation*
    - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2x ULN

    *In most cases of Grade 3 AST or ALT elevation, study treatment(s) will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment(s), a discussion between the investigator and the BMS Medical Monitor/designee must occur.
- Any Grade 4 drug-related AE or laboratory abnormality (including but not limited to creatinine, AST, ALT, or Total Bilirubin), except for the following events which do not require discontinuation:
  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia or leukopenia or asymptomatic amylase or lipase
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 3 calendar days of their onset
  - Grade 4 drug-related endocrinopathy AEs, such as, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the BMS Medical Monitor/designee.
- 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 requiring 10 mg per day or greater prednisone or equivalent for more than 12 weeks
- 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 AEs are allowed. (Note: Protocol AE management algorithms provide guidance to initiate steroid

taper when AE has resolved to ≤ Grade 1. Therefore, persistent Grade ≥ 2 AEs necessitating delay for > 10 weeks would require discontinuation).

– Dosing delays lasting > 10 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the BMS Medical Monitor/designee.

Prior to re-initiating treatment in a participant with a dosing delay lasting > 10 weeks, the BMS Medical Monitor/designee must be consulted. Efficacy assessments must continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 4 weeks or more frequently if clinically indicated during such dosing delays.

8.1.2 Discontinuation of BMS-986205

BMS-986205 treatment should be permanently discontinued for the following:

- Any event requiring discontinuation of nivolumab as in Section 8.1.1
- Any event requiring more than 1 dose reduction of BMS-986205 (see Section 7.4.2)
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the participant with continued BMS-986205 dosing
- For participants who delay BMS-986205 but continue nivolumab with or without BCG, any dose delay of BMS-986205 lasting > 10 weeks will result in the discontinuation of BMS-986205 only and participants may continue treatment with nivolumab with or without BCG.
- Any occurrence of serotonin syndrome

8.1.3 Discontinuation of BCG

BCG treatment should be permanently discontinued for the following:

- Any event requiring discontinuation of nivolumab 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 treatment with or without BMS-986205 if intolerance to BCG develops.

8.1.4 Post Study Treatment Study Follow-up

Per Protocol Amendment 04, efficacy follow-up is not required. Participants, on efficacy follow-up at the time of Protocol Amendment 04 implementation at each site, will conclude study participation.

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

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

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 (Section 2).
- 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.

If a participant shows pulmonary-related signs (hypoxia, fever) or symptoms (eg, dyspnea, cough, fever) consistent with possible pulmonary AEs, the participant should be immediately evaluated to rule out pulmonary toxicity, according to the suspected pulmonary toxicity management algorithm in the BMS-936558 (nivolumab) Investigator Brochure (see also Appendix 5). In addition, blood methemoglobin levels should be evaluated to rule out methemoglobinemia (see Section 7.4.7) and CBC measured to rule out anemia in participants with dyspnea.

Some of the assessments referred to in this section may not be captured as data in the eCRF. 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.

This study will consist of three phases: screening, treatment, and follow-up.

Screening Phase:

- Begins by establishing the participant's initial eligibility and signing of the informed consent form (ICF).

Treatment Phase:

- Begins with the randomization request to the IRT. Based on categories related to the availability of BCG and/or strain at the time of participant randomization, the participant is assigned to one of the 3 following arms: nivolumab (Arm A), nivolumab + BCG (Arm B), or nivolumab + BMS-986205 (Arm C) (see Figure 5.1-1); nivolumab + BMS-986205 + BCG (Arm D) will be paused after the safety lead-in.
- Ends when the participant is discontinued from study therapy or completes 52 weeks of study therapy. For a complete list of reasons for treatment discontinuation, see Section 8.

Follow-up Phase

- Begins when the decision to discontinue a participant from study therapy is made (no further treatment with study therapy) or when 12 months (52 weeks) of study therapy has been completed, and ends when safety follow-up is completed by participant.

9.1 Efficacy Assessments

Per Protocol Amendment 04, efficacy assessments will be conducted per the local standard of care.

Complete Response (CR) Definition

CR will be determined throughout the duration of the study by the investigator. Determination of CR will be based on the local standard of care.

Recurrence Definition

Recurrence will be determined in all participants throughout the duration of the study by the investigator according to the local standard of care.

Progression Definition

Progression will be determined in all participants throughout the duration of the study by the investigator according to the local standard of care.

9.1.1 Imaging Assessment for the Study

Per Protocol Amendment 04, efficacy assessments will be conducted per the local standard of care.

9.1.2 Cystoscopy

Per Protocol Amendment 04, efficacy assessments will be conducted per the local standard of care.

9.1.3 Urine Cytology

Per Protocol Amendment 04, efficacy assessments will be conducted per the local standard of care.

9.1.4 Bladder Biopsy

Per Protocol Amendment 04, efficacy assessments will be conducted per the local standard of care.

Complete resection of all papillary disease (Ta/T1) is required for all participants within 10 weeks (70 days) of randomization. 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. 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.

Random sampling of the bladder mucosa for the detection of occult CIS should also be performed prior to randomization if possible. Biopsies should be obtained from the bladder dome, right and left lateral walls, posterior wall, trigone, and prostatic urethra (in male participants).

If the tumor tissue was obtained > 70 days prior to the anticipated randomization date, a repeat cystoscopy is required to ensure the participant does not have recurrent papillary disease. The repeat cystoscopy must be completed ≤ 70 days prior to randomization. If there is evidence of papillary NMIBC on the repeat cystoscopy, TURBT is required and the participant's eligibility needs to be reassessed and the baseline disease stage will be updated to take account of all TURBT findings. Tumor tissue samples collected during the repeat biopsy (1-10 hematoxylin and eosin [H&E] stained slides, with at least 1 slide/disease site) confirming the diagnosis of high-risk NMIBC must be submitted to the independent PRC prior to randomization. At least one slide containing muscularis propria will be submitted. 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.

9.2 Adverse Events

The definitions of an AE or 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.

Immune-mediated adverse events are AEs consistent with an immune-mediated mechanism or immune-mediated component for which non-inflammatory etiologies (eg, infection or tumor progression) have been ruled out. IMAEs can include events with an alternate etiology which 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

The collection of non-serious AE information should begin at the initiation of study treatment and at the time points specified in the Schedule of Activities (Section 2). All non-serious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 100 days following discontinuation of study treatment. Non-serious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the participants.

Sections 5.6.1 and 5.6.2 in the IBs for nivolumab and BMS-986205 represent the Reference Safety Information to determine expectedness of serious adverse events for expedited reporting. Following the participant's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures.

All SAEs must be collected that occur during the screening period and within 100 days of the last dose of study treatment. For participants randomized and never treated with study drug, SAEs should be collected for 30 days from the date of randomization.

If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up cystoscopy). 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.

- 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 section.
- 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 within 24 hours of this 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 last dose.

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

Adverse events 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.

9.2.3 Follow-up of AEs and SAEs

- Non-serious 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 non-serious AEs that cause interruption or discontinuation of study treatment and for those present at the end of study treatment as appropriate.
- All identified non-serious AEs must be recorded and described on the non-serious 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 non-serious AEs of special interest (as defined in Section 9.2), and 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, until 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 IB 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 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.

In most cases, the study treatment will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety). Please call the BMS Medical Monitor within 24 hours of awareness of the pregnancy.

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.

9.2.6 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the non-serious 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 vs low hemoglobin value).

9.2.7 Potential Drug Induced Liver Injury (DILI)

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

Potential drug induced liver injury is defined as:

1) ALT or AST elevation > 3 times ULN

AND

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

AND

3) No other immediately apparent possible causes of aminotransferase elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, preexisting 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 non-serious or serious AE, as appropriate, and reported accordingly.

9.2.9 Adverse Events of Special Interest

Adverse events of special interest (AEOSI) have been defined for this protocol. BMS requires expedited reporting by the investigator of these AEOSI to BMS. These are:

- Hemophagocytic lymphohistiocytosis (HLH; also known as histiocytosis haematophagic)
- Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome

These AEOSI, whether related or not related to study drug, must be reported to BMS or designee within 24 hours of awareness of the event. These AEOSI are medically important events. The reporting system for SAEs should be used (see Section 9.2.4 and Appendix 3). HLH and DRESS syndrome may both pose diagnostic challenges due to varying clinical manifestations and signs and symptoms that may overlap with other clinical events. To assist investigators in identifying constellations of clinical symptoms that may be consistent with one of these diagnoses, standardized scoring criteria are provided in Appendix 12. Formal evaluation and documentation of diagnostic scores based on these systems is not required; investigators should use their best clinical judgment as informed by these provided criteria to determine if a participant has experienced one of these AEOSI.

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.

Overdoses that meet the regulatory definition of SAE will be reported as an SAE (see Appendix 3).

In the event of an overdose the investigator/treating physician should:

1) Contact the Medical Monitor/designee immediately
2) Closely monitor the participant for AEs/SAEs and laboratory abnormalities
3) Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

9.4 Safety

Planned time points for all safety assessments are listed in the Schedule of Activities (Section 2). Safety assessments include AEs, physical examinations, vital signs, performance status, oxygen

saturation, ECGs, assessment of signs and symptoms, laboratory tests, and pregnancy tests as outlined in the Schedule of Activities.

9.4.1 Clinical Safety Laboratory Assessments

- Investigators must document their review of each laboratory safety report.
- All clinical safety laboratory assessments will be performed locally per the Schedule of Activities. These laboratory assessments are identified in Table 9.4.1-1.

Table 9.4.1-1: Clinical Laboratory Assessments

Hematology	
Hemoglobin	
Hematocrit	
Total leukocyte count, including differential	
Platelet count	
Methemoglobin **- screening, every cycle for participants in Arms C and D, and as clinically indicated**	
G6PD levels - **screening only**	
Serum Chemistry	
Aspartate aminotransferase (AST)	Sodium
Alanine aminotransferase (ALT)	Potassium
Total bilirubin	Chloride
Alkaline phosphatase (ALP)	Calcium
Gamma-glutamyl transferase (only when alkaline phosphatase is ≥ Grade 2)	Phosphate
	Magnesium
Direct bilirubin	Creatinine
Albumin	Creatinine clearance (CLcr) - **screening only**
Lactate dehydrogenase (LDH)	Blood Urea Nitrogen (BUN) or Serum Urea Level
Uric acid	
TSH (reflex to free T3 and T4 if abnormal)	Glucose
Urinalysis (at screening)	
Protein	
Glucose	
Blood	
Leukocyte esterase and/or WBC	
Specific gravity	
pH	
Urinalysis (at visits 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, RBCs, or bacteria	

Table 9.4.1-1: Clinical Laboratory Assessments

Serology (at screening)
Serum for hepatitis C antibody (if Hepatitis C antibody is positive reflex to hepatitis C RNA) or hepatitis C RNA, hepatitis B surface antigen, HIV-1 and HIV-2 antibodies. (Testing for HIV-1 and HIV-2 must be performed at sites where mandated by local requirements [Appendix 11])
C-reactive protein
Other Analyses
Pregnancy test (women of child-bearing potential [WOCBP] only: minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [HCG]), Section 2).
Follicle stimulating hormone (FSH) screening -only required to confirm menopause in women < age 55 (if needed to document postmenopausal status as defined in Appendix 4)

9.4.2 Imaging Safety Assessment

Not applicable.

9.5 Pharmacokinetics

9.5.1 Background

Pharmacokinetics of BMS-986205

Preliminary PK data are available from participants who received BMS-986205 in Study CA017003 at doses of 25 to 400 mg during monotherapy. Following BMS-986205 administration with a light meal, the median Tmax was 3 to 4 hours (ranging from 1 to 8 hours). Geometric mean apparent clearance (CL/F) values on Day 14 ranged from 12.5 to 20.8 L/h. Accumulation based on AUC(0-24h) between Days 1 and 14 ranged from 2.1- to 3.6-fold, supportive of once daily dosing of BMS-986205. Based on the observed accumulation index of AUC, an effective half-life in the range of 26 hours to 51 hours can be estimated. Following a single dose administration of 100 mg BMS-986205, the mean terminal half-life of BMS-986205 was determined to be 98 hours. Full details on the clinical pharmacology aspects of BMS-986205 can be found in the BMS-986205 IB.

Pharmacokinetics of Nivolumab

The PK of nivolumab were studied in participants over a dose range of 0.1 to 10 mg/kg administered as a single dose or as multiple doses of nivolumab every 2 or 3 weeks. The geometric mean (% CV%) CL was 9.5 mL/h (49.7%), geometric mean volume of distribution at steady state (Vss) was 8.0 L (30.4%), and geometric mean elimination half-life was 26.7 days (101%). Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg Q2W, and systemic accumulation was approximately 3 fold. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks. The clearance of nivolumab increased with increasing body weight. The PPK analysis suggested that the following factors had no clinically important effect on the CL of nivolumab: age (29 to 87 years), gender, race, baseline LDH, PD-L1. A PPK analysis suggested no difference in CL of nivolumab based on age, gender, race, tumor type, baseline tumor size, and hepatic impairment.

