Official Title of Study:

A Phase 3, Open-label, Randomized Study of Nivolumab Combined with Ipilimumab, or with Standard of Care Chemotherapy, versus Standard of Care Chemotherapy in Participants with Previously Untreated Unresectable or Metastatic Urothelial Cancer

NCT Number: NCT03036098

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CLINICAL PROTOCOL CA209901

A Phase 3, Open-label, Randomized Study of Nivolumab Combined with Ipilimumab, or with Standard of Care Chemotherapy, versus Standard of Care Chemotherapy in Participants with Previously Untreated Unresectable or Metastatic Urothelial Cancer

(CheckMate 901: CHECKpoint pathway and nivolu**MA**b clinical **T**rial **E**valuation **901)**

Protocol Amendment Number: 05

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Protocol Amendment 05	27-Apr-2023	This amendment updates the substudy final analysis strategy for progression free survival (PFS) to coincide with the overall survival (OS) final analysis, regardless of the number of PFS events reached at this time. This change is being made due to the actual substudy PFS event rate being lower than initially anticipated with a projected delay of approximately 3 years. Therefore, it is not possible for the originally planned number of PFS events to be reached simultaneously with the planned number of OS events as currently specified for the final analysis in the protocol. Thus, this amendment will allow for the final analysis for OS and PFS to occur after only the required number of OS (at least 356) events have been reached in the substudy. There is no update of OS endpoint or corresponding analysis.
Administrative Letter 16	11-Jul-2022	The purpose of this letter is to notify regarding change/addition in study personnel.
Administrative Letter 15	07-Dec-2021	The purpose of this letter is to notify regarding change/addition in study personnel.
Administrative Letter 14	11-Nov-2021	The purpose of this letter is to notify regarding change/addition in study personnel.
Administrative Letter 13	29-Oct-2021	The purpose of this letter is to notify regarding change/addition in study personnel.
Administrative Letter 12	15-Jan-2021	The purpose of this letter is to notify regarding change/addition in study personnel.
Revised Protocol 04	20-Mar-2020	This revision, solely limited to substudy, elevates overall survival (OS) as a primary endpoint with progression free survival (PFS), OS interim analysis has been added, and PFS interim analysis has been removed. To ensure sufficient power for the primary endpoints, 300 cisplatin-eligible participants have been added to the substudy.
Administrative Letter 11	20-May-2019	The purpose is to clarify that an error was discovered in Rev Prot 03 (dated 09 APR 2019) such that Table 9.8.1, Biomarker Sampling Schedule (All Participants) is incorrect because the KEY superscript “c” was incorrectly applied in the table to the “Whole blood (gene expression)” column instead of the intended “PBMC” column. Key “c” notes “Not collected in China, Argentina, Brazil, Chile, Peru, or Australia for Whole Blood (Gene Expression)”. As indicated in the Lab Manual, there should be no restrictions to Whole blood (gene expression) collection, and therefore no Key for the “Whole Blood for gene expression” column
Revised Protocol 03	09-Apr-2019	This revision removes PFS as a co-primary objective and endpoint and adds OS in PD-L1 positive (≥ 1%) as a primary population, adds 100 cisplatin-ineligible participants to the primary study, and revises the timing of the OS interim analysis for the primary study. The timing of the interim analysis for the substudy is revised as well.
Administrative Letter 09	06-Aug-2018	The purpose is to update nivolumab dosing information in revised protocol 02 to be consistent with Investigator Brochure v17; to align Section 7.1.3.1 with Tables 2.4 and 2.5 with respect to allowing additional cycles of gemcitabine if local practice and to address a typographical error.

Document	Date of Issue	Summary of Change
Administrative Letter 03	14-Sep-2017	This letter serves to update Study Director information, clarify statements in the protocol to ensure alignment across the protocol sections and correct typographical errors within the current CA209901 Revised Protocol 02.
Administrative Letter 01	10-Jul-2017	A typographical error was discovered in an exploratory endpoint for PD-L1 expression in the substudy in Revised Protocol 02 for Study CA209901. The investigational treatment to be assessed in this substudy is "nivolumab combined with SOC chemotherapy", not "nivolumab combined with ipilimumab."
Revised Protocol 02	21-Apr-2017	Incorporates Amendment 03
Amendment 03	21-Apr-2017	1. Added substudy, Arms C and D. 2. Updated tumor tissue requirement 3. Updated treatment duration to 24 months 4. Section added regarding BICR assessments 5. Appendix 3, RECIST criteria updated.
Amendment 02	21-Apr-2017	Country specific amendment
Revised Protocol 01	19-Dec-2016	Incorporated Amendment 01
Amendment 01	19-Dec-2016	1. Added procedures to be collected on Day 8 (prior to gemcitabine dosing) 2. Added details regarding requests for optional archive tissue sample (radical cystectomy) 3. Revised renal function criteria for cisplatin-eligible participants. 4. Added Appendix 9 for country specific requirements for Germany 5. Additional clarifications for consistency throughout.
Original Protocol	14-Nov-2016	Not Applicable

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 05:

This amendment updates the substudy final analysis strategy to be overall survival (OS) events-driven, with the progression free survival (PFS) final analysis being conducted at the same time as the OS final analysis based on the available PFS events at that time (time-driven).

This change is being made due to the actual substudy PFS event rate being lower than initially anticipated with a projected delay of approximately 3 years. This is mainly due to the high percentage of subjects censored for PFS. The reason for censoring was mainly due to subsequent anti-cancer therapy prior to progression. This high percentage of censoring is related to the treatment landscape change for this patient population during the conduct of this study with the introduction of avelumab maintenance therapy after initial platinum-based chemotherapy.

Therefore, it is not possible for the originally planned number of PFS events to be reached simultaneously with the planned number of at least 356 OS events as currently specified for the final analysis in the protocol. Thus, this amendment will allow for the final analysis for OS and PFS to occur after only the required number of OS events have been reached in the substudy.

This amendment incorporates the changes from the approved Administrative Letter 16, which are detailed in the Document History, but not listed in the Summary of Key Changes below.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 05		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 10.1.3.1: Progression Free Survival	Updated description of progression free survival (PFS) statistical analysis and added PFS power table corresponding to the expected number of PFS events at the time of final OS analysis.	To align with the updated substudy final analysis testing strategy. Only general power estimates are kept in the updated sentences.
Section 10.1.3.2: Overall Survival	Updated numbers of cure fraction for Arm C and Arm D from 0.20 to 0.234 and 0.234 to 0.20, respectively.	To update a mismatch of the cure rates in the protocol.
Section 10.1.4: Analysis Timing Projections Table 10.1.4-1: Populations and Projected Timing for Analysis of Primary Endpoints: Primary Study and Secondary Study	Added description of substudy OS and PFS final analysis. In Table 10.1.4-1: • For the Substudy OS and PFS (Final Analysis) endpoint, changed the criterion from "At least 460 PFS and 356 OS events" to "At least 356 OS events."	To align with the updated substudy final analysis testing strategy. In Table 10.1.4-1: • To align with the updated substudy final analysis testing strategy.
Appendix 8	Updated text for investigator oversight in subsection: Institutional Review Board/Independent Ethics Committee.	For clarification.
	Added additional requirements in Informed Consent Process subsection.	Clarified the investigator's obligations in the informed consent process.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 05		
Section Number & Title	**Description of Change**	**Brief Rationale**
	Added new sections: BMS Commitment to Diversity in Clinical Trials and Data Protection, Data Privacy, and Data Security.	Added to align with BMS commitment to diversity in clinical trials and to comply with European Union Clinical Trials Regulation (EU-CTR) requirement.
	Updated text for Source Documents.	Clarified definition of source data.
	Updated first paragraph to Case Report Forms subsection.	Updated description of terms “participant” and “subject.”
	Updated description of monitoring plan in Monitoring subsection.	The COVID-19 pandemic resulted in the need to revise site monitoring language to specifically allow for remote monitoring.
	Defined duration of records storage within Records Retention subsection.	Clarified duration of records storage.
	Added instructions for partially used study interventions/empty containers within Return of Study Treatment subsection.	Clarified instructions for study intervention reconciliation and disposal.
	Added new sections for Study and Site Closure and Dissemination of Clinical Study Data.	To define study and site closure and describe BMS policy for dissemination of study data.
All	Minor formatting and typographical corrections.	Minor, therefore not been summarized.

TABLE OF CONTENTS

1 SYNOPSIS

Protocol Title: A Phase 3, Open-label, Randomized Study of Nivolumab Combined with Ipilimumab, or with Standard of Care Chemotherapy, versus Standard of Care Chemotherapy in Participants with Previously Untreated Unresectable or Metastatic Urothelial Cancer

(CheckMate 901: CHECKpoint pathway and nivolu**MA**b clinical **T**rial **E**valuation **901)**

Study Phase: Phase 3

Rationale:

Urothelial carcinoma (UC) of the bladder is the ninth most common cancer in the world, and the fifth most common malignancy in the United States. Approximately 20% to 25% of all patients with UC of the bladder develop metastatic disease, resulting in an estimated 15,580 deaths in 2014 in the US.

Cisplatin is among the most active agents in urothelial carcinoma and cisplatin-based combination chemotherapy is the treatment of choice for patients with metastatic urothelial bladder cancer. Of the commonly used regimens such as gemcitabine plus cisplatin or MVAC (methotrexate, vinblastine, doxorubicin, plus cisplatin) gemcitabine and cisplatin treatment was associated with a better safety profile and improved tolerability and has become a standard regimen for patients with metastatic UC.

Management guidelines therefore support the use of cisplatin-based regimens in the treatment of unresectable or metastatic UC.[1,2] However, in clinical practice, more than 50% of all patients with unresectable or metastatic UC have contraindications for treatment with cisplatin. Renal dysfunction (usually defined as a creatinine clearance of < 60 ml/minute), poor performance status and advanced age are relatively common and preclude cisplatin chemotherapy. While no standard treatment has been defined for cisplatin-unfit patients, carboplatin-containing regimens are considered appropriate alternatives vs cisplatin-based therapy, based on performance status and kidney function defined by glomerular filtration rate (GFR).

Although the combination of gemcitabine plus carboplatin is commonly used in cisplatin-ineligible patients, to date, combination regimens that do not include cisplatin have never been shown to improve survival. Median survival with gemcitabine plus carboplatin in cisplatin-ineligible subjects is only 8 to 9 months either due to lower efficacy of carboplatin compared with cisplatin or due to these patients' lower state of general health. In fact, patients who are not candidates for cisplatin-containing chemotherapy regimens have significantly worse outcomes with regard to response to treatment and overall survival (OS), and there is no consensus on the standard chemotherapy treatment for cisplatin-unfit patients.

Despite the initial chemosensitivity of UC of the bladder, responses generally are short-lived; the median survival of patients with metastatic disease is approximately 14 months. Visceral metastases and poor performance status are adverse prognostic factors associated with a lower likelihood of response to chemotherapy and shorter survival.

While the tolerability of treatment has improved over the past 30 years, improvement in efficacy has not kept pace, underscoring the urgent need for novel approaches in the treatment of metastatic UC of the bladder. Optimally, novel agents with improved efficacy and tolerability may eliminate the need to evaluate patients with metastatic bladder cancer in separate cisplatin-eligible and cisplatin-ineligible cohorts in the future.

Research Hypothesis for the Primary Study: The study aims to demonstrate that treatment with nivolumab combined with ipilimumab will improve efficacy in cisplatin-ineligible participants with previously untreated unresectable or metastatic UC.

Research Hypothesis for Substudy

The study aims to demonstrate that treatment with nivolumab combined with SOC chemotherapy will improve efficacy in cisplatin-eligible participants with previously untreated, unresectable or metastatic UC.

Study Population: Males and females, age ≥ 18 years, with previously untreated unresectable or metastatic UC are eligible for inclusion. Eligible subjects may either have de novo unresectable or metastatic UC, or previously diagnosed localized muscle invasive bladder cancer (MIBC) with radical cystectomy and treatment with chemotherapy in the neo-adjuvant or adjuvant setting following radical cystectomy, who experience progression ≥ 12 months following chemotherapy.

Key Inclusion/Exclusion

Inclusion:

- Histological or cytological evidence of metastatic or surgically unresectable transitional cell carcinoma (TCC) of the urothelium involving the renal pelvis, ureter, bladder or urethra. Minor histologic variants (< 50% overall) are acceptable (TCC must be the dominant histology). Measurable disease by CT or MRI per RECIST 1.1 criteria.
- No prior systemic chemotherapy for metastatic or surgically unresectable UC with the following exceptions: (i) Prior intravesical therapy completed at least greater than 4 weeks prior to the initiation of study treatment. (ii) Prior neoadjuvant chemotherapy, radiation or prior adjuvant platinum-based chemotherapy following radical cystectomy with recurrence ≥ 12 months from completion of therapy.
- Cisplatin-ineligible participants will be defined by any one of the following criteria:[3]
  i. Impaired renal function
  ii. Common Terminology Criteria for Adverse Events (CTCAE) version 4, ≥ Grade 2 audiometric hearing loss
  iii. CTCAE version 4, ≥ Grade 2 peripheral neuropathy

  Participants eligible for Cisplatin-based chemotherapy must exhibit adequate renal function
- Participants must have an evaluable tumor tissue (fresh biopsy [within 2 years]) prior to enrollment period. In order to be treated, a participants must be classified as PD-L1 ≥ 1% or PD-L1 < 1% as determined by a central laboratory during the screening period.

- Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0 or 1. See Appendix 2 for ECOG Performance Status scale
- Adequate hematologic and liver function

Exclusion

- ECOG PS ≥ 2
- Disease that is suitable for local therapy administered with curative intent.
- Active brain metastases or leptomeningeal metastases
- Active, known or suspected autoimmune disease
- Participants may not have received live/attenuated vaccines within 30 days prior to first study treatment.

Objectives and Endpoints:

Table 1: Objectives and Endpoints: Primary Study

Objectives	Endpoints
Primary	
• To compare Overall Survival (OS) of nivolumab combined with ipilimumab versus standard of care (SOC) chemotherapy in cisplatin-ineligible participants with previously untreated, unresectable or metastatic urothelial carcinoma (UC).	• Primary endpoint of OS in cisplatin-ineligible randomized participants
• To compare OS of nivolumab combined with ipilimumab versus standard of care (SOC) chemotherapy in PD-L1 positive (≥ 1%) participants with previously untreated, unresectable or metastatic UC.	• Primary endpoint of OS in PD-L1 positive (≥ 1%) randomized participants by immunohistochemistry (IHC)
Secondary	
• To compare OS of nivolumab combined with ipilimumab versus SOC chemotherapy in all randomized participants with previously untreated, unresectable or metastatic UC.	• OS in all randomized participants
• To evaluate Progression-Free Survival (PFS) of nivolumab combined with ipilimumab versus SOC chemotherapy in cisplatin-ineligible randomized participants, in PD-L1 positive (≥1%) randomized participants and in all randomized participants with previously untreated, unresectable or metastatic UC.	• PFS by blinded independent central review (BICR) (using RECIST 1.1) in cisplatin-ineligible randomized participants, in PD-L1 positive (≥1%) randomized participants and in all randomized participants
• To evaluate changes from baseline in Health-Related QOL (HRQoL) of nivolumab combined with ipilimumab versus SOC chemotherapy in all randomized participants with previously untreated, unresectable or metastatic UC.	• European Organisation for Research and Treatment of Care (EORTC) QLQ-C30 Global Health Status score in all randomized participants

Table 1: Objectives and Endpoints: Primary Study

Objectives	Endpoints
Exploratory	
• To estimate objective response rate (ORR) (using RECIST 1.1) of nivolumab combined with ipilimumab versus SOC chemotherapy.	• ORR by BICR (using RECIST 1.1)
• To assess the efficacy (OS, PFS, and ORR) of nivolumab combined with ipilimumab versus SOC chemotherapy in cisplatin-eligible participants with previously untreated,	• OS, PFS, and ORR by BICR (using RECIST 1.1) in cisplatin-eligible participants with previously untreated, unresectable or metastatic UC
• To assess the safety and tolerability of nivolumab combined with ipilimumab versus SOC chemotherapy.	• AEs, clinical laboratory values, vital signs, or other safety biomarkers
• To assess changes in reported global health outcomes based on EuroQol's EQ-5D-5L.	• EQ-5D-5L index score, EQ-5D-5L dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety), and EQ-5D-5L visual analog scale (VAS).
• To evaluate HRQoL as assessed by EORTC QLQ-C30.	• QLQ-C30 Functional scales; QLQ-C30 Symptom scales
• To evaluate whether PD-L1 expression is a predictive biomarker of efficacy (ORR) of nivolumab combined with ipilimumab as first-line therapy in participants with previously untreated, unresectable or metastatic UC.	• ORR by BICR (using RECIST 1.1) by PD-L1 expression at ≥ 1% expression by immunohistochemistry (IHC)
• To characterize the pharmacokinetics of nivolumab combined with ipilimumab as first-line therapy in participants with previously untreated, unresectable or metastatic UC.	• PK parameters, exposure-response relationship between select PK measures of exposure and safety and efficacy endpoints, if applicable
• To characterize the immunogenicity of nivolumab combined with ipilimumab as first-line therapy in participants with previously untreated, unresectable or metastatic UC.	• Incidence of anti-nivolumab and anti-ipilimumab antibody levels and their potential relationship with safety and efficacy endpoints
• To evaluate the pharmacodynamic and immunomodulatory activity of nivolumab combined with ipilimumab.	• Including but not limited to correlative analyses between gene expression profiling, flow cytometric analyses of peripheral blood mononuclear cells (PBMCs), myeloid derived suppressor cells and serum soluble factor analysis in peripheral blood samples and ORR, PFS, and OS
• To investigate the association between biomarkers in the peripheral blood and tumor tissue with efficacy.	• Including but not limited to correlative analyses between baseline and on-treatment soluble factors (eg, CXCL9, CXCL10, gamma interferon signature, baseline PD-L1/PD-L2, mutational analyses in tumor tissue) with ORR, PFS, and OS

Table 2: Objectives and Endpoints: Substudy

Objectives	Endpoints
Primary	
• To compare PFS of nivolumab combined with SOC chemotherapy versus SOC chemotherapy in cisplatin-eligible participants with previously untreated, unresectable or metastatic urothelial carcinoma (UC)	• PFS by BICR (using RECIST 1.1) in cisplatin-eligible participants with previously untreated, unresectable or metastatic UC
• To compare OS of nivolumab combined with SOC chemotherapy versus SOC chemotherapy in cisplatin-eligible participants with previously untreated, unresectable or metastatic UC	• OS in cisplatin-eligible participants with previously untreated, unresectable or metastatic UC
Secondary	
• To evaluate changes from baseline in Health-Related QOL (HRQoL) of nivolumab combined with SOC chemotherapy versus SOC chemotherapy in cisplatin-eligible participants with previously untreated, unresectable or metastatic UC.	• European Organisation for Research and Treatment of Care (EORTC) QLQ-C30 Global Health Status score
• To evaluate whether PD-L1 expression is a predictive biomarker of efficacy (PFS and OS) of nivolumab combined with SOC chemotherapy as first-line therapy in cisplatin-eligible participants with previously untreated, unresectable or metastatic UC.	• PFS by BICR (using RECIST 1.1) and OS by PD-L1 expression at ≥ 1% expression by immunohistochemistry (IHC)
Exploratory	
• To estimate ORR (using RECIST 1.1) of nivolumab combined with SOC chemotherapy versus SOC chemotherapy.	• ORR by BICR (using RECIST 1.1)
• To assess the safety and tolerability of nivolumab combined with SOC chemotherapy versus SOC chemotherapy.	• AEs, clinical laboratory values, vital signs, or other safety biomarkers
• To assess changes in reported global health outcomes based on EuroQol's EQ-5D-5L.	• EQ-5D-5L index score, EQ-5D-5L dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety), and EQ-5D-5L VAS.
• To evaluate HRQoL as assessed by EORTC QLQ-C30.	• QLQ-C30 Functional scales; QLQ-C30 Symptom scales
• To evaluate whether PD-L1 expression is a predictive biomarker of efficacy (ORR) of nivolumab combined with SOC chemotherapy as first-line therapy in participants with previously untreated, unresectable or metastatic UC.	• ORR by BICR (using RECIST 1.1) by PD-L1 expression at ≥ 1% expression by immunohistochemistry (IHC)
• To characterize the pharmacokinetics of nivolumab combined with SOC chemotherapy as first-line therapy in participants with previously untreated, unresectable or metastatic UC.	• PK parameters, exposure-response relationship between select PK measures of exposure and safety and efficacy endpoints, if applicable

Table 2: Objectives and Endpoints: Substudy

Objectives	Endpoints
• To characterize the immunogenicity of nivolumab combined with SOC chemotherapy as first-line therapy in participants with previously untreated, unresectable or metastatic UC.	• Incidence of anti-nivolumab antibody levels and their potential relationship with safety and efficacy endpoints
• To evaluate the pharmacodynamic and immunomodulatory activity of nivolumab combined with SOC chemotherapy.	• Including but not limited to correlative analyses between gene expression profiling, flow cytometric analyses of PBMCs, myeloid derived suppressor cells and serum soluble factor analysis in peripheral blood samples and ORR, PFS, and OS
• To investigate the association between biomarkers in the peripheral blood and tumor tissue with efficacy.	• Including but not limited to correlative analyses between baseline and on-treatment soluble factors (eg, CXCL9, CXCL10, gamma interferon signature, baseline PD-L1/PD-L2, mutational analyses in tumor tissue) with ORR, PFS, and OS

Overall Design: This will be a randomized, open-label, Phase 3 study comparing combination therapy of nivolumab (1 mg/kg 30 minute IV infusion) plus ipilimumab (3 mg/kg 30 minute IV infusion) administered every 3 weeks for up to four doses, followed by nivolumab monotherapy (480 mg 30 minute IV infusion) administered every 4 weeks, versus the standard of care (SOC; gemcitabine-cisplatin or gemcitabine-carboplatin) in participants with previously untreated unresectable or metastatic UC.

In addition a substudy of treatment with nivolumab 360 mg in combination with SOC (cisplatin-gemcitabine) every 3 weeks for up to 6 cycles followed by nivolumab monotherapy (480 mg every 4 weeks) versus SOC alone (up to 6 cycles) will be evaluated in cisplatin-eligible participants with previously untreated unresectable or metastatic UC.

Primary Study:

Prior to initiation of the substudy, participants will be randomized 1:1 to treatment Arm A or B and stratified by PD-L1 status < 1%, cisplatin-eligibility, and liver metastasis.

- Arm A (nivolumab 1 mg/kg plus ipilimumab 3 mg/kg [N1 + I3], followed by nivolumab monotherapy)
- Arm B (standard of care [SOC] platinum chemotherapy doublet, 3 week cycles, up to 6 cycles).

Participants in Arm A will receive combination therapy (N1+I3) for up to 4 doses (Part 1), followed by nivolumab monotherapy (480 mg every 4 weeks; Part 2). Monotherapy will begin 6 weeks following the last dose of combination therapy and continue until confirmed disease progression, unacceptable toxicity, or participant withdrawal of consent, or 24 months, whichever comes first. Participants randomized to Arm B, may receive SOC treatment (6 cycles of

gemcitabine/cisplatin) or gemcitabine/carboplatin (only cisplatin-ineligible participants). Participants in Arm B will receive up to 6 cycles of SOC chemotherapy.

In Part 1 of Arm A, a minimum of 1 combination cycle of nivolumab and ipilimumab is required before participants can proceed to monotherapy. Participants in Arm A experiencing AEs related to combination dose therapy that do not meet dose discontinuation criteria, may proceed to nivolumab monotherapy dosing (Part 2) without completing all 4 combination doses, after consultation with BMS Medical Monitor, on a case-by-case basis. In Arm B, participants assigned to receive cisplatin-gemcitabine, may be eligible to switch to carboplatin-gemcitabine following a minimum of 1 cycle of cisplatin-gemcitabine, and after consultation with the medical monitor.

Substudy

Once the substudy begins (following IRT configuration), cisplatin-eligible participants will be randomized across Arms A through D, and stratified by PD-L1 status < 1%, cisplatin-eligibility, and liver metastasis. Cisplatin-ineligible participants will continue to be randomized 1:1 to Arms A or B.

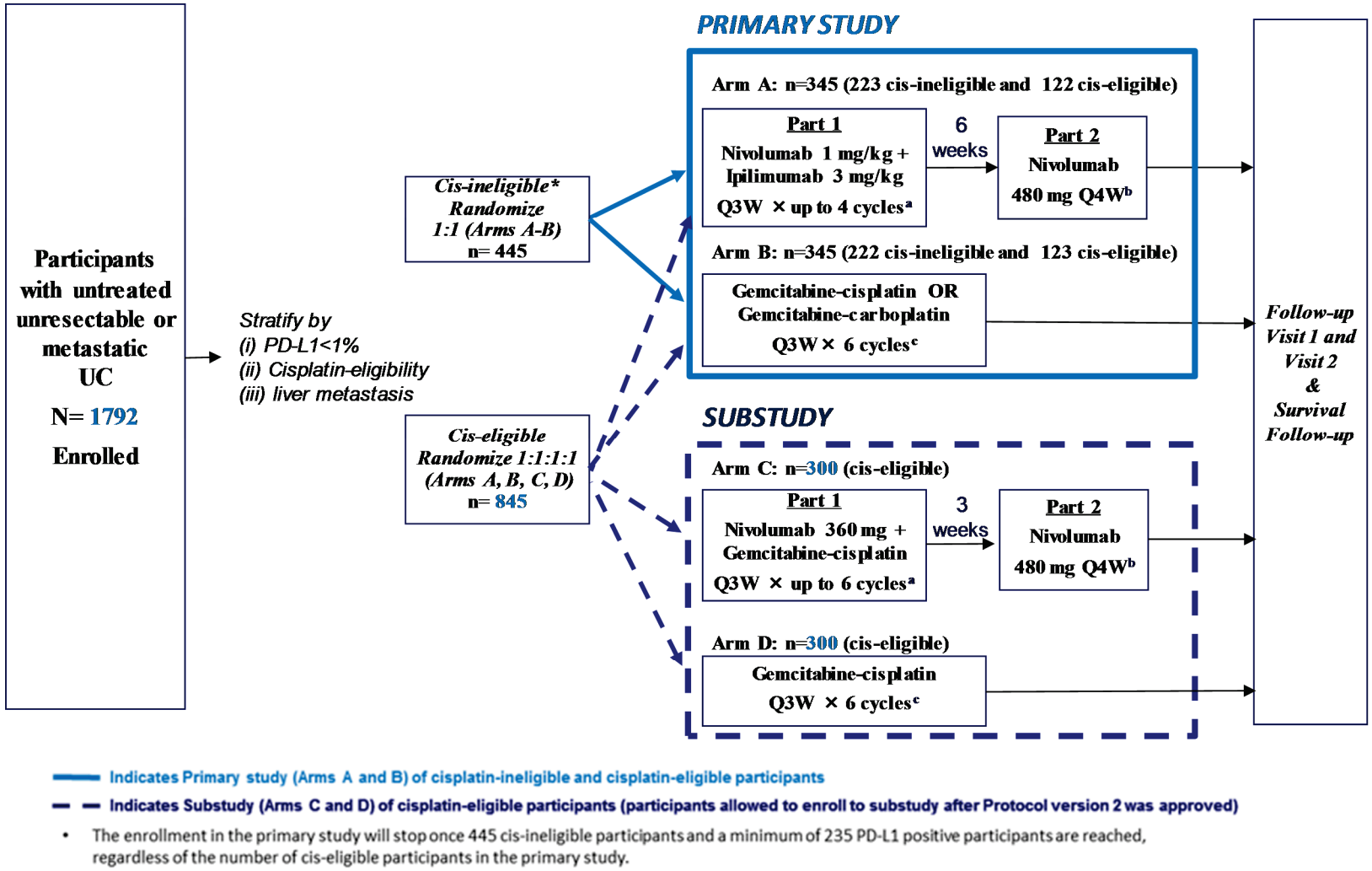
The substudy consists of Arms C and D:

- Arm C: Nivolumab (360 mg + Gemcitabine-cisplatin) every 3 weeks for up to 6 cycles, followed by nivolumab monotherapy (480 mg) every 4 weeks. Monotherapy will begin 3 weeks following the last dose of combination therapy and continue until confirmed disease progression, unacceptable toxicity, or participant withdrawal of consent, or 24 months, whichever comes first.
- Arm D: Gemcitabine- cisplatin for 6 cycles.

Once at least 445 cisplatin-ineligible participants and 235 PD-L1 positive (≥ 1%) participants are enrolled, enrollment of the primary study (Arms A and B) will stop (see Section 10.1). Only cisplatin-eligible will continue to be enrolled into the substudy (Arms C and D).

The study design schematic is presented in Figure 1.

Figure 1: Study Design Schematic



[a] Arm A and Arm C: In Part 1, a minimum of 1 cycle of combination therapy is required before proceeding to nivolumab monotherapy dosing (Part 2). Participants should be dosed no less than 19 days between combination treatment cycles (Arm A),

[b] **In Arm A, monotherapy should begin 6 weeks following the last combination dose. In Arm C, monotherapy will begin 3 weeks following the last combination therapy.** During monotherapy participants should be dosed no less than 26 days between monotherapy treatments. Participants in Arms A and C will be treated until confirmed progression of disease, unacceptable toxicity, withdrawal of consent, or up to 24 months of treatment, whichever occurs first.

[c] Arms B and D participants will receive up to a maximum of 6 cycles per protocol. Additional optional cycles of SOC may be given per local guidelines. See Section 7.1.3.1.

NOTES: All participants will be randomized 1:1 to Arms A or B during the primary study, prior to substudy initiation. Following initiation of the substudy, cisplatin-eligible patients will be randomized to Arms A, B, C or D. Cisplatin-ineligible patients are not eligible for Arms C and D treatment.

Once at least 445 cisplatin-ineligible participants and at least 235 PD-L1 positive (≥ 1%) participants by IHC are enrolled into Arms A or B of the primary study, the primary study will cease enrollment (Arms A and B). Cisplatin-eligible participants will continue enrollment into Arms C and D.

Randomized participants will be evaluated for progression beginning at Week 9 (± 1 week) and then every 8 weeks (± 1 week) for 48 weeks, followed by evaluations every 12 weeks thereafter, until progression or end of treatment, whichever occurs later.

Primary endpoints in the primary study: Overall Survival in cisplatin-ineligible participants and in PD-L1 positive (≥ 1%) participants by IHC; key secondary endpoint: Overall Survival in all randomized participants (hierarchical testing procedure) and Progression Free Survival.

Primary endpoints in the substudy: Progression Free Survival and Overall Survival in cisplatin-eligible participants.

Number of Participants:

Approximately 1290 previously untreated unresectable or metastatic UC participants will be randomized:

- 445 cisplatin-ineligible participants will be randomized in a 1:1 ratio to receive nivolumab plus ipilimumab vs SOC chemotherapy;
- 245 cisplatin-eligible participants will be randomized in a 1:1 ratio to receive nivolumab plus ipilimumab vs SOC chemotherapy;
  - Of these 690 primary study participants, 235 PD-L1 positive (≥ 1%) participants by IHC are expected to be randomized
- 600 cisplatin-eligible participants will be randomized in a 1:1 ratio to receive nivolumab plus SOC chemotherapy vs SOC chemotherapy.