Although ECOG status, baseline glomerular filtration rate (GFR), albumin and body weight had an effect on nivolumab CL, the effect was not clinically meaningful.

Full details on the clinical pharmacology aspects of nivolumab can be found in the nivolumab IB.

9.5.2 Immunogenicity Assessments

Per Protocol Amendment 04, ONLY immunogenicity assessments will be collected. Samples for anti-drug antibody (ADA) assessments will be collected from all participants receiving study treatment. Immunogenicity samples will be analyzed for anti-nivolumab antibody. Given that BMS-986205 is a small molecule, the immunogenicity of BMS-986205 will not be evaluated.

Table 9.5.2-1 lists a detailed sampling schedule to be followed for the assessment of immunogenicity for all study treatments, where applicable. Treatment assignments will be released to the bioanalytical laboratory in order to minimize unnecessary analysis of samples. All on-treatment immunogenicity sample collections are intended to align with days on which nivolumab and BMS-986205 are co-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.

Separate detailed instructions for the collection, processing, handling, labeling, storage, and shipment of immunogenicity samples will be provided in the laboratory procedures manual.

Table 9.5.2-1: Anti-drug Antibody Sampling Schedule for Nivolumab

Study Day of Sample Collection (1 cycle = 4 weeks)	**Event**	**Time Relative to Dosing[a] Hour:Minutes**	**ADA Blood Sample[b]**
			Nivolumab (Serum)
Cycle 1, Day 1	Predose[c]	00:00	X
Cycle 3, Day 1	Predose[c]	00:00	X
Cycle 6, Day 1	Predose[c]	00:00	X
Cycle 10, Day 1	Predose[c]	00:00	X
First 2 Follow-up Visits[d]	FU1		X
	FU2		X

Abbreviations: FU = follow-up; ADA=anti-drug antibody

[a] For nivolumab samples, the time of collection is relative to the start of nivolumab infusion.

[b] ADA samples will be collected for nivolumab only. No ADA sample collection is required for BMS-986205.

[c] Predose samples should be collected just prior to administration of nivolumab (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.

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

9.6 Pharmacodynamics

Per Protocol Amendment 04, pharmacodynamics will not be collected.

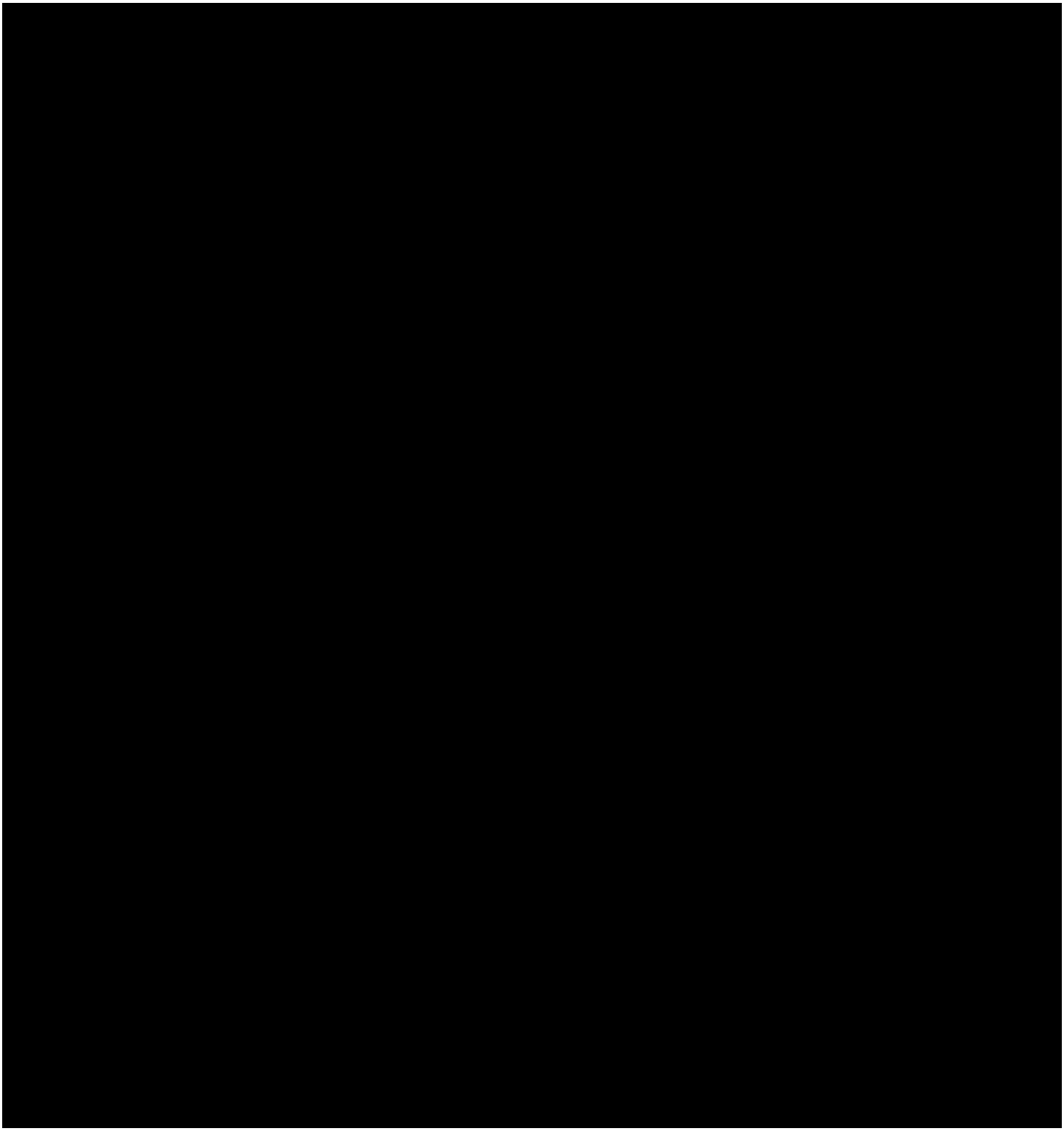
9.7 Pharmacogenomics

See Section 9.8.

9.8 Biomarkers

Per Protocol Amendment 04, biomarkers will not be collected.

[redacted]



9.9 Health Economics OR Medical Resource Utilization and Health Economics

Per Protocol Amendment 04, health economics/medical resource utilization and health economics parameters will not be evaluated.

9.10 Immunogenicity Assessments

See Table 9.5.2-1 for timing of blood sampling for immunogenicity assessments.

Nivolumab immunogenicity will be reported for ADA positive status (such as persistent positive, other positive, only last sample positive, or baseline positive) and ADA negative status, relative to baseline. In addition, presence of neutralizing antibody may be reported, if applicable. The effect of immunogenicity on safety may be explored.

9.11 Other Assessments

9.11.1 Patient-reported Outcomes

Per Protocol Amendment 04, patient-reported outcomes will not be evaluated.

10 STATISTICAL CONSIDERATIONS

Per Protocol Amendment 04, only safety and immunogenicity analyses will be conducted.

10.1 Sample Size Determination

Per Protocol Amendment 04, sample size will be limited to the participants enrolled as of 02-Jun-2021. The following sample size considerations refer to the original study design.

The sample size of this study is calculated in order to estimate the CR rate in treated participants with CIS randomized to receive either nivolumab monotherapy, nivolumab combined with intravesical BCG, or nivolumab combined with BMS-986205.

Using modified randomization based on BCG availability and BCG strain, as described in Section 7.2, it is expected that approximately 100 CIS participants will be treated each in Arm A and C and 150 CIS participants in Arm B. It is expected that approximately 8 CIS participants will be treated in Arm D during the safety lead-in. Table 10.1-1 summarizes the different boundaries of the exact 95% CI (based on Clopper-Pearson method) for different observed CR rates in 100 and 150 CIS treated participants. For example, if at least 40 participants with CR in a treatment group are observed among the 100 CIS treated participants (ie, CR rate ≥ 40%), then the lower bound of the 95% CI is above 30%.

Table 10.1-1: Observed Complete Response Rate and Exact 95% Confidence Interval in the CIS Population

Observed CR (CR rate [%]) (N=100)	95% Exact CI	Observed CR (CR rate [%]) (N=150)	95% Exact CI
25 (25%)	(16.9% - 34.7%)	37 (24.7%)	(18.0% - 32.4%)
30 (30%)	(21.2% - 40.0%)	45 (30.0%)	(22.8% - 38.0%)

Table 10.1-1: Observed Complete Response Rate and Exact 95% Confidence Interval in the CIS Population

Observed CR (CR rate [%]) (N=100)	95% Exact CI	Observed CR (CR rate [%]) (N=150)	95% Exact CI
35 (35%)	(25.7% - 45.2%)	53 (35.3%)	(27.7% - 43.6%)
40 (40%)	(30.3% - 50.3%)	60 (40.0%)	(32.1% - 48.3%)
45 (45%)	(35.0% - 55.3%)	68 (45.3%)	(37.2% - 53.7%)
50 (50%)	(39.8% - 60.2%)	75 (50.0%)	(41.7% - 58.3%)
55 (55%)	(44.7% - 65.0%)	82 (54.7%)	(46.3% - 62.8%)
60 (60%)	(49.7% - 69.7%)	90 (60%)	(51.7% - 67.9%)

An initial evaluation of efficacy and safety will be performed for each treatment group when 34 CIS participants in each treatment group have been treated and followed up to 6 months. If ≤ 9 (26%) participants achieve CR at 6 months, the treatment group may not be considered promising and accrual in this treatment group may then be stopped based on the recommendation of the DMC and decision of the Sponsor. If ≥ 10 (29%) participants achieve CR at 6 months, the treatment group will be considered promising and accrual in this treatment group could then continue to full enrollment. If the true CR rate at 6 months for a treatment group is 20%, there is a probability of 87% of observing ≤ 9 CR among 34 first CIS participants. If the true CR rate at 6 months for a treatment group is 40%, there is only a probability of 7% of observing ≤ 9 CR among 34 first CIS participants. These probabilities were considered appropriate in light of recent efficacy results of another anti-PD1 monotherapy regimen in the same indication showing an encouraging CR rate of 40.2% [95% CI: 30.6-50.4].[79]

CIS participants will be randomized in a 1:1:1 ratio (dependent on BCG availability) after safety lead-in completion. Enrollment in the safety lead-in will be staggered so that the safety lead-in phase for Arm B is adequately assessed prior to the enrollment of Arm D. Once the number of participants for the safety lead-in is reached in Arm D, accrual will only continue in the 3 other arms. Once 34 CIS treated participants in a given treatment group have been followed for at least 6 months, an initial evaluation of efficacy and safety for that treatment group will be conducted. Accrual will not be stopped prior to this initial evaluation.

The primary analysis of the primary endpoint CR rate will be performed when all CIS treated participants with CR in each treatment group have had at least 12 months of follow up from the time of initial CR.

10.2 Populations for Analyses

Per Protocol Amendment 04, only safety and immunogenicity assessments will be conducted.

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled Participants	All participants who sign informed consent and are registered into IRT
Treated	All randomized participants who received at least one dose of any study medication.
Immunogenicity	All treated participants with available ADA data.

10.3 Statistical Analyses

The statistical analysis plan (SAP) will be developed and finalized before 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.

A description of the participant population will be included in the statistical output and reported, including subgroup of age, gender, and race.

10.3.1 Efficacy Analyses

Per Protocol Amendment 04, formal efficacy analyses will not be conducted. Descriptive summary statistics may be provided for internal dissemination only.

10.3.2 Safety Analyses

All safety analyses will be performed on the Treated Population.

Safety analyses will be performed in all treated participants and for each treatment group. Descriptive statistics of safety will be presented using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 by treatment group. All on-study AEs, treatment-related AEs, SAEs, and treatment-related SAEs will be tabulated using worst grade per NCI CTCAE v 4.03 criteria by system organ class and preferred term. On-study lab parameters including hematology, chemistry, liver function, and renal function will be summarized using worst grade NCI CTCAE v 4.03 criteria.

Additional safety analyses will be described in the SAP finalized before database lock.

10.3.3 Other Analyses

Immunogenicity analyses will be described in the SAP finalized before database lock.

10.3.4 Initial Evaluation of Efficacy and Safety

Not applicable per Protocol Amendment 04.