Overall, approximately 445 cisplatin-ineligible participants (per eligibility criteria see Section 6.1) and 545 cisplatin-eligible participants will be randomized. Enrollment assumptions are a fixed accrual rate of 5 participants per month (2 cisplatin-ineligible participants per month) during the first 6 months, 14 participants per month (8 cisplatin-ineligible participants per month) between 6 and 12 months, and 30 participants per months between 12 and 18 months (19 cisplatin-ineligible participants per month) and 37 participants per months thereafter (26 cisplatin-ineligible participants per month). In addition, as of month 11, cisplatin-eligible participants are equally randomized to both primary study and substudy. Therefore once enrollment in the primary study is closed, the accrual rate in the substudy is assumed to be 21 cisplatin-eligible participants per month.

Assuming a 28% screen failure rate, it is estimated that approximately 1792 participants will be enrolled in order to have 445 cisplatin-ineligible participants randomized in the primary study and 600 cisplatin-eligible participants randomized in the sub study.

Treatment Arms and Duration:

Participants in Arm A (combination therapy [N1+I3], followed by nivolumab monotherapy) will be treated until confirmed progression of disease, unacceptable toxicity, withdrawal of consent, or up to a maximum of 24 months, whichever comes first.

Participants in Arm B or Arm D will be treated until confirmed progression of disease, unacceptable toxicity, withdrawal of consent, or up to 6 cycles of SOC therapy, whichever occurs first.

Participants in Arm C will be treated with up to 6 cycles of nivolumab (360 mg) in combination with gemcitabine-cisplatin. Beginning 3 weeks following the last dose of combination therapy, participants will be treated with nivolumab monotherapy (480 mg Q4W) until confirmed progression of disease, unacceptable toxicity, withdrawal of consent, or up to a maximum of 24 months, whichever comes first.

Study treatment:

Study Drug for CA209901		
Medication	**Potency**	**IP/Non-IP**
BMS-936558-01 (Nivolumab) Solution for Injection[a]	100 mg (10 mg/mL)	IP
Ipilimumab Solution for Injection	200 mg (5 mg/mL)	IP
Carboplatin Solution for Injection	450 mg/vial (10 mg/mL)[b]	IP
Gemcitabine Powder for Solution for Infusion	1000 mg/vial[b]	IP
Cisplatin	100 mg/vial (1 mg/mL)[b]	IP

[a] May be labeled as either "BMS-936558-01" or "Nivolumab".

[b] These products may be obtained by the investigational sites as local commercial product in certain countries if allowed by local regulations. In these cases, products may be a different pack size/potency than listed in the table. These products should be prepared/stored/administered in accordance with the package insert or summary of product characteristics (SmPC).

REFERENCES

1 Witjes JA, Comperat E, Cowan NC, De Santis M et al. Guidelines on muscle-invasive and metastatic bladder cancer. EAU European Association of Urology 2014, www.uroweb.org.

2 NCCN Clinical Practice guidelines in Oncology. Bladder Cancer Version 2.2014. www.nccn.org.

3 Galsky MD, Hahn NM, Rosenberg J, et al. A consensus definition of patients with metastatic urothelial carcinoma who are unfit for cisplatin-based chemotherapy. Lancet Oncol. 2011 Mar;12(3):211-4.

2 SCHEDULE OF ACTIVITIES

Table 2-1: Screening Procedural Outline for All Participants (CA209901)

Procedure	Screening Visit (within 45 days)[a]	Notes
Informed Consent	X	Must be obtained prior to performing any screening procedures. Register in Interactive Response system to obtain participant number. Study allows for re-enrollment of a participant that has discontinued the study as a pre-treatment failure. If re-enrolled, the participant must be re-consented and assigned a new participant number from IRT.
Inclusion/Exclusion Criteria	X	Assessed during screening period and (re-enrollment if applicable). Must be confirmed prior to randomization
Medical History	X	
Previous anti-cancer treatment	X	Includes chemotherapy, radiotherapy, surgery, intravesical BCG, targeted therapy
Assessment of Signs and Symptoms	X	Within 14 days prior to randomization
Physical Examination, Measurements, Vital Signs and ECOG Performance Status	X	Height, weight, and ECOG Performance Status (Appendix 2), and hearing assessment (per local standard of care) within 14 days prior to randomization. BP, HR, temperature at screening and within 72 hours prior to first dose.
Serious Adverse Event Assessment	X	Serious Adverse Events from time of consent. See Section 9.2 and Appendix 3
Laboratory Tests	X	Must be performed within 14 days prior to randomization CBC w/differential; Chemistry panel including: AST, ALT, ALP, total bilirubin, blood urea nitrogen (BUN) or serum urea level, creatinine, phosphate, Ca, Na, K, Cl, Mg, LDH, glucose, albumin, amylase, lipase Thyroid panel including TSH, Free T4, Free T3 (if not available, total T3 and T4 acceptable) Hepatitis B/C (HBV sAG, HCV antibody or HCV RNA) (sites in Germany see Appendix 9)
Chemotherapy eligibility	X	Local evaluation of participant status for cisplatin treatment must be determined before randomization
ECG	X	Within 14 days prior to randomization

Table 2-1: Screening Procedural Outline for All Participants (CA209901)

Procedure	Screening Visit (within 45 days)[a]	Notes
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 treatment.
Concomitant Medication Collection	X	Within 14 days prior to randomization
Tumor Tissue Sample	X	Participants must have PD-L1 status from immunohistochemistry (IHC) testing performed by the central laboratory during the screening period. Results may take up to 14 days. Sufficient tumor tissue must be obtained and sent to central laboratory (tissue block or a minimum of 15 formalin-fixed, paraffin-embedded (FFPE) slides, obtained from core biopsy, punch biopsy, excisional biopsy or surgical specimen). Participants must provide a fresh tumor biopsy from the primary disease site or a metastatic site. If fresh tissue cannot be provided, a tissue block (or at least 15 FFPE slides) from the latest surgical resection (eg, radical cystectomy) can be accepted if collected within 2 years prior to enrollment period and the participant did not receive systemic anticancer agents or radiotherapy (except prior to palliative radiotherapy) since collection of sample. Samples received must be suitable for testing to verify PD-L1 status. For exploratory purposes, an additional block of archival tissue (or 15 FFPE slides) from prior radical cystectomy (if available) will be requested.

Table 2-1: Screening Procedural Outline for All Participants (CA209901)

Procedure	Screening Visit (within 45 days)[a]	Notes
Tumor Assessment	X	CT with IV contrast of the chest/abdomen/pelvis and all other known/suspected sites of disease should be imaged during the screening period. If CT iodinated contrast is contraindicated, a non-contrast CT of the chest and contrast enhanced MRI abdomen and pelvis and all other known or suspected sites of disease should be imaged (See Section 7.7.3.1). MRI of brain with and without gadolinium is required to rule out brain metastases (CT with or without contrast acceptable if prohibited for medical reasons). RECIST 1.1 criteria (Appendix 4) Radiographic tumor assessment must be performed within 28 days prior to randomization.
Contact IRT	X	IRT contact must occur as follows: For participant number assignment at the time informed consent is obtained. Participant must receive the first dose of study medication within 3 days from randomization.

Note: 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.

[a] Screening assessments must be completed ≤ 45 days of signing ICF (or within the timeframes as specified in the table).

Table 2-2: On Treatment Procedural Outline for Arm A, Part 1: Ipilimumab/Nivolumab Combination Treatment (CA209901)

Procedure	Day 1 of each cycle[a] (Q3 weeks for 4 cycles)	Notes: If a dose is delayed, the procedures scheduled for that same time point should also be delayed to coincide with when that time point's dosing actually occurs (with the exception of tumor assessments, which should occur as scheduled).
Safety Assessments		
Review of Concomitant Medications	Continuously	Record at each visit.
Targeted Physical Examination, Physical Measurements, Vital Signs, ECOG Performance Status	X	Weight, BP, HR, temperature and Performance Status Obtain vital signs within 72 hours prior to dosing
Serious Adverse Events Assessment	Continuously	Adverse events will be graded according to the NCI-CTCAE version 4.
Adverse Events Assessment	Continuously	Adverse events will be graded according to the NCI-CTCAE version 4.
Laboratory Tests	X	On site/ local laboratory testing should be done within 72 hours prior to each dose. For the first dose visit, labs need not be repeated if they were preformed within 72 hours and the results are available and have been reviewed for eligibility. CBC w/differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, phosphate, glucose, and albumin if clinically indicated) Thyroid Function Testing (TSH with reflexive free T3 and free T4 if TSH is abnormal, if free T3 and free T4 are not available then Total T3 and Total T4 are acceptable), to be evaluated every 3 weeks during combination cycle (see Section 9.4)
Pregnancy Test (WOCBP only)	X	Serum or urine within 24 hours prior to first dose and then every 4 weeks (± 1 week) regardless of dosing schedule.
Patient Reported Outcomes Assessment		
EORTC QLQ-C30	See notes	Assessed following randomization but prior to dosing on C1D1, and prior to dosing on C2D1 and C4D1.
EQ-5D-5L	See notes	Assessed following randomization but prior to dosing on C1D1, and prior to dosing on C2D1 and C4D1.

Table 2-2: On Treatment Procedural Outline for Arm A, Part 1: Ipilimumab/Nivolumab Combination Treatment (CA209901)

Procedure	Day 1 of each cycle[a] (Q3 weeks for 4 cycles)	Notes: If a dose is delayed, the procedures scheduled for that same time point should also be delayed to coincide with when that time point's dosing actually occurs (with the exception of tumor assessments, which should occur as scheduled).
Efficacy Assessments		
Tumor Assessment	See notes	Tumor assessments will occur on Week 9 (± 1 week) and then every 8 weeks (± 1 week). After 48 weeks, tumor assessments will occur every 12 weeks (± 1 week). Post-baseline tumor assessments will continue until progression is assessed by the investigator **and** confirmed by BICR or treatment is discontinued (whichever occurs later). CT with IV contrast of the chest, abdomen, pelvis and all other known or suspected sites of disease should be imaged. If CT iodinated contrast is contraindicated, a non-contrast CT of the chest and contrast enhanced MRI abdomen, pelvis and all other known or suspected sites of disease should be imaged. (See Section 7.7.3.1). Use same imaging method as was used at screening/baseline. Participants with a history of brain metastasis should have surveillance MRI with and without gadolinium approximately every 12 weeks, or sooner if clinically indicated. (CT with or without contrast acceptable if prohibited for medical reasons). If a dose is delayed, the tumor assessments should occur as scheduled.
Pharmacokinetic /Immunogenicity Assessments		
PK samples	X	See Table 9.5-1 and Table 9.5-2
Immunogenicity blood samples	X	See Table 9.5-1 and Table 9.5-2
Biomarker Assessments		
Serum sample: Soluble Biomarkers	X	See Table 9.8-1
Whole Blood Sample (SNP)	X	See Table 9.8-1
Whole Blood Sample (Gene Expression)	X	See Table 9.8-1

Table 2-2: On Treatment Procedural Outline for Arm A, Part 1: Ipilimumab/Nivolumab Combination Treatment (CA209901)

Procedure	Day 1 of each cycle[a] (Q3 weeks for 4 cycles)	Notes: If a dose is delayed, the procedures scheduled for that same time point should also be delayed to coincide with when that time point's dosing actually occurs (with the exception of tumor assessments, which should occur as scheduled).
Myeloid Derived Suppressor Cells (MDSC)	X	See Table 9.8-1
Peripheral Blood Mononuclear Cells (PBMCs)	X	See Table 9.8-1
ctDNA	X	See Table 9.8-1
Collection of tumor tissue for biomarker research upon disease progression and at C2D15	X	Tumor tissue submission during Cycle 2 (C2D15) and after progression, is highly recommended, but optional. Biopsy is not required per protocol. See Table 9.8-1
Clinical Drug Supplies		
IRT Drug Vial Assignment	X	
Dispense Study Drug	X	Nivolumab 1 mg/kg (30 min IV) and ipilimumab 3mg/kg (30 min IV) Q3 weeks for up to 4 doses.[a] The dosing calculations should be based on the body weight. If the participant's weight on the day of dosing differs by > 10% from weight used to calculate the previous dose, the dose must be recalculated. All doses should be rounded to the nearest milligram.

[a] Nivolumab and Ipilimumab Combination Therapy, 1 cycle = 3 weeks. Participants should be dosed no less than 19 days from previous dose in Part 1 of Arm A. Participants will receive up to 4 doses of combination treatment and then switch to nivolumab monotherapy treatment (to begin 6 weeks following the last combination dose received. Participants in Arm A experiencing AEs related to combination dose therapy (Part 1) that do not meet dose discontinuation criteria, may proceed to nivolumab monotherapy dosing (Part 2) without completing all 4 combination doses, after consultation with BMS Medical Monitor, on a case-by-case basis.

Table 2-3: On Treatment Procedural Outline for Arms A and C, Part 2 Nivolumab Monotherapy Treatment (CA209901)

Procedure	Day 1 of each cycle (Q4 weeks)[a]	Notes: If a dose is delayed, the procedures scheduled for that same time point should also be delayed to coincide with when that time point's dosing actually occurs (with the exception of tumor assessments, which should occur as scheduled).
Safety Assessments		
Review Concomitant Medications	Continuously	Record at each visit
Targeted Physical Examination, Physical Measurements, Vital Signs, ECOG Performance Status	X	Weight, BP, HR, temperature, and ECOG Performance Status Obtain vital signs within 72 hours prior to dosing
Severe Adverse Events Assessment	Continuously	Adverse events will be graded according to the NCI-CTCAE version 4.
Adverse Events Assessment	Continuously	Adverse events will be graded according to the NCI-CTCAE version 4.
Laboratory Tests	X	On site/ local laboratory testing should be done within 72 hours prior to each dose. For the first dose visit, labs need not be repeated if they were preformed within 72 hours and the results are available and have been reviewed for eligibility. CBC w/differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, phosphate, glucose (and albumin if clinically indicated) Thyroid Function Testing (TSH with reflexive free T3 and free T4 if TSH is abnormal, if free T3 and free T4 are not available then Total T3 and Total T4 are acceptable) to be evaluated every 8 weeks during nivolumab treatment (see Section 9.4).
Pregnancy Test (WOCBP only)	X	Serum or urine within 24 hours prior to first dose and then every 4 weeks (± 1 week) regardless of dosing schedule.
Patient Reported Outcomes Assessment		
EORTC QLQ-C30	X	Assessed prior to dosing on Day 1 of each monotherapy dosing cycle for the first 6 months of study, then every 12 weeks (every 3 cycles) for the remainder of the treatment period.
EQ-5D-5L	X	Assessed prior to dosing on Day 1 of each monotherapy dosing cycle for the first 6 months of study, then every 12 weeks (every 3 cycles) for the remainder of the treatment period.

Table 2-3: On Treatment Procedural Outline for Arms A and C, Part 2 Nivolumab Monotherapy Treatment (CA209901)

Procedure	Day 1 of each cycle (Q4 weeks)[a]	Notes: If a dose is delayed, the procedures scheduled for that same time point should also be delayed to coincide with when that time point's dosing actually occurs (with the exception of tumor assessments, which should occur as scheduled).
Efficacy Assessments		
Tumor Assessment	See Notes	Tumor assessments will occur on Week 9 (± 1 week) and then every 8 weeks (± 1 week). After 48 weeks, tumor assessments will occur every 12 weeks (± 1 week). Post-baseline tumor assessments will continue until progression is assessed by the investigator **and** confirmed by BICR or treatment is discontinued (whichever occurs later). CT with IV contrast of the chest, abdomen, pelvis and all other known or suspected sites of disease should be imaged. If CT iodinated contrast is contraindicated, a non-contrast CT of the chest and contrast enhanced MRI abdomen, pelvis and all other known or suspected sites of disease should be imaged. (See Section 7.7.3.1). Use same imaging method as was used at screening/baseline. Participants with a history of brain metastasis should have surveillance MRI with and without gadolinium approximately every 12 weeks, or sooner if clinically indicated. (CT with or without contrast acceptable if prohibited for medical reasons). If a dose is delayed, the tumor assessments should occur as scheduled.
Pharmacokinetic /Immunogenicity Assessments		
PK samples	X	Table 9.5-1
Immunogenicity blood samples	X	Table 9.5-1
Biomarker Assessments		
Serum sample: Soluble Biomarkers	X	See Table 9.8-1
Whole Blood Sample (SNP)	X	See Table 9.8-1
Whole Blood Sample (Gene Expression)	X	See Table 9.8-1
Myeloid Derived Suppressor Cells (MDSC)	X	See Table 9.8-1

Table 2-3: On Treatment Procedural Outline for Arms A and C, Part 2 Nivolumab Monotherapy Treatment (CA209901)

Procedure	Day 1 of each cycle (Q4 weeks)[a]	Notes: If a dose is delayed, the procedures scheduled for that same time point should also be delayed to coincide with when that time point's dosing actually occurs (with the exception of tumor assessments, which should occur as scheduled).
Peripheral Blood Mononuclear Cells (PBMCs)	X	See Table 9.8-1
ctDNA	X	See Table 9.8-1
Collection of tumor tissue for biomarker research upon disease progression	X	Tumor tissue submission during Cycle 2 (C2D15) and after progression is highly recommended, but optional. Biopsy is not required per protocol. See Table 9.8-1
Clinical Drug Supplies		
IRT Drug Vial Assignment	X	
Dispense Study Drug	X	Nivolumab 480 mg Q4 weeks[a] (30 min IV) until disease progression (See Sections 9.1.4 and 7.4.5, and Appendix 4).

[a] Participants should be dosed no less than 26 days from previous dose in Part 2 of the study (monotherapy treatment). Monotherapy should begin 6 weeks following the last combination dose received for Arm A and 3 weeks after the last combination therapy cycle for Arm C.

Table 2-4: On Study Assessments Treatment Arm B and Arm D (Cisplatin-Eligible) Doublet Gemcitabine-Cisplatin Chemotherapy (CA209901)

Procedure	Cycle 1 Day 1	Each Subsequent Cycle Day1	Notes: 1 cycle = 3 weeks, up to 6 cycles maximum[a] If a dose is delayed, the procedures scheduled for that same time point should also be delayed to coincide with when that time point's dosing actually occurs (with the exception of tumor assessments, which should occur as scheduled).
Safety Assessments			
Review of Concomitant Medications	Continuously		Record at each visit.
Targeted Physical Examination, Physical Measurements, Vital Signs, Performance Status	X*	X*	Weight, BP, HR, temperature and Performance Status Obtain vital signs within 72 hours prior to dosing *Also to be collected prior to gemcitabine dosing on Day 8 of each cycle, except Performance Status.
Serious Adverse Event Assessments	--------Continuously------		Adverse events will be graded according to the NCI-CTCAE version 4.
Adverse Event Assessments	--------Continuously------		Adverse events will be graded according to the NCI-CTCAE version 4.
Laboratory Tests	X*	X*	On site/ local laboratory testing should be done within 72 hours prior to each dose. For the first dose visit, labs need not be repeated if they were preformed within 72 hours and the results are available and have been reviewed for eligibility. CBC w/differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, phosphate, glucose, amylase, lipase (and albumin if clinically indicated) *CBC required prior to gemcitabine dosing on Day 8 of each cycle.
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 2-4: On Study Assessments Treatment Arm B and Arm D (Cisplatin-Eligible) Doublet Gemcitabine-Cisplatin Chemotherapy (CA209901)

Procedure	Cycle 1 Day 1	Each Subsequent Cycle Day1	Notes: 1 cycle = 3 weeks, up to 6 cycles maximum[a] If a dose is delayed, the procedures scheduled for that same time point should also be delayed to coincide with when that time point's dosing actually occurs (with the exception of tumor assessments, which should occur as scheduled).
Patient Reported Outcomes Assessments			
EORTC QLQ-C30	X	See notes	Assessed following randomization but prior to dosing on Day 1 of treatment, and prior to dosing on C2D1, C4D1 and C6D1. For participants who continue with additional treatment due to local guidelines, assessments should continue every 2 cycles starting with C8D1.
EQ-5D-5L	X	See notes	Assessed following randomization but prior to dosing on Day 1 of treatment, and prior to dosing on C2D1, C4D1 and C6D1. For participants who continue with additional treatment due to local guidelines, assessments should continue every 2 cycles starting with C8D1.
Efficacy Assessments			
Tumor Assessment	See notes		Tumor assessments will occur on Week 9 (± 1 week) and then every 8 weeks (± 1 week). After 48 weeks, tumor assessments will occur every 12 weeks (± 1 week). Post-baseline tumor assessments will continue until progression is assessed by the investigator **and** confirmed by BICR or treatment is discontinued (whichever occurs later). CT with IV contrast of the chest, abdomen, pelvis and all other known or suspected sites of disease should be imaged. If CT iodinated contrast is contraindicated, a non-contrast CT of the chest and contrast enhanced MRI abdomen, pelvis and all other known or suspected sites of disease should be imaged. (See Section 7.7.3.1). Use same imaging method as was used at screening/baseline. Participants with a history of brain metastasis should have surveillance MRI approximately with and without gadolinium every 12 weeks, or sooner if clinically indicated. (CT with or without contrast acceptable if prohibited for medical reasons). If a dose is delayed, the tumor assessments should occur as scheduled.
Biomarker Assessments			
Serum sample: Soluble Biomarkers	X	See notes	See Table 9.8-1
Whole Blood Sample (SNP)	X	See notes	See Table 9.8-1

Table 2-4: On Study Assessments Treatment Arm B and Arm D (Cisplatin-Eligible) Doublet Gemcitabine-Cisplatin Chemotherapy (CA209901)

Procedure	Cycle 1 Day 1	Each Subsequent Cycle Day1	Notes: 1 cycle = 3 weeks, up to 6 cycles maximum[a] If a dose is delayed, the procedures scheduled for that same time point should also be delayed to coincide with when that time point's dosing actually occurs (with the exception of tumor assessments, which should occur as scheduled).
Whole Blood Sample (Gene Expression)	X	See notes	See Table 9.8-1
Myeloid Derived Suppressor Cells (MDSC)	X	See notes	See Table 9.8-1
Peripheral Blood Mononuclear Cells (PBMCs)	X	See notes	See Table 9.8-1
ctDNA	X	See notes	See Table 9.8-1
Collection of tumor tissue for biomarker research upon disease progression	See notes		Tumor tissue submission during Cycle 2 (C2D15) and after progression is highly recommended, but optional. Biopsy is not required per protocol. See Table 9.8-1
Clinical Drug Supplies			
IRT Drug Vial Assignment	X	X	
Dispense Study Drug	X	X	Gemcitabine at a dose of 1000 mg/m^2 for a 30-minute IV infusion on Days 1 and 8 of a 3-week treatment cycle for up to 6 cycles. Cisplatin at a dose of 70 mg/m^2 as a 30 to 120-minute IV infusion on Day 1 of a 3-week treatment cycle for up to 6 cycles.[a] Dosing calculations should be based on the body surface area calculation and may be capped per local standards. The dose may remain the same if the participant's weight is within 10% of the baseline weight or prior dose weight.

[a] Note that additional cycles may be permitted as per local guidelines.

Table 2-5: On Study Assessments Treatment Arm B (Cisplatin-Ineligible) Doublet Gemcitabine/Carboplatin Chemotherapy (CA209901)

Procedure	Cycle 1 Day 1	Each Subsequent Cycle Day1	Notes: 1 cycle = 3 weeks, up to 6 cycles maximum[a] If a dose is delayed, the procedures scheduled for that same time point should also be delayed to coincide with when that time point's dosing actually occurs (with the exception of tumor assessments, which should occur as scheduled).
Safety Assessments			
Review of Concomitant Medications	Continuously		Record at each visit.
Targeted Physical Examination, Physical Measurements, Vital Signs, Performance Status	X*	X*	Weight, BP, HR, temperature, and Performance Status Obtain vital signs within 72 hours prior to dosing *Also to be collected prior to gemcitabine dosing on Day 8 of each cycle, except Performance Status
Serious Adverse Event Assessments	-------Continuously------		Adverse events will be graded according to the NCI-CTCAE version 4.
Adverse Event Assessments	-------Continuously------		Adverse events will be graded according to the NCI-CTCAE version 4.
Laboratory Tests	X*	X*	On site/ local laboratory testing should be done within 72 hours prior to each dose. For the first dose visit, labs need not be repeated if they were preformed within 72 hours and the results are available and have been reviewed for eligibility. CBC w/differential , LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, phosphate, glucose, amylase, lipase (and albumin if clinically indicated) *CBC required prior to gemcitabine dosing on Day 8 of each cycle
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 2-5: On Study Assessments Treatment Arm B (Cisplatin-Ineligible) Doublet Gemcitabine/Carboplatin Chemotherapy (CA209901)

Procedure	Cycle 1 Day 1	Each Subsequent Cycle Day1	Notes: 1 cycle = 3 weeks, up to 6 cycles maximum[a] If a dose is delayed, the procedures scheduled for that same time point should also be delayed to coincide with when that time point's dosing actually occurs (with the exception of tumor assessments, which should occur as scheduled).
Patient Reported Outcomes Assessments			
EORTC QLQ-C30	X	See notes	Assessed following randomization but prior to dosing on Day 1 of treatment, and prior to dosing on C2D1, C4D1 and C6D1. For participants who continue with additional treatment due to local guidelines, assessments should continue every 2 cycles starting with C8D1.
EQ-5D-5L	X	See notes	Assessed following randomization but prior to dosing on Day 1 of treatment, and prior to dosing on C2D1, C4D1 and C6D1 For participants who continue with additional treatment due to local guidelines, assessments should continue every 2 cycles starting with C8D1.
Efficacy Assessments			
Tumor Assessment	See notes	See notes	Tumor assessments will occur on Week 9 (± 1 week) and then every 8 weeks (± 1 week). After 48 weeks, tumor assessments will occur every 12 weeks (± 1 week). Post-baseline tumor assessments will continue until progression is assessed by the investigator **and** confirmed by BICR or treatment is discontinued (whichever occurs later). If CT iodinated contrast is contraindicated, a non-contrast CT of the chest and contrast enhanced MRI abdomen, pelvis and all other known or suspected sites of disease should be imaged. (See Section 7.7.3.1) Use same imaging method as was used at screening/baseline. CT with IV contrast of the chest, abdomen, pelvis and all other known or suspected sites of disease should be imaged. Participants with a history of brain metastasis should have surveillance MRI with and without gadolinium approximately every 12 weeks, or sooner if clinically indicated. (CT with or without contrast acceptable if prohibited for medical reasons). If a dose is delayed, the tumor assessments should occur as scheduled.
Biomarker Assessments			
Serum sample: Soluble Biomarkers	X	See notes	See Table 9.8-1
Whole Blood Sample (SNP)	X	See notes	See Table 9.8-1

Table 2-5: On Study Assessments Treatment Arm B (Cisplatin-Ineligible) Doublet Gemcitabine/Carboplatin Chemotherapy (CA209901)

Procedure	Cycle 1 Day 1	Each Subsequent Cycle Day1	Notes: 1 cycle = 3 weeks, up to 6 cycles maximum[a] If a dose is delayed, the procedures scheduled for that same time point should also be delayed to coincide with when that time point's dosing actually occurs (with the exception of tumor assessments, which should occur as scheduled).
Whole Blood Sample (Gene Expression)	X	See notes	See Table 9.8-1
Myeloid Derived Suppressor Cells (MDSC)	X	See notes	See Table 9.8-1
Peripheral Blood Mononuclear Cells (PBMCs)	X	See notes	See Table 9.8-1
ctDNA	X	See notes	See Table 9.8-1
Collection of tumor tissue for biomarker research upon disease progression	See notes		Tumor tissue submission during Cycle 2 (C2D15) and after progression is highly recommended, but optional. Biopsy is not required per protocol. See Table 9.8-1
Clinical Drug Supplies			
IRT Drug Vial Assignment	X	X	
Dispense Study Drug	X	X	Gemcitabine at a dose of 1000 mg/m^2 for a 30-minute IV infusion on Days 1 and 8 of a 3-week treatment cycle for up to 6 cycles.[a] Carboplatin: AUC4.5/5 (see Section 7.1.3.2) Dosing calculations should be based on the body surface area calculation and may be capped per local standards. The dose may remain the same if the participant's weight is within 10% of the baseline weight or prior dose weight.

[a] Note that additional cycles may be permitted as per local guidelines.

Table 2-6: On Study Assessments Treatment Substudy: (Arm C, Part 1) Nivolumab + Doublet Gemcitabine-Cisplatin Chemotherapy (CA209901)

Procedure	Cycle 1 Day 1	Each Subsequent Cycle Day 1	**Notes:** 1 cycle = 3 weeks, for a maximum of 6 cycles. **If a dose is delayed, the procedures scheduled for that same time point should also be delayed to coincide with when that time point's dosing actually occurs (with the exception of tumor assessments, which should occur as scheduled).**
Safety Assessments			
Review of Concomitant Medications	Continuously		Record at each visit.
Targeted Physical Examination, Physical Measurements, Vital Signs, Performance Status	X*	X*	Weight, BP, HR, temperature and Performance Status Obtain vital signs within 72 hours prior to dosing *Also to be collected prior to gemcitabine dosing on Day 8 of each cycle, except Performance Status.
Serious Adverse Event Assessments	------Continuously------		Adverse events will be graded according to the NCI-CTCAE version 4.
Adverse Event Assessments	------Continuously------		Adverse events will be graded according to the NCI-CTCAE version 4.
Laboratory Tests	X*	X*	On site/ local laboratory testing should be done within 72 hours prior to each dose. For the first dose visit, labs need not be repeated if they were preformed within 72 hours and the results are available and have been reviewed for eligibility. CBC w/differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, phosphate, glucose, amylase, lipase (and albumin if clinically indicated) Thyroid Function Testing (TSH with reflexive free T3 and free T4 if TSH is abnormal, total T3 and T4 acceptable if Free T3 T4 are not available) to be evaluated every 3 weeks during treatment with nivolumab (see Section 9.4). *CBC required prior to gemcitabine dosing on Day 8 of each cycle.
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 2-6: On Study Assessments Treatment Substudy: (Arm C, Part 1) Nivolumab + Doublet Gemcitabine-Cisplatin Chemotherapy (CA209901)

Procedure	Cycle 1 Day 1	Each Subsequent Cycle Day 1	**Notes:** 1 cycle = 3 weeks, for a maximum of 6 cycles. **If a dose is delayed, the procedures scheduled for that same time point should also be delayed to coincide with when that time point's dosing actually occurs (with the exception of tumor assessments, which should occur as scheduled).**
Patient Reported Outcomes Assessments			
EORTC QLQ-C30	X	See notes	Assessed following randomization but prior to dosing on C1D1, and prior to dosing at C2D1 and C4D1.
EQ-5D-5L	X	See notes	Assessed following randomization but prior to dosing on C1D1, and prior to dosing at C2D1 and C4D1.
Efficacy Assessments			
Tumor Assessment	See notes		Tumor assessments will occur on Week 9 (± 1 week) and then every 8 weeks (± 1 week). After 48 weeks, tumor assessments will occur every 12 weeks (± 1 week). Post-baseline tumor assessments will continue until progression is assessed by the investigator **and** confirmed by BICR or treatment is discontinued (whichever occurs later). CT with IV contrast of the chest, abdomen, pelvis and all other known or suspected sites of disease should be imaged. If CT iodinated contrast is contraindicated, a non-contrast CT of the chest and contrast enhanced MRI abdomen, pelvis and all other known or suspected sites of disease should be imaged. (See Section 7.7.3.1) Use same imaging method as was used at screening/baseline. Participants with a history of brain metastasis should have surveillance MRI approximately with and without gadolinium every 12 weeks, or sooner if clinically indicated. (CT with or without contrast acceptable if prohibited for medical reasons). If a dose is delayed, the tumor assessments should occur as scheduled.
Biomarker Assessments			
Collection of tumor tissue for biomarker research upon disease progression	See notes		Tumor tissue submission during Cycle 2 (C2D15) and after progression is highly recommended, but optional. Biopsy is not required per protocol. See Table 9.8-1
Serum	X	See notes	See Table 9.8-1
Whole Blood Sample (SNP)	X	See notes	See Table 9.8-1

Table 2-6: On Study Assessments Treatment Substudy: (Arm C, Part 1) Nivolumab + Doublet Gemcitabine-Cisplatin Chemotherapy (CA209901)

Procedure	Cycle 1 Day 1	Each Subsequent Cycle Day 1	**Notes:** 1 cycle = 3 weeks, for a maximum of 6 cycles. **If a dose is delayed, the procedures scheduled for that same time point should also be delayed to coincide with when that time point's dosing actually occurs (with the exception of tumor assessments, which should occur as scheduled).**
Whole Blood Sample (Gene Expression)	X	See notes	See Table 9.8-1
Myeloid Derived Suppressor Cells (MDSC)	X	See notes	See Table 9.8-1
Peripheral Blood Mononuclear Cells (PBMCs)	X	See notes	See Table 9.8-1
ctDNA	X	See notes	See Table 9.8-1
Clinical Drug Supplies			
IRT Drug Vial Assignment	X	X	
Dispense Study Drug	X	X	Nivolumab 360 mg Day 1 of each Q 3 weeks (30 min IV) Gemcitabine at a dose of 1000 mg/m^2 for a 30-minute IV infusion on Days 1 and 8 of a 3-week treatment cycle for up to 6 cycles. Cisplatin at a dose of 70 mg/m^2 as a 30 to 120-minute IV infusion on Day 1 of a 3-week treatment cycle for up to 6 cycles. Dosing calculations should be based on the body surface area calculation and may be capped per local standards. The dose may remain the same if the participants weight is within 10% of the baseline weight or prior dose weight. 3 weeks following the last combination dose (nivolumab + gemcitabine-cisplatin) participants will follow assessments and treatment in nivolumab maintenance Table 2-3

Table 2-7: Follow-Up Period (All Participants) CA209901

Procedure	Follow Up, Visits 1 and 2[a]	Survival Follow-Up Visits [b]	Notes
Safety Assessments			
Targeted Physical Examination	X		To assess for potential late emergent study drug related issues
Vital Signs	X		Weight, BP, HR, temperature and Performance Status
Adverse Events Assessment	X	X	In survival period only to include toxicities from study therapy.
Review of Concomitant Medication	X	X	Document Subsequent Cancer Therapy
Laboratory Tests	X		On site/local laboratory testing; CBC w/differential, LFTs, BUN, creatinine, amylase, lipase and TSH (+ reflex Free T4 and Free T3 , total T3 and T4 acceptable if Free T3 T4 are not available) for) for FU 1, repeat at FU 2 if study drug related toxicity persists.
Pregnancy Test (WOCBP only)	X		Serum or urine
Exploratory Biomarker Testing			
Exploratory Serum Biomarkers	X		Collect serum at Follow-Up Visit 1 and Follow-Up Visit 2 visit. Sample collection upon disease progression is optional, but highly recommended. See Table 9.8-1
Collection of tumor tissue for biomarker research upon disease progression	X		Tumor tissue submission after progression is highly recommended, but optional. Biopsy is not required per protocol. See Table 9.8-1
Pharmacokinetic Samples and Immunogenicity Assessments			
PK samples	X		See Table 9.5-1 and Table 9.5-2
Immunogenicity blood sample	X		See Table 9.5-1 and Table 9.5-2

Table 2-7: Follow-Up Period (All Participants) CA209901

Procedure	Follow Up, Visits 1 and 2[a]	Survival Follow-Up Visits [b]	Notes
Efficacy Assessments			
Tumor Assessment	X	X	Only for participants without progression, and no longer on study therapy. Tumor assessments will occur on Week 9 (± 1 week) and then every 8 weeks (± 1 week). After 48 weeks, tumor assessments will occur every 12 weeks (± 1 week), until disease progression even if the participant has initiated subsequent anti-cancer therapy. CT with IV contrast of the chest, abdomen, pelvis and all other known or suspected sites of disease should be imaged. If CT iodinated contrast is contraindicated, a non-contrast CT of the chest and contrast enhanced MRI abdomen, pelvis and all other known or suspected sites of disease should be imaged. (See Section 7.7.3.1). Use same imaging method as was used at screening/baseline. Participants with a history of brain metastasis should have surveillance MRI with and without gadolinium approximately every 12 weeks, or sooner if clinically indicated. (CT with or without contrast acceptable if prohibited for medical reasons).
Outcomes Research Assessment			
EORTC QLQ-C30	X		Assessment at clinical visit
EQ-5D-5L	X	X	Assessment at clinical visit, or can be collected over the phone for Survival Follow-Up visits.
Participant Status			
Survival Status	X	X	Every 3 months after FU 2; may be accomplished by visit, phone contact or email, to include assessment of subsequent anti-cancer therapy.

[a] Follow Up visits 1 (FU1) and 2 (FU2) are in clinic visits. Follow-up visit 1 (FU1) = 30 days from the last dose (± 7 days) or coincides with the date of discontinuation (± 7 days) if date of discontinuation is greater than 35 days after last dose, Follow-up visit 2 (FU2) = 90 days (± 7 days) from follow-up visit 1

[b] Survival Follow Up Visits may be conducted in clinic or via telephone contact: Every 3 Months (± 7 days) from FU2

3 INTRODUCTION

CA209901 is a Phase 3, open-label, randomized study of nivolumab combined with ipilimumab or standard of care chemotherapy, versus standard of care chemotherapy in participants with previously untreated unresectable or metastatic urothelial carcinoma (UC). Eligible participants may either have *de novo* previously untreated unresectable or metastatic UC, or previously diagnosed localized muscle invasive bladder cancer (MIBC) with radical cystectomy and treatment with chemotherapy or radiation therapy in the neo-adjuvant or adjuvant setting and progression ≥ 12 months following receiving chemotherapy.

3.1 Study Rationale

UC of the bladder is the ninth most common cancer in the world[1] and the fifth most common malignancy in the United States.[2] Approximately 20% to 25% of all patients with UC of the bladder develop metastatic disease, resulting in an estimated 15,580 deaths in 2014 in the United States.[3]

Cisplatin has been used for the treatment of UC since the 1970s, with initial reports describing response rates ranging from 30% to 70% for advanced UC treated with cisplatin-containing regimens.[4,5,6] These response rates were higher than observed with other chemotherapeutic agents at the time, establishing cisplatin as a preferred first-line agent in this disease. The M-VAC (methotrexate, vinblastine, adriamycin, and cisplatin) regimen, developed in the early 1980's, became a treatment standard based on data from two large randomized trials demonstrating improved survival with MVAC compared with single agent cisplatin or CISCA (cisplatin, adriamycin, and cyclophosphamide), respectively.[7,8] However, the toxicity of MVAC (myelosuppression, fever/neutropenia and mucositis)[7] limited the widespread use of this regimen in elderly patients with comorbidities.

In an effort to improve on the response and toxicity of MVAC, cisplatin-containing doublets incorporating other chemotherapeutic agents were tested.[9,10] Of the commonly used regimens such as gemcitabine plus cisplatin, or MVAC (methotrexate, vinblastine, doxorubicin, plus cisplatin) gemcitabine plus cisplatin treatment was associated with a better safety profile and improved tolerability and has become a standard regimen for patients with metastatic UC.[11,12]

Management guidelines therefore support the use of cisplatin-based regimens in the treatment of unresectable or metastatic UC.[13,14] However, in clinical practice, more than 50% of all patients with unresectable or metastatic UC have contraindications for treatment with cisplatin. Renal dysfunction, poor performance status, and advanced age are relatively common and preclude cisplatin chemotherapy.[15] An expert consensus statement was released in 2011 with the goal of defining unfit patients.[16] According to this definition, unfit patients would meet at least one of the following criteria: Eastern Cooperative Oncology Group performance status of 2, creatinine clearance less than 60 mL/min, grade ≥ 2 hearing loss, grade ≥ 2 neuropathy, and/or New York Heart Association Class III heart failure.[16]

A randomized study compared two carboplatin-containing regimens, M-CAVI and gemcitabine/carboplatin, in this population of cisplatin "unfit" patients.[17] Although median survival was comparable, toxicity was significantly lower with gemcitabine/carboplatin, establishing it as an appropriate first-line regimen in this patient population.

Although the combination of gemcitabine plus carboplatin is commonly used in cisplatin-ineligible patients, to date, combination regimens that do not include cisplatin have never been shown to improve survival. Median survival with gemcitabine plus carboplatin in cisplatin-ineligible patients is only 8 to 9 months,[17] either due to lower efficacy of carboplatin compared with cisplatin or due to these patients' lower state of general health. In fact, patients who are not candidates for cisplatin-containing chemotherapy regimens have significantly worse outcomes with regard to response to treatment and overall survival (OS).

Despite the initial chemosensitivity of UC of the bladder, responses generally are short-lived; the median survival of patients with metastatic disease is approximately 14 -15 months.[12] Visceral metastases and poor performance status are adverse prognostic factors associated with a lower likelihood of response to chemotherapy and shorter survival.[18]

While the tolerability of treatment has improved over the past 30 years, improvement in efficacy has not kept pace, underscoring the urgent need for novel approaches in the treatment of metastatic UC of the bladder. Optimally, novel agents with improved efficacy and tolerability may eliminate the need to evaluate patients with metastatic UC in separate cisplatin-eligible and cisplatin-ineligible cohorts in the future.

3.1.1 Research Hypothesis

3.1.1.1 Research Hypothesis for Primary Study

The study aims to demonstrate that treatment with nivolumab combined with ipilimumab will improve efficacy in cisplatin-ineligible and/or PD-L1 positive (PD-L1 ≥ 1%) participants with previously untreated, unresectable or metastatic UC.

3.1.1.2 Research Hypothesis for Substudy

The study aims to demonstrate that treatment with nivolumab combined with SOC chemotherapy will improve efficacy in cisplatin-eligible participants with previously untreated, unresectable or metastatic UC.

3.1.2 Rationale for Immunotherapy in UC

UC is an immunogenic malignancy. Immunotherapy has played a major role in the treatment of superficial bladder cancer since the introduction of intravesical bacillus Calmette-Guérin (BCG); randomized trials have demonstrated treatment with intravesical BCG results in lower recurrence rates and significantly superior survival rates.[19] While the mechanism of action of BCG remains poorly defined, studies support an immunological mechanism including the 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.[20] Multiple studies have shown that bladder cancer specimens harbor tumor infiltrating lymphocytes;[21,22] immunohistochemical

staining for intratumoral CD8 T cells in tissue samples from 69 patients with bladder cancer (pT2, pT3, or pT4) demonstrated that patients with higher numbers of CD8 tumor infiltrating lymphocytes within the tumor (8 or more) had better disease-free survival ($P < 0.001$) and overall survival ($P = 0.018$) than did patients with similar-staged bladder cancer and fewer intratumoral CD8 tumor infiltrating lymphocytes.[22]

Despite the immunogenicity of bladder cancer, patients with bladder cancer also exhibit tumor-associated immunologic suppression. Patients with bladder cancer exhibit a tumor-associated immunologic suppression, particularly evident as an impaired T-cell response, which may worsen with advanced tumor stage.[23,24,25] Bladder cancer specimens have been shown to be infiltrated by T regulatory cells, and to express high levels of inhibitory cytokines.[24] In addition, aberrant expression of T-cell coregulatory molecules, known to inhibit the immune response, have been demonstrated on bladder cancer cells and tumor infiltrating lymphocytes and have correlated with clinical outcomes.[26]

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.

Immune checkpoint inhibition blockade has demonstrated intriguing activity in localized bladder cancer.

Ipilimumab has been explored pre-cystectomy in a pilot trial of patients with clinically localized bladder cancer. In this trial, 12 patients were treated with 2 doses of ipilimumab (n = 6 treated with 3 mg/kg and n = 6 treated with 10 mg/kg).[27] Most drug-related adverse events (AEs) were Grade 1 or 2, all patients demonstrated an increase in $CD4^{+}$ $ICOS^{hi}$ T cells in tumor tissue and systemic circulation, and 8/12 patients had down-staging of their disease on final pathology review. The efficacy and safety of first-line gemcitabine, cisplatin plus ipilimumab for metastatic UC is being investigated in a Phase 2 trial (NCT01524991).

High levels of programmed death 1 (PD-1) ligand 1 (PD-L1) expression have been noted in UC, 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 sample (28-30). PD-1 and PD-L1 immune checkpoint inhibitors appear to show benefit in patients with disease progression on platinum-based therapy. [28] Recently, atezolizumab (anti-PD-L1) 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. In an open-label, multicenter Phase 1/2 expansion cohort in patients with metastatic UC, nivolumab elicited a response rate of 24.4% with acceptable safety, regardless of tumor PD-L1 expression, in patients who had received one or more prior lines of chemotherapy (CheckMate 032; NCT01928394).[29] In a larger study in unresectable or metastatic UC, CheckMate 275, nivolumab had clinically meaningful efficacy and a manageable safety profile.[30] At 7 months of median follow-up, 24.4% of patients remain on therapy. Confirmed overall response rate (ORR) was 19.6% (95% CI 15.0–24.9), with Grade 3-4 treatment-related adverse events occurring in 18%

of patients (Grade 5, 1%), mainly fatigue and diarrhea (2% each). The combination of nivolumab and ipilimumab demonstrated acceptable safety and high activity in patients with advanced, platinum refractory UC in study CA209032. At 7.9 months minimum follow-up, 23.9% of patients remain on therapy. BICR confirmed overall response rate (ORR) was 37.0% (95% CI 27.1–47.7), with Grade 3-4 treatment-related adverse events occurring in 39.1% of patients (no Grade 5 SAE), mainly diarrhea (9.8% each) and elevated alanine aminotransferase (6.5%), and only 13% discontinuations due to treatment-related AEs (Please see Section 5.5.1).

Taken together, these data suggest that combination therapy with nivolumab and ipilimumab may provide the most favorable benefit-risk among the regimens studied and support the further development of the N1I3 combination as first-line therapy in metastatic UC.

3.1.3 Rationale for Cisplatin-ineligible Subpopulation being a Primary Analysis Population

Management guidelines support the use of cisplatin-based regimens in metastatic UC.[13,14] In real-world clinical practice, up to 50% of patients with UC are not eligible or are considered unfit for cisplatin-based standard chemotherapy because of impaired renal function, performance status, or comorbidity.[15,16] Hence, evaluation of treatment approaches in all-comer trials with over-enrollment of cisplatin-eligible patients may not be applicable to the cisplatin unfit population.

While no standard treatment has been defined for cisplatin-unfit patients, carboplatin-containing regimens are considered appropriate alternatives vs cisplatin-based therapy, based on performance status and kidney function defined by GFR.[17] However, patients who are not candidates for cisplatin-containing chemotherapy regimens have significantly worse outcomes with regard to response to treatment and OS, and there is no consensus on the standard chemotherapy treatment for cisplatin-unfit patients. In view of the limited success of carboplatin-based chemotherapy more effective and better tolerated treatments are needed for cisplatin-ineligible patients (a primary analysis population in this study).

3.1.4 Rationale for PD-L1 Positive Subpopulation being a Primary Analysis Population

The treatment options for tumors have been evolving rapidly with new data emerging dramatically. For locally advanced unresectable and metastatic UC, newly approved immunotherapies have recently become available, including Keytruda[31] and Tecentriq[32] in PD-L1 positive untreated metastatic UC. In a second-line setting, data from CA209-032 also provided supportive evidence for application in first-line metastatic UC.[33] In light of such data, this study CA209-901 was revised (revised protocol 03) to remove PFS as a primary endpoint and add OS in PD-L1 positive (≥ 1%) patients as a primary population.

The rationale for this revision were based on the available evidence. First, the median PFS of single agent immunotherapy were reported as 2.3 months for pembrolizumab[31] and 2.7 months for atezolizumab[34] in untreated cisplatin-ineligible metastatic UC, and 3.55 months for nivolumab in study CA209-275[35] and 4.86 months for nivolumab in combination with ipilimumab in study

CA209-032 in previously platinum-treated metastatic UC,[33] which may not be comparable with the gemcitabine-carboplatin regimen (7.5 months) in cisplatin-ineligible patients. On the other hand, the above mentioned studies presented efficacy of ORR especially in PD-L1 positive metastatic UC. In single immunotherapy agent studies, Keynote-052 showed an ORR of 47% for PD-L1 CPS ≥ 10[31] and IMvigor-210, ORR of 28.1% for PD-L1 ≥ 5% in ICs.[32] Furthermore, a nivolumab with ipilimumab combined regimen in CA209-032 demonstrated strong incremental efficacy in PD-L1 ≥ 1% patients (ORR 54.8%), but limited benefit (ORR 21.4%) in PD-L1 negative cisplatin pre-treated metastatic UC.[33] The clinical efficacy of OS in PD-L1 positive metastatic UC was also supported by CA209-032 with OS 24.08 months in PD-L1 positive (14.88 months in PD-L1 negative).[33] The application of pembrolizumab and atezolizumab are restricted in PD-L1 positive untreated metastatic UC.[31,32] In consideration of this evidence, this current revision removed PFS a primary endpoint and added OS in PD-L1 positive (≥1%) as a primary endpoint for the primary study.

3.1.5 Rationale for Arm B and Arm D: Gemcitabine-Cisplatin/Gemcitabine-Carboplatin Combination Chemotherapy

Currently cisplatin, the taxanes and gemcitabine are employed in the management of advanced bladder cancer. Combinations of 2 or 3 of these agents have shown clinical benefit, of which commonly used combinations include Gemcitabine plus cisplatin and dose-dense MVAC (3). While studies have noted the superiority of MVAC over other cisplatin-containing regimens, the significant toxicity of MVAC with increased rates of myelosuppression, neutropenic fever, and mucositis limits the use of this regimen in the elderly and patients with comorbidities.[7]

A large Phase 3 trial randomized 405 patients with stage IV UC to gemcitabine plus cisplatin or standard MVAC.[12] Both arms had similar response rates (RRs) (46%–49%) and OS (13.8–14.8 months), with improved toxicity profile in the gemcitabine plus cisplatin arm. Fewer deaths were noted in the gemcitabine plus cisplatin arm compared to MVAC arm (1% vs. 3%) although this did not reach statistical significance. A 5-year update analysis confirmed that gemcitabine plus cisplatin was not inferior to MVAC in terms of survival (OS: 13% vs. 15.3%; PFS: 9.8% vs 11.3%, respectively). The similar disease outcomes and favorable toxicity profile of gemcitabine plus cisplatin have established this regimen as an appropriate first-line treatment for patients with previously untreated, unresectable or metastatic UC in the US and Europe. Accordingly, to maintain homogeneity of treatment in the comparator arm, gemcitabine plus cisplatin was included as SOC chemotherapy for cisplatin-eligible patients randomized to SOC arm.

In clinical practice, more than 50% of all patients with unresectable or metastatic UC have contraindications for treatment with cisplatin. Renal dysfunction (usually defined as a creatinine clearance of < 60 ml/minute), poor performance status, and advanced age are relatively common and preclude cisplatin chemotherapy. While no standard treatment has been defined for cisplatin-unfit patients, carboplatin-containing regimens are considered appropriate alternatives vs cisplatin-based therapy, based on performance status and kidney function defined by GFR. Hence, gemcitabine plus carboplatin was included as SOC chemotherapy for cisplatin-ineligible patients randomized to SOC arm.

3.1.6 Rationale For Exclusion Of ECOG Performance Status ≥2

The relationship between comorbidities, treatment-related toxicities, and efficacy of therapy is complex and has not been adequately explored in patients with advanced solid tumors. Poor functional status has been associated with increased toxic effects and decreased efficacy in patients with metastatic UC who are treated with cisplatin-based chemotherapy.[18] Limited to no safety information is available with regard to combination of ipilimumab 3 mg/kg with nivolumab 1 mg/kg in patients with ≥ PS 2 across a range of solid tumors evaluated within the nivolumab program.

Accordingly, patients with comorbidities and poor functional status (ECOG PS 2 or greater) will be excluded from this study out of concern for inability to tolerate combination of higher dose of ipilimumab (3 mg/kg) in the combination regimen of the treatment arm.

3.1.7 Rationale For Shorter Infusion Times Of Nivolumab And Ipilimumab Dosing In Part 1

Long infusion times place a burden on patients and treatment centers. Establishing that nivolumab and ipilimumab can be safely administered using shorter infusion times of 30-minute duration will diminish the burden, provided that there is no change in the safety profile. Nivolumab and ipilimumab have been administered at up to 10 mg/kg with infusion duration of 60 minutes and 90 minutes, respectively.

Establishing that nivolumab can be safely administered using a shorter infusion time (30 minutes) is under investigation. Previous clinical studies of nivolumab monotherapy have used a 60-minute infusion duration wherein, nivolumab has been safely administered up to 10 mg/kg over long treatment periods. Infusion reactions including high-grade hypersensitivity reactions have been uncommon across nivolumab clinical program. In CA209010, a dose association was observed for infusion site reactions and hypersensitivity reactions (1.7% at 0.3 mg/kg, 3.7% at 2 mg/kg, and 18.5% at 10 mg/kg). All the events were Grade 1-2 and were manageable. An infusion duration of 30 minutes for 3 mg/kg nivolumab (30% 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. The safety of nivolumab 3 mg/kg administered as a 30-min infusion was assessed in CA209153 in patients (n = 322) 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 patients administered nivolumab over a 30-minute infusion compared with that reported for patients with the 60-minute infusion. Thus, it was shown that nivolumab can be safely infused over 30 minutes.

Similarly, ipilimumab at 10 mg/kg has been safely administered over 90 minutes. In participants with advanced Stage II or Stage IV melanoma (CA184022 study), where ipilimumab was administered up to a dose of 10 mg/kg, on-study drug related hypersensitivity events (Grade 1/2) were reported in 1 participant (1.4%) in the 0.3 mg/kg and in 2 participants (2.8%) in the 10 mg/kg group. There were no drug-related hypersensitivity events reported in the 3 mg/kg group. Across the 3 treatment groups, no Grade 3/4 drug-related hypersensitivity events were reported and there were no reports of infusion reactions. Ipilimumab 10 mg/kg monotherapy has also been safely

administered as a 90-minute infusion in a large Phase 3 study in prostate cancer (CA184043) and as adjuvant therapy for Stage III melanoma (CA184029), with infusion reactions occurring in participants. Administering 3 mg/kg of ipilimumab represents approximately one-third of the 10 mg/kg dose. Similarly, shortened infusion duration of 30 minutes for ipilimumab is not expected to present additional safety concerns.[36]

Overall, infusion reactions including high-grade hypersensitivity reactions have been uncommon across clinical studies of nivolumab, ipilimumab, and nivolumab/ipilimumab combinations. Furthermore, a 30-minute break after the first infusion for the combination cohort will ensure the appropriate safety monitoring before the start of the second infusion. Overall, a change in safety profile is not anticipated with 30-minute infusions of nivolumab, ipilimumab, or combination treatment.

3.1.8 Rationale For Shorter Infusion Times With Nivolumab 480 Mg Flat Dose In Part 2

Long infusion times place a burden on participants and treatment centers. Establishing that nivolumab can be safely administered 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 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), a dose association was observed for infusion site reactions and hypersensitivity reactions (1.7% at 0.3 mg/kg, 3.7% at 2 mg/kg and 18.5% at 10 mg/kg). 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 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 min infusion compared with that reported for participants with the 60 min infusion. An infusion duration of 30 minutes for 1 mg/kg nivolumab and 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.

As of Sep 2016, 4 patients in the nivolumab clinical development programs have received nivolumab 480 mg Q4W for at least 1 dose. Clinical evaluation of this dose regimen is in its early stages and no safety summary is available. BMS has a clinical safety program that monitors symptoms potentially related to infusion-related reactions reported on the day of infusion and the following day. For the 4 patients treated with 480 mg nivolumab as a 30-minute infusion, there have been no reports of any symptoms that may potentially be linked to infusion reactions on the day of infusion or the following day.

3.1.9 Rationale for 360 mg Flat Dose Nivolumab plus Gemcitabine-Cisplatin Chemotherapy (Substudy, Arm C)

The interaction of a tumor with the immune system is complex. Tumors and the tumor microenvironment are known to express a variety of factors that impede a robust immune response from eliminating the tumor. Soluble and membrane-bound factors have been shown to inhibit the cytolytic activity of tumor infiltrating T-cells (e.g., PD-L1 expression; TGF-beta). In addition, some tumor-derived factors are able to enhance immune system counter-regulatory systems (e.g., increased T-regulatory cells). Finally, suboptimal tumor antigen delivery and presentation has been postulated as another mechanism by which tumors can successfully evade immune system recognition.

Cancer therapeutics such as chemotherapy may modulate tumor/immune-system interactions in favor of the immune system. Chemotherapy can result in tumor cell death with a resultant increase in tumor antigen delivery to antigen-presenting cells. Tumor cell death may also lead to a reduction in soluble and membrane-bound factors inhibiting tumor-infiltrating T-cells. Chemotherapy may also disrupt immune system regulatory networks by decreasing numbers of T-regulatory cells.

Nivolumab added to chemotherapy has been evaluated in several cohorts of chemotherapy-naive patients with advanced NSCLC in study CA209012. Nivolumab 10 mg/kg was combined with gemcitabine + cisplatin and pemetrexed + cisplatin. Nivolumab 10 mg/kg, and 5 mg/kg, were combined with paclitaxel and carboplatin.

The safety profile of nivolumab combined with platinum-doublet chemotherapy reflects additive toxicities of the individual agents, which were manageable using established safety guidelines (Table 3.1.9-1). The frequency of most immune-related select AEs was higher than what has been observed for nivolumab monotherapy. However, these treatment-related AEs, including pneumonitis, were effectively managed and did not lead to any deaths.

Table 3.1.9-1: Treatment-related AEs Reported in (10% of all NSCLC Patients Treated with Nivolumab plus Platinum-based Chemotherapy

Treatment-related AE, n (%)	Total (n=56)	
	All Grades	Grade 3/4
Patients with any AE	53 (95)	25 (45)
Fatigue	40 (71)	3 (5)
Nausea	26 (46)	1 (2)
Decreased appetite	20 (36)	1 (2)
Alopecia	17 (30)	0
Anemia	15 (27)	2 (4)
Rash	14 (25)	2 (4)
Diarrhea	12 (21)	1 (2)
Arthralgia	12 (21)	0
Constipation	11 (20)	0

Table 3.1.9-1: Treatment-related AEs Reported in (10% of all NSCLC Patients Treated with Nivolumab plus Platinum-based Chemotherapy

Treatment-related AE, n (%)	Total (n=56)	
	All Grades	Grade 3/4
Peripheral neuropathy	11 (20)	0
Dysgeusia	8 (14)	0
Hypersensitivity	8 (14)	1 (2)
Vomiting	8 (14)	0
Mucosal inflammation	7 (12)	0
Myalgia	7 (12)	0
Pneumonitis	7 (12)	4 (7)
Infusion-related reaction	6 (11)	0
Leukopenia	6 (11)	0
Lymphopenia	6 (11)	0
Peripheral sensory neuropathy	6 (11)	0
Pruritus	6 (11)	0
Treatment related AEs leading to discontinuation	11(2)	

The observed response rates of nivolumab and chemotherapy (Table 3.1.9-2) were similar to that of platinum-doublet chemotherapy alone, though the duration of responses is longer. The median duration of response across all the nivolumab + chemotherapy cohorts was 27.3 weeks. The 1-year survival rate for all cohorts combined is 71%.

Table 3.1.9-2: Efficacy in First-Line Nivolumab + Chemotherapy

	Nivo/Gem/Cis (n=12)	Nivo/Pem/Cis (n=15)	Nivo/Pac/Carbo (n=29)	Nivo/Chemo (n=56)
ORR, n (%)	4 (33%)	7 (47%)	13 (45%)	24 (43%)
Median DOR (wks)	45	24.4	27.3	27.3
PFS rate at 24 wks	51%	71%	43%	52%
Median PFS (wks)	24.7	29.7	21.4	24.7
OS rate at 12 mos	50%	87%	72%	71%
OS rate at 18 mos	33%	60%	62%	55%
Median OS (wks)	50.5	83.4	89.6	83.4

Participants will be evaluated with the combination of nivolumab and chemotherapy (gemcitabine+cisplatin) as follows:

- Cisplatin-eligible metastatic urothelial carcinoma participants (Sub-study, Arm C)
  - nivolumab + gemcitabine with cisplatin (up to 6 cycles), followed by nivolumab maintenance therapy for those without disease progression following combination therapy
    NOTE: The chemotherapy backbone is as in Arms B and D

As the PK of nivolumab is linear, the corresponding flat dose of nivolumab for an every 6-week schedule is 360 mg. The simulated steady state concentration at trough (C_{minss}), peak (C_{maxss}), and average (C_{avgss}) with 480 mg are less than 10 mg/kg every 2 weeks. Thus, these regimens are expected to be safe and tolerable.

3.2 Background

3.2.1 Bladder Cancer

UC of the bladder is the ninth most common cancer in the world (1)[1], and the fifth most common malignancy in the United States.[2] Approximately 20% to 25% of all patients with UC of the bladder develop metastatic disease, resulting in an estimated 15,580 deaths in 2014 in the United States.[3] Nonmuscle-invasive tumors account for 75–85% of bladder neoplasms while the remaining 15–25% are muscle-invasive or metastatic at the time of initial presentation.[37] In 2015, an estimated 74,000 patients were diagnosed with bladder cancer in the USA and approximately 16,000 patients succumbed to the disease. Bladder cancer is more common in men with nearly a 3:1 incidence. The vast majority of cases are urothelial carcinoma (previously known as transitional cell carcinoma) while mixed histologies and pure variant histologies, such as adenocarcinoma and squamous cell carcinoma, comprise a smaller subset.[2] While urothelial cancers predominantly arise in the bladder, given that the urothelium extends from the renal pelvis to the urethra, such cancers can arise from any of these locations in the genitourinary tract. Once invasive into the muscularis propria, urothelial cancer of the bladder is an aggressive disease that requires multimodal treatment with surgery or radiation therapy with or without chemotherapy. Despite multimodality treatment, more than 50% of patients will develop metastatic disease. The median survival of patients with metastatic urothelial cancer of the bladder is only 12–14 months.[12]

Chemotherapy is standard treatment for metastatic UC. Cisplatin is among the most active agents in UC and cisplatin-based combination chemotherapy is the treatment of choice for patients with metastatic urothelial bladder cancer. Commonly used regimens such as gemcitabine plus cisplatin or MVAC (methotrexate, vinblastine, doxorubicin, plus cisplatin) yield objective responses in 50% to 60% of patients, with complete responses in 10% to 20%. However, gemcitabine and cisplatin treatment was associated with a better safety profile and improved tolerability and has become a standard regimen for patients with metastatic UC.