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12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
ADA	anti-drug antibody
AE	adverse event
AEOSI	adverse events of special interest
AIDS	acquired immunodeficiency syndrome
AJCC	American Joint Committee on Cancer
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APC	antigen-presenting cell
AST	aspartate aminotransferase
AUA	American Urological Association
AUC	area under the concentration-time curve
AUC(0-T)	area under the concentration-time curve from time zero to the time of the last quantifiable concentration
BCG	Bacillus Calumette-Guerin
BCRP	breast cancer resistance protein
β-HCG	beta-human chorionic gonadotrophin
BMS	Bristol-Myers Squibb
BUN	blood urea nitrogen
C	Celsius
Cavgss	average concentration at steady state
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
CIS	carcinoma in situ
CL	clearance
CLcr	creatinine clearance
Cmax	maximum observed concentration
Cmaxss	maximum observed concentration at steady state
Cminss	minimum observed concentration at steady state

Term	Definition
CMV	cytomegalovirus
CONSORT	Consolidated Standards of Reporting Trials
COVID 19	coronavirus disease 2019
CR	complete response
CRF	case report form, paper or electronic
CT	computed tomography
CTAg	clinical trial agreement
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
CTLA-4	cytotoxic T-lymphocyte-associated protein-4
CYP	cytochrome p-450
DC	dendritic cell
DDI	drug-drug interaction
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DRESS	drug reaction with eosinophilia and systemic symptoms
EC50	half maximal effective concentration
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EFS	event-free survival
eg	exempli gratia (for example)
EOI	end of infusion
EU	European Union
EAU	European Association of Urology
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
FU, F/U	follow-up

Term	Definition
G6PD	glucose 6-phosphate dehydrogenase
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GM-CSF	granulocyte macrophage-colony stimulating factor
h	hour
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCG	human chorionic gondotropin
HCV	hepatitis C virus
HG	high grade
HIPAA	Health Insurance Portability and Accountability Act (US)
HIV	human Immunodeficiency Virus
HLH	hemophagocytic lymphohistiocytosis; also known as histiocytosis haematophagic
IB	Investigator Brochure
IC50	half maximal inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonisation
IDO	indoleamine-1,2-dioxygenase 1
ie	id est (that is)
IEC	Independent Ethics Committee
IFN	interferon
IHC	imunohistochemistry
IL	interleukin
IMAE	immune mediated adverse event
IMP	investigational medicinal products
I-O	immuno-oncology(ic)
IP	investigational product
IRB	Institutional Review Board
IRT	Interactive Response Technology

Term	Definition
IU	International Unit
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
kg	kilogram
L	liter
LAM	lactation amenorrhea method
LDH	lactate dehydrogenase
mg	milligram
MIBC	Muscle-invasive bladder cancer
min	minute
mL	milliliter
MLR	mixed lymphocyte reaction
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
µg	microgram
N	number of subjects or observations
N/A	not applicable
NCI	National Cancer Institute
NMIBC	non-muscle-invasive bladder cancer
NSCLC	non-small cell lung cancer
NYHA	New York Heart Association
ORR	objective response rate
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD-1	programmed cell death protein 1
PD-L1	programmed cell death-ligand 1
P-gp	permeability glycoprotein
PK	pharmacokinetics
PO	per os (by mouth route of administration)

Term	Definition
PPK	population pharmacokinetics
PR	partial response
PRC	Pathology Review Committee
PRO	patient-reported outcome
PS	Performance Status
PSA	prostate-specific antigen
Q2W	every 2 weeks
Q4W	every 4 weeks
QD	quaque die, once daily
QLQ-NMIBC24	Quality of Life Questionnaire - Non-Muscle Invasive Bladder Cancer 24
QoL	quality of life
R&D	Research and Development
RBC	red blood cell
RCC	renal cell carcinoma
RNA	ribonucleic acid
RT-PCR	reverse transcription-polymerase chain reaction
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SmPC	Summary of Product Characteristics
[redacted]	[redacted]
SOC	standard of care
SUSAR	suspected unexpected serious adverse reaction
TaHG	high-grade Ta tumor
TCR	tumor cell receptor
TIL	tumor-infiltrating lymphocyte
Tmax	time of maximum observed concentration
TNF	tumor necrosis factor
TRAIL	TNF-related apoptosis-inducing ligand
Treg	regulatory T-cell

Term	Definition
TSH	thyroid stimulating hormone
TTR	time to response
TURBT	transurethral resection of the bladder tumor
UC	urothelial cancer, urothelial carcinoma
UK	United Kingdom
ULN	Upper limit of normal
US	United States
USPI	United States Prescribing Information
UTI	urinary tract infection
VAS	visual analog scale
Vss	volume at steady state
WBC	white blood cell
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 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)
- 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/Independent Ethics Committee (IRB/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 Brochure 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 (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 commercial supply, or a specialty pharmacy)	The investigator or designee accepts responsibility for documenting traceability and study treatment integrity in accordance with requirements applicable 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 (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 or commercial supply, or a specialty pharmacy)	It is the investigator's or designee's responsibility to dispose of all containers 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.

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 <u>Meeting</u> 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 <u>NOT</u> 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 Investigator's Brochure (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 post-menopausal 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 CHILD BEARING 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.*

Note: For WOCBP participants treated with BMS-986205 in this study, hormone-based contraceptives are <u>not</u> considered highly effective methods of contraception since potential interactions of BMS-986205 with hormonal contraceptives are not known at this time. This constraint applies to Arms C and D in this study.

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly*[a]
• **Not acceptable in WOCBP participants treated with BMS-986205 in this study (Arms C and D):** 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
• **Not acceptable in WOCBP participants treated with BMS-986205 in this study (Arms C and D):** Progestogen-only hormonal contraception associated with inhibition of ovulation[b] – oral – injectable • **Not acceptable in WOCBP participants treated with BMS-986205 in this study (Arms C and D):** Hormonal methods of contraception including oral contraceptive pills containing a combination of estrogen and progesterone, vaginal ring, injectables, implants and intrauterine hormone-releasing system (IUS)[b,c] –
Highly Effective Methods That Are User Independent
• **Not acceptable in WOCBP participants treated with BMS-986205 in this study (Arms C and D):** Implantable progestogen-only hormonal contraception associated with inhibition of ovulation [b] • 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. The absence of such interactions is not known for BMS-986205 when administered with nivolumab. Therefore, for participants of child-bearing potential who receive these 2 medications, intrauterine hormone-releasing systems are not acceptable methods of contraception.

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.

Male participants with female partners of childbearing potential are eligible to participate if they agree to the following during the treatment and until the end of relevant systemic exposure. This constraint applies to Arms C and D in this study.

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- Male participants are required to use a synthetic or latex condom during any sexual activity with WOCBP for study duration and until end of relevant systemic exposure defined as 1 month (approximately 4 weeks) after the end of study treatment. This applies even if the participant has undergone a successful vasectomy.
- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 1 month (approximately 4 weeks) after the end of treatment in the male participant.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male latex or synthetic condom during each episode of

penile penetration during the treatment and until 1 month (approximately 4 weeks) after the end of study treatment.

- Refrain from donating sperm for the duration of the study treatment and until 1 month (approximately 4 weeks) after the end of study treatment.

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 FOR STUDIES UNDER CTCAE VERSION 4.0

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.

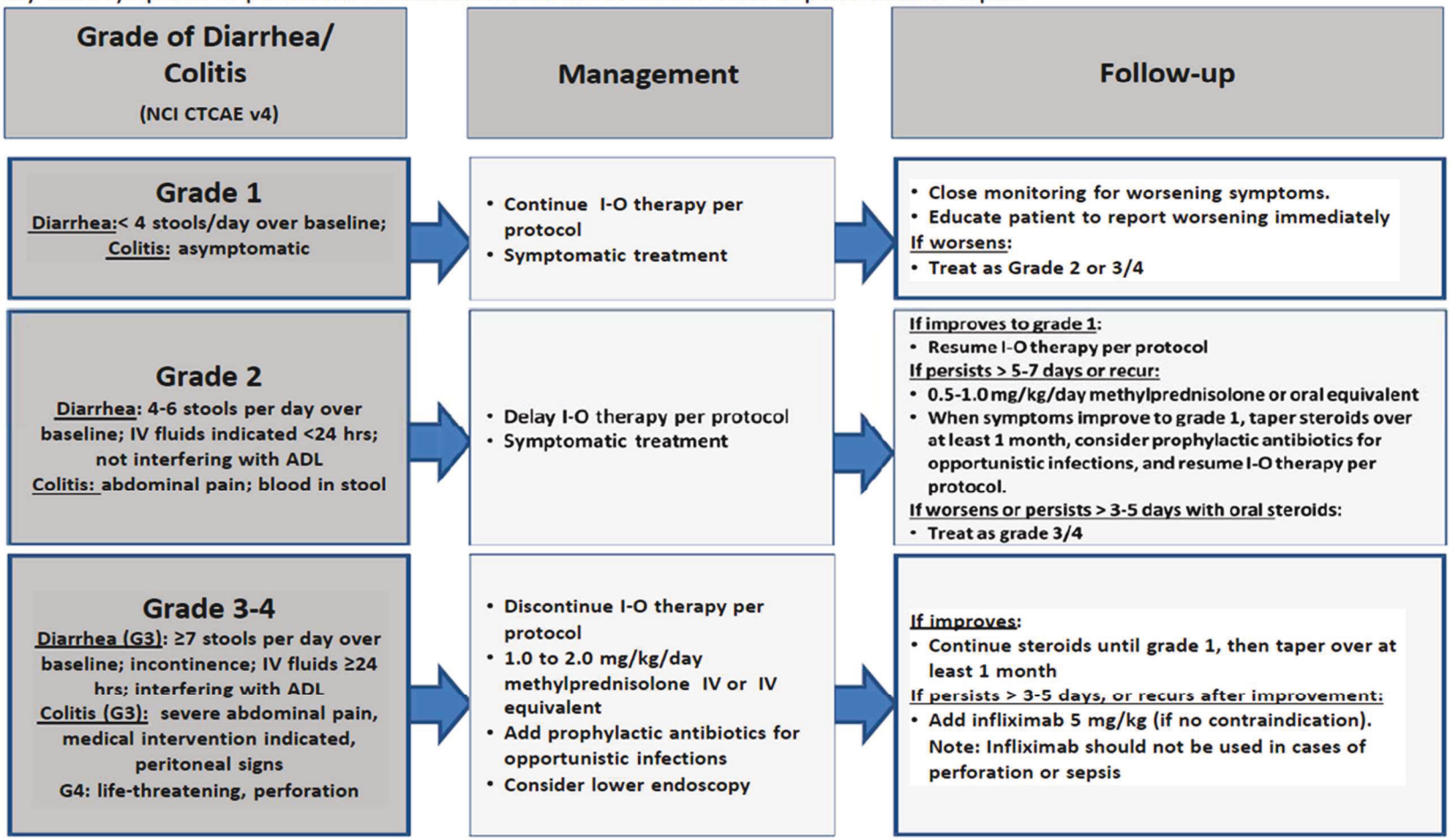
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the 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 (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

28-Sep-2020

Renal Adverse Event Management Algorithm

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

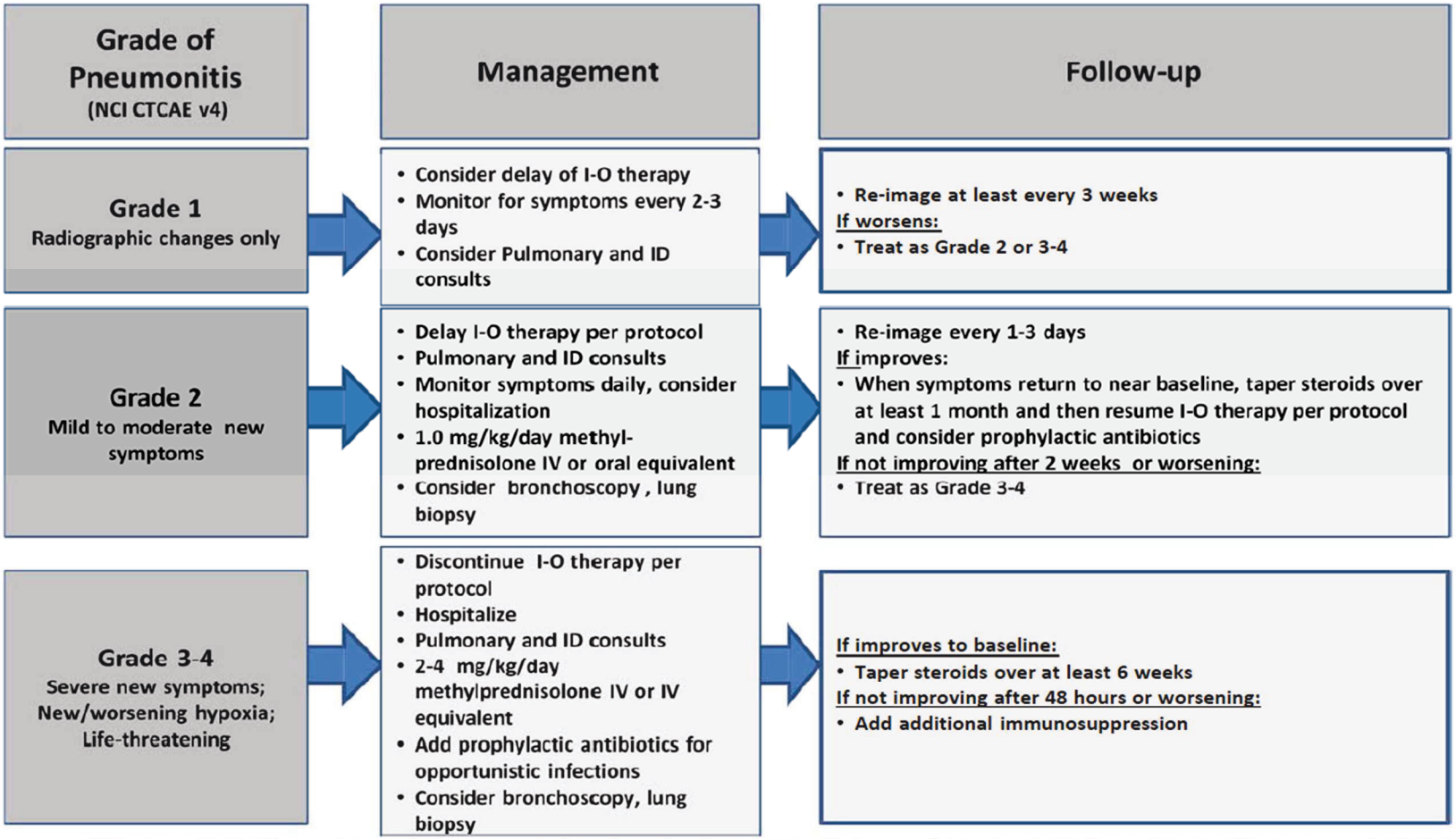
Grade of Creatinine Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 Creatinine > ULN and > than baseline but ≤ 1.5x baseline	• Continue I-O therapy per protocol • Monitor creatinine weekly	If returns to baseline: •Resume routine creatinine monitoring per protocol If worsens: •Treat as Grade 2 or 3/4
Grade 2-3 Creatinine > 1.5x baseline to ≤ 6x ULN	• Delay I-O therapy per protocol • Monitor creatinine every 2-3 days • 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent • Consider renal biopsy with nephrology consult	If returns to Grade 1: •Taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy and routine creatinine monitoring per protocol If elevations persist > 7 days or worsen: •Treat as Grade 4
Grade 4 Creatinine > 6x ULN	• Discontinue I-O therapy per protocol • Monitor creatinine daily • 1.0-2.0 mg/kg/day methylprednisolone IV or IV equivalent • Consult nephrologist • Consider renal biopsy	If returns to Grade 1 : Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections

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

28-Sep-2020

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.

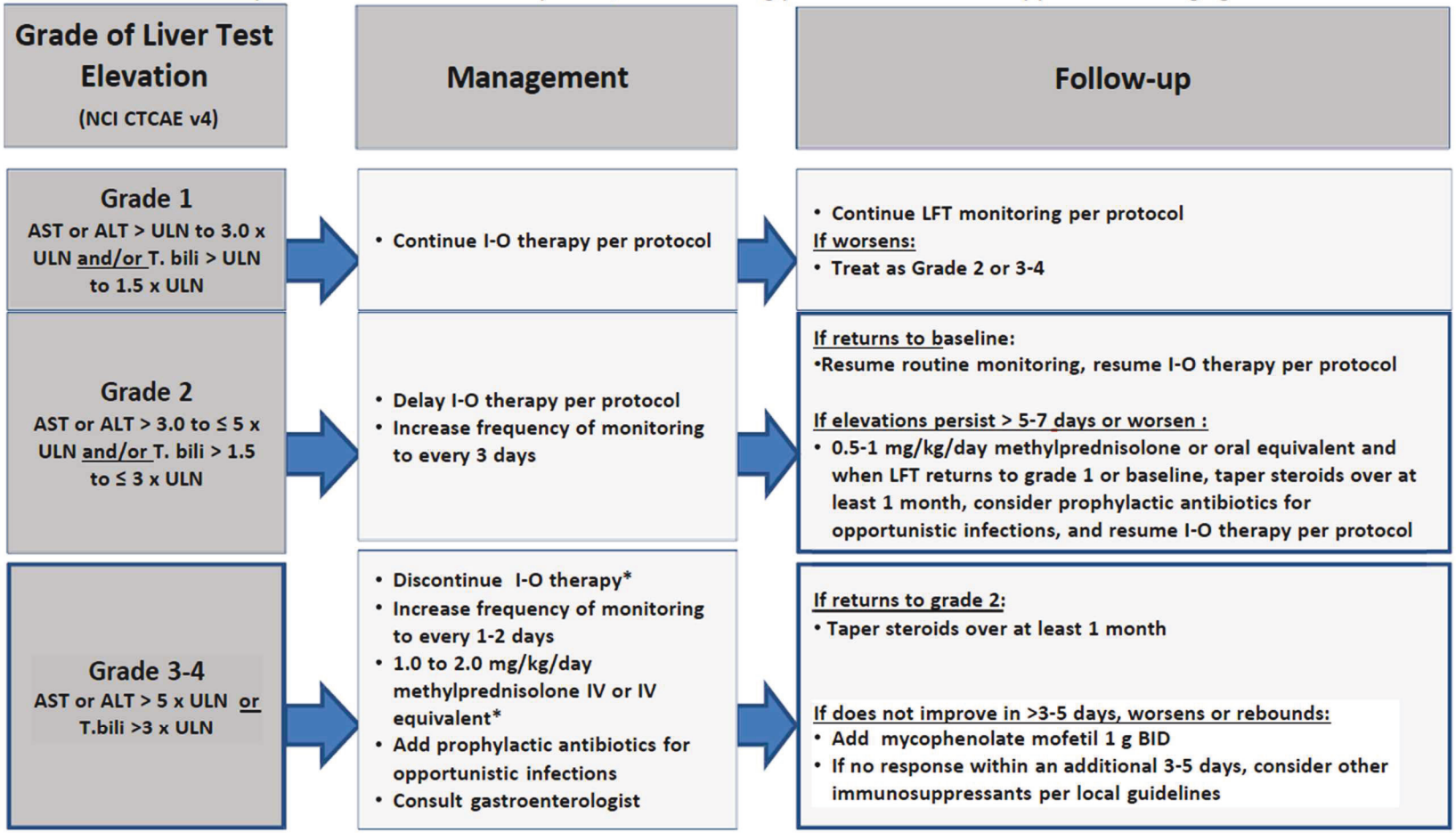


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

28-Sep-2020

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.



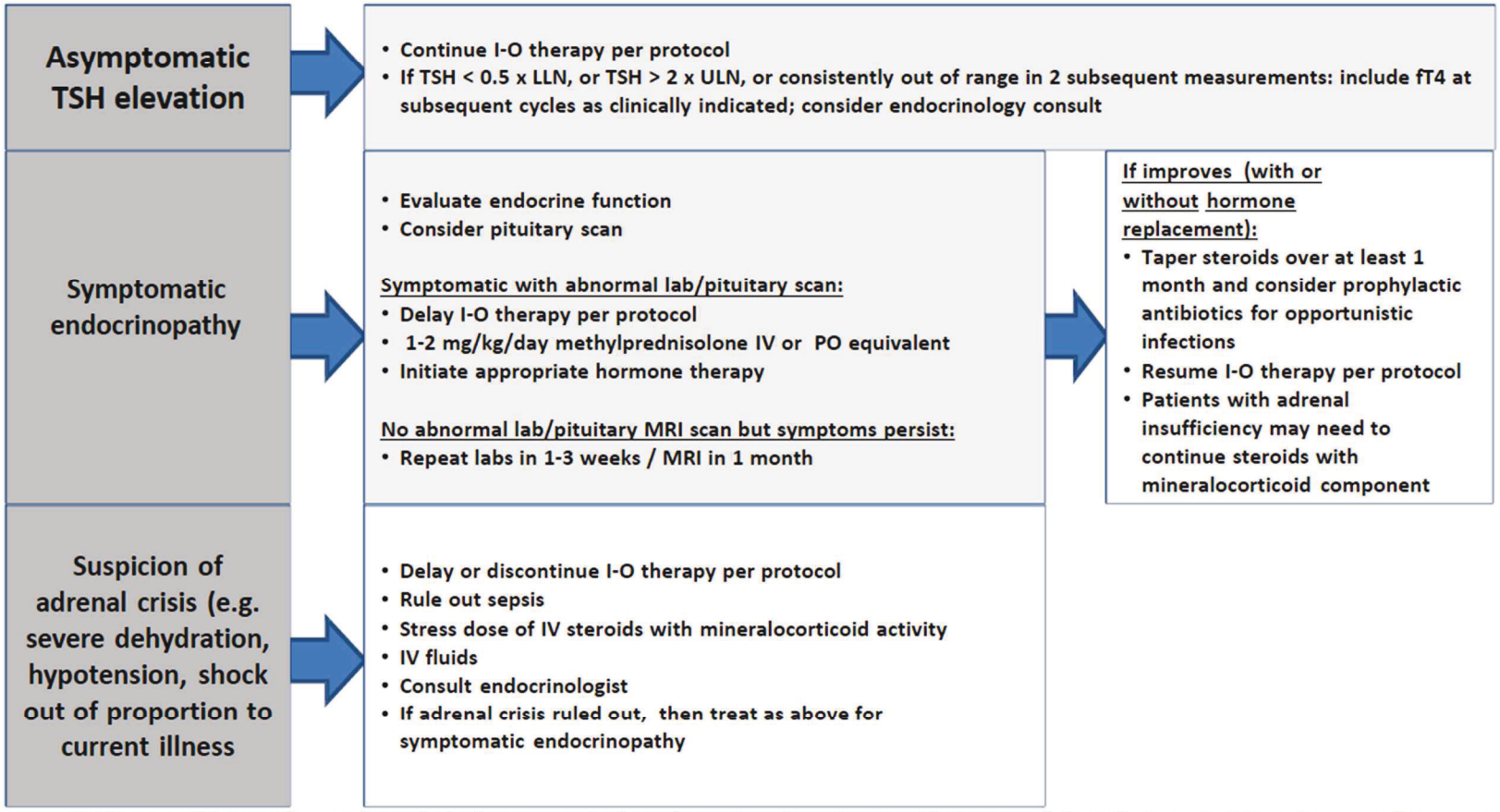
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

*The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

28-Sep-2020

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.