Treatment of cisplatin-ineligible or "unfit" patients. In clinical practice, more than 50% of all patients with unresectable or metastatic UC have contraindications for treatment with cisplatin.

Renal dysfunction (usually defined as a creatinine clearance of < 60 ml/minute), poor performance status, and advanced age are relatively common and preclude cisplatin chemotherapy. While no standard treatment has been defined for cisplatin-unfit patients, carboplatin-containing regimens are considered appropriate alternatives vs cisplatin-based therapy, based on performance status and kidney function defined by GFR. Although the combination of gemcitabine plus carboplatin is commonly used in cisplatin-ineligible patients, patients who are not candidates for cisplatin-containing chemotherapy regimens have significantly worse outcomes with regard to response to treatment and OS, and there is no consensus on the standard chemotherapy treatment for cisplatin-unfit patients.

To date, combination regimens that do not include cisplatin have never been shown to improve survival. Despite the initial chemosensitivity of UC of the bladder, responses generally are short-lived; the median survival of patients with metastatic disease is approximately 14 months. Visceral metastases and poor performance status are adverse prognostic factors associated with a lower likelihood of response to chemotherapy and shorter survival.

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.[38,39,40] Current immunotherapy efforts attempt to break the apparent tolerance of the immune system to tumor cells and antigens by either 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).[41] 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.[42] PD-1 signaling has been shown to inhibit CD-28-mediated upregulation of IL-2, IL-10, IL-13, interferon-γ (IFN-γ) and Bcl-xL. PD-1 expression 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.[43] 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 CMV re stimulation assay with human 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 versus 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).[44]

3.2.3 Ipilimumab Mechanism of Action

CTLA-4, an activation-induced T-cell surface molecule, is a member of the CD28:B7 immunoglobulin superfamily that competes with CD28 for B7. CTLA-4 mediated signals are inhibitory and turn off T cell-dependent immune responses.[45] Ipilimumab is a fully human monoclonal IgG1κ that binds to the CTLA-4 antigen expressed on a subset of T cells from human and nonhuman primates. The proposed mechanism of action for ipilimumab is interference of the interaction of CTLA-4 with B7 molecules on APCs, with subsequent blockade of the inhibitory modulation of T-cell activation promoted by the CTLA 4/B7 interaction.

3.2.4 Nivolumab plus Ipilimumab Evidence

The combination of nivolumab and ipilimumab was chosen because of preclinical and clinical evidence supporting synergy between these two established checkpoint blockade inhibiting monoclonal antibodies.

Preclinical data indicate that the combination of PD-1 and CTLA-4 receptor blockade may improve antitumor activity. In vitro combinations of nivolumab plus ipilimumab increase IFN-γ production 2-fold to 7-fold over either agent alone in a mixed lymphocyte reaction.[46] Several preclinical syngeneic tumor models showed that combined treatment with anti-murine PD-1 and anti-murine CTLA-4 monoclonal antibody (mAb) resulted in increased antitumor responses over either mAb alone which were greatest when the antibodies were given together rather than sequentially.[46] In some instances, combined treatment resulted in tumor-free mice that exhibited long-lived tumor immunity when re-challenged with tumor cells.[46] In a murine melanoma vaccine model, blockade with either CTLA-4 or PD-1 antibodies increased the proportion of CTLA-4 and PD-1-expressing CD4/CD8 tumor infiltrating T effector cells, and dual blockade increased tumor infiltration of T effector cells and decreased intratumoral T regulatory cells, as compared to either agent alone.[47]

The combination of nivolumab and ipilimumab was initially studied in participants with unresectable or metastatic melanoma in the Phase 1 dose escalation study CA209004. In this study, the 3 mg/kg nivolumab plus 3 mg/kg ipilimumab dosing regimen exceeded the maximum tolerated dose (MTD) per protocol.[48] In CA209004, while both Cohort 2 (1 mg/kg nivolumab + 3 mg/kg ipilimumab) and Cohort 2a (3 mg/kg nivolumab + 1 mg/kg ipilimumab) had similar clinical activity, a dose of 1 mg/kg nivolumab every 3 weeks combined with 3 mg/kg of ipilimumab every 3 weeks for a total of four doses, followed by nivolumab 3 mg/kg every 2 weeks until progression was chosen.[46] This dose level has been approved in participants with advanced melanoma in the US based on the Phase 3 study CA209067 which demonstrated that the combination of nivolumab

and ipilimumab had increased benefit compared to either nivolumab or ipilimumab monotherapy in participants with advanced melanoma.[49]

The combination of nivolumab with ipilimumab is being studied in the Phase 1 study CA209016.[50] Participants with mRCC (favorable/intermediate MSKCC score; Karnofsky performance status > 80%; untreated or any number of prior therapies) were randomized to receive

- nivolumab 3 mg/kg + ipilimumab 1 mg/kg (arm N3 + I1) or
- nivolumab 1 mg/kg + ipilimumab 3 mg/kg (arm N1 + I3) IV Q3W for 4 doses followed by nivolumab 3 mg/kg IV Q2W until progression/toxicity.

The primary objective was to assess safety/tolerability; secondary objective was to assess antitumor activity. Participants were randomized to N3 + I1 (n = 21) and N1 + I3 (n = 23). Most patients (n = 34; 77%) had prior systemic therapy (N3 + I1: 16; N1 + I3: 18). The confirmed ORR was 43% (N3 + I1) and 48% (N1 + I3). Duration of response (DOR) was 4.1+ to 42.1+ weeks (7 of 9 responses ongoing) in N3 + I1, and 12.1+ to 35.1+ weeks (9 of 11 responses ongoing) in N1 + I3. Best response of stable disease (SD) was seen in 5 (24%) patients (N3 + I1) and 8 (35%) pts (N1 + I3). Median PFS was 36.6 weeks (N3 + I1) and 38.3 weeks (N1 + I3); these data are still immature, with 11 of 21 events reported for N3 + I1 and 10 of 23 events reported for N1 + I3.[51]

The safety of nivolumab combined with ipilimumab was assessed in study CA209016. Treatment-related adverse events (AEs) were seen in 83 of 94 patients (88%), including 39 of 47 (83%) in N3 + I1 and 44 of 47 (94%) in N1 + I3. The most frequently reported drug-related AEs in participants treated with 3 mg/kg nivolumab + 1 mg/kg ipilimumab included fatigue (23 participants, 48.9%), rash and pruritus (12 participants, 25.5% each), and diarrhea and nausea (11 participants, 23.4% each); the majority were Grade 1- 2. The most frequently reported drug-related AEs in participants treated with 1 mg/kg nivolumab + 3 mg/kg ipilimumab included fatigue (30 participants, 63.8%); nausea and diarrhea (20 participants, 42.6% each), and lipase increased (16 participants, 34.0%). The majority were Grade 1-2.

Treatment-related AEs leading to discontinuation (21% vs 11%), and treatment-related SAEs (34% vs 21%) all occurred more commonly in participants in the N1 + I3 arm than in the N3 + I1 arm, respectively.[51]

In the Phase 1 study CA209004, ascending doses of nivolumab have been studied concomitantly with ascending doses of ipilimumab in participants with unresectable or metastatic melanoma. In each arm in this multi-arm study, ipilimumab was administered once every 3 weeks for 4 doses with nivolumab administered once every 3 weeks for 8 doses. Starting at week 24, ipilimumab and nivolumab were administered once every 12 weeks for 8 doses. The 3 initial dose-escalation cohorts consisted of Cohort 1 (nivolumab 0.3 mg/kg plus ipilimumab 3 mg/kg; n = 14), Cohort 2 (nivolumab 1.0 g/kg plus ipilimumab 3 mg/kg; n = 17) and Cohort 3 (nivolumab 3.0 mg/kg plus ipilimumab 3 mg/kg; n = 6). Later, the study was amended to include Cohort 2a which evaluated nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (n = 16).

As of the 15-Feb-2013 clinical cut-off in CA209004, of the 52 participants evaluable for response, 21 participants (40%) had an objective response by modified World Health

Organization (mWHO) criteria. In an additional 2 participants (4%) there was an unconfirmed objective response. In Cohort 1 (0.1 mg/kg nivolumab + 3 mg/kg ipilimumab), 3 out of 14 evaluable participants had an objective response by mWHO (21%); 1 complete response (CR) and 2 participants with a partial response (PR) with an additional PR observed by immune-related mWHO criteria (irPR).[52] In Cohort 2 (1 mg/kg nivolumab + 3 mg/kg ipilimumab), 9 out of 17 evaluable participants had an objective response by mWHO (53%; 3 CRs (18%), 6 PRs (35%) with two additional participants experiencing immune-related SD (irSD). In Cohort 2a (3 mg/kg nivolumab + 1 mg/kg ipilimumab), 6 out of 15 response evaluable participants had an objective response rate by mWHO (40%; 1 CR (7%), 5 PRs (33%) with 2 additional uPRs (13%) and 2 irSDs and 1 irPR). In Cohort 3 (3 mg/kg nivolumab + 3 mg/kg ipilimumab), 3 out of 6 evaluable participants had an objective response by mWHO (50%; 3 PRs (50%) with 1 additional irPR and 1 irSD.

Preliminary analysis revealed 16 of the 52 evaluable participants (31%) had > 80% reduction in the size of target tumor lesions by the week 12 evaluation. This is compared to < 2% for 3 mg/kg ipilimumab monotherapy based on CA184020 (N = 540) and < 3% for nivolumab monotherapy based on CA209003 (N = 94, 0.1-10 mg/kg).

The following DLTs were observed in Cohort 1 - Grade 3 elevated AST/ALT (1 participant); in Cohort 2 - Grade 3 uveitis (1 participant) and Grade 3 elevated AST/ALT (1 participant) and in Cohort 3 - Grade 4 elevated lipase (2 participants) and Grade 3 elevated lipase (1 participant). Based on these data, Cohort 2 was identified as the maximum tolerated dose (MTD) and Cohort 3 exceeded the MTD.

A total of 53 melanoma participants were treated with nivolumab combined with ipilimumab in CA209004 across cohorts 1, 2, 2a, and 3. At least one AE regardless of causality has been reported in 98% of participants treated. The most common (reported at > 10% incidence) treatment related AEs (any Grade %; Grade 3-4 %: 93; 53) are rash (55; 4), pruritus (47; 0), vitiligo (11; 0), fatigue (38; 0), pyrexia (21, 0), diarrhea (34; 6), nausea (21, 0), vomiting (11, 2), ALT increased (21; 11), AST increased (21; 13), lipase increased (19; 13), amylase increased (15, 6), headache (11, 0), and cough (13, 0).

The majority of AEs leading to discontinuation (regardless of causality) were Grade 3 or 4 (reported in 11 of 53 participants, 21%). Grade 3 events included lipase increased, ALT increased, AST increased, troponin I increased, colitis, diverticular perforation, pancreatitis, tachycardia, renal failure acute, choroiditis, autoimmune disorder, and pneumonitis. One participant each discontinued due to Grade 4 events of blood creatinine increased and AST increased. No drug-related deaths were reported.[53]

3.3 Benefit/Risk Assessment

3.3.1 Benefit/Risk Assessment for Primary Study

Metastatic UC is an aggressive disease; patients have a median survival of approximately 15 months when treated with modern chemotherapy regimens. While objective response rates to frontline therapy are generally high, nearly all patients with metastatic, unresectable UC will

progress. Therefore, new therapeutic options that will result in durable responses are urgently needed in metastatic UC. Several lines of evidence, as outlined in Section 3.1.2, strongly support the investigation of immunotherapy agents to improve outcomes for patients with metastatic, unresectable UC.

Safety and efficacy have been demonstrated with both single agent nivolumab and ipilimumab. The combination of dual check-point blockade with both of these agents administered together has an efficacy advantage over either single agent alone. Same day sequential administration of nivolumab (1 mg/kg) followed by ipilimumab (3 mg/kg) was initially evaluated in advanced/metastatic melanoma in 2 studies, the Phase 2 study CA209069 and the Phase 3 study CA209067, and demonstrated statistically significant and clinically meaningful improvements in progression-free survival (PFS) and objective response rate (ORR) compared to nivolumab or ipilimumab monotherapy.[51,54] and served as the basis for an application to extend the indication of Opdivo® to include the use of nivolumab and ipilimumab in combination for the treatment of advanced melanoma (United States Packaging Insert [USPI] for nivolumab and Summary of Product Characteristics [SmPC] for nivolumab). Subsequently, nivolumab plus ipilimumab has also demonstrated clinical activity in several tumor types, including renal cell cancer (RCC),[55] NSCLC,[56] small cell lung cancer (SCLC),[57] and gastric cancer.[58]

Results to date suggest that the safety profile of nivolumab plus ipilimumab combination therapy is consistent with the mechanisms of action of nivolumab and ipilimumab. The nature of the AEs is similar to that observed with either agent used as monotherapy; however, both frequency and severity of most AEs are increased with the combination. The adverse event profile of nivolumab 1 mg/kg combined with ipilimumab 3 mg/kg characterized by immune-related toxicities, such as diarrhea, rash, pneumonitis, liver toxicity, and endocrinopathies. These events were mostly low grade and manageable with well-established treatment algorithms that included the use of corticosteroids.

Extensive details on the safety profile of nivolumab are available in the Investigator Brochure, and will not be repeated herein.

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

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

Additional details on the safety profile of nivolumab, and ipilimumab, including results from other clinical studies, are also available in the nivolumab IB[51] and ipilimumab IB,[59] respectively.

3.3.2 Benefit/Risk Assessment for Substudy

The potential benefit of nivolumab, (which was recently approved by FDA for advanced or metastatic UC patients who progressed on first line or recent peri-operative platinum therapy) in combination with platinum-doublet chemotherapy over standard-of-care platinum-based first-line chemotherapy is supported by both CheckMate 012 as well as data with other PD-1 inhibitors, eg pembrolizumab in Keynote 021. The response rate observed from the two studies ranges from 33% to 55% regardless of PD-L1 expression levels. In KN021, which to date is the only randomized study, albeit with a very small sample size, the addition of a PD-1 inhibitor significantly increased ORR and prolonged PFS. All published data to date indicate that a similar magnitude of benefit is observed with IO/chemo combinations regardless of PD-L1 expression level. Together, these data suggest that addition of nivolumab to platinum-doublet chemotherapy could provide benefit over doublet alone in a broad population of patients. The platinum-based chemotherapy regimens have similar clinical activity and well described safety profiles, characterized by myelosuppression and other regimen-specific non-hematologic toxicities, such as peripheral neuropathy, nausea/vomiting, and renal impairment. The safety profile of PD-1 agent plus platinum-doublet chemotherapy reflects additive toxicities of the individual agents, which were manageable using established safety guidelines. The frequency of most immune-related, select AEs was higher with nivolumab/pembrolizumab plus platinum-doublet chemotherapy compared to platinum-doublet. However, these treatment-related AEs, including pneumonitis, were effectively managed and did not lead to any deaths.

The potential benefit of nivolumab combined with platinum-doublet chemotherapy in the treatment of cisplatin-eligible metastatic UC patients compared to SOC platinum-based first-line chemotherapy, will be evaluated in Arms C and D of the sub-study as follows: nivolumab combined with platinum-doublet chemotherapy (Arm C), or platinum doublet chemotherapy (Arm D), stratified by PD-L1 status < 1%, cisplatin-eligibility, and liver metastasis.

To assure an ongoing favorable risk/benefit assessment for participants enrolled onto CA209901, an independent Data Monitoring Committee (DMC) will be utilized to monitor the safety and clinical activity of the treatments throughout the conduct of the trial, until the primary end-point for the sub-study is reached (See Section 5.5.1).

4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints: Primary Study

Objectives	Endpoints
Primary	
• To compare Overall Survival (OS) of nivolumab combined with ipilimumab versus standard of care (SOC) chemotherapy in cisplatin-ineligible participants with previously untreated, unresectable or metastatic urothelial carcinoma (UC).	• Primary endpoint of OS in cisplatin-ineligible randomized participants
• To compare OS of nivolumab combined with ipilimumab versus standard of care (SOC) chemotherapy in PD-L1 positive (≥ 1%) participants with previously untreated, unresectable or metastatic UC.	• Primary endpoint of OS in PD-L1 positive (≥ 1%) randomized participants by immunohistochemistry (IHC)
Secondary	
• To compare OS of nivolumab combined with ipilimumab versus SOC chemotherapy in all randomized participants with previously untreated, unresectable or metastatic UC.	• OS in all randomized participants
• To evaluate Progression-Free Survival (PFS) of nivolumab combined with ipilimumab versus SOC chemotherapy in cisplatin-ineligible randomized participants, in PD-L1 positive (≥1%) randomized participants and in all randomized participants with previously untreated, unresectable or metastatic UC.	• PFS by blinded independent central review (BICR) (using RECIST 1.1) in cisplatin-ineligible randomized participants, in PD-L1 positive (≥1%) randomized participants and in all randomized participants
• To evaluate changes from baseline in Health-Related QOL (HRQoL) of nivolumab combined with ipilimumab versus SOC chemotherapy in all randomized participants with previously untreated, unresectable or metastatic UC.	• European Organisation for Research and Treatment of Care (EORTC) QLQ-C30 Global Health Status score in all randomized participants
Exploratory	
• To estimate objective response rate (ORR) (using RECIST 1.1) of nivolumab combined with ipilimumab versus SOC chemotherapy.	• ORR by BICR (using RECIST 1.1)
• To assess the efficacy (OS, PFS, and ORR) of nivolumab combined with ipilimumab versus SOC chemotherapy in cisplatin-eligible participants with previously untreated, unresectable or metastatic UC.	• OS, PFS, and ORR by BICR (using RECIST 1.1) in cisplatin-eligible participants with previously untreated, unresectable or metastatic UC
• To assess the safety and tolerability of nivolumab combined with ipilimumab versus SOC chemotherapy.	• AEs, clinical laboratory values, vital signs, or other safety biomarkers
• To assess changes in reported global health outcomes based on EuroQol's EQ-5D-5L.	• EQ-5D-5L index score, EQ-5D-5L dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety), and EQ-5D-5L visual analog scale (VAS).

Table 4-1: Objectives and Endpoints: Primary Study

Objectives	Endpoints
• To evaluate HRQoL as assessed by EORTC QLQ-C30.	• QLQ-C30 Functional scales; QLQ-C30 Symptom scales
• To evaluate whether PD-L1 expression is a predictive biomarker of efficacy (ORR) of nivolumab combined with ipilimumab as first-line therapy in participants with previously untreated, unresectable or metastatic UC.	• ORR by BICR (using RECIST 1.1) by PD-L1 expression at ≥ 1% expression by immunohistochemistry (IHC)
• To characterize the pharmacokinetics of nivolumab combined with ipilimumab as first-line therapy in participants with previously untreated, unresectable or metastatic UC.	• PK parameters, exposure-response relationship between select PK measures of exposure and safety and efficacy endpoints, if applicable
• To characterize the immunogenicity of nivolumab combined with ipilimumab as first-line therapy in participants with previously untreated, unresectable or metastatic UC.	• Incidence of anti-nivolumab and anti-ipilimumab antibody levels and their potential relationship with safety and efficacy endpoints
• To evaluate the pharmacodynamic and immunomodulatory activity of nivolumab combined with ipilimumab.	• Including but not limited to correlative analyses between gene expression profiling, flow cytometric analyses of peripheral blood mononuclear cells (PBMCs), myeloid derived suppressor cells and serum soluble factor analysis in peripheral blood samples and ORR, PFS, and OS
• To investigate the association between biomarkers in the peripheral blood and tumor tissue with efficacy.	• Including but not limited to correlative analyses between baseline and on-treatment soluble factors (eg, CXCL9, CXCL10, gamma interferon signature, baseline PD-L1/PD-L2, mutational analyses in tumor tissue) with ORR, PFS, and OS

Table 4-2: Objectives and Endpoints: Substudy

Objectives	Endpoints
Primary	
• To compare PFS of nivolumab combined with SOC chemotherapy versus SOC chemotherapy in cisplatin-eligible participants with previously untreated, unresectable or metastatic urothelial carcinoma (UC)	• PFS by BICR (using RECIST 1.1) in cisplatin-eligible participants with previously untreated, unresectable or metastatic UC
• To compare OS of nivolumab combined with SOC chemotherapy versus SOC chemotherapy in cisplatin-eligible participants with previously untreated, unresectable or metastatic UC	• OS in cisplatin-eligible participants with previously untreated, unresectable or metastatic UC
Secondary	
• To evaluate changes from baseline in Health-Related QOL (HRQoL) of nivolumab combined with SOC chemotherapy versus SOC chemotherapy in cisplatin-eligible participants with previously untreated, unresectable or metastatic UC.	• European Organisation for Research and Treatment of Care (EORTC) QLQ-C30 Global Health Status score
• To evaluate whether PD-L1 expression is a predictive biomarker of efficacy (PFS and OS) of nivolumab combined with SOC chemotherapy as first-line therapy in cisplatin-eligible participants with previously untreated, unresectable or metastatic UC.	• PFS by BICR (using RECIST 1.1) and OS by PD-L1 expression at ≥ 1% expression by immunohistochemistry (IHC)
Exploratory	
• To estimate ORR (using RECIST 1.1) of nivolumab combined with SOC chemotherapy versus SOC chemotherapy.	• ORR by BICR (using RECIST 1.1)
• To assess the safety and tolerability of nivolumab combined with SOC chemotherapy versus SOC chemotherapy.	• AEs, clinical laboratory values, vital signs, or other safety biomarkers
• To assess changes in reported global health outcomes based on EuroQol's EQ-5D-5L.	• EQ-5D-5L index score, EQ-5D-5L dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety), and EQ-5D-5L VAS.
• To evaluate HRQoL as assessed by EORTC QLQ-C30.	• QLQ-C30 Functional scales; QLQ-C30 Symptom scales
• To evaluate whether PD-L1 expression is a predictive biomarker of efficacy (ORR) of nivolumab combined with SOC chemotherapy as first-line therapy in participants with previously untreated, unresectable or metastatic UC.	• ORR by BICR (using RECIST 1.1) PD-L1 expression at ≥ 1% expression by immunohistochemistry (IHC)
• To characterize the pharmacokinetics of nivolumab combined with SOC chemotherapy as first-line therapy in participants with previously untreated, unresectable or metastatic UC.	• PK parameters, exposure-response relationship between select PK measures of exposure and safety and efficacy endpoints, if applicable
• To characterize the immunogenicity of nivolumab combined with SOC chemotherapy as first-line therapy in participants with previously untreated, unresectable or metastatic UC.	• Incidence of anti-nivolumab antibody levels and their potential relationship with safety and efficacy endpoints

Table 4-2: Objectives and Endpoints: Substudy

Objectives	Endpoints
• To evaluate the pharmacodynamic and immunomodulatory activity of nivolumab combined with SOC chemotherapy.	• Including but not limited to correlative analyses between gene expression profiling, flow cytometric analyses of PBMCs, myeloid derived suppressor cells and serum soluble factor analysis in peripheral blood samples and ORR, PFS, and OS
• To investigate the association between biomarkers in the peripheral blood and tumor tissue with efficacy.	• Including but not limited to correlative analyses between baseline and on-treatment soluble factors (eg, CXCL9, CXCL10, gamma interferon signature, baseline PD-L1/PD-L2, mutational analyses in tumor tissue) with ORR, PFS, and OS

5 STUDY DESIGN

5.1 Overall Design

This will be a randomized, open-label, Phase 3 study comparing combination therapy of nivolumab (1 mg/kg 30 minute IV infusion) plus ipilimumab (3 mg/kg 30 minute IV infusion) administered every 3 weeks for up to four doses, followed by nivolumab monotherapy (480 mg 30 minute IV infusion) administered every 4 weeks, versus the standard of care (SOC; gemcitabine-cisplatin or gemcitabine-carboplatin) in participants with previously untreated unresectable or metastatic UC.

In addition a substudy of treatment with nivolumab (360 mg) in combination with SOC (cisplatin-gemcitabine) for up to 6 cycles followed by nivolumab monotherapy (480 mg) versus SOC alone (up to 6 cycles) will be evaluated in cisplatin-eligible participants with previously untreated unresectable or metastatic UC will be evaluated.

Primary Study:

Prior to initiation of the substudy, participants will be randomized 1:1 to treatment Arm A or B and stratified by PD-L1 status < 1%, cisplatin-eligibility, and liver metastasis.

- Arm A (nivolumab 1 mg/kg plus ipilimumab 3 mg/kg [N1 + I3], followed by nivolumab monotherapy)
- Arm B (standard of care [SOC] platinum chemotherapy doublet, 3 week cycles, up to 6 cycles).

Participants in Arm A will receive combination therapy (N1+I3) for up to 4 doses (Part 1), followed by nivolumab monotherapy (480 mg every 4 weeks; Part 2). Monotherapy will begin 6 weeks following the last dose of combination therapy and continue until confirmed disease progression, unacceptable toxicity, or participant withdrawal of consent, or 24 months from first dose, whichever comes first. Participants randomized to Arm B may receive up to 6 cycles of SOC treatment (gemcitabine/cisplatin for cisplatin-eligible participants or gemcitabine/carboplatin for cisplatin-ineligible participants, additional cycles may be permitted as per local guidelines).

In Part 1 of Arm A, a minimum of 1 combination cycle of nivolumab and ipilimumab is required before participants can proceed to monotherapy. Participants in Arm A experiencing AEs related to combination dose therapy that do not meet dose discontinuation criteria, may proceed to nivolumab monotherapy dosing (Part 2) without completing all 4 combination doses, after consultation with BMS Medical Monitor, on a case-by-case basis. In Arm B, participants assigned to receive cisplatin-gemcitabine, may be eligible to switch to carboplatin-gemcitabine following a minimum of 1 cycle of cisplatin-gemcitabine, and after consultation with the Medical Monitor.

Substudy

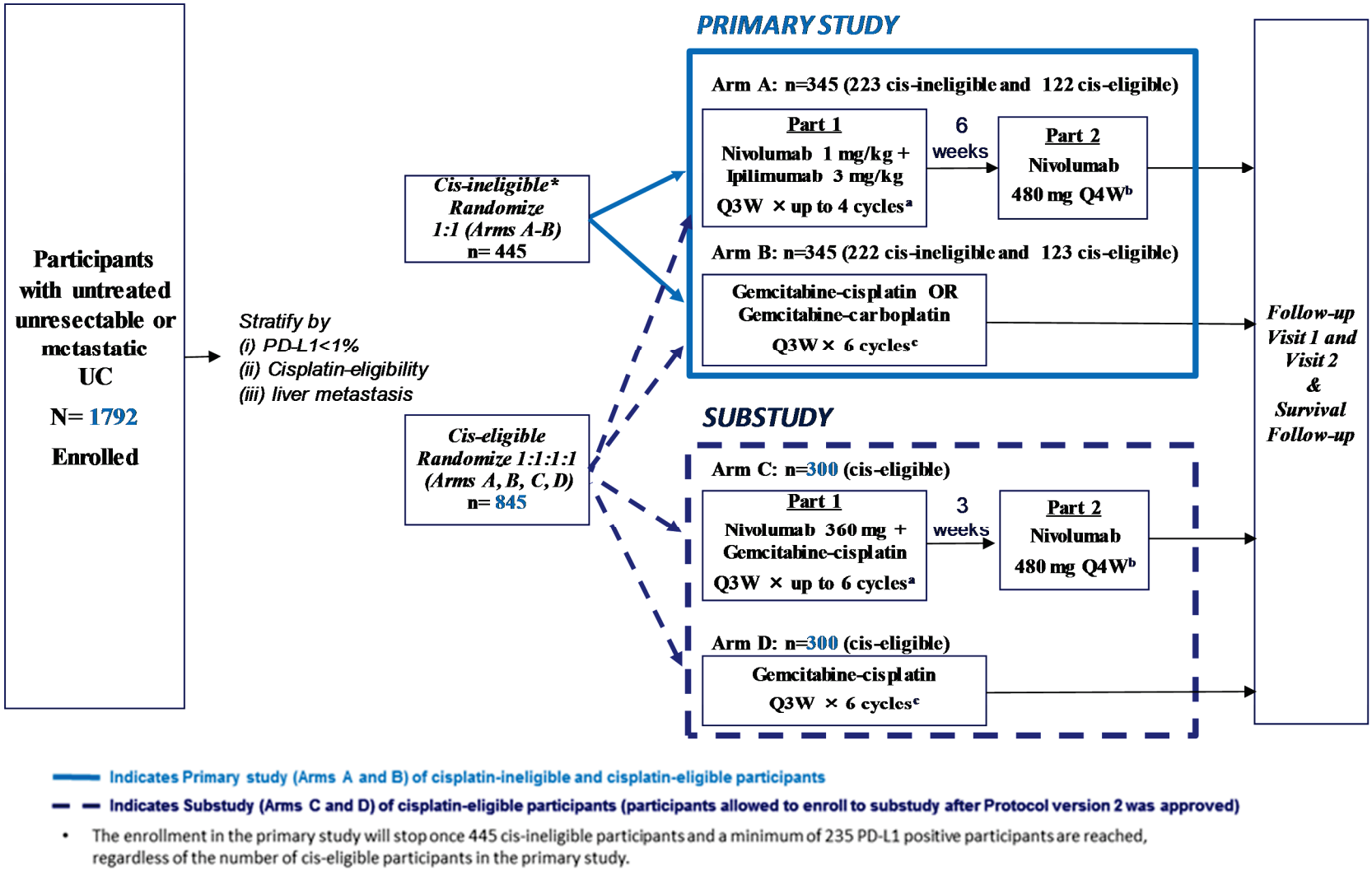
The substudy consists of Arms C and D:

- Arm C: Nivolumab (360 mg) in combination with gemcitabine-cisplatin) every 3 weeks for up to 6 cycles, followed by nivolumab monotherapy (480 mg) every 4 weeks. Monotherapy will begin 3 weeks following the last dose of combination therapy and continue until confirmed disease progression, unacceptable toxicity, participant withdrawal of consent, or 24 months from first dose, whichever comes first.
- Arm D: Gemcitabine-cisplatin for up to 6 cycles (additional cycles may be permitted as per local guidelines).

Once the substudy is initiated, cisplatin-ineligible participants will continue to be randomized 1:1 to Arms A or B. Cisplatin-eligible participants will be randomized across Arms A through D, and stratified by PD-L1 status < 1%, cisplatin-eligibility, and liver metastasis. Once approximately 445 cisplatin-ineligible participants and 235 PD-L1 positive participants are enrolled into Arms A and B, enrollment of the primary study (Arms A and B) will stop (see Section 5.2). Only cisplatin-eligible will continue to be enrolled into the substudy (Arms C and D).

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

Figure 5.1-1: Study Design Schematic



[a] Arm A and Arm C: In Part 1, a minimum of 1 cycle of combination therapy is required before proceeding to nivolumab monotherapy dosing (Part 2). Participants should be dosed **no less than 19 days between combination treatment** cycles for Arm A combination therapy.