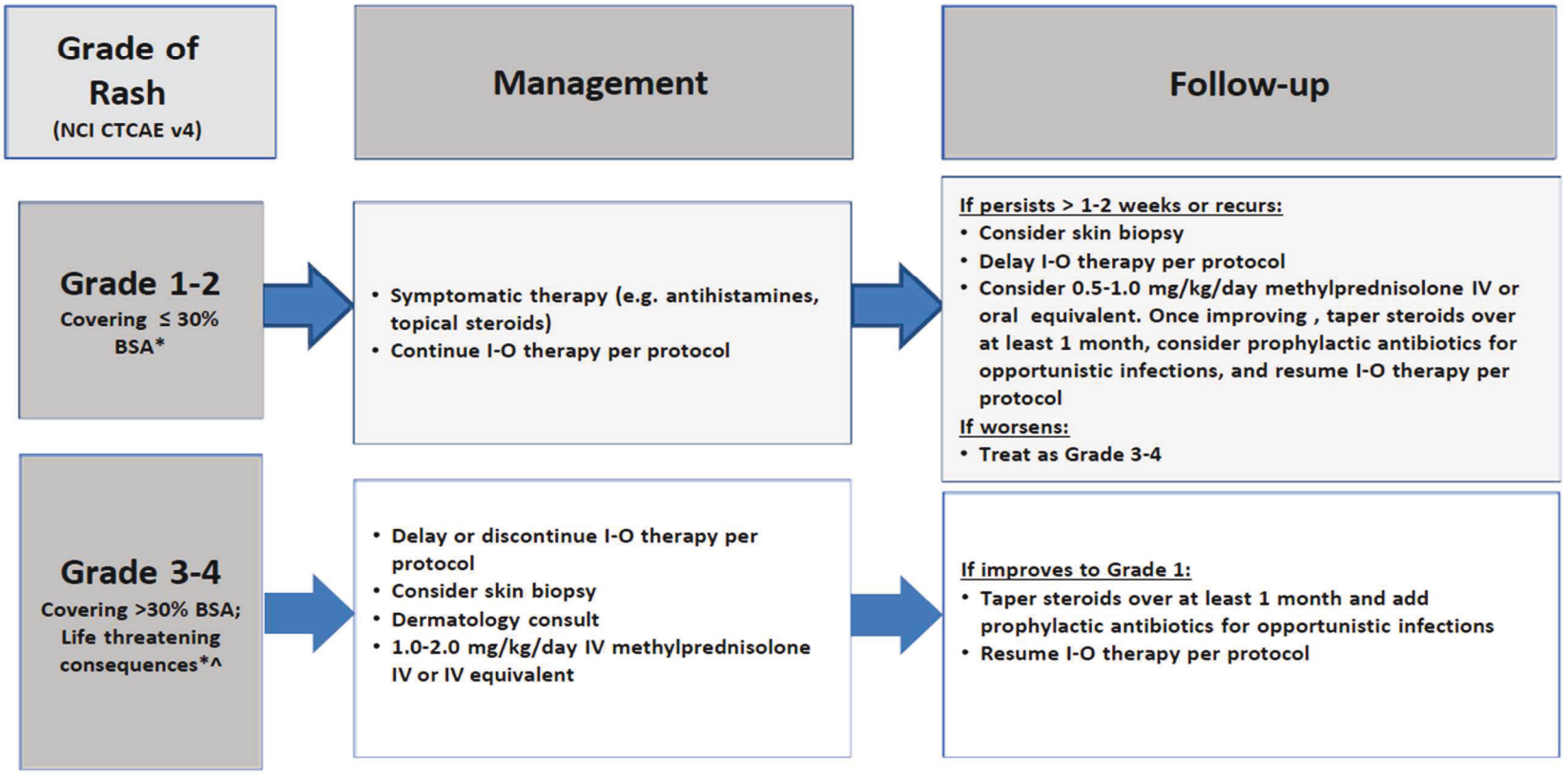


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

28-Sep-2020

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, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

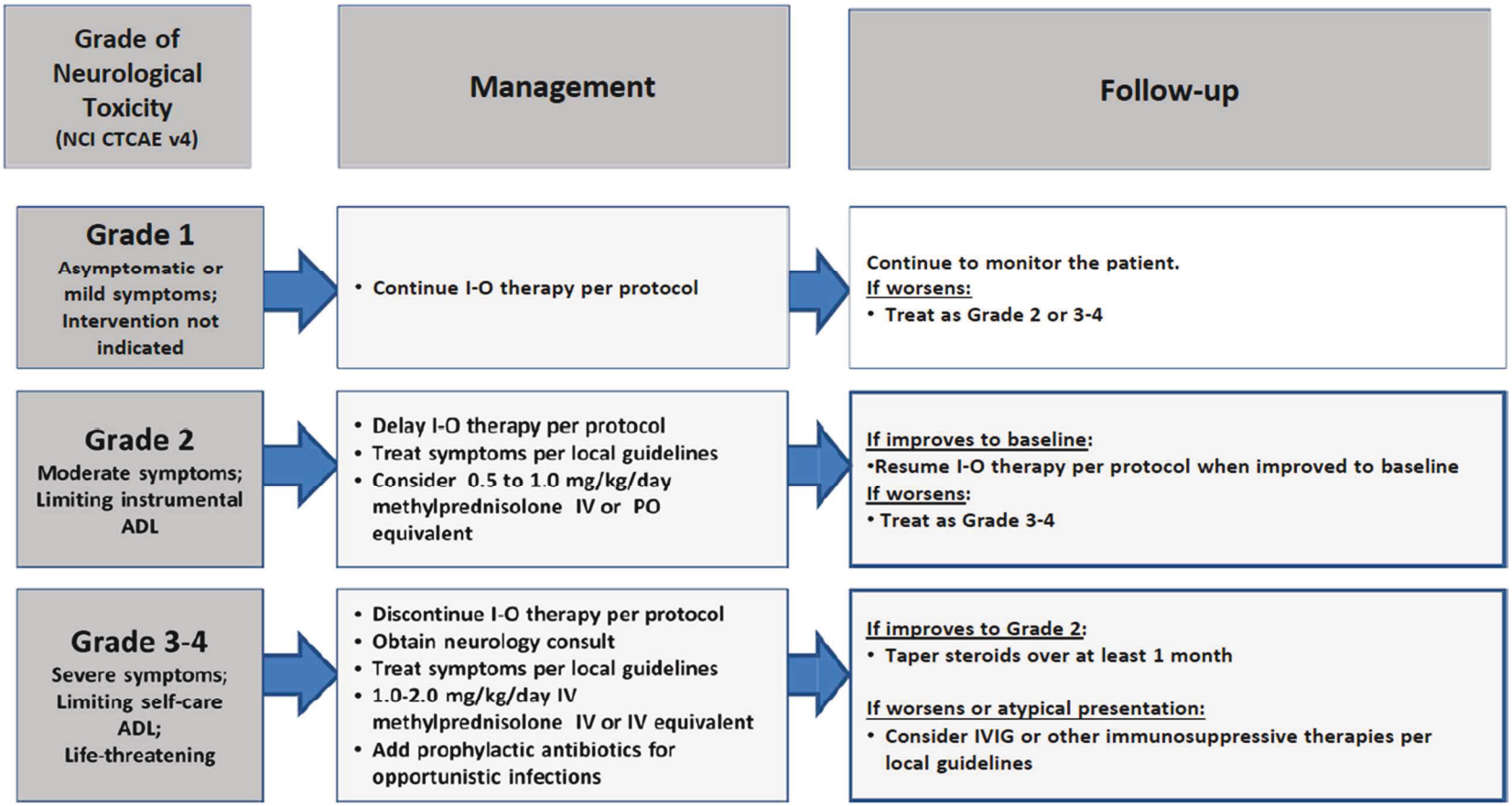
*Refer to NCI CTCAE v4 for term-specific grading criteria.

^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

28-Sep-2020

Neurological Adverse Event Management Algorithm

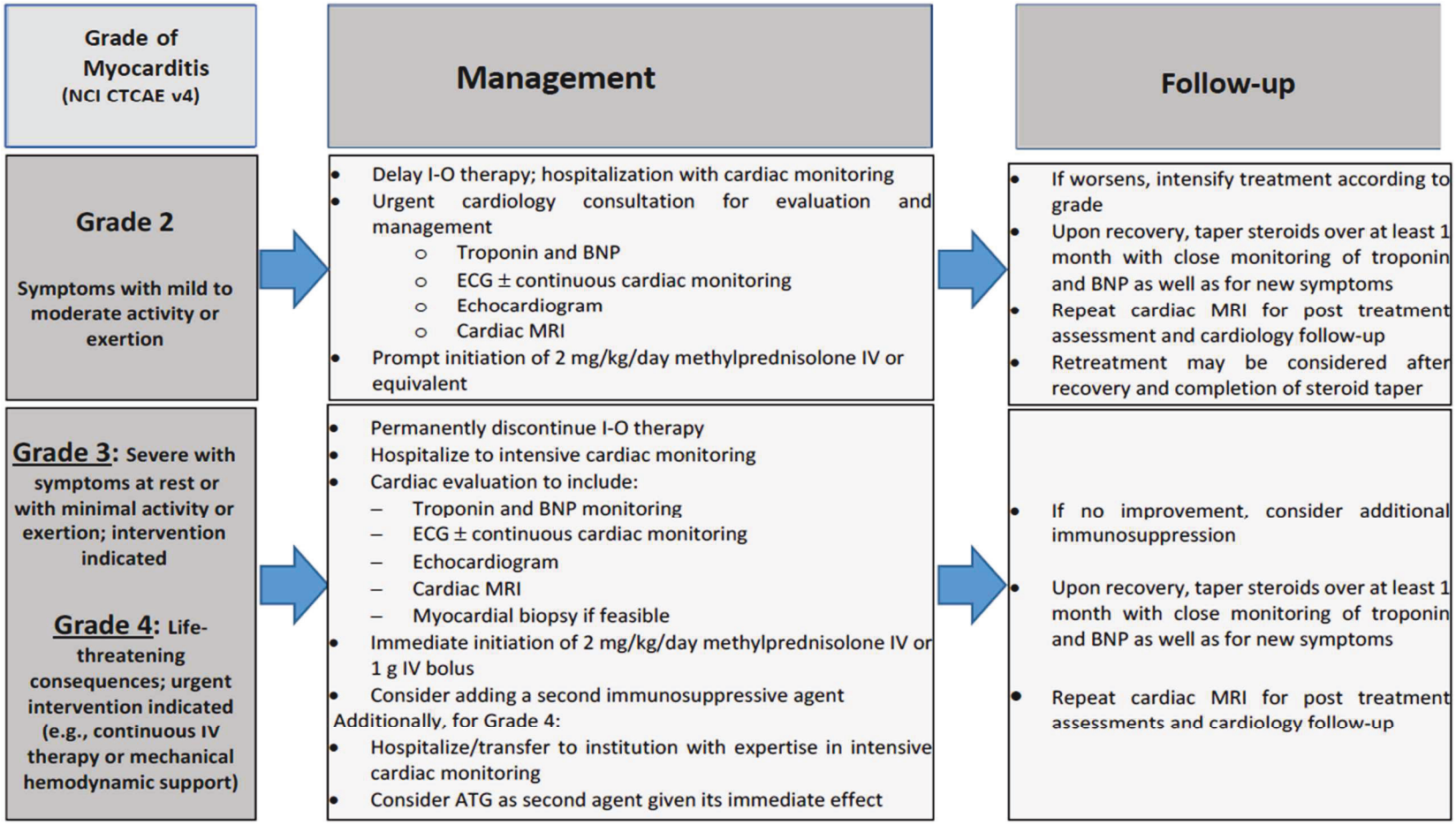
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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

28-Sep-2020

Myocarditis Adverse Event Management Algorithm



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once 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.
ATG = anti-thymocyte globulin; BNP = B-type natriuretic peptide; ECG = electrocardiogram; IV = intravenous; MRI = magnetic resonance imaging

28-Sep-2020

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 CYP3A4, CYP1A2 AND CYP2B6 GUIDANCE

The lists below are not meant to be all inclusive. Please consult individual drug labels for further information. Additional information is also available at:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

Table 1: Classification of In Vivo Inhibitors of CYP Enzymes

CYP Enzymes	Strong Inhibitors[a] ≥ 5-fold Increase in AUC or > 80% Decrease in CL	Moderate Inhibitors[b] ≥ 2 but < 5-fold Increase in AUC or 50-80% Decrease in CL	Weak Inhibitors[c] ≥ 1.25 but < 2-fold Increase in AUC or 20-50% Decrease in CL
CYP3A	Boceprevir, clarithromycin, conivaptan, grapefruit juice,[d] indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil,[e] nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole	Amprenavir, aprepitant, atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice,[d] imatinib, verapamil	Alprazolam, amiodarone, amlodipine, atorvastatin, bicalutamide, cilostazol, cimetidine, cyclosporine, fluoxetine, fluvoxamine, ginkgo,[f] goldenseal,[f] isoniazid, nilotinib, oral contraceptives, ranitidine, ranolazine, tipranavir/ritonavir, zileuton
CYP1A2	ciprofloxacin, enoxacin, fluvoxamine[g], zafirlukast	methoxsalen, mexiletine, oral contraceptives	acyclovir, allopurinol, cimetidine, peginterferon alpha-2a, piperine, zileuton

Abbreviations: AUC = area under the concentration-time curve; CYP = cytochrome P450.
Please note that this is not an exhaustive list.

[a] A strong inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a substrate for that CYP by equal or more than 5-fold.

[b] A moderate inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 5-fold but equal to or more than 2-fold.

[c] A weak inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 2-fold but equal to or more than 1.25-fold.

[d] The effect of grapefruit juice varies widely among brands and is concentration, dose, and preparation dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (eg, high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (eg, low dose, single strength).

[e] Withdrawn from the United States market because of safety reasons.

[f] Herbal product.

[g] Strong inhibitor of CYP1A2 and CYP2C19, and moderate inhibitor of CYP2D6 and CYP3A

Table 2: Classification of In Vivo Inducers of CYP Enzymes

CYP Enzymes	Strong Inducers ≥ 80% Decrease in AUC	Moderate Inducers 50-80% Decrease in AUC	Weak Inducers 20-50% Decrease in AUC
CYP3A	Avasimibe,[a] carbamazepine, phenytoin, rifampin, St. John's wort[b]	Bosentan, efavirenz, etravirine, modafinil, nafcillin	Amprenavir, aprepitant, armodafinil, echinacea,[c] pioglitazone, prednisone, rufinamide
CYP1A2		Phenytoin[d], rifampin[e], ritonavir[f], smoking, teriflunomide	

Please note that this is not an exhaustive list.

[a] Not a marketed drug.

[b] The effect of St. John's wort varies widely and is preparation dependent.

[c] Herbal product.

[d] Strong inducer of CYP3A and moderate inducer of CYP1A2, CYP2C19.

[e] Strong inducer of CYP2C19, CYP3A, and moderate inducer of CYP1A2, CYP2B6, CYP2C8, CYP2C9.

[f] Strong inducer of CYP2C19 and moderate inducer of CYP1A2, CYP2B6, CYP2C9.

Abbreviations: AUC = area under the concentration-time curve; CYP = cytochrome P450.

Table 3: Examples of Sensitive In Vivo CYP Substrates and CYP Substrates with Narrow Therapeutic Range

CYP Enzymes	Sensitive Substrates[a]	Substrates with Narrow Therapeutic Range[b]
CYP3A	Alfentanil, aprepitant, budesonide, buspirone, conivaptan, darifenacin, darunavir, dasatinib, dronedarone, eletriptan, eplerenone, everolimus, felodipine, indinavir, fluticasone, lopinavir, lovastatin, lurasidone, maraviroc, midazolam, nisoldipine, quetiapine, saquinavir, sildenafil, simvastatin, sirolimus, tolvaptan, tipranavir, triazolam, vardenafil	Alfentanil, astemizole,[c] cisapride,[c] cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine[c]
CYP2B6	Bupropion, efavirenz	

Abbreviations: AUC = area under the concentration-time curve; CYP = cytochrome P450.

Please note that this is not an exhaustive list.

[a] Sensitive CYP substrates refers to drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a known CYP inhibitor.

[b] CYP substrates with narrow therapeutic range refers to drugs whose exposure-response relationship indicates that small increases in their exposure levels by the concomitant use of CYP inhibitors may lead to serious safety concerns (eg, Torsades de Pointes).

[c] Withdrawn from the United States market because of safety reasons.

APPENDIX 8 MEDICATIONS ASSOCIATED WITH QT PROLONGATION

The list below is not meant to be all inclusive. Please consult individual drug labels for further information.

quinidine, procainamide, disopyramide,
amiodarone, sotalol, ibutilide, dofetilide,
erythromycins, clarithromycin,
chlorpromazine, haloperidol, mesoridazine, thioridazine, pimozide,
cisapride, bepridil, droperidol, methadone, arsenic, chloroquine, domperidone,
halofantrine, levomethadyl, pentamidine, sparfloxacin, lidoflazine

APPENDIX 9 P-GP AND BCRP GUIDANCE

The list below is not meant to be all inclusive. Please consult individual drug labels for further information. Additional information is also available at:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm

Table 1: Examples of In Vivo Substrates for Selected Transporters

Transporter	Gene	Substrate
P-gp	*ABCB1*	Aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, everolimus, fexofenadine, imatinib, lapatinib, maraviroc, nilotinib, posaconazole, ranolazine, saxagliptin, sirolimus, sitagliptin, talinolol, tolvaptan, topotecan
BCRP	*ABCG2*	Methotrexate, mitoxantrone, imatinib, irrinotecan, lapatinib, rosuvastatin, sulfasalazine, topotecan

Please note that this is not an exhaustive list.
Abbreviations: BCRP = breast cancer resistance protein; P-gp = P-glycoprotein.

APPENDIX 10 AGENTS KNOWN TO CAUSE METHEMOGLOBINEMIA

- Acetanilid
- p-Amino salicylic acid
- Aniline, aniline dyes
- Benzene derivatives
- Clofazimine
- Chlorates
- Chloroquine
- Dapsone
- Local anesthetic agents
  - Benzocaine
  - Lidocaine
  - Prilocaine
- Menadione
- Metoclopramide
- Methylene blue*
- Naphthoquinone
- Naphthalene
- Nitrites
  - Amyl nitrite
  - Farryl nitrite
  - Sodium nitrite
  - Nitroglycerin
  - Nitric oxide
- Nitrobenzene
- Paraquat
- Phenacetin
- Phenazopyridine
- Primaquine
- Rasburicase
- Resorcinol
- Sulfonamides

* While methylene blue is a recognized treatment for methemoglobinemia, it is an agent with oxidant potential (and may worsen the clinical situation) since in individuals with glucose-6-phosphate dehydrogenase deficiency, it induces acute hemolysis that can further decrease oxygen delivery to the tissues. Paradoxically, in high doses, methylene blue can also increase methemoglobinemia.

APPENDIX 11 COUNTRY SPECIFIC REQUIREMENTS

Argentina, Czech Republic, France, Germany, Spain, and Any Other Countries Where Exclusion of HIV Positive Participants Is Locally Mandated

	Country-specific language
Section 2 Schedule of Activities, Table 2-1: Screening Procedural Outline - 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".
Section 9.4 Safety Assessments (baseline laboratory assessments)	Add "HIV" test to Baseline local laboratory assessments to be done within 14 days prior to first dose.

APPENDIX 12 DIAGNOSTIC CRITERIA FOR HLH AND DRESS SYNDROME

Table 1. Diagnostic criteria for HLH used in the HLH-2004 trial*

The diagnosis of HLH† may be established:
A. Molecular diagnosis consistent with HLH: pathologic mutations of *PRF1*, *UNC13D*, *Munc18-2*, *Rab27a*, *STX11*, *SH2D1A*, or *BIRC4*
or
B. Five of the 8 criteria listed below are fulfilled:
1. Fever ≥ 38.5°C
2. Splenomegaly
3. Cytopenias (affecting at least 2 of 3 lineages in the peripheral blood)
Hemoglobin < 9 g/dL (in infants < 4 weeks: hemoglobin < 10 g/dL)
Platelets < 100×10^3/mL
Neutrophils < 1×10^3/mL
4. Hypertriglyceridemia (fasting, > 265 mg/dL) and/or hypofibrinogenemia (< 150 mg/dL)
5. Hemophagocytosis in bone marrow, spleen, lymph nodes, or liver
6. Low or absent NK-cell activity
7. Ferritin > 500 ng/mL‡
8. Elevated sCD25 (α-chain of sIL-2 receptor)§

*Adapted from Henter et al.

†In addition, in the case of familial HLH, no evidence of malignancy should be apparent.

‡Although the HLH-2004 protocol uses ferritin > 500 ng/mL, we generally view ferritin > 3000 ng/mL as concerning for HLH and ferritin > 10 000 as highly suspicious.

§Elevations above age-adjusted, laboratory-specific normal levels (defined as > 2 SD from the mean) appear more meaningful than the original designation of > 2400 U/mL because of variations between laboratories.

Jordan et al. How I treat hemophagocytic lymphohistiocytosis. Blood. 2011;118(15):4041. Epub 2011 Aug 9

Table 2 **Scoring system for classifying HSS/DRESS cases as definite, probable, possible, or no case**

Score	−1	0	1	2	Min.	Max.
Fever ≥ 38·5 °C	No/U	Yes			−1	0
Enlarged lymph nodes		No/U	Yes		0	1
Eosinophilia		No/U			0	2
Eosinophils			0·7–1·499 × 10^9 L^{-1}	≥ 1·5 × 10^9 L^{-1}		
Eosinophils, if leucocytes < 4·0 × 10^9 L^{-1}			10–19·9%	≥ 20%		
Atypical lymphocytes		No/U	Yes		0	1
Skin involvement					−2	2
Skin rash extent (% body surface area)		No/U	> 50%			
Skin rash suggesting DRESS	No	U	Yes			
Biopsy suggesting DRESS	No	Yes/U				
Organ involvement[a]					0	2
Liver		No/U	Yes			
Kidney		No/U	Yes			
Lung		No/U	Yes			
Muscle/heart		No/U	Yes			
Pancreas		No/U	Yes			
Other organ		No/U	Yes			
Resolution ≥ 15 days	No/U	Yes			−1	0
Evaluation of other potential causes						
Antinuclear antibody						
Blood culture						
Serology for HAV/HBV/HCV						
Chlamydia/mycoplasma						
If none positive and ≥ 3 of above negative			Yes		0	1
Total score					−4	9

U, unknown/unclassifiable; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus. [a]After exclusion of other explanations: 1, one organ; 2, two or more organs. Final score < 2, no case; final score 2–3, possible case; final score 4–5, probable case; final score > 5, definite case.

Kardaun SH, et al. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? SHBr J Dermatol. 2007 Mar;156(3):609-11.

APPENDIX 13 REVISED PROTOCOL SUMMARY OF CHANGE HISTORY

Overall Rationale for the Revised Protocol 03, 01-Nov-2019

In the context of its natural history, carcinoma in situ (CIS) in intravesical bacillus Calmette-Guerin (BCG)-unresponsive patients persists despite surgical treatment, and participants entering a study with a CIS diagnosis will likely have residual CIS post-TURBT. For BCG-unresponsive disease, complete response (CR) rate and duration of response in patients with CIS in a single treatment arm can be attributed to treatment. Therefore, the focus of study CA2099UT has been limited to participants with CIS, and the sample size for each arm has been increased in order to enable a statistically robust analysis of CR rate and duration of response. These study endpoints for single-arm, registrational studies in the BCG-unresponsive non-muscle-invasive bladder cancer (NMIBC) population are in accordance with the the FDA Guidance in this population.[1]

Due to global shortages of intravesical BCG, only 1 BCG-containing arm (Arm B) will be expanded, after safety lead-in, instead of 2 (Arm B and Arm D). Accordingly, after completion of the safety lead-in to Arm D, enrollment in that arm will be paused.

In addition, randomization was modified to include both BCG availability and strain based on the following reasons:

- different BCG strains are standard of care in varying regions,
- some countries have more than one strain approved, and
- the TICE strain is the only strain approved in the US and is approved for use in many other countries.

Three BCG-based randomization categories (No BCG available, TICE BCG available, non-TICE BCG available) will ensure reasonable balance between the 3 treatment arms. The number of non-TICE BCG-treated participants will be limited to ≤ 70 to ensure at least 80 TICE BCG-treated participants in Arm B.

Based on these key changes, subsequent revisions were made to sample size, 6 month decision point CR estimates, etc., throughout the protocol. Several appendices were updated as well.

Summary of key changes of Revised Protocol 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
1 Synopsis 3 Introduction 3.1 Study Rationale 5.1 Overall Design 5.1-1 Study Diagram 5.1.1 Safety Lead-in Phase 5.1.2 Randomization Phase 5.4.9 Rationale for Modified Randomization	Revised study design to pause enrollment into Arm D once the safety lead-in is completed. Introduced modified randomization to account for BCG availability.	In the context of a global shortage of intravesical BCG, only 1 BCG-containing arm (Arm B) will be expanded after safety lead-in instead of 2 (Arms B, D). Availability of BCG is incorporated into randomization in order to allow sites without BCG available to enroll participants.

Summary of key changes of Revised Protocol 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
7.2 Method of Treatment Assignment 9.0 Study Assessment and Procedures, Treatment Phase 10.1 Sample Size Determination		The modified randomization will allow efficacy data from all arms to be mature around the same time.
1 Synopsis 3 Introduction 3.1.1 Research Hypothesis 3.2.1 Indication Background Table 4-1 Objectives and Endpoints 5.1 Overall Design 5.1.2 Randomization Phase [through-out] 5.2 Number of Participants 5.3 End of Study Definition 6.1 Inclusion Criteria (3) 7.2 Method of Treatment Assignment 8.1.4 Post Study Treatment Study Follow-up 9.0 Study Assessment and Procedures, Follow-up Phase 9.1 Efficacy Assessments 9.8.3 Urine Markers 10.2 Populations for Analyses	Removed eligibility for non-CIS participants. Deleted the endpoint of event free survival (EFS) in non-CIS participants In 6.1, removed Ta or T1 alone from eligibility.	In the context of a global shortage of intravesical BCG and the FDA guidance on registrational studies in BCG-unresponsive NMIBC, patients with CIS are being prioritized. Non-CIS participants will not be eligible, and the associated EFS endpoint was removed.
1 Synopsis Table 2-2 On-treatment Procedural Outline for Arms A and C (CA2099UT) Table 2-3 On-treatment Procedural Outline for Arms B and D (CA2099UT) Table 2-4 Follow-up Procedural Outline (CA2099UT) 5.1 Overall Design	Revised language from Methemoglobin “should” to “must” be assessed. Revised language from a negative pregnancy test “should” be to “must” be documented within 24 hours prior to start of each dose of nivolumab. Revised language from “should” to “efficacy assessments must occur” until disease recurrence or progression, per PRC, based on a positive urinary cytology or bladder biopsy. Imaging changed from “should” to “must” be performed per instructions.	The assessments are not optional so more explicit language was used.
1 Synopsis 5.1 Overall Design 5.1-1 Study Diagram 5.1.2 Randomization Phase, Part 2 5.1.2 Randomization Phase, Part 3	Increased N in Arms A, B, and C. Revised 6-month decision point CR numbers for CIS participants.	Only CIS participants will be enrolled and the number of participants per arm will be increased to enable more robust evaluation of CR rate on each arm, with subsequent