[b] In Arm A, monotherapy should begin 6 weeks following the last combination dose. **In Arm C, monotherapy will begin 3 weeks following the last combination therapy. During monotherapy participants should be dosed no less than 26 days between monotherapy treatments.** Participants in Arms A and C will be treated until confirmed progression of disease, unacceptable toxicity, withdrawal of consent, or up to 24 months of treatment, whichever occurs first.

[c] Arms B and D participants will receive up to a maximum of 6 cycles per protocol. Additional optional cycles of SOC may be given per local guidelines. See Section 7.1.3.1.

NOTES: All participants will be randomized 1:1 to Arms A or B during the primary study, prior to substudy initiation. Following initiation of the substudy, cisplatin-eligible patients will be randomized to Arms, A, B, C or D. Cisplatin-ineligible patients are not eligible for Arms C and D treatment.

Once at least 445 cisplatin-ineligible participants and at least 235 PD-L1 positive (≥ 1%) participants by IHC are randomized into Arms A and B of the primary study, the primary study will cease enrollment (Arms A and B). Cisplatin-eligible participants will continue enrollment into Arms C and D.

Randomized participants will be evaluated for progression beginning at Week 9 (± 1 week) and then every 8 weeks (± 1 week) for 48 weeks, followed by evaluations every 12 weeks thereafter, until progression or end of treatment, whichever occurs later.

Primary endpoints in the primary study: Overall Survival in cisplatin-ineligible participants and in PD-L1 positive (≥ 1%) participants by IHC; key secondary endpoint: Overall Survival in all randomized participants (hierarchical testing procedure) and Progression Free Survival.

Primary endpoints in the substudy: Progression Free Survival and OS primary endpoints in cisplatin-eligible participants.

5.1.1 Data Monitoring Committee and Other External Committees

A Data Monitoring Committee (DMC) will be established to provide oversight of safety and efficacy considerations in protocol CA209901. Additionally, the DMC will provide advice to the sponsor regarding actions the committee deems necessary for the continuing protection of participants enrolled in the study. The DMC will be charged with assessing such actions in light of an acceptable benefit/risk profile for nivolumab. The DMC will act in an advisory capacity to BMS and will monitor participant safety and evaluate the available efficacy data for the study. Details regarding the responsibilities of the DMC including frequency of meetings will be included in the DMC charter. The oncology therapeutic area of BMS has primary responsibility for design and conduct of the study.

When required, adjudicated events will be submitted to the DMC and Health Authorities for review on a specified timeframe in accordance with the adjudication documentation.

5.1.1.1 Blinded Independent Central Review Committee

A blinded independent central review (BICR) will be utilized in this study for determination of BICR-assessed PFS and ORR endpoints. All available tumor assessment scans for all randomized participants will be reviewed. Details of BICR procedures will be specified in the Imaging Manual.

Additional activities and medical monitoring to ensure participant safety include:

- Education of investigators and representatives of the sponsor on the nivolumab AE profile and management of potential immune-related adverse events through well-defined treatment algorithms.
- Ongoing safety monitoring by the BMS Medical Monitor, as well as assessment and review of safety signals across the entire nivolumab program through the BMS medical surveillance team (MST).
- Appropriate contraceptive methods (as outlined in Appendix 6) and pregnancy testing during the mandatory contraceptive period.

5.2 Number of Participants

Assuming a 28% screen failure rate, it is estimated that approximately 1792participants with previously untreated unresectable or metastatic UC will be enrolled with approximately 1290 participants randomized to the primary study and substudy:

- 445 cisplatin-ineligible participants will be randomized in a 1:1 ratio to receive nivolumab plus ipilimumab vs SOC chemotherapy (primary study);
- 245 cisplatin-eligible participants will be randomized in a 1:1 ratio to receive nivolumab plus ipilimumab vs SOC chemotherapy (primary study);
  - Of these 690 primary study participants, 235 PD-L1 positive (≥ 1%) participants by IHC are expected to be randomized
- 600 cisplatin-eligible participants will be randomized in a 1:1 ratio to receive nivolumab plus SOC chemotherapy vs SOC chemotherapy (substudy).

With revised protocol 04, randomization to the substudy is increased by 300 cisplatin eligible participates to ensure adequate power of dual primary endpoints OS and PFS.

Overall, approximately 445 cisplatin-ineligible participants (per eligibility criteria see Section 6.1) and 845 cisplatin-eligible participants will be randomized. Enrollment assumptions are a fixed accrual rate of 5 participants per month (2 cisplatin-ineligible participants per month) during the first 6 months, 14 participants per month (8 cisplatin-ineligible participants per month) between 6 and 12 months, and 30 participants per months between 12 and 18 months (19 cisplatin-ineligible participants per month) and 37 participants per months thereafter (26 cisplatin-ineligible participants per month). In addition, as of month 11, cisplatin-eligible participants are equally randomized to both primary study and substudy. Therefore once enrollment in the primary study is closed, the accrual rate in the substudy is assumed to be 18 cisplatin-eligible participants per month.

Based on the above information, it will take approximately 28 months to randomize 690 participants in the primary study (including 445 cisplatin-ineligible participants and 235 PD-L1 positive (≥ 1%) participants), given that an estimated 34% of the participants randomized in the primary study would be PD-L1 positive, and 44 months from substudy initiation (ie, 54 months from first participants randomized in the study) to randomize 600 cisplatin-eligible participants in the substudy.

Details regarding sample size calculation are found in Section 10.1.

Once at least 445 cisplatin-ineligible participants and at least 235 PD-L1 positive (≥ 1%) participants by IHC are randomized into Arms A and B of the primary study, the primary study will cease enrollment (Arms A and B).

5.3 End of Study Definition

The start of the trial is defined as first participant first screening visit. End of trial is defined as last participant last visit on the Schedule of Activities. Study completion is defined as the final date on which data for the primary endpoint was or is expected to be collected, if this is not the same.

5.4 Scientific Rationale for Study Design

A 2-arm open-label, randomized study will be employed to hierarchically demonstrate that treatment with nivolumab combined with ipilimumab will improve overall survival (OS) in (i) the high unmet need, primary population of cisplatin-ineligible, previously untreated, unresectable or metastatic UC participants as compared to standard of care (SOC) gemcitabine-plus-carboplatin chemotherapy and the high unmet need, primary population of PD-L1 positive (≥ 1%), previously untreated, unresectable or metastatic UC participants as compared to standard of care (SOC) gemcitabine-plus-carboplatin chemotherapy and (ii) all randomized participants as compared to SOC chemotherapy. The sample size of the primary study accounts for the comparison of the primary endpoint (OS) in the two primary populations (cisplatin-ineligible participants and PD-L1 positive (≥ 1%) participants by IHC) followed by all randomized participants.

5.4.1 Rationale for Duration of Treatment with Nivolumab and Ipilimumab

The optimal duration of immunotherapy is currently unknown. However, 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 different clinical trials in different tumor types with nivolumab or nivolumab combined to ipilimumab indicates that most of the responses are generally occurring early, with a median time to response of 2-4 months. [60,61] A recent analysis in a melanoma study suggests the majority of patients who discontinue nivolumab and/or ipilimumab for toxicity maintain disease control in the absence of further treatment.[62] Furthermore, a limited duration of ipilimumab including only 4 induction doses resulted in long term survival in patients with metastatic melanoma, with a sustained plateau in survival starting at around Year 3.[63]

For these reasons, in study CA209901, treatment with nivolumab will be given for up to 24 months in the absence of disease progression or unacceptable toxicity. Chemotherapy will be given as per the study dosing schedule. Participants who complete 24 months of nivolumab and have subsequent disease progression may reinitiate nivolumab at the same dose and schedule given previously on study and continue such treatment for up to 1 additional year provided criteria for treatment beyond progression (Section 7.4.5) are met.

5.5 Justification for Dose

5.5.1 Rationale for Nivolumab and Ipilimumab Dose and Schedule

In CheckMate 032 (NCT01928394), an open-label, multicenter Phase 1/2 study of patients with metastatic UC who progressed after prior platinum-based therapy, patients with locally advanced or metastatic UC previously treated with platinum-based therapy for metastatic disease were included in the study. Patients were treated with either of two combination schedules, nivolumab 1 mg/kg + ipilimumab 3 mg/kg (N1I3) or nivolumab 3 mg/kg + ipilimumab 1 mg/kg (N3I1) every 3 weeks for four cycles, followed by nivolumab 3 mg/kg every 2 weeks, or nivolumab monotherapy 3 mg/kg (N3) every 2 weeks. All patients were treated until disease progression or unacceptable toxicity. The primary endpoint was investigator-assessed objective response rate (ORR) by RECIST v1.1. Secondary endpoints included safety, duration of response (DoR), and overall survival (OS).

Investigator-assessed ORR was 38.0%, 26.9%, and 25.6% in N1I3, N3I1 and N3 groups, respectively after a minimum follow-up of 7.9 months in N1I3 (n=92) group, 38.8 months in the N3I1 group (n=104) and 37.7 months in N3 group (n=78).[64] The investigator- assessed median DOR was 22.93, 22.34, and 30.52 months in N1I3, N3I1, and N3 arms, respectively. The BICR assessed ORR was 37.0% and 20.5% in the N1I3 and N3 arms, respectively. The frequency of drug-related grade 3-4 adverse events were higher in both combination groups (39.1% in N1I3, 30.8% in N3I1) than in the N3 group (26.9%). Treatment-related adverse events led to discontinuation in 13.0% (N1I3), 12.5% (N3I1), and 3.8% (N3) of patients. One death not related to disease progression was reported in the N3I1 group (pneumonitis), one was reported in the N3 group (pneumonitis and thrombocytopenia), and none reported in the N1I3 group.

Taken together, these data suggest that combination therapy with nivolumab and ipilimumab may provide the most favorable benefit-risk among the regimens studied and support the further development of the N1I3 combination as first-line therapy in metastatic UC.

5.5.2 Rationale for Flat Dose 480 mg Nivolumab every 4 weeks in Part 2 of Arms A and C (Nivolumab Monotherapy)

Nivolumab monotherapy has been extensively studied in a number of tumor types including NSCLC, melanoma, renal cell carcinoma (RCC), and colorectal cancer (CRC) with body weight normalized dosing (mg/kg). Nivolumab pharmacokinetics (PK) and exposures of participants in these studies have been characterized by population pharmacokinetic (PPK) analysis of data collected together with PK data from several Phase 1, 2, and 3 clinical studies of nivolumab monotherapy in solid tumors. PPK analyses have shown that the PK of nivolumab are linear, with dose proportional exposures over a dose range of 0.1 mg/kg to 10 mg/kg, and are similar across tumor types. Nivolumab clearance and volume of distribution were found to increase with increasing body weight, but the increase was less than proportional, indicating that a mg/kg dose represents an over-adjustment for the effect of body weight on nivolumab PK. Given the relationship between nivolumab PK and body weight, a flat dose is expected to lead to lower exposures in heavier participants, relative to the exposures in lighter participants.

Using the PPK model, nivolumab steady-state trough, peak and time-averaged concentration (Cminss, Cmaxss, and Cavgss, respectively) were predicted for a flat nivolumab dose of 240 mg Q2W and compared to those following administration of 3 mg/kg Q2W in NSCLC, melanoma, and RCC participants. A dose of 240 mg nivolumab is identical to a dose of 3 mg/kg for participants weighing ~ 80 kg, which is the approximate median body weight of participants in the Phase 2 and 3 BMS clinical studies of nivolumab monotherapy. Using a PPK model, the overall distributions of nivolumab exposures (Cavgss, Cminss, Cmaxss, and Cmin1) are comparable after treatment with either 3 mg/kg or 240 mg nivolumab. The predicted range of nivolumab exposures (median and 90% prediction intervals) resulting from a 240 mg flat dose across the 35 to 160 kg weight range is maintained well below the corresponding exposures observed with the well tolerated 10 mg/kg nivolumab Q2W dosage. Given the similarity of nivolumab PK across tumor types and the similar exposures predicted following administration of a 240 mg flat dose compared to 3 mg/kg, it is expected that the safety and efficacy profile of nivolumab following a flat dose will be similar to that of 3 mg/kg nivolumab dose.

Across the various tumor types in the BMS clinical program, nivolumab has been shown to be safe and well tolerated up to a dose level of 10 mg/kg, and the relationship between nivolumab exposure produced by 3 mg/kg and efficacy has been found to be relatively flat. Taken together, the PK, safety, and efficacy data indicate that the safety and efficacy profile of flat nivolumab dose every 2 weeks will be similar to that of a 3 mg/kg nivolumab every 2 weeks.

While 480 mg Q4W is predicted to provide greater (approximately 40%) maximum steady state concentrations and lower (approximately 15 to 20%) steady state trough concentrations, these exposures are predicted to be within the exposure ranges observed at doses up to 10 mg/kg Q2W used in the Phase 1 nivolumab clinical program, and are not considered to put participants at

increased risk. Similar to the nivolumab Q2W dosing monotherapy regimen, the exposures predicted following administration of nivolumab 480 mg Q4W, are on the flat part of the exposure-response curves for previously investigated tumors, melanoma and NSCLC, and are not predicted to affect efficacy. Based on these data, nivolumab 480 mg Q4W is expected to have similar efficacy and safety profiles to nivolumab 3 mg/kg Q2W.

In this study, 6 weeks after the last combination dose is administered, participants will receive flat dose 480 mg nivolumab every 4 weeks (Q4W), which provides a more convenient dosing regimen for participants. Based on PK modeling and simulations, administration of nivolumab 480 mg Q4W will be started after steady state is achieved with the combination regimen.

Hence, doubling the dose of nivolumab from 240 mg to 480 mg would extend the dosing interval from 2 weeks to 4 weeks.

Thus, a flat dose of 480 mg every 4 weeks is recommended for investigation in the nivolumab monotherapy phase (Part 2) of this study.

6 STUDY POPULATION

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

6.1 Inclusion Criteria

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 participant care.

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

2) Target Population

a) Histological or cytological evidence of metastatic or surgically unresectable transitional cell carcinoma (TCC) of the urothelium involving the renal pelvis, ureter, bladder or urethra. Minor histologic variants (< 50% overall) are acceptable (TCC must be the dominant histology).

b) All participants must have measurable disease by CT or MRI per RECIST 1.1 criteria. See Appendix 4.

c) Prior systemic chemotherapy for metastatic or surgically unresectable UC is not allowed.

NOTE: (i) Prior intravesical therapy is permitted if completed at least 4 weeks prior to the initiation of study treatment. (ii) Prior neoadjuvant chemotherapy, radiation or prior adjuvant platinum-based chemotherapy or radiation following radical cystectomy with recurrence ≥12 months from completion of therapy is permitted.

d) Participants ineligible for cisplatin-based chemotherapy will be defined by **any <u>one</u>** of the following criteria:

i. Impaired renal function (glomerular filtration rate [GFR] ≥ 30 but < 60 mL/min); GFR should be assessed by direct measurement (ie, creatinine clearance) or, if not available, by calculation from serum/plasma creatinine (Cockcroft-Gault formula)

ii. Common Terminology Criteria for Adverse Events (CTCAE) version 4, ≥ Grade 2 hearing loss (assessed per local standard of care)

iii. CTCAE version 4, ≥ Grade 2 peripheral neuropathy

Cisplatin-ineligible patients will receive gemcitabine-carboplatin treatment.

e) Participants eligible for Cisplatin-based chemotherapy must exhibit adequate renal function as follows:

GFR ≥ 60 mL/min (assessed by direct measurement (i.e. creatinine clearance) or, if not available, by calculation using the Cockcroft-Gault formula):

Female CrCl = [(140 - age in years) × weight in kg × 0.85] / [72 x serum creatinine in mg/dL]

Male CrCl = [(140 - age in years) × weight in kg × 1.00] / [72 x serum creatinine in mg/dL]

f) Participants must provide a fresh tumor biopsy from the primary disease site or a metastatic site. If fresh tissue cannot be provided, a tissue block (or at least 15 FFPE slides), from the most recent surgical resection (eg, radical cystectomy) can be accepted if collected within 2 years prior to enrollment period and the participant did not receive systemic anticancer agents or radiotherapy since collection of sample. The PD-L1 stained tissue sections will be assessed by a pathologist and membranous PD-L1 expression scored in tumor cells if a minimum of a hundred (100) evaluable tumor cells are present. Additional information regarding biopsy samples see Section 9.8.1.

g) Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1, See Appendix 2 for ECOG Performance Status Score

h) Adequate hematologic and liver function (using CTCAE v4). (All baseline laboratory requirements will be assessed and should be obtained within 14 days prior to randomization)

a) WBC ≥ 2000/ μ L

b) Neutrophils ≥ 1500/ μ L

c) Platelets ≥ 100 × 10^3/ μ L

d) Hemoglobin ≥ 9.0 g/dL

e) AST ≤ 3 × ULN

f) ALT ≤ 3 × ULN

g) Total bilirubin ≤ 1.5 × ULN (except in participants with Gilbert Syndrome, who can have total bilirubin < 3.0 mg/dL).

i) 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 and inclusion/exclusion criteria reassessed.

j) Prior palliative radiotherapy must have been completed at least 2 weeks prior to study drug administration. Participants must have measurable disease outside the radiation field to be eligible and the tumor sample be collected before (but not after) palliative RT if it is from the irradiated area. Participants with progression in a previously radiated field will also be eligible.

3) Age and Reproductive Status

a) Males and Females, ages ≥ 18 years or age of majority

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 for the duration of treatment with study treatment(s) plus 5 half-lives of study treatment, plus 30 days (duration of ovulatory cycle) for a total of 5 months post-treatment completion.

e) WOCBP must also agree to follow instructions for method(s) of contraception from the time of enrollment for the duration of treatment with chemotherapy plus 5 half-lives of chemotherapy plus 30 days (duration of ovulatory cycle) for a total of 30 days post treatment completion or a duration specified by the local labels of the chemotherapy drugs received, whichever is longer.

f) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception (Appendix 6) for the duration of treatment with study treatment(s) plus 5 half-lives of the study treatment plus 90 days (duration of sperm turnover) for a total of 7 months post-treatment completion. In addition, male participants must be willing to refrain from sperm donation during this time.

g) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with chemotherapy plus 5 half-lives of chemotherapy plus 90 days (duration of sperm turnover) for a total of 90 days post treatment completion or a duration specified by the local labels of the chemotherapy drugs received, whichever is longer.

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

Investigators shall counsel WOCBP, and male participants who are sexually active with WOCBP, on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise on the use of highly effective methods of contraception, (Appendix 6 which have a failure rate of < 1% when used consistently and correctly.

6.2 Exclusion Criteria

1) Target Disease Exceptions

a) Has disease that is suitable for local therapy administered with curative intent.

b) Active brain metastases or leptomeningeal metastases. Participants with brain metastases are eligible if these have been treated and there is no magnetic resonance imaging (MRI except where contraindicated in which CT scan is acceptable) evidence of progression for at least 4 weeks after treatment is complete and within 28 days prior to first dose of study drug administration. Cases must be discussed with the Medical Monitor. Brain lesions are not considered measurable disease.

c) There must also be no requirement for immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration.

2) Medical History and Concurrent Diseases

a) 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 prostate, cervix or breast.

b) Any serious or uncontrolled medical disorder that, in the opinion of the investigator, may increase the risk associated with study participation or study drug administration, impair the ability of the participant to receive protocol therapy, or interfere with the interpretation of study results.

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

d) Participants with active, known or suspected autoimmune disease. Participants with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

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

f) Uncontrolled adrenal insufficiency.

g) New York Heart Association (NYHA) Functional Classification of Heart Failure: Class III or Class IV (Appendix 7)[65]

h) ECOG PS ≥ 2

i) 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.

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

k) 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. Sites in Germany see Appendix 9.

l) 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.

m) Participants who have had a history of acute diverticulitis, intra-abdominal abscess, GI obstruction and abdominal carcinomatosis which are known risk factors for bowel perforation.

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

3) Physical and Laboratory Test Findings

a) Positive test for hepatitis B virus surface antigen (HBV sAg) or hepatitis C virus ribonucleic acid (RNA) or hepatitis C antibody (HCV antibody) indicating acute or chronic infection.

4) Allergies and Adverse Drug Reaction

a) History of allergy or hypersensitivity to study drug components

5) Prior Investigational Agents

a) Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways.

b) Use of an investigational agent within 4 weeks of Day 1 visit

6) Other Exclusion Criteria

a) Prisoners or participants who are involuntarily incarcerated. (Note: under certain specific circumstances a person who has been imprisoned may be included or permitted to continue as a participant. Strict conditions apply and Bristol-Myers Squibb approval is required.)

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

c) Participants may not have received live/attenuated vaccines within 30 days prior to first study treatment.

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 first study treatment.

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 but are not subsequently randomized. 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 (i.e., participant has not been randomized). If re-enrolled, the participant must be re-consented.

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

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

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

7 TREATMENT

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

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

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

In this protocol, investigational products are:

- Nivolumab
- Ipilimumab
- Gemcitabine
- Cisplatin
- Carboplatin

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

Table 7-1: Study Treatments for CA209901

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	100 mg (10 mg/mL)[a]	IP	Open-Label	10 mL per vial (10 vials/carton)	Store at 2° - 8 °C. Protect from light and freezing.
Ipilimumab Solution for Injection	200 mg (5 mg/mL)	IP	Open-Label	40 mL per vial (4 vials/carton)	Store at 2° - 8 °C. Protect from light and freezing.
Carboplatin Solution for Injection	450 mg/vial (10 mg/mL)[b]	IP	Open-label	Clear, colorless or slightly yellow solution	As per market conditions
Carboplatin Solution for Injection (China Source)	150 mg/vial (10 mg/mL)	IP	Open-label	Clear, colorless or slightly yellow solution	As per market conditions
Gemcitabine Concentrate for Solution for Infusion	1000 mg/ vial[b]	IP	Open-label	Clear, colorless, or light straw colored solution	As per market conditions
Gemcitabine Powder for Solution for Infusion	1000 mg/vial[b]	IP	Open-label	White to off-white plug or powder	As per market conditions
Cisplatin Concentration for Solution for Infusion	100 mg/vial (1 mg/mL)[b]	IP	Open-label	Clear, colorless solution	As per market conditions

[a] May be labeled as either "BMS-936558-01" or "Nivolumab."

[b] These products may be obtained by the investigational sites as local commercial product in certain countries if allowed by local regulations. In these cases, products may be a different pack size/potency than listed in the table. 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 as follows:

Table 7.1-1: Selection and Timing of Dose

Study Treatment	Unit Dose Strength(s)/Dosage Level(s)	Dosage Formulation Frequency of Administration	Route of Administration
Arm A: Part 1	Nivolumab (1 mg/kg) plus Ipilimumab (3 mg/kg)	Combination: D1W1 every 3 weeks for up to 4 doses	Nivolumab 30 min IV infusion Ipilimumab 30 min IV infusion
Arm A: Part 2	Nivolumab (480 mg)	Monotherapy beginning 6 weeks following last combination dose, every 4 weeks	Nivolumab 30 min IV infusion
Arm B*	Gemcitabine (1000 mg/m^2) plus Cisplatin (70 mg/m^2)	Gem: Days 1 and 8 of each 3-week cycle and Cis: Day 1 of each 3-week cycle For up to 6 cycles	Gemcitabine: 30 min IV infusion Cisplatin: 30-120 min IV infusion
	Gemcitabine (1000 mg/m^2) plus Carboplatin (AUC 4.5/5)	Gem: Days 1 and 8 of each 3-week cycle and Carb: Day 1 of each 3-week cycle For up to 6 cycles	Gemcitabine: 30 min IV infusion Carboplatin: 30 min IV infusion
Arm C* Part 1	Nivolumab (360 mg) plus Gemcitabine (1000 mg/m^2) plus Cisplatin 70 mg/m^2	Nivo: 360 mg Day 1 of each 3-week cycle Gem: Days 1 and 8 of each 3-week cycle and Cis: Day 1 of each 3-week cycle For up to 6 cycles	Nivolumab 30 min IV infusion Gemcitabine 30 min IV infusion Cisplatin 30-120 min IV infusion Nivolumab should be administered first.
Arm C Part 2	Nivolumab (480 mg)	Monotherapy beginning 3 weeks following last combination dose, every 4 weeks	Nivolumab 30 min IV infusion
Arm D*	Gemcitabine (1000 mg/m^2) plus Cisplatin (70 mg/m^2)	Gem: Days 1 and 8 of each 3-week cycle and Cis: Day 1 of each 3-week cycle For up to 6 cycles	Gemcitabine: 30 min IV infusion Cisplatin: 30-120 min IV infusion

Note: Carboplatin dosing to be calculated per the Calvert formula, see Section 7.1.3.2.

*Only applies to chemotherapy drugs - Infusion duration and premedications may follow local guidelines.

The first treatment in any cohort, will be within 3 days following randomization (see Schedule of Activities, Section 2).

7.1.1 Nivolumab and Ipilimumab

7.1.1.1 Arm A: Part 1 Study Drug Administration - Nivolumab and Ipilimumab Combination Therapy (Cycles 1-4)

Participants randomized to Arm A, will receive nivolumab plus ipilimumab combination therapy for up to 4 cycles. For each infusion, nivolumab is to be administered first. Participants should receive nivolumab at a dose of 1 mg/kg as a 30-minute IV infusion, on Day 1 of each treatment cycle every 3 weeks for up to 4 doses (Cycles 1-4). In Part 1, a minimum of 1 combination cycle of nivolumab and ipilimumab is required, for the participant to proceed to Part 2, nivolumab monotherapy. Participants experiencing AEs related to combination dose therapy (Part 1) that do not meet dose discontinuation criteria for nivolumab,, may proceed to nivolumab monotherapy dosing (Part 2) without completing all 4 combination doses, after consultation with BMS Medical Monitor.

During Part 1 in Arm A, participants may be dosed no less than 19 days between doses. If dosing is delayed, both nivolumab and ipilimumab must be delayed together. If dosing is resumed after a delay, both nivolumab and ipilimumab must be resumed on the same day.

Participants may be dosed up to 2 days before or 3 days after the scheduled date if necessary, so long as the dosing intervals are respected (no less than 19 days in Part 1, and no less than 26 days in Part 2). Subsequent dosing should be based on the actual date of administration of the previous dose of drug.

The nivolumab infusion must be promptly followed by a saline flush to clear the line of nivolumab before starting the ipilimumab infusion.

The second infusion in the combination will always be ipilimumab, and will start after the infusion line has been flushed, filters changed and the participant has been observed to ensure no infusion reaction has occurred. The time in between infusions is expected to be approximately 30 minutes but may be more or less depending on the situation. Participants should receive ipilimumab at a dose of 3 mg/kg as a 30-minute IV infusion, on Day 1 of each treatment cycle every 3 weeks for 4 doses (Cycles 1-4).

Dosing calculations for the combination phase should be based on the body weight assessed at screening. It is not necessary to re-calculate subsequent doses if the participant weight is within 10% of the weight used to calculate the previous dose. All doses should be rounded to the nearest milligram. The risk/benefit profile for nivolumab has primarily been investigated using a 60-minute infusion and for ipilimumab a 90-minute infusion. Long infusion times place a burden on participants and treatment centers. Establishing that these agents can be safely administered using shorter infusion times will diminish some of this burden. Both nivolumab and ipilimumab have been administered safely at doses ranging up to 10 mg/kg over these treatment durations. Overall, infusion reactions including high-grade hypersensitivity reactions have been uncommon across multiple clinical studies, and all have been managed by following the safety algorithms. Infusion duration of 30 minutes for 3 mg/kg nivolumab (30% of the dose provided at 10 mg/kg) is not expected to present any safety concerns compared with the prior experience at 10 mg/kg

nivolumab dose infused over the 60-minute duration. Similarly, a shortened infusion duration of 30 minutes for ipilimumab is not expected to present additional safety concerns.[66]

When given as a single agent, there is a low rate of infusion reactions. The incidence is less than 1% for ipilimumab (Yervoy® FDA Label) and for nivolumab 3%. In the CA209069 study, in which nivolumab and ipilimumab were given sequentially, hypersensitivity/infusion reactions occurred at 3.2% for the combination and at 2.2% for ipilimumab. No Grade 3 or Grade 4 hypersensitivity/infusion reactions were observed in either the combination or single agent ipilimumab treatment groups.[67]

Participants should be carefully monitored for infusion reactions during nivolumab/ipilimumab administration. If an acute infusion reaction is noted, participants should be managed according to Section 7.4.3.

7.1.1.2 Arm A and C: Part 2 Study Drug Administration - Nivolumab Monotherapy

Starting 6 weeks after the last combination dose in Arm A Part 1, or 3 weeks following the last combination dose in Arm C Part 1, participants will be administered a flat dose of 480 mg nivolumab on Day 1 of each treatment cycle given IV over approximately 30 minutes every 4 weeks (Q4W) until unacceptable toxicity or disease progression.

Participants may be dosed up to 2 days before or 3 days after the scheduled date if necessary, however participants should be dosed no less than 26 days between treatments. Subsequent dosing should be based on the actual date of administration of the previous dose of drug. Every effort should be made to adhere to the protocol treatment schedule of administration of nivolumab every 4 weeks in the monotherapy phase. In extenuating circumstances in which the participant cannot make the dosing schedule within the 3-day window, the BMS Medical Monitor should be contacted.

Premedications are not recommended for the first dose of nivolumab.

7.1.2 Study Drug Preparation and Infusion

Instructions for dilution of nivolumab injection are provided in the pharmacy manual, or IB. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

Instructions for dilution of ipilimumab injection are provided in the pharmacy manual or IB.

Separate infusion bags and filters should be used when administering nivolumab and ipilimumab on the same day.

Ipilimumab is to be administered as a 30 minute IV infusion. It is not to be administered as an IV push or bolus injections. Care must be taken to assure sterility of the prepared solutions, since the drug product does not contain any antimicrobial preservatives or bacteriostatic agents. At the end of the infusion, flush the line with a sufficient quantity of normal saline or 5% dextrose solution.

Doses of nivolumab and or ipilimumab may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment. Dosing visits are not skipped, only delayed. In the event infusion duration in the SmPC varies from the protocol, the SmPC or local administration standards will take precedence.

7.1.3 Arm B: Platinum Doublet Chemotherapy

Participants randomized to Arm B, may receive either gemcitabine/cisplatin or gemcitabine/carboplatin. Cisplatin-ineligible participants will only receive gemcitabine/ carboplatin (see Section 6.1).

Participants may be dosed up to 3 days before or after the scheduled date if necessary. Subsequent dosing should be based on the actual date of administration of the previous dose of drug.

7.1.3.1 Gemcitabine/Cisplatin

Participants will receive gemcitabine at a dose of 1000 mg/m^2 for a 30-minute IV infusion on Days 1 and 8 with cisplatin at a dose of 70 mg/m^2 as a 30 to 120-minute IV infusion on Day 1 of a 3-week treatment cycle for up to 6 cycles. As noted in Table 2-5, additional cycles may be permitted as per local guidelines.

Dosing calculations should be based on the body surface area calculation and may be capped per local standards. The dose may remain the same if the participant's weight is within 10% of the baseline weight or prior dose weight.

Cisplatin will be administered to participants following the end of the gemcitabine infusion. Pretreatment hydration for cisplatin can follow local standard of care, or 1 to 2 liters of fluid (per local standards) infused IV for 8 to 12 hours prior to cisplatin infusion is recommended. Adequate hydration and urinary output must be maintained for at least 24 hours following cisplatin administration. Administration and monitoring should be performed according to local standards. Use of mannitol following the cisplatin infusion should also follow local standards-of-care.