Summary of key changes of Revised Protocol 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
5.1.3 Data Monitoring Committee and Other External Committees 5.2 Number of Participants 10.3.4 Initial Evaluation of Efficacy and Safety		revisions to the decision point numbers.
1 Synopsis Table 7-1 Study Treatments for CA2099UT	From Potency column, deleted 100 mg and 40 mg.	This administrative update clarifies that potency is expressed as 10mg/mL, not mg.
1 Synopsis 5.1 Overall Design	Added that participants should remain on their same BCG strain throughout the study whenever possible.	To enable the clearest interpretation of safety and efficacy data, it is preferred that participants remain on one BCG strain.
1 Synopsis 5.3 End of Study Definition	Revised end of study for the primary completion definition for the CR rate of CIS participants to 12 months after the initial CR for all participants. Reworded definitions for study completion and added end of trial and end of study definition. Changed time period to achieve full enrollment from 22 to 37 months.	The end of study changed due to the drop of EFS endpoint. Revised Study Completion and added End of Trial for consistency with US NIH Clinical Trial Registry and The EU Clinical Trial Registry, respectively; added end of study for consistency with internal BMS guidance. Revised timing based on current projection.
Table 2-1 Screening Procedural Outline (CA2099UT) 9.1.4 Bladder Biopsy	Specified that tumor tissue samples for diagnosis are 1-10 hematoxylin and eosin (H&E) stained slides, with at least 1 slide/disease site, representing the diagnosis of high-risk NMIBC (CIS, CIS with TaHG, or CIS with T1).	Provided clarity on the slides needed for diagnosis.
Table 2-1 Screening Procedural Outline (CA2099UT) 6.1 Inclusion Criteria 9.1.4 Bladder Biopsy	Specified that if tumor tissue was obtained > 70 days prior to randomization, participants must have a repeat cystoscopy ≤ 70 days prior to randomization. Disease stage will be updated to take account of all TURBT findings.	Revised language that if tissue collection timelines exceed 70 days, additional time is allowed for completion of repeat cystoscopy to confirm participant eligibility.
Table 2-2 On-treatment Procedural Outline for Arms A and C (CA2099UT) Table 2-3 On-treatment Procedural Outline for Arms B and D (CA2099UT) Table 2-4 Follow-up Procedural Outline (CA2099UT)	Added that PK samples of BMS-986205 will be analyzed for select metabolites. [redacted]	Select metabolite analysis was added to support future exposure-response analysis. For ease of understanding.

Summary of key changes of Revised Protocol 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 4-1 Objectives and Endpoints 9.5.2 Pharmacokinetics and Immunogenicity Assessments Table 9.5.2-1 Pharmacokinetic and Anti-drug Antibody Sampling Schedule for Nivolumab and PK Sampling Schedule for BMS-986205 and Select Metabolites		
Table 2-2 On-treatment Procedural Outline for Arms A and C (CA2099UT) Table 2-3 On-treatment Procedural Outline for Arms B and D (CA2099UT) 9.11.1 Patient-reported Outcomes	Changed timing of health outcomes questionnaires assessments from every 4 weeks following randomization to D1 of every cycle.	To clarify the timing.
3 Introduction	Added the new generic name "linrodostat mesylate" to BMS-986205	To remain current and transparent.
5.1 Overall Design 5.1.2 Randomization Phase, Part 2 5.2 Number of Participants	Removed text on 2 arms continuing to full enrollment.	For consistency with changes made throughout protocol.
5.1.2 Randomization Phase, Part 1	Corrected text to indicate that the randomization phase begins after the safety lead-in participants begin treatment rather than after safety lead-in enrollment. Added statement that if BCG shortage resolves, randomization will switch to Arms A, B, or C in a 1:1:1 ratio.	Corrected misstatement. Allows for adjustments if BCG shortage resolves.
5.4.6 Rationale for Complete Response Rate in Participants with Carcinoma in Situ as a Primary Endpoint 5.4.7 Rationale for EFS in All Non-CIS Participants as a Co-primary Endpoint	Revised Section 5.4.6 Heading to change "Co-Primary" to "Primary." Deleted Section 5.4.7 to remove EFS endpoint.	Enrollment limited only to CIS participants so EFS of non-CIS participants removed as co-primary endpoint.
5.5.3 Justification for Administration of BMS-986205 with Food	Updated text based on a definitive food effect assessment in normal healthy volunteers.	Provide most recent data.
7.2 Method of Treatment Assignment 9 Study Assessment and Procedures, Treatment Phase 10.3.1 Efficacy Analyses	Revised randomization to be based on BCG availability (No BCG available vs TICE BCG available vs Non-TICE BCG available). Specified that for the purposes of randomization, any BCG strain that becomes approved in the US during the	Modified randomization to utilize available BCG in the context of a global shortage of intravesical BCG. Added analyses for Arm B to assess the primary and secondary endpoints on the

Summary of key changes of Revised Protocol 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
	conduct of the study will be included in the category of TICE BCG available.	subgroup of participants receiving BCG TICE strain.
7.4.6 Management Algorithms	Added algorithm on myocarditis to Appendix 6.	Provide new algorithm per recent Nivolumab Investigator Brochure.
9.3 Overdose	Clarified that only overdose occurrences that meet regulatory SAE definitions are to be reported as SAE.	Made consistent with Appendix 3.
10.1 Sample Size Determination 10.1-1 Observed Complete Response Rate and Exact 95% Confidence Interval in the CIS Population	Removed Arm D and revised sample size to enable most robust assessment of CR rate in each arm. Increased number of participants at the early decision point (from 27 to 34). Revised the decision-marking CR criteria from ≥ 11 to ≥ 10 participants. Removed text related to Arm D enrollment.	[redacted]. The protocol is being revised to address the BCG shortage and improve the ability of the study to demonstrate efficacy. Given the recent KEYNOTE-057 report of ~40% overall CR rate and ~30% 6 month CR rate, 30% CR rate at 6 months may be clinically meaningful in terms of improving upon existing SOC.
Appendix 4 WOCBP Definitions and Methods of Contraception	Moved hormonal methods of contraception from User Independent to User Dependent. Added additional detail.	Meets current standards.
Appendix 5 Management Algorithms for Immuno-Oncology Agents	Added algorithm on myocarditis and replaced all algorithms with updated versions.	Meets current standards.
All	Minor formatting and typographical corrections.	Minor, therefore have not been summarized.

Overall Rationale for the Revised Protocol 02, 10-May-2019

The purpose of this revised protocol is to increase the window for screening procedures, [redacted], make random bladder biopsies at screening optional, allow for urine cytology to be tested on a voided specimen, and increase the window for repeat TURBT for participants with stage T1 disease from 4 to 8 weeks to be consistent with professional society guidelines. Yearly upper tract imaging is added to be consistent with NCCN guidelines, and histologic confirmation of tumor progression identified on imaging and/or clinical examination is added. Clarification is provided regarding the exclusion criterion for prior systemic chemotherapy and immunotherapy, which applies only if these therapies were administered for the treatment of urothelial carcinoma. A subsection was added to the protocol describing the adverse events of special interest of Hemophagocytic lymphohistiocytosis (HLH)

and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome. Language was added to clarify condom requirements for males who are sexually active with WOCBP to prevent seminal transmission of investigational agents. Secondary items incorporated into this revised protocol include clarifications regarding timing and need for some laboratory testing and some protocol-specific activities, excluding participants who have received a live/attenuated vaccine within 30 days of first treatment, prohibiting live/attenuated vaccines during treatment and until 100 days post last dose, and making minor clarifications and edits throughout the protocol to ensure consistency between sections.

This revised protocol applies in all countries, at all sites, to all future participants enrolled in the study, and where applicable, to all participants currently enrolled in the study.

Summary of key changes of Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Synopsis, Key Inclusion Criteria Section 2, Schedule of Activities, Table 2-1 Screening Procedural Outline 5.1 Overall design 6.1 Inclusion Criteria (3, 3b, 3c) 9.1.2 Cystoscopy 9.1.3 Urine Cytology 9.1.4 Bladder Biopsy [redacted]	Increased window for diagnostic pathology slides from 8 weeks/56 days to 10 weeks/70 days Increased window for screening cystoscopy and urine cytology from 8 weeks/56 days to 10 weeks/70 days Increased window for complete resection from 8 weeks/56 days to 10 weeks/70 days	Increased window to allow additional time for completion of all screening activities including collection and evaluation of diagnostic biopsy slides and determination of PD-L1 status
Synopsis, Key Inclusion Criteria 5.1 Study Design 6.1 Inclusion Criteria (3) 9.1.4 Bladder Biopsy	Changed diagnostic pathology slides timing to prior to randomization	Provides consistent language throughout protocol
Synopsis, Key Inclusion Criteria 6.1 Inclusion Criteria (3b [i])	Extended time for repeat TURBT after the initial TURBT to 8 weeks	Aligns with global practice patterns
Synopsis, Key Inclusion Criteria 6.1 Inclusion Criteria (3b [iii]) 9.1.4 Bladder Biopsy	Random sampling of bladder mucosa during screening changed from required to optional with added details about timing In 9.1.4, added text on random bladder biopsies in CIS participants at 26 weeks	Based on extensive feedback from study investigators, random bladder biopsies are no longer performed as part of routine care in this patient population. The first four randomized participants in this study required a separate, additional surgical procedure to obtain random bladder biopsies prior to randomization, thereby placing them at increased risk and increasing the burden

Summary of key changes of Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
		on participants and investigators. As a result, random bladder biopsies at screening have been changed from required to optional. For CIS participants not undergoing random bladder biopsy at screening, requirement was added for inclusion of random biopsies during the mandatory 26 week bladder biopsy to fully stage the participant's response to therapy. Because these biopsies will be performed in conjunction with an already required procedure, no additional burden will be placed on the participant or investigator.
Synopsis, Key Inclusion Criteria 6.1 Inclusion Criteria (3b [iv]) 9.1.3 Urine Cytology	Added voided specimen (except for first morning urination) as an option for obtaining urine cytology	Requirement for bladder wash cytology placed additional burden on investigator and participant as in some cases, a separate, additional catheterization procedure was necessary to obtain the cytology specimen. Allowing for either a voided specimen or bladder wash specimen removes the need for catheterization in circumstances where the participant is not being catheterized for another reason.
Synopsis, Key Inclusion Criteria 6.2 Exclusion Criteria (2e)	Specified prior systemic chemotherapy or immunotherapy for UC	Provides clarification that prior systemic chemotherapy or immunotherapy is only an exclusion if it was administered to treat UC
Synopsis, Key Exclusion Criteria 6.2 Exclusion Criteria (2 [i])	Added exclusion for participants who had received a live/attenuated vaccine within 30 days of first treatment	Reflects new required content
Synopsis, Overall Design Section 2, Schedule of Activities, Table 2-3 On-treatment Procedural Outline for Arms B and D	Extends cystoscopy and bladder biopsy for CIS participants (± 5 weeks) at week 26 and 52 In Table 2.3 Footnote b, added clarification on the timing of BCG administration after TURBT/bladder biopsy	Allows for greater flexibility in scheduling week 26 and week 52 cystoscopy and bladder biopsy in CIS participants receiving BCG
Synopsis, Study Treatment 6.1 Inclusion Criteria (3d) 7.1.2 BMS-986205 Dosing	Deleted text about BMS-986205 only in tablet formulation	Allow treatment with alternative modes of administration (eg, crushed tablets) as detailed in IB and pharmacy manual
Section 2, Schedule of Activities, Table 2-1 Screening Procedural Outline	[redacted]	Allows for participants with limited remaining tumor tissue to be enrolled into the study