Premedications: Antiemetic premedication will be administered according to local standards. Recommended antiemetic treatments are dexamethasone (dosing according to local standards; an equivalent dose of another corticosteroid may be substituted) and a 5-HT3 receptor antagonist (type per investigator discretion and local standards-of-care). Additional use of antiemetic premedications may be employed at the discretion of the Investigator.

Doses of gemcitabine and/or cisplatin may be interrupted, delayed, reduced, or discontinued depending on how well the participant tolerates the treatment. See the following sections for more details: 7.4.2.2 (dose delays); 7.4.1.2, 7.4.1.3, and 7.4.1.4 (dose reductions); 8.1.2.2 (retreatment), and 8.1.1.2 (dose discontinuations).

All participants who will be receiving cisplatin should have audiometric testing performed prior to initiation of therapy and prior to subsequent doses of cisplatin, or as per local standards of care.

Participants who discontinue cisplatin alone may, at the investigator's discretion, be switched to gemcitabine/carboplatin for the remainder of the platinum doublet cycles (up to 6 cycles in total).

Dosing for gemcitabine/carboplatin for such participants should follow the instructions in the Gemcitabine/Carboplatin section below.

7.1.3.2 Gemcitabine/Carboplatin

Participants will receive gemcitabine at a dose of 1000 mg/m^2 as a 30-minute IV infusion on Days 1 and 8 with carboplatin at a dose of AUC 4.5/5 as a 30-minute IV infusion, on Day 1 of a 3-week cycle, for up to 6 cycles, or at doses per the local prescribing information.

Gemcitabine dosing calculations should be based on the body surface area calculation. The dose may remain the same if the participant's weight is within 10% of the baseline weight or prior dose weight.

Carboplatin should be given following gemcitabine on Day 1 of each cycle, and the carboplatin dose will be calculated using the Calvert formula as follows:

- Carboplatin dose (mg) = Target AUC x [CrCl (ml/min) + 25]
- Creatinine clearance (CrCl) calculation is based on the Cockroft-Gault formula) and should include the most recent serum creatinine and most recent weight. NOTE: If calculation of the CrCl by the Cockroft-Gault formula yields a result of > 125 mL/min, then a CrCl should be calculated by an alternative formula per institutional standards or capped at 125 mL/min.
- The dose of carboplatin may be capped per local standards.

Premedications: Oral antiemetic premedication will be administered according to local standards. Recommended antiemetic treatments are dexamethasone (dosing according to local standards; an equivalent dose of another corticosteroid may be substituted) and a 5-HT3 receptor antagonist (type per investigator discretion and local standards of care). Additional use of antiemetic premedications may be employed at the discretion of the investigator per local standards of care.

Doses of gemcitabine and/or carboplatin may be interrupted, delayed, reduced, or discontinued depending on how well the participant tolerates the treatment. See the following sections for more details: 7.4.2.2 (dose delays); 7.4.1.2, 7.4.1.3, and 7.4.1.4 (dose reductions); 8.1.2.2 (retreatment), and 8.1.1.2 (dose discontinuations).

7.1.4 Arm C: Nivolumab plus Platinum-Doublet Chemotherapy

Participants will receive nivolumab at a dose of 360 mg as 30 minute IV infusion on Day 1, followed by gemcitabine at a dose of 1000 mg/m^2 for a 30 minute IV infusion with cisplatin at a dose of 70 mg/m^2 as a 30 to 120-minute IV infusion, of a 3-week treatment cycle for up to 6 cycles. Gemcitabine will also be administered at a dose of 1000 mg/m^2 for a 30 minute IV infusion on Day 8 of each 3-week treatment cycle. In the event infusion duration in the SmPC varies from the protocol, the SmPC or local administration standards will take precedence.

At the time of discontinuation of gemcitabine/cisplatin, participants who have not experienced disease progression will continue to receive nivolumab at a dose of 480 mg as 30 minute IV infusion on Day 1 of a 4 week treatment cycle. Treatment will continue until progression,

unacceptable toxicity, withdrawal of consent, or up to a maximum of 24 months, whichever occurs first.

Dosing calculations should be based on the body surface area calculation and may be capped per local standards. The dose may remain the same if the participant's weight is within 10% of the baseline weight or prior dose weight.

Cisplatin will be administered to patients following the end of the gemcitabine infusion. Pretreatment hydration for cisplatin can follow local standard of care, or 1 to 2 liters of fluid (per local standards) infused IV for 8 to 12 hours prior to cisplatin infusion is recommended. Adequate hydration and urinary output must be maintained for at least 24 hours following cisplatin administration. Administration and monitoring should be performed according to local standards. Use of mannitol following the cisplatin infusion should also follow local standards-of-care.

Premedications: Antiemetic premedication will be administered according to local standards. Recommended antiemetic treatments are dexamethasone (dosing according to local standards; an equivalent dose of another corticosteroid may be substituted) and a 5-HT3 receptor antagonist (type per investigator discretion and local standards-of-care). Additional use of antiemetic premedications may be employed at the discretion of the Investigator.

Doses of gemcitabine and/or cisplatin may be interrupted, delayed, reduced, or discontinued depending on how well the participant tolerates the treatment. See the following sections for more details: 7.4.2.2 (dose delays); 7.4.1.2, 7.4.1.3, and 7.4.1.4 (dose reductions); 8.1.2.2 (retreatment), and 8.1.1.2 (dose discontinuations).

All participants who will be receiving cisplatin should have audiometric testing performed prior to initiation of therapy and prior to subsequent doses of cisplatin, or as per local standards of care.

Participants who discontinue cisplatin alone may, at the investigator's discretion, be switched to gemcitabine/carboplatin for the remainder of the platinum doublet cycles (up to 6 cycles in total). Dosing for gemcitabine/carboplatin for such participants should follow the instructions in the Gemcitabine/Carboplatin Section 7.1.3.2.

Beginning 3 weeks following the last combination dose, participants in Arm C will begin nivolumab monotherapy as described in Section 7.1.1.2.

7.1.5 Arm D: Platinum-Doublet Chemotherapy (Cisplatin-Eligible)

Dosing for participants randomized to Arm D will be the same as that outlined in Section 7.1.3.1 above. In the event infusion duration in the SmPC varies from the protocol, the SmPC or local administration standards will take precedence.

7.2 Method of Treatment Assignment

All participants will be centrally 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.

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

7.3 Blinding

This is an open-label study; however, 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 Dose reductions

7.4.1.1 Nivolumab or Ipilimumab Dose Modification

Dose reductions or dose escalations of nivolumab or ipilimumab are not permitted.

7.4.1.2 Platinum Doublet Chemotherapy Dose Reductions

Dose reductions of platinum doublet chemotherapy may be required, and will be performed according to Table 7.4.1.2-1 or per institutional guidelines. Chemotherapy dose reductions are permanent; once the dose of any chemotherapy agent is reduced, it may not be re-escalated in subsequent cycles. The dose reductions for each agent in the platinum doublet chemotherapy regimen are not linked and may be adjusted independently as summarized below.

Table 7.4.1.2-1: Dose Modifications of Chemotherapeutic Agents

Dose Level	Gemcitabine	Cisplatin	Carboplatin
Starting dose	1000 mg/m² (with cisplatin) or 1000 mg/m² (with carboplatin)	70 mg/m²	AUC 4.5/5 with gemcitabine
First dose reduction	750 mg/m² (with cisplatin) or 750 mg/m² (with carboplatin)	56 mg/m²	AUC 4 with gemcitabine
Second dose reduction	500 mg/m² (with cisplatin) or 500 mg/m² (with carboplatin)	38 mg/m²	AUC 3 with gemcitabine
Third dose reduction	Discontinue	Discontinue	Discontinue

Any participant with two prior dose reductions for one agent who experiences a toxicity that would cause a third dose reduction must be discontinued from that agent.

7.4.1.3 Platinum Doublet Chemotherapy - Dose Reductions for Hematologic Toxicity

Dose adjustments are based on nadir blood counts (assessed as per local standards) since the preceding drug administration. After the first cycle, growth factors may be used to assist hematologic recovery. Use local standards of care in the use of these supportive measures. Additionally, prophylactic antibiotics may be used according to local standards of care. Please report any antibiotic or growth factor use on the eCRF.

7.4.1.4 Platinum Doublet Chemotherapy - Dose Reductions for Non-Hematologic Toxicities

All dose reductions should be made based on the worst grade toxicity. Participants experiencing toxicity meeting dose-delay criteria during the previous cycle should have their chemotherapy delayed until retreatment criteria are met (per Section 8.1.2.2) and then reduced for all subsequent cycles by 1 dose level or discontinued as appropriate. Dose levels for the two drugs in the platinum-doublet chemotherapy regimen are not linked and may be reduced independently.

7.4.2 Dose Delay Criteria

7.4.2.1 Nivolumab or Ipilimumab Dose Delay Criteria

Regardless of whether or not the event is attributed to nivolumab or ipilimumab, both study drugs must be delayed until treatment can resume. Tumor assessments for all participants should continue as per protocol even if dosing is delayed.

Nivolumab and ipilimumab administration should be delayed for the following:

- Grade 2 non-skin, drug-related adverse event, with the exception of fatigue
- Grade 2 drug-related creatinine, AST, ALT and/or Total Bilirubin abnormalities
- Grade 3 skin, drug-related adverse event
- Grade 3 drug-related laboratory abnormality, with the following exceptions:
  - Grade 3 lymphopenia or asymptomatic amylase or lipase does not require dose delay
  - Grade ≥ 3 AST, ALT, Total Bilirubin will require dose discontinuation (see Section 8.1.1.1)
- 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/ipilimumab should be re-evaluated weekly or more frequently if clinically indicated and resume nivolumab dosing when re-treatment criteria are met.

7.4.2.2 Platinum Doublet Chemotherapy Dose Delay

Treatment of both drugs in the platinum doublet chemotherapy regimen selected should be delayed for any of the following on the Day 1 of each cycle:

- Absolute neutrophil count (ANC) ≤ 1500/µL
- Platelets < 100,000/mm^3
- Any Grade ≥ 2 non-skin, non-hematologic, drug-related adverse event (excluding Grade 2 alopecia, Grade 2 fatigue, and Grade 2 laboratory abnormalities other than Grade 2 LFT increases if baseline within normal limits)
- Any Grade ≥ 3 skin, drug-related adverse event
- Any Grade ≥ 3 drug-related laboratory abnormality, with the following exceptions for lymphopenia, AST, ALT, or total bilirubin:
  - Grade 3 lymphopenia does not require dose delay.

  - If a participant has a baseline AST, ALT or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity.
  - If a participant has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication. Investigators should consult local labeling for the chemotherapy drugs being administered to any given participant for additional guidance on dose delays.

In addition, participants receiving cisplatin with gemcitabine must discontinue cisplatin if the calculated creatinine clearance decreases to < 50 mL/min (based on the Cockroft Gault formula). Gemcitabine may be continued, and the platinum agent may, at the investigator's discretion, be switched to carboplatin for the remainder of the platinum doublet cycles (up to 6 cycles in total) when the participant meets retreatment criteria, as specified in Section 8.1.2.2.

Based on institutional guidelines, Day 8 gemcitabine dosing for participants receiving gemcitabine with cisplatin or carboplatin may be delayed for any of the following:

- ANC < 1,000/mm^3
- Platelets < 75,000/mm^3

If any adverse event meeting the dose delay criteria above is felt to be related to only one particular agent in the platinum doublet chemotherapy regimen, then that agent alone may be omitted for that cycle while the other agent is given. In order to maintain synchronized dosing of the regimen, the omitted agent should be resumed with the next scheduled cycle once the AE has improved and retreatment criteria are met. Please refer to Section 8.1.2.2 to determine if dose reduction of the resumed agent is required.

If both drugs in the platinum doublet chemotherapy regimen are delayed, then the participant should be re-evaluated weekly or more frequently if clinically indicated until re-treatment criteria are met (as per Section 8.1.2.2).

7.4.2.3 Dose Delay Criteria for Nivolumab plus Platinum-Doublet Chemotherapy

In Arm C, dosing of all drugs should be delayed if any criteria for delay of Arms A (Section 7.4.2.1) or Arm B (Section 7.4.2.2, Gemcitabine-cisplatin chemotherapy) are met. After participants have completed 6 cycles of SOC gemcitabine-cisplatin chemotherapy, and are on nivolumab maintenance therapy, dose delay criteria for nivolumab monotherapy (see Section 7.4.2.1 should apply.

7.4.3 Treatment of Nivolumab or Ipilimumab Related Infusion Reactions

Since nivolumab and ipilimumab contain only human immunoglobulin protein sequences, each is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus,

arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the BMS Study Medical Monitor and reported as an SAE if it meets the criteria. Infusion reactions should be graded according to NCI CTCAE (Version 4) 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 nivolumab or ipilimumab 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 nivolumab or ipilimumab 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 infusions. 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 nivolumab or ipilimumab. 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 drug 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).

7.4.4 Management Algorithms for Immuno-Oncology Agents

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 ipilimumab are considered 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
- Hepatic
- Endocrinopathy
- Skin
- Neurological
- Myocarditis

The above algorithms are found in both the nivolumab and ipilimumab Investigator Brochures, as well as in **Appendix 5**.

7.4.5 Treatment Beyond Progression

Accumulating evidence indicates a minority of participants treated with immunotherapy may derive clinical benefit despite initial evidence of PD.[68]

Participants treated with study drug(s) will be permitted to continue treatment beyond initial RECIST 1.1 defined PD in both Part 1 (combination) and Part 2 (monotherapy), assessed by the investigator up to a maximum of 24 months from date of first dose as long as they meet the following criteria:

- Investigator-assessed clinical benefit
- Tolerance of study drug
- Stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases)

- Participant provides written informed consent prior to receiving additional nivolumab treatment. All other elements of the main consent including description of reasonably foreseeable risks or discomforts, or other alternative treatment options will still apply
- Radiographic assessment/scan(s) should continue in accordance with the Section 2 Schedule of Activities for the duration of the treatment beyond progression and should be submitted to the central imaging vendor.

If the investigator feels that the participant continues to achieve clinical benefit by continuing treatment, the participant should remain on the trial and continue to receive monitoring according to the Time and Events Schedule.

For the participants who continue study therapy beyond progression, further progression is defined as an additional 10% increase in tumor burden with a minimum 5 mm absolute increase from time of initial PD. This includes an increase in the sum of diameters of all target lesions and/ or the diameters of new measurable lesions compared to the time of initial PD. Treatment should be discontinued permanently upon documentation of further progression.

New lesions are considered measureable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). Any new lesion considered non-measureable at the time of initial progression may become measureable and therefore included in the tumor burden if the longest diameter increases to at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). In situations where the relative increase in total tumor burden by 10% is solely due to inclusion of new lesions which become measurable, these new lesions must demonstrate an absolute increase of at least 5 mm.

7.5 Preparation/Handling/Storage/Accountability

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 (e.g., required diluents, administration sets).

Further guidance and information for infusion preparation are provided in the pharmacy manual or product specific IB.

7.5.1 Retained Samples for Bioavailability / Bioequivalence

Not Applicable.

7.6 Treatment Compliance

Study treatment compliance will be periodically monitored by drug accountability. Drug accountability should be reviewed by the site study staff at each visit to confirm treatment compliance.

7.7 Concomitant Therapy

7.7.1 Prohibited and/or Restricted Treatments

Treatment with any of the following medications or interventions concomitantly or within 28 days of starting nivolumab or ipilimumab:

1. Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways
2. Any concurrent anti-neoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, non-palliative surgical resection or standard or investigational agents for treatment of unresectable or metastatic UC)
3. Use of an investigational agent within 4 weeks of Day 1 visit
4. The following medications are prohibited during the study:
    a. Immunosuppressive agents (except to treat a drug-related adverse event)
    b. Systemic corticosteroids > 10 mg daily prednisone equivalent (except as stated in Section 7.7.2 below or to treat a drug-related adverse event)
    c. Intravesical therapy lasting for >1 instillation
    d. Any live/attenuated vaccine (eg, varicella, zoster, yellow fever, rotavirus, oral polio, and measles, mumps, rubella) during treatment and until 100 days post last dose
    e. Any botanical preparation (eg herbal supplements or traditional Chinese medicines) intended to treat the disease under study or provide supportive care. Use of marijuana and its derivatives for treatment of symptoms related to cancer or cancer treatment are permitted if obtained by medical prescription or if its use (even without a medical prescription) has been legalized locally.

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, as is a short dose of corticosteroids (< 3 weeks) to prevent a reaction to the IV contrast used for CT scans (see Section 7.7.3).

Palliative (limited-field) radiation therapy and palliative surgical resection are permitted, if the following criteria are met:

1) The participant will be considered to have progressed at the time of palliative therapy and must meet criteria to continue with treatment beyond progression (Section 7.4.5). Transurethral resection of bladder tumors (TURBT) should be discussed on a case by case basis with BMS Medical Monitor as some TURBTs may be allowed without considering the patient as progressing (eg, TURBT of lower risk non-muscle invasive lesion).
2) The case is discussed with the BMS Medical Monitor or Study Director.

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 (≤ 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.

The use of dexamethasone or other steroid as antiemetic premedication is permitted for the chemotherapy containing arms as described in Sections 7.1.3.2 and 7.1.4.

Bisphosphonates and RANK-ligand inhibitors for bone metastases are allowed to be initiated while on study as per institutional SOC guidelines.

7.7.3.1 Imaging Restriction and Precautions

It is the local imaging facility's responsibility to determine, based on participant attributes (eg, allergy history, diabetic history and renal status), the appropriate imaging modality and contrast regimen for each participant. Imaging contraindications and contrast risks should be considered in this assessment. Participants with renal insufficiency should be assessed as to whether or not they should receive contrast and if so, what type and dose of contrast is appropriate. Specific to MRI, participants with severe renal insufficiency (ie, estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2) are at increased risk of nephrogenic systemic fibrosis. MRI contrast should not be given to this participant population. In these participants, an MRI with and without gadolinium abdomen and pelvis, and CT without contract. In participants, who are excluded from an MRI, a CT (chest, abdomen, and pelvis) without contrast is acceptable. In addition, participants are excluded from MRI if they have tattoos, metallic implants, pacemakers, etc.

For brain MRI, if MRI is prohibited because of medical reasons (eg. metallic implants), CT with or without contrast agents would be acceptable.

Subsequent assessments should use the same imaging method as was used at baseline.

7.8 Treatment After the End of the Study

At the conclusion of the study, participants who continue to demonstrate clinical benefit will be eligible to receive BMS supplied study treatment. Study treatment will be provided via an

extension of the study, a rollover study requiring approval by responsible health authority and ethics committee or through another mechanism at the discretion of BMS.

BMS reserves the right to terminate access to BMS supplied study treatment if any of the following occur: a) the study is terminated due to safety concerns; b) the development of the nivolumab is terminated for other reasons, including but not limited to lack of efficacy and/or not meeting the study objectives; c) the participant can obtain medication from a government sponsored or private health program. In all cases BMS will follow local regulations

8 DISCONTINUATION CRITERIA

8.1 Discontinuation from Study Treatment

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

- Participant's request to stop study treatment. Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant
- Termination of the study by Bristol-Myers Squibb (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
- Additional protocol specified criteria for discontinuation (see Section 8.1.1)

Refer to the Schedule of Activities 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 the event a normal healthy female participant becomes pregnant during a clinical trial, the study treatment must be discontinued immediately. 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 case report form (CRF) page.

8.1.1 Dose Discontinuation

8.1.1.1 Discontinuation of Nivolumab or Ipilimumab

The assessment for discontinuation of nivolumab should be made separately from the assessment made for discontinuation of ipilimumab. Although there is overlap among the discontinuation criteria, if discontinuation criteria are met for ipilimumab but not for nivolumab, treatment with nivolumab may continue if ipilimumab is discontinued.

If a participant in any of the nivolumab/ipilimumab combination arms meets criteria for discontinuation and investigator is unable to determine whether the event is related to both or one study drug, the participant should discontinue both nivolumab and ipilimumab and be taken off the treatment phase of the study.

Study 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 re-treatment period OR requires systemic treatment
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, or recurs with the following exceptions for laboratory abnormalities, diarrhea, colitis, neurologic toxicity, drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, infusion reactions, and endocrinopathies:
  - Grade 3 drug-related diarrhea, colitis, neurologic toxicity, uveitis, pneumonitis, bronchospasm, myocarditis, 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
    - Any drug-related liver function test (LFT) abnormality that meets the following criteria require 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 drug(s) will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of

study drug(s), a discussion between the investigator and the BMS Medical Monitor/designee must occur.

- Any Grade 4 drug-related adverse event 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 72 hours of their onset
  - Grade 4 drug-related endocrinopathy adverse events, 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.
- Any event that leads to delay in dosing lasting > 8 weeks from the previous dose requires discontinuation, with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related adverse events are allowed.
  - Dosing delays lasting > 6 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the BMS Medical Monitor.

Prior to re-initiating treatment in a participant with a dosing delay lasting > 8 weeks, the BMS Medical Monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.

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

For participants in Arm C, if the investigator is unable to determine whether an adverse event is due to nivolumab or -to platinum doublet chemotherapy, then all drugs must be discontinued.

8.1.1.2 Platinum Doublet Chemotherapy Dose Discontinuation

Except where specified below, both chemotherapy drugs in the platinum doublet chemotherapy regimen should be discontinued for any of the following:

- Any Grade ≥ 3 peripheral neuropathy
- Grade ≥ 3 drug-related thrombocytopenia associated with clinically significant bleeding
- Any drug-related liver function test (LFT) abnormality that meets the following criteria requires discontinuation:
  - AST or ALT > 5-10 × ULN for > 2 weeks
  - AST or ALT > 10 × ULN

  - Total bilirubin > 5× ULN
  - Concurrent AST or ALT > 3× ULN and total bilirubin > 2 × ULN
- Any cisplatin-related decrease in creatinine clearance to < 50 mL/min (using the Cockroft Gault formula) requires discontinuation of cisplatin.
- Any drug-related adverse event which recurs after two prior dose reductions for the same drug-related adverse event (as specified in Sections 7.4.1.3 and 7.4.1.4) requires discontinuation of the drug(s) which was/were previously dose reduced.
- Any Grade ≥ 3 drug-related hypersensitivity reaction or infusion reaction requires discontinuation of the drug(s) felt to be causing the reaction. The drug not felt to be related to the hypersensitivity reaction or infusion reaction may be continued.
- Any Grade 4 drug-related adverse event which the investigator deems is inappropriate to be managed by dose reduction(s) requires discontinuation of the drug(s) felt to be causing the event. The drug not felt to be related to the event may be continued.
- Any event that leads to delay in dosing of any study drug(s) for > 6 weeks from the previous dose requires discontinuation of that drug(s) with the following exception:
  - **Dosing delays lasting > 6 weeks from the previous dose that occur for drug-related reasons may be allowed if approved by the BMS Medical Monitor.**
  - Dosing delays lasting > 6 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the BMS medical monitor. Prior to re-initiating treatment in a participant with a dosing delay lasting > 6 weeks, the BMS medical monitor must be consulted. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the participant with continued platinum doublet chemotherapy dosing. Investigators should consult local labeling for the chemotherapy drugs being administered to any given participant for additional guidance on dose discontinuation.

Note that participants receiving gemcitabine/cisplatin who discontinue cisplatin alone may, at the investigator's discretion, be switched to gemcitabine/carboplatin for the remainder of the platinum doublet cycles (up to 6 cycles in total).

For participants in Arm C, if the investigator is unable to determine whether an adverse event is due to nivolumab or to platinum doublet chemotherapy, then all drugs must be discontinued.

8.1.2 Criteria to Resume Treatment

8.1.2.1 Criteria to Resume Nivolumab or Ipilimumab

Participants may resume treatment with study drug 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 Grade 2 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.

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

8.1.2.2 Criteria to Resume Treatment with Platinum Doublet Chemotherapy

- Participants may resume treatment with platinum doublet chemotherapy when the ANC returns to > 1500/µl, the platelet count returns to ≥ 100,000/mm^3, and all other drug-related toxicities have returned to baseline or Grade ≤ 1 (or Grade ≤ 2 for alopecia and fatigue).
- If a participant fails to meet criteria for re-treatment, then re-treatment should be delayed, and the participant should be re-evaluated weekly or more frequently as clinically indicated. Any participant who fails to recover from toxicity attributable to platinum doublet chemotherapy to baseline or Grade ≤ 1 (except Grade 2 alopecia and fatigue) within 6 weeks from the last dose given should discontinue the drug(s) that caused the delay.

8.1.3 Post Study Treatment Follow-up

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

BMS may request that survival data be collected on all randomized participants outside of the protocol defined window (Schedule of Activities, Section 2). At the time of this request, each

participant will be contacted to determine their survival 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 (e.g., 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.

9.1 Efficacy Assessments

Study evaluations will take place in accordance with the Schedule of Activities (Section 2).

9.1.1 Overall Survival

OS is defined as the time between the date of randomization and the date of death from any cause. For participants without documentation of death, OS will be censored on the last date the participant was known to be alive ("last known alive date"). OS will be censored for participants at the date of randomization if they were randomized but had no follow-up. OS will be followed continuously while participants are on the study drug and every 3 months via in-person or phone contact after participants discontinue the study drug.

The overall survival rate at time T is defined as the probability that a participant is alive at time T following randomization.

9.1.2 Progression-Free Survival

PFS will be estimated based on BICR assessments. PFS is defined as the time from the date of randomization to the date of first documented disease progression, based on BICR assessments (as per RECIST 1.1), or death due to any cause, whichever occurs first. Clinical deterioration in the absence of progression per RECIST 1.1 is not considered progression for the purpose of determining PFS. Participants who die without a reported prior progression will be considered to have progressed on the date of their death. Participants who did not progress or die will be censored on the date of their last evaluable tumor assessment. Participants who did not have any on study tumor assessments and did not die will be censored on the date they were randomized. Participants who started any subsequent anti-cancer therapy, including tumor-directed radiotherapy and tumor-directed surgery, without a prior reported progression will be censored at the last evaluable tumor assessment prior to/on initiation of the subsequent anti-cancer therapy.

The progression free survival rate at time T is defined as the probability that a participant has not progressed and is alive at time T following randomization.

9.1.3 Objective Response Rate

The ORR is defined as the number of participants with a best overall response (BOR) of a confirmed complete response (CR) or partial response (PR) using the RECIST 1.1 criteria based on BICR assessments divided by the number of randomized participants for each treatment group. The BOR is defined as the best response designation, as determined by BICR, recorded between the date of randomization and the date of progression, as assessed by BICR per RECIST 1.1 or the date of subsequent anticancer therapy (including tumor-directed radiotherapy and tumor-directed surgery), whichever occurs first. For participants without documented progression or subsequent therapy, all available response designations will contribute to the BOR determination.

9.1.4 Imaging Assessment for the Study

Baseline assessments should be performed within 28 days prior to randomization utilizing CT or MRI. In addition to chest, abdomen, pelvis, and brain, all known, or suspected, sites of disease should be assessed at baseline.

Participants who cannot receive IV contrast for CT at the start of study should be imaged by MRI of abdomen/pelvis with IV contrast and CT of chest without contrast. Subsequent assessments should include chest, abdomen, and pelvis, and all known sites of disease and should use the same imaging method as was used at baseline. Participants initially imaged with CT of chest, abdomen, and pelvis with IV contrast who can no longer receive contrast can be monitored by CT of chest, abdomen, and pelvis without IV contrast. Participants in all cohorts will be evaluated for tumor response at the following intervals and time points:

- First tumor assessment should be performed at Week 9 (± 1 week) following first dose. Subsequent tumor assessments should occur every 8 weeks (± 1 week) up to first 48 weeks, then every 12 weeks until disease progression or treatment discontinuation, whichever is later

Tumor assessments for all participants should continue as per protocol even if dosing is delayed.

Tumor assessments for ongoing study treatment decisions will be completed by the investigator using RECIST (Response Evaluation Criteria in Solid Tumors) 1.1 criteria.

Images will be submitted to an imaging core lab. Sites should be trained prior to scanning the first study participant. Image acquisition guidelines and submission process will be outlined in the CA209901 Imaging Manual to be provided by the core lab.

9.1.4.1 BICR Assessment Of Progression

Post-baseline tumor assessments will be performed at the time points described above until progression assessed by the investigator **and** confirmed by BICR or treatment is discontinued (whichever occurs later). In the case of study drug treatment beyond a BICR confirmed progression, scans should continue to be submitted for BICR assessment, but subsequent progression does not need to be confirmed by BICR.

Sites should submit all scans (protocol specified imaging and any additional imaging that may demonstrate tumor response or progression, including scans performed at unscheduled time points and/or at an outside institution), for BICR on a rolling basis, preferably within 7 days of scan acquisition, throughout the duration of the study. BICR will review scans on a rolling basis and remain blinded to treatment arm and investigator assessment of submitted scans.

When progression per RECIST 1.1 criteria is assessed by the investigator, the site will inform the imaging core lab, so that the BICR assessment of progression can be expedited. The BICR review will be completed and the results provided to the site within approximately 5 business days of receipt of the scans, provided there are no pending imaging queries to the site.

Participants whose progression is not confirmed by the BICR will be required to continue tumor assessments (if clinically feasible) according to the protocol-specified schedule or sooner if clinically indicated until the BICR confirms progression on a subsequent tumor assessment. Also, if participants discontinue treatment without radiographic progression, tumor assessments will continue according to the protocol specified schedule, as noted in Section 2, until progression has been confirmed by BICR.

All study treatment decisions will be based on the investigator's assessment of tumor images and not on the BICR assessment. The BICR assessment of progression is only relevant for determining when tumor assessments for a given participant are no longer required to be submitted to the imaging vendor.

9.1.5 Patient Report Outcomes

Outcomes research data including health related quality of life and patient reported symptom burden provide a more complete understanding of the impact of treatment by incorporating the patients' perspective. These data offer insights into the patient experience that may not be captured through physician reporting. The EQ-5D-5L will be collected in order to assess the impact of nivolumab on generic health related quality of life and the data will be used for populating health economic models most notably, cost effectiveness analysis. The EORTC QLQ-C30 will be collected in order to assess cancer specific health related quality of life. The combination of the generic scale for general health status and economic evaluation and the cancer specific scale will provide a robust outcomes research package. EORTC QLQ-C30 and the EQ-5D-5L will be collected according to the Schedule of Activities.

The EORTC QLQ-C30 is a 30-item instrument comprising five functional scales (Physical, Role, Cognitive, Emotional and Social), three symptom scales (Fatigue, Pain, and Nausea/Vomiting), a Global Health Status/QoL scale, and six single items (Constipation, Diarrhea, Insomnia, Dyspnea, Appetite Loss, and Financial Difficulties). Except for the overall health status and global QoL items, responses for all items are 4-point categorical scales ranging from 1 (Not at all) to 4 (Very much). The overall health status/QoL responses are 7-point Likert scales. It has gone through appropriate psychometric testing and is available in over 81 languages.

General health status will be measured using the EQ-5D-5L. The EQ-5D-5L is a standardized instrument for use as a measure of self-reported general health status. The EQ-5D-5L comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety) and a visual

analog rating scale (VAS). The utility data generated from the EQ-5D-5L is recommended for and commonly used in cost effectiveness analysis.

9.2 Adverse Events

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

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

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

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 case report form.

Contacts for SAE reporting specified in Appendix 3.

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

The collection of non-serious AE information should begin at initiation of study treatment until [the follow-up contact], at the time points specified in the Schedule of Activities (Section 2). 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 Investigator Brochure (IB) 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 discontinuation of dosing. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

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 eCRF 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.

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. (In order to prevent reporting bias, participants should not be questioned regarding the specific occurrence of one or more AEs.)

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 will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up (as defined in Section 8.3).

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

9.2.4 Regulatory Reporting Requirements for SAEs

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

Sponsor or designee will be reporting adverse events to regulatory authorities and ethics committees according to local applicable laws including European Directive 2001/20/EC and FDA Code of Federal Regulations 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.

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/assigned to treatment and never treated with study drug, SAEs should be collected for 30 days from the date of randomization.

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 versus 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) AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)

AND

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

AND

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

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.

9.3 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see Section 9.2).

9.4 Safety

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

At screening, a medical history will be obtained to capture relevant underlying conditions. The screening examinations should include weight, height, ECOG Performance Status, blood pressure (BP), heart rate (HR), temperature, and hearing assessments (per standard of care). Screening assessments should be performed in the time frames as indicated in the Schedule of Activities.

Screening local laboratory assessments should be done within 14 calendar days prior to first treatment and are to include: CBC with differential, Chemistry panel including LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Na, K, Cl, Mg, phosphate, LDH, glucose, albumin.

The following screening local laboratory assessments should be done within 28 calendar days prior to first treatment: thyroid panel including TSH, free T3, and free T4 (if free T3 and free T4 are not available then Total T3 and Total T4 are acceptable) and Hepatitis B and C testing (HBV sAg and HCV Ab or HCV RNA). Sites in Germany see Appendix 9.

While on-study the following local laboratory assessments are to be done within 3 calendar days prior to each dose on Day 1: CBC with differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Na, K, Cl, Mg, phosphate, LDH, glucose. Albumin will be assessed as clinically indicated in all four treatment arms. Amylase and lipase are

to be monitored on-treatment in Arm B and D participants and during Part 1 of Arm C only. CBC with differential should be performed prior to gemcitabine dosing on Day 8 (see Section 7.4.2.2).

Thyroid function testing (TSH with reflexive fT3 and fT4 if free T3 and free T4 are not available then Total T3 and Total T4 are acceptable) is to be done every 3 weeks (following each combination dose infusion) during the on-treatment Part 1 of Arm A (ie, during the period of same day sequential dosing with nivolumab 1 mg/kg followed by ipilimumab 3 mg/kg), then every 8 weeks for participants receiving nivolumab at 480 mg every 4 weeks.

Participants will be evaluated for safety if they have received any study drug. Toxicity assessments will be continuous during the treatment phase as well as during the first two safety follow-up visits. Once participants reach the survival follow-up phase, either in-person visits or documented telephone calls/email correspondence to assess the participant's status are acceptable.

Adverse events and laboratory values will be graded according to the NCI-CTCAE version 4.

On-study weight, ECOG performance status, and vital signs should be assessed at each on-study visit prior to dosing. Vital signs should also be taken as per institutional standard of care prior to, during and after infusions. The start and stop time of the study therapy infusions and any interruptions or infusion rate reductions should be documented.

Physical examinations are to be performed as clinically indicated. If there are any new or worsening clinically significant changes since the last exam, report changes on the appropriate non-serious or serious adverse event page.

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 adverse events, 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 and in Appendix 5 of this protocol.

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.

9.4.1 Electrocardiograms

All participants who have met the eligibility criteria are required to have a 12-lead ECG performed during Screening. This will serve as a baseline assessment in the event of any on-study cardiac events. If clinically indicated, additional ECGs may be obtained during the study.

9.4.2 Clinical Safety Laboratory Assessments

Investigators must document their review of each laboratory safety report.

Please refer to the Schedule of Activities in Section 2 for details related to the required laboratory assessments.

9.4.3 Imaging Safety Assessment

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

9.5 Pharmacokinetic

Although ECOG status, baseline glomerular filtration rate (GFR), albumin and body weight had an effect on nivolumab CL, the effect was not clinically meaningful. When nivolumab is administered in combination with ipilimumab 3 mg/kg, the CL of nivolumab was increased by 24%, whereas there was no effect on the clearance of ipilimumab. Additionally, PPK and exposure response (ER) analyses have been performed to support use of 240 mg Q2W dosing in addition to the 3 mg/kg Q2W regimen. Using the PPK and ER models, exposure, safety and efficacy of nivolumab at 240 mg flat dose was identical to a dose of 3 mg/kg. Full details on the clinical pharmacology aspects of nivolumab can be found in the Investigator Brochure.

Samples for PK and immunogenicity assessments will be collected for all participants receiving nivolumab and ipilimumab as described in Table 9.5-1 and from participants receiving nivolumab and platinum doublet chemotherapy as described in Table 9.5-2. All time points are relative to the start of study drug administration. All on-treatment time points are intended to align with days on which study drug is administered. If it is known that a dose is going to be delayed, then the predose sample should be collected just prior to the delayed dose. However, if a predose sample is collected but the dose is subsequently delayed, an additional predose sample should not be collected. Further details of sample collection, processing, and shipment will be provided in the laboratory procedures manual.

Blood samples should be drawn from a site other than the infusion site (ie, contralateral arm) on days of infusion. All samples collected pre-dose should be taken just prior to the administration from the contralateral arm (ie, the arm not used for the infusion). If the infusion was interrupted, the interruption details will also be documented on the CRF. Blood samples will be processed to collect serum and stored preferably at -70°C (samples may be stored at -20°C up to 2 months). Further details of pharmacokinetic sample collection and processing will be provided to the site in the lab manual.

Blood samples for immunogenicity analyses of nivolumab and/or ipilimumab will be collected according to the schedule given in Table 9.5-1 and Table 9.5-2. Samples collected from participants will be evaluated for the development of Anti-Drug Antibody (ADA) for nivolumab and/or ipilimumab by validated immunoassays. Samples may also be analyzed for neutralizing ADA response to nivolumab and/or ipilimumab.

Table 9.5-1: Pharmacokinetic and Immunogenicity Sample Collections for Arm A (CA209901)

Part[a]	Study Day[b]	Time (Event)	Time (Relative to Start of Nivolumab Infusion) Hours:Min	Pharmacokinetic Blood Sample for Nivolumab	Immunogenicity Blood Sample for Nivolumab	Pharmacokinetic Blood Sample for Ipilimumab	Immunogenic Blood Sample for Ipilimumab
1	C1D1	(Predose)[c]	00:00	X	X	X	X
1	C1D1	(EOI-nivo)[d]	00:90	X			
1	C1D1	(EOI-ipi)[d]	00:90			X	
1	C2D1	(Predose)[c]	00:00	X	X	X	X
1	C2D1	(EOI-nivo)[d]	00:90	X			
1	C2D1	(EOI-ipi)[d]	00:90			X	
1	C3D1	(Predose)[c]	00:00	X	X	X	X
1	C3D1	(EOI-nivo)[d]	00:90	X			
1	C3D1	(EOI-ipi)[d]	00:90			X	
2[a]	C5D1[a]	(Predose)[c]	00:00	X	X	X	X
2	C5D1	(EOI-nivo)[d]	00:30	X			
2	C9D1	(Predose)[c]	00:00	X	X		

Table 9.5-1: Pharmacokinetic and Immunogenicity Sample Collections for Arm A (CA209901)

Part[a]	Study Day[b]	Time (Event)	Time (Relative to Start of Nivolumab Infusion) Hours:Min	Pharmacokinetic Blood Sample for Nivolumab	Immunogenicity Blood Sample for Nivolumab	Pharmacokinetic Blood Sample for Ipilimumab	Immunogenic Blood Sample for Ipilimumab
2	CXD1: Every4th cycle after C9D1 in Part 2 (ie, C13D1, C17D1, etc.)	(Predose)[c]	00:00	X	X		
Follow-up	First 2 Follow-up Visits (Approximately up to 100 Days from the Discontinuation of Study Drug)	NA		X	X		

[a] Cycle numbering is consecutive from start of treatment. Part 1 indicates first 12 weeks (or 4 cycles) of combination treatment (nivolumab + ipilimumab). Part 2, indicates nivolumab monotherapy period beginning 6 weeks following last combination dose. "**C5D1" here represents the first dose of nivolumab monotherapy, regardless of cycle number.**

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

[c] Predose: All predose samples for nivolumab and ipilimumab should be taken prior to the start of nivolumab infusion. (preferably within 30 minutes). If it is known that a dose is going to be delayed, then 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] EOI-nivo and EOI-ipi: End of Infusion samples for nivolumab and ipilimumab, respectively. **For sequential dosing, both EOI samples should be collected immediately (preferably within 2 - 5 minutes) prior to the end of the ipilimumab infusion (~ 90 min from the start of the nivolumab infusion).** If the end of infusion is delayed, the collection of the EOI samples should be delayed accordingly. EOI samples may not be collected from the same IV access as drug was administered, refer to the laboratory manual for additional instructions.

Table 9.5-2: Pharmacokinetic (PK) and Immunogenicity Sample Collections - Nivolumab + Platinum Doublet Chemotherapy Arm C

Part[a]	Study Day[b]	Time (Event)	Time (Relative to Start of Nivolumab Infusion) Hours:Min	Pharmacokinetic Blood Sample for Nivolumab	Immunogenicity Blood Sample for Nivolumab
1	C1D1	Predose[c]	00:00	X	X
1	C1D1	EOI-nivo[d]	00:30	X	
1	C4D1	Predose[c]	00:00	X	X
1	C6D1	Predose[c]	00:00	X	X
2[a]	C7D1[a]	Predose[c]	00:00	X	X
2	C12D1	Predose[c]	00:00	X	X
2	D1 of every 6th Cycle after C12D1 (Part 2) until discontinuation of study treatment or maximum up to 2 years of treatment	Predose[c]	00:00	X	X
Follow-up	First 2 Follow-up Visits (Approximately up to 100 Days from the Discontinuation of Study Drug)	NA		X	X

[a] Cycle numbering is consecutive from start of treatment. Part 1 indicates first 6 cycles of treatment (nivolumab + platinum doublet chemotherapy dosing). Part 2 indicates nivolumab monotherapy period beginning 3 weeks following the last combination dose. "**C7D1" here represents the first dose of nivolumab monotherapy, regardless of cycle number.**

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

[c] Predose samples should be collected just before the administration of the first drug (preferably within 30 minutes). If it is known that a dose is going to be delayed, then 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] EOI-nivo End of Infusion samples for nivolumab, EOI samples should be collected immediately (preferably within 2 - 5 minutes) prior to the end of the nivolumab infusion (~ 30 min from the start of the nivolumab infusion). If the end of infusion is delayed, the collection of the EOI samples should be delayed accordingly. EOI samples may not be collected from the same IV access as drug was administered, refer to the laboratory manual for additional instructions.

9.6 Pharmacodynamics

See Section 9.8.

9.7 Pharmacogenomics

See Section 9.8.

9.8 Biomarkers

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

Table 9.8-1: Biomarker Sampling Schedule (All Participants)

Collection Timing[a]	Tumor Biopsy	MDSCs[b]	Serum	Whole Blood (Gene Expression)	PBMCs[c]	ctDNA	Whole Blood (SNP)
Screening	X						
C1D1		X	X	X	X	X	X
C2D1			X				
C2D15	X[d]						
C4D1		X	X	X	X	X	
C5D1			X				
C6D1		X	X	X	X	X	
C8D1			X		X		
C10D1		X	X	X	X	X	
FU visit 1 & 2			X				
Upon Progression	X[e]	x[e]	x[e]	x[e]	x[e]	x[e]	

[a] Biomarker sampling occurs prior to dosing of study drug and can occur up to 5 days prior to dosing.

[b] Collected in US, Canada, and European countries only.

[c] Not collected in China, Argentina, Brazil, Chile, or Peru, for PBMC.

[d] This is an optional biopsy, post-second dosing of combination therapy (if possible 2 weeks post-C2D1 or 1 week pre-C3D1).

[e] Sample collection upon disease progression is optional, but highly recommended.

9.8.1 Additional Research Collection

This protocol will include both sample collection and residual sample storage for additional research (AR).

For All US sites:

Additional research is mandatory for all study participants.

- If the IRB/ethics committees and site agree to the mandatory additional research retention and/or collection, then the study participant must agree to the mandatory additional research as a requirement for inclusion in the study.

For non-US Sites

Additional research is optional for all study participants, except where retention and/or collection is prohibited by local laws or regulations, ethics committees, or institutional requirements.

This collection for additional research is intended to expand the translational R&D capability at Bristol-Myers Squibb, and will support as yet undefined research aims that will advance our

understanding of disease and options for treatment. It may also be used to support health authority requests for analysis, and advancement of pharmacodiagnostic development to better target drugs to the right patients. This may also include genetic/genomic exploration aimed at exploring disease pathways, progression and response to treatment etc.

All requests for access to samples or data for additional research will be vetted through a diverse committee of the study sponsor's senior leaders in Research and Development (or designee) to ensure the research supports appropriate and well-defined scientific research activities.

Residual samples of tumor tissue (baseline and on-treatment,) whole blood, serum samples, and PBMC samples will be retained from selected time points for additional research purposes (see Table 9.8.1-1).

Samples kept for future research will be stored at [redacted] an independent, BMS-approved storage vendor.

- The manager of these samples will ensure they are properly used throughout their usable life and will destroy the samples at the end of the scheduled storage period, no longer than fifteen (15) years after the end of the study or the maximum allowed by applicable law.
- Transfers of samples by research sponsor to third parties will be subject to the recipient's agreement to establish similar storage procedures.

Samples will be stored in a coded fashion, and no researcher will have access to the key. The key is securely held by the Investigator at the clinical site, so there is no direct ability for a researcher to connect a sample to a specific individual.

Further details of sample collection and processing will be provided to the site in the procedure manual.

Table 9.8.1-1: Residual Sample Retention for Additional Research Schedule

Sample Type	Time Points for which residual samples will be retained
Tumor Biopsy	Pre-treatment, C2D15 (optional), upon progression (optional)
Whole blood sample (SNP)	C1D1
Whole blood sample (Gene Expression)	C1D1, C4D1, C6D1, C10D1, upon progression (optional)
Serum sample	C1D1, C2D1, C4D1, C5D1, C6D1, C8D1, C10D1, FU visits 1 and 2, upon progression (optional)
PBMC	C1D1, C4D1, C6D1, C8D1, and C10D1, upon progression (optional)

9.8.2 Immunogenicity Assessments

Blood samples for immunogenicity analysis will be collected according to the schedule given in Table 9.5-1. Samples collected from prospective participants will be evaluated for development of Anti-Drug Antibody (ADA) by a validated electrochemiluminescent (ECL) immunoassay.

Samples may also be analyzed for neutralizing antibodies and PK samples may be used for ADA analysis in the event of insufficient volume, to complete immunogenicity assessment, or to follow up on suspected immunogenicity-related AEs.

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

9.8.3 Tumor Tissue Specimens

Pre-treatment tumor tissue specimens in the form of a paraffin-embedded block or a minimum of 15 unstained slides will be submitted to central lab for PD-L1 IHC assessment prior to randomization. Participants must provide a fresh tumor biopsy from the primary disease site. If fresh tissue cannot be provided, a tissue block (or at least 15 FFPE slides) from the latest surgical resection (eg, radical cystectomy) can be accepted if collected within 2 years prior to enrollment period, and the participant did not receive systemic anticancer agents or radiotherapy since collection of sample. The PD-L1 stained tissue sections will be assessed by a pathologist and membranous PD-L1 expression scored in tumor cells if a minimum of a hundred (100) evaluable tumor cells are present. Participants with tumor samples containing less than a hundred tumor cells per tissue section will not be randomized, but participants with positive, negative or indeterminate (membrane staining is obscured by high cytoplasmic staining) PD-L1 expression will be stratified based on their expression. Participants with "indeterminate" PD-L1 expression, will be included as PD-L1 negative. In addition, this pre-treatment tumor sample may be used to assess other putative predictive biomarkers of nivolumab/ipilimumab efficacy and/or to better characterize the tumor-immune microenvironment within the resected tissue. Various molecular markers with potential predictive value for the treatment of bladder cancer with nivolumab/ipilimumab and other immunotherapies are currently under investigation and may be assessed in this study. These tumor tissue biomarkers include, but are not limited to PD-1, PD-L2, TILs or subpopulations of TILs and a Th1 immune mRNA expression signature. In addition, other methods of measuring tumor PD-L1 expression may also be assessed. These pre-treatment tumor samples may also be used to further characterize the tumor-immune microenvironment through assessment of markers that may be associated with the efficacy of nivolumab/Ipilimumab combination treatment, including but not limited to other T-cell checkpoint receptors and ligands (eg, Lag-3, Tim-3), intratumoral immune cell subsets, including macrophages, natural killer (NK) cells and B cells. It is highly recommended to collect an on-treatment biopsy sample in metastatic sites (e.g. lymph nodes) one week prior to the third combination dosing. Tumor tissue collection at relapse is also highly recommended. Although these on-treatment and relapse biopsies are optional, they are absolutely needed to understand the reasons of disease relapse, the mechanism of action of nivolumab/ipilimumab and how to benefit patients with optimal treatment strategies. They may be used for the assessment of markers implicated in resistance to immunotherapeutic agents, including but not limited to other T cell checkpoint receptors and ligands (eg, Lag-3, Tim-3) and intratumoral immune cell subsets, including but not limited to, T regulatory cells and myeloid derived suppressor cells. These samples may also be used to investigate the effect of nivolumab/ipilimumab on the expression of potentially relevant predictive and/or prognostic bladder cancer biomarkers. Both the pre- and on-treatment tumor samples and the sample collected

upon recurrence may be retrospectively profiled for gene expression/mutation status, as well as for the expression of other immune or bladder cancer related genes, RNAs, miRNA and proteins, or for the presence of immune cell populations using a variety of methodologies inclusive of, but not limited to IHC, qRT-PCR, genetic mutation detection and fluorescent in-situ hybridization (FISH).

9.8.4 Peripheral Blood Markers

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

9.8.5 Single Nucleotide Polymorphisms (SNPs)

Whole blood will be collected from all participants prior to treatment to generate genomic DNA for Single Nucleotide Polymorphism (SNP) analyses. These analyses will focus on SNPs within genes associated with PD1 and other immunoregulatory signaling pathways to determine if natural variation within those genes is associated with response to nivolumab/ipilimumab and/or with adverse events during treatment.

9.8.6 Serum-Soluble Factors

Blood samples for exploratory serum biomarker analyses will be drawn at specified time points. Additionally, serum samples will be collected when clinically safe and feasible, upon occurrence of a Grade 3 drug-related AE and/or any lab abnormality regarded as a drug-related SAEs. Serum samples may be assessed by ELISA, seromics, microRNA profiling, circulating tumor DNA measurements, metabolomics and/or other relevant multiplex-based protein assay methods for immune-related factors that will predict for nivolumab/ipilimumab benefit or correlate with treatment-related adverse events. Numerous potential serum/plasma-based biomarkers are currently under investigation for their potential to predict or correlate with safety or efficacy to nivolumab/ipilimumab combination or other immunotherapies, including but not limited to levels of soluble PD-L1, anti-tumor antibodies, cytokines, chemokines, inflammatory factors, NKG2D ligands (eg, soluble MICA), circulating tumor DNA, and microRNAs (such as, but not limited to, miR-513 and miR19b. Myeloid Derived Suppressor Cells (MDSC) Myeloid derived suppressor cells are an immune cell population capable of suppressing T cell activation and proliferation. Low pre-treatment MDSC levels in peripheral blood may be associated with better overall survival in bladder cancer participants treated with the combination nivolumab/ipilimumab. MDSCs will be measured at baseline and on-treatment to assess pharmacodynamic changes or associations with outcome.

9.8.7 Peripheral Blood Mononuclear Cells (PBMCs)

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

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

9.8.8 Plasma

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

9.8.9 Whole Blood Gene Expression

The expression level of genes related to response to nivolumab/ipilimumab therapy will be quantified using molecular methods such as Affymetrix by microarray and/or quantitative reverse transcription polymerase chain reaction (RT-PCR) analysis in whole blood samples. Analysis may include, but not necessarily be limited to, genes associated with immune-related pathways, such as T cell activation and antigen processing and presentation.

9.9 Health Economics OR Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters will not be evaluated in this study.

10 STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

Details on accrual assumptions are in Section 5.2.

Primary Study:

The sample size of the primary study accounts for 2 primary comparisons of the primary endpoint (OS): in cisplatin-ineligible participants and in PD-L1 positive (≥ 1%) participants with previously untreated unresectable or metastatic UC.

The overall alpha for the primary study is 0.05, which is split with 0.02 to evaluate OS in cisplatin-ineligible participants and 0.03 to evaluate OS in PD-L1 positive (≥ 1%) participants, accounting for one formal interim analysis in each primary population.

Substudy:

The sample size of the substudy accounts for the dual-primary efficacy endpoints: PFS based on BICR assessments and OS, evaluated in cisplatin-eligible participants with previously untreated unresectable or metastatic UC.

The overall alpha for the substudy is 0.05, which is split with 0.01(two-sided) to evaluate PFS and 0.04(two-sided) to evaluate OS. No interim analysis of PFS is planned. One formal OS interim analysis at 75% information fraction and one final analysis are planned to assess efficacy.

Primary Study and Substudy:

For the primary study and substudy, simulation models incorporating aspects of immunotherapy-like delayed separation (observed as late separation of survival curves between the experimental and SOC arms), long term survival benefits (observed as a long-lasting plateau towards the tail of the survival curve) and potential access to immunotherapy as second line therapy among participants randomized into the SOC chemotherapy arm post first-line progression were developed for sample size estimation. Sample size calculations for this study design were done using EAST 6 (v. 6.3.1) and R.

Overall approximately 445 cisplatin-ineligible participants (per eligibility criteria see Section 6.1) and 845 cisplatin-eligible participants will be randomized. Of the 845 cisplatin-eligible participants, approximately 245 will be randomized in the primary study and 600 will be randomized in the substudy.

The primary analysis in the primary study is based on the number of OS events observed in each primary population (cisplatin-ineligible participants and PD-L1 positive (≥ 1%) participants by IHC). Once at least 445 cisplatin-ineligible participants and at least 235 PD-L1 positive participants are randomized into Arms A and B of the primary study, the primary study will cease enrollment (Arms A and B). (This is regardless of the number of cisplatin-eligible participants randomized in the primary study.) Subsequent cisplatin-eligible participants will only be randomized to the substudy.

10.1.1 Sample Size Justification for the Primary Overall Survival Endpoints in the Primary Study

The primary study accounts for two primary comparisons of the primary endpoint (OS): in cisplatin-ineligible participants and in PD-L1 positive (≥ 1%) participants with previously untreated unresectable or metastatic UC.

The overall alpha for this primary study is 0.05, which is split with 0.02 to evaluate OS in cisplatin-ineligible participants and 0.03 to evaluate OS in PD-L1 positive (≥ 1%) participants, accounting for one formal interim analysis in each primary population.

10.1.1.1 Overall Survival in Cisplatin-ineligible Participants

One of the primary objectives of the primary study is to compare OS of nivolumab combined with ipilimumab to SOC chemotherapy in cisplatin-ineligible participants with previously untreated, unresectable or metastatic UC. The number of events and power of this comparison were

calculated assuming a non-proportional hazard model with a 3-month delayed treatment effect and a 0.23 cure fraction in the nivolumab combined with ipilimumab arm (weighted average of estimated OS cure rate of 20% in PD-L1 negative (<1%) participants and 30% in PD-L1 positive (≥ 1%) participants) and a 0.10 cure fraction in the SOC chemotherapy arm.

Approximately 348 events (i.e., deaths), observed among the 445 randomized cisplatin-ineligible participants, provides 80% power to detect an average HR of 0.71 with an overall type 1 error of 0.02 (two-sided). The average HR of 0.71 corresponds to a 40.8% increase in the median OS, assuming a median OS of 13.0 months[17] in the SOC chemotherapy arm (median estimate assuming a median OS of 11 months in cisplatin-ineligible participants increased by 2 months for use of PD-1/PD-L1 in the refractory setting) and 18.3 months in the experimental treatment arm, taking into account 3-month delayed treatment effect and cure rates in each arm as specified above.

One formal interim analysis of OS in cisplatin-ineligible participants is planned in this primary study. This interim analysis is planned after 278 observed events (i.e., deaths) corresponding to 80% of the targeted OS events for final analysis and it is expected to happen 41 months from the randomization of the first participant. The alpha allocation for the interim and final analyses is based on the Lan-DeMets alpha spending function approach using an O'Brien Fleming stopping boundary controlling for a two-sided overall type 1 error of 2%. The stopping boundary will depend on the actual number of deaths at the time of the interim analysis and the final analysis.

Under the assumptions for accrual and OS distribution stated above, it will take approximately 55 months from the randomization of the first participant to observe the required number of OS events for the final OS analysis (28 months for accrual and 27 months for minimum follow-up). It is projected that an observed hazard ratio of 0.77 or less would results in a statistically significant improvement of nivolumab combined with ipilimumab at the final analysis of OS in cisplatin-ineligible participants.

10.1.1.2 Overall Survival in PD-L1 Positive (≥ 1%) Participants

One of the primary objectives of the primary study is to compare OS of nivolumab combined with ipilimumab to SOC chemotherapy in PD-L1 positive (≥ 1%) participants by IHC with previously untreated, unresectable or metastatic UC. The number of events and power of this comparison were calculated assuming a non-proportional hazard model with a 3-month delayed treatment effect, a 0.30 cure fraction in the nivolumab combined with ipilimumab arm and a 0.13 cure fraction in the SOC chemotherapy arm (weighted average of estimated OS cure rate of 10% in cisplatin-ineligible participants and 20% in cisplatin-eligible participants), accounting for use of second-line immunotherapy.

Approximately 163 events (i.e., deaths), observed among the 235 randomized PD-L1 positive (≥ 1%) participants by IHC, provides 84% power to detect an average HR of 0.61 with an overall type 1 error of 0.03 (two-sided). The average HR of 0.61 corresponds to a 70.2% increase in the median OS, assuming a median OS of 14.1 months (weighted average of estimated median OS of 13 months in cisplatin-ineligible participants and 16 months in cisplatin-eligible participants, both being increased by 2 months for use of PD-1/PD-L1 in the refractory setting) in the SOC

chemotherapy arm and 24.0 months in the experimental treatment arm, taking into account 3-month delayed treatment effect and cure rates in each arm as specified above.

One formal interim analysis of OS in PD-L1 positive (≥ 1%) participants is planned in this primary study. This interim analysis is planned after 130 observed events (i.e., deaths) corresponding to 80% of the targeted OS events for final analysis and it is expected to happen 41 months from the randomization of the first participant. The alpha allocation for the interim and final analyses is based on the Lan-DeMets alpha spending function approach using an O'Brien Fleming stopping boundary controlling for a two-sided overall type 1 error of 3%. The stopping boundary will depend on the actual number of deaths at the time of the interim analysis and the final analysis.

Under the assumptions for accrual and OS distribution stated above, it will take approximately 52 months from the randomization of the first participant to observe the required number of OS events for the final OS analysis (28 months for accrual and 24 months for minimum follow-up). It is projected that an observed hazard ratio of 0.70 or less would results in a statistically significant improvement of nivolumab combined with ipilimumab at the final analysis of OS in PD-L1 positive (≥ 1%) participants by IHC.

10.1.2 Sample Size Justification for the Secondary Overall Survival Endpoint in All Randomized Participants in the Primary Study

Under the accrual projection detailed in the Section 5.2, Number of Participants, it is estimated that approximately 690 participants will be randomized in the primary study, with an estimated 445 cisplatin-ineligible participants and 245 cisplatin-eligible participants.

One of the secondary objectives of the primary study is to compare OS of nivolumab combined with ipilimumab to SOC chemotherapy in all randomized participants with previously untreated, unresectable or metastatic UC. The HR in the all randomized participants is expected to be in a range. The number of events and power of this comparison were calculated assuming a non-proportional hazard model with a 3-month delayed treatment effect, a 0.23 cure fraction (per weighted average) in the nivolumab combined with ipilimumab arm and a 0.13 cure fraction (per weighted average) in the SOC chemotherapy arm.

One formal interim is planned in the all randomized participants. The interim and final analyses are planned at the corresponding time of the interim and final analysis of the primary comparisons.

Assuming an average HR of 0.75, at the final OS analysis of the primary comparisons (approximately 55 months from the randomization of the first participant), it is expected to observe approximately 518 events (i.e., deaths) among the 690 randomized participants in the two respective treatment arms. This would lead to a 90% power for the all randomized comparison with an overall type 1 error of 0.05 (two-sided). The average HR of 0.75 corresponds to a 33% increase in the median OS, assuming a median OS of 13.9 months in the SOC chemotherapy arm[11,17] (increased by 2 months for use of PD-1/PD-L1 in the refractory setting) and 18.5 months in the experimental treatment arm.

At the interim analysis, it is expected to observe 414 events (80.0% of the targeted OS events for final analysis).

The alpha allocation for the interim and final analyses is based on the Lan-DeMets alpha spending function approach using an O'Brien Fleming stopping boundary controlling for a two-sided overall type 1 error passed from the primary comparisons. The stopping boundary will depend on the actual number of deaths at the time of the interim analysis and the final analysis.

10.1.3 Sample Size Justification for the Dual Primary Endpoints of Progression Free Survival and Overall Survival in Cisplatin-eligible Randomized Participants in the Substudy

The substudy accounts for dual primary endpoints: PFS as per BICR and OS. Overall alpha is set at 0.05, which is split with 0.01 to evaluate PFS and 0.04 to evaluate OS.

10.1.3.1 Progression Free Survival

One of the primary objectives of the substudy is to compare PFS (based on BICR assessments) of nivolumab combined with SOC chemotherapy to SOC chemotherapy in cisplatin-eligible participants with previously untreated, unresectable or metastatic UC. The number of events and power were calculated assuming a non-proportional hazards model with a 3-month delayed treatment effect, a 0.20 cure fraction in Arm C and a 0.15 cure fraction in the Arm D.

For the comparison of PFS endpoint using log rank test, 460 PFS events among the 600 randomized cisplatin-eligible participants will show a statistically significant difference between the treatment arms with 70% power under a two-sided experiment-wise alpha = 0.01 when the average HR of the experimental arm to SOC arm is 0.7. This HR of 0.7 is equivalent to demonstrating a 42% improvement in median PFS, assuming a median PFS of 7.7 months[11] in the SOC chemotherapy arm and a median PFS of 10.9 months in the experimental treatment arm. No interim analysis of PFS is planned for this substudy.

If OS superiority is demonstrated in interim analysis for the substudy, formal testing of PFS will be performed. The significance level of the PFS will depends on the number of PFS events occur at time of the interim analysis. The hierarchical testing procedure under the group sequential testing setting will be employed to control the overall type 1 error. It is projected that approximately 368 PFS events may occur (80% of total events) at the time of OS interim analysis.