Summary of key changes of Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-2 On-treatment Procedural Outline for Arms A and C Table 2-3 On-treatment Procedural Outline for Arms B and D Table 2-4 Follow-up Procedural Outline [redacted]		
Section 2, Schedule of Activities, Table 2-1 Screening Procedural Outline	All testing, except viral, CRP, and G6DP, within 14 days prior to randomization	Provides clarification for timing of laboratory studies
Section 2, Schedule of Activities, Table 2-1 Screening Procedural Outline	G6PD testing to be done within 28 days prior to randomization	Aligns with global capabilities for G6PD testing
Section 2, Schedule of Activities, Table 2-2 On-treatment Procedural Outline for Arms A and C Table 2-3 On-treatment Procedural Outline for Arms B and D	Physical examination revised to only as clinically indicated starting from Cycle 1 Day 1	Full physical examination is required at screening; performing as clinically indicated at time points after screening decreases burden on participants and investigators
Section 2, Schedule of Activities, Table 2-2 On-treatment Procedural Outline for Arms A and C Table 2-3 On-treatment Procedural Outline for Arms B and D	Specified that CBC with differential, chemistry panel, and thyroid testing must be done within 72 hours prior to nivolumab dosing	Provides clarification for timing of laboratory studies
Section 2, Schedule of Activities, Table 2-2 On-treatment Procedural Outline for Arms A and C Table 2-3 On-treatment Procedural Outline for Arms B and D	Added that participants may continue BMS-986205 dosing until methemoglobin result is available unless clinical signs or symptoms of methemoglobinemia are present	Provides clarification for BMS-986205 dosing while methemoglobin results are pending
Section 2, Schedule of Activities, Table 2-2 On-treatment Procedural Outline for Arms A and C	Methemoglobin testing can be stopped if BMS-986205 is discontinued and prior methemoglobin level is ≤ to ULN	Methemoglobinemia is no longer a risk if participant discontinued BMS-986205

Summary of key changes of Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-3 On-treatment Procedural Outline for Arms B and D		
Section 2, Schedule of Activities, Table 2-2 On-treatment Procedural Outline for Arms A and C Table 2-3 On-treatment Procedural Outline for Arms B and D Table 2-4 Follow-up Procedural Outline 9.1.1 Imaging Assessment for the Study	Specified upper tract imaging every 52 weeks (± 3 weeks); added new row to 2-4	Consistent with NCCN guidelines on follow-up of high-risk NMIBC patients
Section 2, Schedule of Activities, Table 2-2 On-treatment Procedural Outline for Arms A and C Table 2-3 On-treatment Procedural Outline for Arms B and D 9.1.4 Bladder Biopsy	Added that any abnormality suspicious for recurrent papillary tumor or CIS must be biopsied and evaluated Random biopsy changed to mandatory in CIS participants at 26 weeks if not performed prior to randomization and details of the biopsy were provided	Provides clarification
Section 2, Schedule of Activities, Table 2-3 On-treatment Procedural Outline for Arms B and D	Specifies timing of urinalysis relative to BCG dosing	Consistent with routine clinical practice
Section 2, Schedule of Activities, Table 2-3 On-treatment Procedural Outline for Arms B and D	Footnote b: added timing of first BCG dose at CID1 (± 3 days) and ± 3 day window for subsequent BCG dosingAdded that BCG treatment should not be given within 14 days after TURBT/bladder biopsy	Provides window for BCG dosing
Section 2, Schedule of Activities, Table 2-4 Follow-up Procedural Outline	Clarified that pregnancy testing is only required at FU1 and FU2 visits, unless increased frequency and/or duration is required per local regulations	Language allows for compliance with guidelines that may differ between countries with respect to frequency and duration of pregnancy testing
Section 2, Schedule of Activities, Table 2-4 Follow-up Procedural Outline 9.11.1 Patient-reported Outcomes	In 2-4, specified administration of PRO assessments prior to any procedures Added EQ-5D-3L through Efficacy Follow-up 9.11.1 only: added minimum important differences (MIDs	Added PRO to Efficacy Follow-up as currently QoL only being collected through Follow-up 2. MIDs included in the protocol for informational purposes

Summary of key changes of Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
6.1 Inclusion Criteria (3b [i]) 9.1.4 Bladder Biopsy	For T1 lesions, increased re-staging TURBT window from within "4" to "8" weeks	Changed to be consistent with AUA and EAU guidelines
6.1 Inclusion Criteria (4f)	For male participants, specified type of condom and expanded their use with any sexual activity	Clarified condom requirements and type of sexual activity for males who are sexually active with WOCBP to prevent seminal transmission. Revised Appendix 4 to make consistent
6.1 Inclusion Criteria	Deleted text on female partners of male participants treated with BMS-986205	For consistency with Appendix 4 Women of Childbearing Potential Definitions; drug interactions with BMS-986205 not a concern in partners
6.2 Exclusion Criteria (2h)	Changed use of investigational agent to within 4 weeks of randomization	Provides consistent language throughout protocol
6.2 Exclusion Criteria (5a) 8.1 Discontinuation from Study Treatment	Added "only in countries where local regulations permit"	Provides clarification
Table 7-1 Study Treatments for CA2099UT 7.1.3 BCG Dosing	Inserted Footnote b in table and text in 7.1.3	Provides clarification as BCG to be obtained as local commercial product in countries where local regulations permit
7.1.3 BCG Dosing	Revised text related to study drug treatment delay and continuation of other study drugs	Provides consistent approach to dose delays
7.7.1.1 Prohibited Treatments	Added "Treatment Arm C and D only" to first bullet because it only applies to BMS-986205	Concomitant use of strong inhibitors or inducers of CYP3A4 and/or CYP1A2 are only prohibited for participants taking BMS-986205
7.7.1.1 Prohibited Treatments	Added prohibitions against live/attenuated vaccines during treatment and until 100 days post last dose and included vaccine examples	Reflects new requirement for BMS nivolumab studies
9.1 Efficacy Assessments, Complete Response	Removed "for cause" describing imaging for CR; specified indeterminate "for response"	Clarification
9.1 Efficacy Assessments (Progression Definition) 9.1.1 Imaging Assessment for the Study	Added histological confirmation of progression detected by imaging and/or clinical examination, if feasible *Note*: 9.1.1 specifies confirmation by PRC	Histologic confirmation (or exclusion) of progression detected on imaging/clinical examination will allow for more accurate determination of progression when imaging/examination suggestive but not conclusive

Summary of key changes of Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
9.1.1 Imaging Assessment for the Study	Specified CT and post-contrast CT/MRI that must be done during screening and through-out the study Deleted 2 paragraphs on contraindications	Clarification Consistent with NCCN guidelines on follow-up of high-risk NMIBC patients
9.2.9 Adverse Events of Special Interest Appendix 12 Diagnostic Criteria for HLH and DRESS Syndrome	Added AE subsection containing Hemophagocytic lymphohistiocytosis (HLH) and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome	HLH and DRESS have been reported (in 1 participant each) with BMS-986205 and nivolumab. These AEs have been determined to be AEOSI requiring expedited reporting. Diagnostic criteria have been added to aid investigators in identifying these adverse events of special interest. Added new Appendix 12 to provide diagnostic criteria
Table 9.4.1-1 Clinical Laboratory Assessments	Added "and/or WBC" to leukocyte esterase in two places	Addresses minor differences in reporting of urinalysis results in different regions
Table 9.5.2-1 PK and ADA Sampling Schedule	Added statement to Footnote c	Provides clarification since only participants in Arm C and Arm D receive BMS-986205
Appendix 2 Study Governance Consideration	Slightly modified definition of "serious breach"; provided additional criteria for the CSR Signatory Investigator; added publication policy	Meets current standards
Appendix 3 AEs and SAEs	Updated definitions and procedures for recording, evaluating, follow-up, and reporting AEs and SAEs	Meets current standards
Appendix 4 Women of Childbearing Potential Definitions	Moved hormonal methods of contraception from User Independent to User Dependent For male participants, specified synthetic or latex condom during any sexual activity	Clarified condom requirements and type of sexual activity for males who are sexually active with WOCBP to prevent seminal transmission. Revised Section 6.1 Inclusion Criteria (4f) to be consistent.
Appendix 5 I-O Treatment Algorithms	Updated treatment algorithms *Note*: Footnotes in Hepatic AE Management Algorithm are consistent with prior 2016 version	Meets current standards
ALL	Minor edits made throughout document to align sections for consistency	Minor, therefore have not been summarized

Overall Rationale for the Revised Protocol 01, 23-Mar-2018

The purpose of this revised protocol is to align language with the FDA Final guidance for BCG Unresponsive Non-Muscle Invasive Bladder Cancer (NMIBC) dated February 2018 [redacted] Secondary items incorporated into this revised protocol include plan for evaluating suspicious urine cytology, allowing randomization of participants with PD-L1 not evaluable tumor tissue, clarification of exclusion criteria, adding CYP1A2 inhibitors and inducers to prohibited and restricted treatments and details added regarding serotonin syndrome, and minor clarifications made throughout document for consistency across sections.

This revised protocol applies in all countries, at all sites, to all future participants enrolled in the study, and where applicable, to all participants currently enrolled in the study.

Summary of key changes of Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Synopsis, Key Inclusion Criteria Section 6.1, Inclusion Criteria	Updated language defining BCG - unresponsive disease	Revised language in alignment with FDA final guidance for BCG Unresponsive NMIBC
[redacted]		
Synopsis, Figure 1 Study Schematic Section 5.1, Figure 5.1-1 Study Schematic	Revised schematic to update stratification factors and add stagger to safety lead-in phase	Revised stratification factors in alignment with FDA final guidance for BCG Unresponsive NMIBC. Stagger of safety lead-in phase allows for adequate assessment of Arm B prior to the enrollment of Arm D.
Synopsis, Study Treatment Section 6.1, Inclusion Criteria Section 7.1.2, BMS-986205 Dosing	Updated language for BMS-986205 formulation and added reference to IB and Pharmacy manual	Ongoing clinical pharmacology studies may expand options available for administration of BMS-986205 (eg crushing tablet). New language refers to IB and Pharmacy manual for updates.
Section 2, Schedule of Activities Table 2-1	ECG and smoking and alcohol history added as part of screening procedure	Language added since ECG is performed at screening and smoking and alcohol history is collected with medical history
Section 2, Schedule of Activities Table 2-4	Revised notes section for subsequent bladder cancer treatment	Revised language to further specify the collection of subsequent

Summary of key changes of Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
		bladder cancer treatment in alignment with FDA final guidance for BCG Unresponsive NMIBC
Section 2, Schedule of Activities Table 2-1, Section 5.1, Schema Overall Design	Language revised to allow participants with tumor tissue that is not evaluable for PD-Ll expression to be randomized	Allows for participants with PD-L1 not evaluable status to be randomized and enter study. Provides expanded opportunity for screened patients to participate in study thereby increasing the eligible study population and potentially providing more generalizable results.
Section 2, Schedule of Activities Table 2-2 and Table 2-3 Section 9.8, Biomarkers Table 9.8-1	Increased windows for cystoscopy, urine cytology and bladder biopsy from ±2 weeks to ± 3 weeks	Window during which to perform efficacy assessments increased to +/- 3 weeks to allow Investigators greater flexibility in scheduling evaluations
[redacted]		
Section 5.1.2, Randomization Phase	Added language detailing classifications and definitions of BCG refractory and BCG early relapsing	Language added since BCG refractory vs Early Relapsing are no longer stratification factors but will still be recorded by investigators for the purpose of analysis
Section 6.1, Inclusion Criteria	Added language to criteria 4f detailing requirements specific to condom use during penile vaginal intercourse	Clarified condom requirements for males who are sexually active with WOCBP. Language made consistent with Appendix 4
Section 5.1, Overall Design Section 5.5.4, Justification for BCG Dose, Section 7.1, Treatments Administered	Language revised to indicate BCG dosing according to prescribing information for BCG strain and preparation administered	BCG will be locally sourced in some countries and provided by sponsor in other countries. As a result, dose will not be based on local SOC but rather will be based on prescribing information for BCG strain/preparation administered.
Section 7.2, Method of Treatment Assignment	Updated language for disease status that will be used to stratify participants at time of randomization	Revised language in alignment with FDA final guidance for BCG Unresponsive NMIBC

Summary of key changes of Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 7.7.1.1, Prohibited Treatments Section 7.7.1.2, Restricted Treatments	Updated language to add CYP1A2 inhibitors and inducers and add details regarding marijuana and concurrent smoking	Clinical pharmacology studies have further clarified the metabolic pathway of BMS-986205 as it relates to CYP1A2
Section 6.2, Exclusion Criteria Section 7.7.2, Other Restrictions and Precautions Section 8.1.2, Discontinuation of BMS-986205	Added language regarding theoretical risk of serotonin syndrome and updated exclusion criteria and discontinuation criteria for serotonin syndrome	There is a theoretical chance that BMS-986205 could cause an increase in serotonin levels in the brain that may contribute to occurrence of serotonin syndrome.
[redacted]		
Section 9.1, Efficacy Assessments	Added language providing detailed plan for evaluating suspicious urine cytology and clarified definitions for complete response and recurrence for participants with suspicious cytology undergoing subsequent evaluation	Revised language in alignment with FDA final guidance for BCG Unresponsive NMIBC
Section 2, Schedule of Activities Table 2-2 & 2-3 Section 9.8, Biomarkers Table 9.8-1 [redacted]	[redacted]	[redacted]
ALL	Minor edits made throughout document to align sections for consistency	Minor, therefore have not been summarized