Under the assumptions for accrual and PFS distribution stated above, it will take approximately 45 and 54 months from the randomization of the first participant in the substudy to observe the required number of PFS events for the interim (if performed) and final PFS analysis (44 months for accrual and 10 months for minimum follow up), respectively.). It is projected that an observed HR of 0.786 or less would result in a statistically significant improvement in the final analysis of PFS. However, the PFS final analysis will be performed at the time of final OS analysis which may be earlier than the planned number of PFS events.

Table 10.1.3.1-1 summarizes the power of PFS corresponding to different potential numbers of PFS events observed at the time of OS final analysis if no PFS interim analysis is performed, for a two-sided total alpha level of 0.01 (without alpha recycling) and 0.05 (with alpha recycling).

Table 10.1.3.1-1: PFS per BICR Power for Different Potential Number of PFS Events at OS Final Analysis (Cis-eligible Randomized Participants)

Potential number of PFS events at OS final analysis	Total alpha	PFS power
405	0.01	59%
	0.05	80%
410	0.01	61%
	0.05	82%
415	0.01	62%
	0.05	83%

10.1.3.2 Overall Survival

One of the primary objectives of the substudy is to compare the OS of nivolumab combined with SOC chemotherapy to SOC chemotherapy in cisplatin-eligible participants with previously untreated, unresectable or metastatic UC. The number of events and power were calculated assuming a non-proportional hazards model with a 3-month delayed treatment effect, a 0.234 cure fraction in Arm C and a 0.20 cure fraction in the Arm D.

For the comparison of OS endpoint using log rank test, at least 356 OS events among the 600 randomized cisplatin-eligible participants are required to show a statistically significant difference in OS between the treatment arms with 85% power under a 2-sided experiment-wise alpha = 0.04 when the average HR of the experimental arm to SOC arm is 0.7. The HR of 0.7 is equivalent to demonstrating a 47% improvement in median OS, assuming a median OS of 16 months[11] in the SOC chemotherapy arm and a median OS of 23.5 months in the experimental treatment arm.

One interim analysis of OS is planned for the substudy when 267 OS events (75% information fraction) have occurred. The alpha allocation for the interim and final analyses is based on the Lan-DeMets alpha spending function approach using an O'Brien Fleming stopping boundary controlling for a 2-sided overall type 1 error of 4%. The stopping boundary will depend on the actual number of OS events at the time of the interim analyses and the final analysis.

Under the assumptions for accrual and OS distribution stated above, it will take approximately 45 and 54 months from the randomization of the first participant in the substudy to observe the required number of OS events for the interim and final OS analyses, respectively. It is projected that an observed HR of 0.74 and 0.8 or less would result in a statistically significant improvement in the interim and final analysis of OS, respectively.

10.1.4 Analysis Timing Projections

As stated above, approximately 1290 participants with previously untreated, unresectable or metastatic UC will be randomized (see Section 5.2).

It will take approximately 28 months to complete the randomization of the primary study and 6 extra months to complete the randomization of the substudy.

Table 10.1.4-1 summarizes populations and the projected timing of primary comparisons and secondary endpoints analyses planned in the primary study and of primary endpoint analysis in the substudy.

It is expected that final OS analysis in each primary population of the primary study will occur at 3 months interval and will have their interim OS analysis at the same time. However, because the OS event rate pattern may be different between cisplatin-ineligible participants and PD-L1 positive participants, the interim OS analyses of the primary study will occur at the same time if the targeted OS events are projected to happen with less than 5 months interval. The same rule will apply for the final OS analyses of the primary study.

The substudy final analysis will be OS driven and will be conducted when the OS final analysis events (at least 356) are reached. The substudy PFS final analysis will be conducted at the same time as the OS final analysis.

Table 10.1.4-1: Populations and Projected Timing for Analysis of Primary Endpoints: Primary Study and Secondary Study

Endpoint	Population	Criteria	Projected timing	Type 1 error
Primary study				
Primary OS in PD-L1 positive (Interim Analysis)	All PD-L1 positive randomized participants in primary study	At least 130 events	41 months[a]	O'Brien Fleming 3% two-sided
Primary OS in PD-L1 positive (Final Analysis)	All PD-L1 positive randomized participants in primary study	At least 163 events	52 months[a]	O'Brien Fleming 3% two-sided
Primary OS in cisplatin-ineligible (Interim Analysis)	All cisplatin-ineligible randomized participants in primary study	At least 278 deaths	41 months[a]	O'Brien Fleming 2% (or 5%) two-sided (for details, see Section 10.3.1.1)
Primary OS in cisplatin-ineligible (Final Analysis)	All cisplatin-ineligible randomized participants in primary study	At least 348 events	55 months[a]	O'Brien Fleming 2% (or 5%) two-sided (for details, see Section 10.3.1.1)
Secondary OS in all randomized (Interim Analysis)[b]	All randomized participants in primary study	At time of interim OS final analysis, in a hierarchical fashion (for details, see Section 10.3.1.2) ~ 414 deaths	41 months[a]	O'Brien Fleming 2% (or 5%) two-sided (for details, see Section 10.3.1.2)
Secondary OS in all randomized (Final Analysis)[b]	All randomized participants in primary study	At time of interim OS final analysis, in a hierarchical fashion (for details, see Section 10.3.1.2) ~ 518 deaths	55 months[a]	O'Brien Fleming 2% (or 5%) two-sided (for details, see Section 10.3.1.2)
Substudy				
Substudy OS (Interim Analysis)	All cisplatin-eligible randomized participants in the substudy	At time of cisplatin-ineligible OS final analysis of primary study ~ 267 OS (75% information fraction) events	55 months (ie, 45 month[c])	O'Brien Fleming 4% two-sided
Substudy OS and PFS (Final Analysis)	All cisplatin-eligible randomized participants in the substudy	At least 356 OS events	64 months (ie, 54 months[c])	O'Brien Fleming 1% (PFS), 4 % (OS) two-sided

[a] Projected timing from first participant's randomization date in primary study.

[b] Under hierarchical testing procedure (See Section 10.3.1 for further details).

[c] Projected timing from first participant's randomization date in substudy.

10.2 Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
All enrolled participants	All participants who signed an informed consent form and were registered into the IRT.
All randomized participants	All randomized participants overall.
Cisplatin-ineligible randomized participants	All randomized participants meeting cisplatin-ineligibility criteria (See Section 6.1) at the time of randomization. This is one of the primary populations for the primary study. Analysis of demography, protocol deviations, baseline characteristics and primary efficacy analysis will be performed for this population.
All randomized participants with PD-L1 at ≥ 1% expression by immunohistochemistry (IHC) in the primary study	All randomized participants with PD-L1 expressing tumor (≥ 1%) who were randomized in the primary study. This is one of the primary populations for the primary study. Analysis of demography, protocol deviations, baseline characteristics and primary efficacy analysis will be performed for this population
All randomized participants in the primary study	All randomized participants in the primary study. This population is considered as the secondary efficacy analysis population for the primary study. Analysis of demography, protocol deviations, baseline characteristics, secondary efficacy analysis and outcome research analysis will be performed for this population.
Cisplatin-eligible randomized participants in the primary study	All randomized participants meeting cisplatin-eligibility criteria (See Section 6.1) at the time of randomization in the primary study. This population is considered as the exploratory efficacy analysis population for the primary study. Analysis of demography, protocol deviations, baseline characteristics, exploratory efficacy analysis and outcome research analysis will be performed for this population.
Cisplatin-eligible randomized participants in the substudy	All randomized participants meeting cisplatin-eligibility criteria (See Section 6.1) at the time of randomization in the substudy. This is the primary efficacy analysis population of the sub-study. Analysis of demography, protocol deviations, baseline characteristics and primary efficacy analysis will be performed for this population.
All treated participants	All participants who received any dose of study therapy. This is the primary dataset for drug exposure and safety analysis.
PK participants	All participants with available serum time-concentration data from randomized participants dosed with nivolumab.
Immunogenicity participants	All participants with available data from randomized participants dosed with nivolumab.
Immunogenicity evaluable participants	All treated participants with baseline and at least one post baseline immunogenicity assessment.
Outcome research participants	All treated participants who have an assessment at baseline and at least one subsequent assessment.

Population	Description
Biomarker participants	All randomized participants with available biomarker data (PD-L1 expression status and other assays).
All randomized participants with PD-L1 expression at ≥ 1% expression by immunohistochemistry (IHC) in the substudy	All randomized participants with PD-L1 expressing tumor (≥ 1%) who were randomized in the substudy. This is the primary dataset for the secondary efficacy analysis in the PD-L1 expressing group in the substudy.

10.3 Statistical Analyses

The statistical analysis plan 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 and unused data. Below is a summary of planned statistical analyses of the primary and secondary endpoints.

10.3.1 Efficacy Analyses

Primary Study:

The primary objective of the primary study is to compare OS (defined in Section 9.1.1 of nivolumab combined with ipilimumab to SOC chemotherapy in the cisplatin-ineligible and in the PD-L1 positive (≥ 1%) randomized participants.

The first secondary objective of the primary study is to compare OS of nivolumab combined with ipilimumab to SOC chemotherapy in all randomized participants in the primary study. This will be measured by the same definition of OS, as specified in Section 10.3.1.1, in the all randomized population in the primary study.

For these 3 comparisons, multiplicity adjustment (as described in Section 10.3.1.1 and 10.3.1.2) will be applied to ensure strong control of the Type I error rate at 0.05.

The second secondary objective of this study is to evaluate PFS in nivolumab combined with ipilimumab versus SOC chemotherapy in the two primary populations and in all randomized participants in the primary study. This will be measured by PFS endpoint defined in Section 10.3.1.2, in the two primary populations and in all randomized participants in the primary study.

The third secondary objective of this study is to evaluate changes from baseline in health-related QOL in nivolumab combined with ipilimumab versus SOC chemotherapy in all randomized participants in the primary study. This will be measured by QLQ-C30 Global Health Status score, as specified in Section 10.3.1.2, in the all randomized population in the primary study.

Substudy:

The primary objective of the substudy is to compare PFS (based on BICR assessments) and OS of nivolumab combined with SOC chemotherapy to SOC chemotherapy in the cisplatin-eligible randomized participants in the substudy. This will be measured by the PFS and OS endpoints defined in Section 10.3.1.1, in the cisplatin-eligible randomized participants in the substudy.

The secondary objectives of this study are:

- To evaluate changes from baseline in health-related QOL in nivolumab combined with SOC chemotherapy versus SOC chemotherapy in the cisplatin-eligible randomized participants in the substudy. This will be measured by QLQ-C30 Global Health Status score, as specified in Section 10.3.1.2, in the cisplatin-eligible randomized population in the substudy.
- To evaluate whether PD-L1 expression is a predictive biomarker of efficacy (PFS and OS) of nivolumab combined with SOC chemotherapy as first-line therapy in cisplatin-eligible participants with previously untreated, unresectable or metastatic UC using Kaplan-Meier survival plot between treatments by PD-L1 expression status (<1% or ≥ 1%).

10.3.1.1 Primary Endpoints

Primary Study:

Overall survival is the primary endpoint in the primary study.

The formal comparison of OS will be conducted in the two primary populations, using a two-sided 0.03 stratified log-rank test (adjusted for interim analysis) in the PD-L1 positive (≥ 1%) participants by IHC and a two-sided 0.02 stratified log-rank test (adjusted for interim analysis) in the cisplatin-ineligible participants, each comparison with the randomization stratification factors as recorded in IRT as stratification factors. At either the interim or final analysis: in case OS in the PD-L1 positive (≥ 1%) participants is significant, its significance level of 0.03 will be passed on to the other primary comparison (ie OS in the cisplatin-ineligible participants will be tested at a local significance level of 0.05 [adjusted for interim analysis]).

Median OS will be estimated via the Kaplan-Meier product limit method. Median survival time along with two-sided 95% CI will be constructed based on a log-log transformed CI for the survival function. Kaplan-Meier plots of OS will be presented. Hazard ratios (HR) and corresponding two-sided (1 - adjusted alpha)% confidence intervals (CI) will be estimated using a Cox proportional hazards model, with treatment arm as a single covariate, stratified by the stratification factors, corresponding to the comparison of OS.

Rates at landmark time will be derived from the KM estimate and corresponding CI will be derived based on Greenwood formula for variance derivation and on log-log transformation applied on the survivor function.

Substudy:

Progression-free survival (PFS) and overall survival (OS) are the dual primary endpoints in the substudy.

The formal comparison of PFS will be conducted using a two-sided 0.01 stratified log-rank test, with the randomization stratification factors as recorded in IRT as stratification factors among cisplatin-eligible randomized participants in the substudy.

The formal comparison of OS will be conducted using a two-sided 0.04 stratified log-rank test, with the randomization stratification factors as recorded in IRT as stratification factors among cisplatin-eligible randomized participants in the substudy.

Median PFS and OSwill be estimated via the Kaplan-Meier product limit method. Median survival time along with two-sided 95% CI will be constructed based on a log-log transformed CI for the survival function. Kaplan-Meier plots of PFS and OS will be presented. HR and corresponding two-sided (1-adjusted alpha) % CI will be estimated using a Cox proportional hazards model, with treatment arm as a single covariate, stratified by the stratification factors, corresponding to the comparison of PFS and OS.

In case OS is significant at either the interim analysis or final analysis, its significance level of 0.04 will be passed on to the PFS primary comparison (ie PFS will be tested at a local significance level of 0.05). If OS superiority is demonstrated in interim analysis, a formal testing of PFS will be performed at the time of the OS interim analysis (hierarchical testing). The significance level of the PFS will depends on the number of PFS events occur at time of the interim analysis. The Lan-DeMets alpha spending function with O'Brien and Fleming type of boundary under the group sequential testing setting will be used to ensure the control of type 1 error. Detailed hierarchical testing procedure can be found in Section 7.5.10 of the SAP with both graphical presentation and the exact significance level if the analysis is conducted at the planned number of events. Similarly, if PFS is tested significant at final analysis, its significance level of 0.01 will be passed on to the OS final analysis (ie OS will be tested at a local significance level of 0.05 at final analysis under group sequential testing procedure and adjusts for the OS interim analysis).

Rates at landmark time will be derived from the KM estimate and corresponding CI will be derived based on Greenwood formula for variance derivation and on log-log transformation applied on the survivor function.

10.3.1.2 Secondary Endpoints

Primary Study:

Overall Survival

If OS superiority is demonstrated in cisplatin-ineligible participants, formal testing of OS among all randomized participants in the primary study will be performed. (If, at a given timepoint, OS in the PD-L1 positive (≥ 1%) population is significant, but not OS in the cisplatin-ineligible population then OS in the all randomized participants will not be tested.) Local significance level will be 0.02 if no significance level was passed from the PD-L1 positive (≥ 1%) population to the cisplatin-ineligible population; 0.05 otherwise. For OS in all randomized participants, one interim analysis is planned; thus the local significance level (0.02 or 0.05) will be adjusted based on the Lan-DeMets alpha spending function approach using an O'Brien Fleming stopping boundary. The stopping boundary will depend on the actual number of deaths at the time of the interim and the final analysis. Analyses of OS among all randomized participants in the primary study will be similar to those conducted towards the assessment of the primary OS objective.

Progression-Free Survival

PFS will be evaluated among each primary population and among all randomized participants in the primary study.

Median PFS will be estimated via the Kaplan-Meier product limit method. Median survival time along with two-sided 95% CI will be constructed based on a log-log transformed CI for the survival function. Kaplan-Meier plots of PFS will be presented. HR and corresponding two-sided 95% CI will be estimated using a Cox proportional hazards model, with treatment arm as a single covariate, stratified by the stratification factors, corresponding to the comparison of PFS.

Analysis for investigator-assessed PFS will be performed similarly.

Rates at landmark time will be derived from the KM estimate and corresponding CI will be derived based on Greenwood formula for variance derivation and on log-log transformation applied on the survivor function.

EORTC QLQ-C30 Global Health Score

The analysis of EORTC QLQ-C30 Global Health Status score will be performed for participants who have an assessment at baseline (Visit 1 assessment prior to administration of drug) and at least 1 subsequent assessment.

For EORTC QLQ-C30 all scales and single items are scored on categorical scales and linearly transformed to 0-to-100 scales, with higher scores for the Global Health Status representing higher levels of Global Health Status. Data will be analyzed as change from baseline scores.

Baseline and change from baseline in EORTC QLQ-C30 Global Health Status score data will be summarized at each of the assessment time points.

Substudy:

EORTC QLQ-C30 Global Health Score

The analysis of EORTC QLQ-C30 Global Health Status score will be performed for participants who have an assessment at baseline (Visit 1 assessment prior to administration of drug) and at least 1 subsequent assessment.

For EORTC QLQ-C30 all scales and single items are scored on categorical scales and linearly transformed to 0-to-100 scales, with higher scores for the Global Health Status representing higher levels of Global Health Status. Data will be analyzed as change from baseline scores.

Baseline and change from baseline in EORTC QLQ-C30 Global Health Status score data will be summarized at each of the assessment time points.

PD-L1 Expression

PD-L1 expression as a predictive biomarker of efficacy (PFS and OS) of nivolumab combined with SOC chemotherapy as first-line therapy in cisplatin-eligible participants with previously untreated, unresectable or metastatic UC will be evaluated by Kaplan-Meier survival plot between treatments by PD-L1 expression status (<1% or ≥ 1%).

10.3.1.3 Exploratory Endpoints

Primary Study and Substudy:

Objective Response Rate

ORR (based on BICR assessments) will be summarized by binomial response rates and their corresponding two-sided 95% exact CIs using Clopper-Pearson method, by treatment group. Analysis for investigator-assessed ORR will be performed similarly.

The BICR-assessed objective response will be further characterized by the time to objective response (TTR) and duration of response (DOR). DOR and TTR will be evaluated for responders (confirmed CR or PR) only.

TTR is defined as the time from randomization to the date of the first confirmed response (CR or PR), as assessed by the BICR.

TTR will be summarized using descriptive statistics for the responders.

DOR is defined as the time between the date of first confirmed response (CR or PR) to the date of the first documented tumor progression as determined by the BICR (using the RECIST 1.1 criteria) or death due to any cause, whichever occurs first. Participants who start subsequent therapy without a prior reported progression will be censored at the last evaluable tumor assessment prior to initiation of the subsequent anticancer therapy. Participants who die without a reported prior progression will be considered to have progressed on the date of their death. Participants who neither progress nor die will be censored on the date of their last evaluable tumor assessment.

DOR will be summarized for the participants who achieved confirmed PR or CR using the Kaplan-Meier (KM) product-limit method. Median values of DOR, along with two-sided 95% CI using Brook-Meyer and Crowley method, will also be calculated.

10.3.2 Safety Analyses

Safety and tolerability will be measured by the incidence of adverse events, serious adverse events, deaths and laboratory abnormalities. Adverse events incidence rate is defined as the proportion of participants with any grade adverse events among participants treated in each treatment arm. Events reported from the first dose up to and including 100 days following the last dose of study treatment could be included in estimating this incidence rate.

The safety analysis will be performed in all treated participants. Select safety analysis will also be performed in cisplatin-ineligible participants and in cisplatin-eligible participants. Additional details will be provided in statistical analysis plan. Descriptive statistics of safety will be presented using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 by treatment arm. All AEs, drug-related AEs, SAEs and drug-related SAEs will be tabulated using the worst grade per NCI CTCAE v4.0 criteria by organ class and preferred term. On-study lab parameters including hematology, coagulation, chemistry, liver function and renal function will be summarized using worst grade per NCI CCAE v4.0 criteria.

10.3.3 Other Analyses

PK, immunogenicity, and biomarker exploratory analyses will be described in the statistical analysis plan finalized before database lock. The population pharmacokinetics analysis and pharmacodynamic analyses will be presented separately from the main clinical study report.

10.3.3.1 Pharmacokinetic Analyses

The nivolumab and ipilimumab concentration data obtained in this study may be combined with data from other studies in the clinical development program to develop or refine a population PK model. This model may be used to evaluate the effects of intrinsic and extrinsic covariates on the PK of nivolumab and to determine measures of individual exposure (such as steady-state peak, trough, and time-averaged concentration). In addition, model determined exposures may be used for exposure-response analyses. Results of population PK and exposure response-analyses will be reported separately.

10.3.3.2 Immunogenicity Analyses

Immunogenicity may be reported for ADA positive status (such as persistent positive, only last sample positive, other positive, baseline positive) and ADA negative status, relative to baseline. In addition, presence of neutralizing antibodies may be reported, if applicable. Effect of immunogenicity on safety, efficacy, biomarkers and PK may be explored. Additional details will be described in the SAP.

10.3.3.3 Biomarker Analyses

Pharmacodynamic Analyses

To assess pharmacodynamic effects in serum, blood RNA, or peripheral cells obtained from participants on each treatment arm, summary statistics for biomarkers of immunoregulatory activity (eg, IFN-inducible proteins, miRNAs, gene expression, immune cells) and their corresponding changes (or percent changes) from baseline will be tabulated by planned study visit. In addition, the time course of biomarker outcomes will be investigated graphically. If there is indication of a meaningful pattern across time, further analysis may be completed to characterize the relationship. Possible associations between changes in biomarker measures of interest and exposure to study drug will be explored graphically.

Pharmacogenomics and Exploratory Analyses

Potential relationships between biomarker data and efficacy or safety endpoints will be investigated as part of an analysis plan aimed at identifying baseline biomarkers that may be used to prospectively identify participants likely (or not likely) to respond to nivolumab and to identify participants who may be predisposed to having adverse reactions to treatment. These exploratory predictive biomarker analyses will be completed with biomarkers measured in blood and in tumor samples and will focus primarily, as outlined in the exploratory objectives, on SNPs in select genes associated with immunity or on the expression of selected proteins in tumor specimens, such as PD-1, and PD-L2. Similar analyses will be completed with data regarding serum-soluble factors, blood RNA and/or immune cell types.

Associations between biomarkers and efficacy measures will be analyzed on all participants treated with at least one dose of study medication and with corresponding efficacy and biomarker measurements. Efficacy measures will include response, PFS, and OS. Demographic and case-history factors will be examined to determine whether stratification or adjustments should be made within the subsequent statistical analyses, and if necessary, the appropriate stratification or adjustment will be made.

Biomarkers will be summarized graphically as they relate to efficacy and safety endpoints, as applicable. Summary statistics will be tabulated. SNP allele frequencies will be summarized. The relationships between binary measures (eg, response) and candidate biomarkers will be investigated using logistic regression. Associations will be summarized in terms of point and interval estimates of hazard ratios, odds ratios, or other statistics, as appropriate for the analyses completed. Models to predict clinical activity based on combinations of biomarkers may also be investigated.

Additional post hoc statistical analyses not specified in the protocol, such as alternative modeling approaches may be completed. All analyses described in this section are based on the availability of the data.

10.3.3.4 Outcome Research Analyses

EORTC QLQ-C30 Functional Scales and Symptom Scales

The analysis of EORTC QLQ-C30 functional scales and symptom scales will be performed for participants who have an assessment at baseline (Visit 1 assessment prior to administration of drug) and at least 1 subsequent assessment.

For EORTC QLQ-C30 all scales and single items are scored on categorical scales and linearly transformed to 0-to-100 scales with higher scores for a functional scale representing higher levels of functioning and higher scores for a symptom scale representing higher level of symptoms. Data will be analyzed as change from baseline scores.

Baseline and change from baseline in the EORTC QLQ-C30 functional scales and symptom scales will be summarized at each of the assessment time points.

In addition:

- The percentage of participants demonstrating a clinically meaningful deterioration (defined as a 10 point change from baseline) will be presented for each scale at each assessment time point. Percentages will be based on number of participants assessed at assessment time point.
- Participant compliance will be described per time point by the proportion of participants who filled out the EORTC QLQ-C30 assessments over the numbers of participant known to be alive and eligible for assessment at these time points.

EuroQol EQ-5D-5L

The analysis of EQ-5D-5L will be performed for participants who have an assessment at baseline (Visit 1 assessment prior to administration of drug) and at least 1 subsequent assessment.

The EQ-5D-5L comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety) and a VAS. The EQ-5D-5L descriptive system will be converted into a single summary index score which provides a simple measure of health on a scale of 0 to 1 (0 = death and 1 = perfect health). EQ-5D-5L data will be described in the following three ways:

Participant's overall health state on a visual analog scale (EQ-VAS) and a summary index (EQ-5D-5L index) at each assessment time point will be summarized using descriptive statistics. (N, mean, standard deviation, median, first and third quartiles, minimum, maximum).

- Proportion of participants reporting problems for the 5 EQ-5D-5L dimensions at each assessment time point will be summarized by level of problem. Percentages will be based on number participants assessed at assessment time point.
- A by-participant listing of EQ-5D-5L with the problem levels for each of the 5 dimensions (mobility, self-care, usual activities, pain / discomfort and anxiety/depression), health state (5 dimensions digits combined in a 5-digit number), EQ-5D-5L index, and EQ-VAS will be provided.

In addition, participant compliance will be described per time point by the proportion of participants who filled out the EQ-5D-5L assessments over the numbers of participant known to be alive and eligible for assessment at these time points.

10.3.4 Interim Analyses

Primary Study:

One interim analysis of OS is planned in each primary population.

It is scheduled after approximately 130 deaths among the PD-L1 positive (≥ 1%) participants and 278 deaths among the cisplatin-ineligible participants (approximately 80% of the targeted OS events in each primary population) have been observed based on above accrual rate and the non-proportional hazards model. These formal comparisons of OS will allow for early stopping for superiority, and the boundaries for declaring superiority will be derived based on the actual number of deaths using Lan-DeMets alpha spending function with O'Brien and Fleming type of boundary in EAST 6 (v 6.3.1). The boundary for declaring superiority in terms of statistical significance for the final analysis after 163 deaths among the PD-L1 positive (≥1%) participants would be 0.70. The boundary for declaring superiority in terms of statistical significance for the final analysis after 348 deaths among the cisplatin-ineligible participants would be 0.77.

Interim analysis is also planned for OS in the all randomized population (secondary endpoint). It is projected that the interim analysis will happen with approximately 414 deaths in the all randomized population (approximately 80% of the 518 projected to occur at the final analysis). The boundaries for declaring superiority will be derived based on the actual number of deaths using Lan-DeMets alpha spending function with O'Brien and Fleming type of boundary in EAST 6 (v 6.3.1).

Note that all deaths available at the time of the database-lock will be used for the primary and secondary analyses (even if it is more than pre-specified).

Substudy:

One interim analysis of OS is planned and is scheduled at the time of the cisplatin-ineligible final OS analysis in the primary study and it is expected after approximately 267 OS events (approximately 75% of the targeted OS events in the substudy) have been observed among cisplatin-eligible randomized participants in the substudy based on above accrual rate and the non-proportional hazards model.

This formal comparison of OS will allow for early stopping for superiority, and the boundaries for declaring superiority will be derived based on the actual number of OS events using Lan-DeMets alpha spending function with O'Brien and Fleming type of boundary in EAST 6 (v 6.3.1). The boundary for declaring superiority in terms of statistical significance for the interim analysis after 267 events would be 0.74.

The Statistical Analysis Plan will further describe the planned interim analyses. An independent statistician external to BMS will perform interim analyses.

In addition to the formal planned interim analyses, the DMC will have access to periodic un-blinded interim reports of efficacy and safety to allow a risk/benefit assessment. Details will be included in the DMC charter.

11 REFERENCES

1 Antoni S, Ferlay J, Soerjomataram I, et al. Bladder Cancer Incidence and Mortality: A Global Overview and Recent Trends. Eur Urol 2016 Jun 28.

2 Collazo-Lorduy A, Galsky MD. Systemic therapy for metastatic bladder cancer in 2016 and beyond. Future Oncol 2016 May;12(9):1179-92. doi: 10.2217/fon-2015-0020. Epub 2016 Feb 29.

3 Abida W, Bajorin DF, and Rosenberg JE. First-Line Treatment and Prognostic Factors of Metastatic Bladder Cancer for Platinum-Eligible Patients. Hematol Oncol Clin N Am 2015;29(2):319-328.

4 Sternberg CN, Yagoda A, Scher HI, et al. Preliminary results of M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) for transitional cell carcinoma of the urothelium. J Urol 1985;133:403–7.

5 Sternberg JJ, Bracken RB, Handel PB, et al. Combination chemotherapy (CISCA) for advanced urinary tract carcinoma. A preliminary report. JAMA 1977;238: 2282–7.

6 Yagoda A. Future implications of Phase 2 chemotherapy trials in ninety-five patients with measurable advanced bladder cancer. Cancer Res 1977;37:2775–80.

7 Loehrer PJ Sr, Einhorn LH, Elson PJ, et al. A randomized comparison of cisplatin alone or in combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma: a cooperative group study. J Clin Oncol 1992;10:1066-73.

8 Logothetis CJ, Dexeus FH, Finn L, et al. A prospective randomized trial comparing MVAC and CISCA chemotherapy for patients with metastatic urothelial tumors. J Clin Oncol 1990;8:1050.

9 Kaufman D, Raghavan D, Carducci M, et al. Phase II trial of gemcitabine plus cisplatin in patients with metastatic urothelial cancer. J Clin Oncol 2000;18:1921–7.

10 Moore MJ, Winquist EW, Murray N, et al. Gemcitabine plus cisplatin, an active regimen in advanced urothelial cancer: a Phase 2 trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 1999;17:2876–81.

11 von der Maase H, Sengelov L, Roberts JT, et al. Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. J Clin Oncol 2005;23:4602–8.

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

[13] Witjes JA, Comperat E, Cowan NC, et al. Guidelines on muscle-invasive and metastatic bladder cancer. EAU European Association of Urology 2015; Available at: https://uroweb.org/guideline/bladder-cancer-muscle-invasive-and-metastatic/

[14] NCCN Clinical Practice guidelines in Oncology. Bladder Cancer Version 2.2014. www.nccn.org.

[15] Galsky MD, Hahn NM, Rosenberg J, et al. Treatment of Patients With Metastatic Urothelial Cancer "Unfit" for Cisplatin-Based Chemotherapy. J Clin Oncol 2011; 29:2432-2438.

[16] Galsky MD, Hahn NM, Rosenberg J, et al. A consensus definition of patients with metastatic urothelial carcinoma who are unfit for cisplatin-based chemotherapy. Lancet Oncology. 2011 March; 12 (3):211-214.

[17] De Santis M, Bellmunt J, Mead G, et al. Randomized Phase 2/3 trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986. J Clin Oncol 2012;30:191–9.

[18] Bajorin DF, Dodd PM, Mazumdar M, et al. Long-term survival in metastatic transitional-cell carcinoma and prognostic factors predicting outcome of therapy. J Clin Oncol 1999 Oct;17(10):3173-81.

[19] Alexandroff AB, Jackson AM, O'Donnell MA, James K. BCG immunotherapy of bladder cancer: 20 years on. Lancet 1999;353:1689-94.

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

[21] Hilmy M, Campbell R, Bartlett JM, et al. The relationship between the systemic inflammatory response, tumor proliferative activity, T-lymphocytic infiltration and COX-2 expression and survival in patients with transitional cell carcinoma of the urinary bladder. British Journal of Cancer 2006;95:1234-8.

[22] Sharma P, Shen Y, Wen S, et al. CD8 tumor-infiltrating lymphocytes are predictive of survival in muscle-invasive urothelial carcinoma. Proceedings of the National Academy of Sciences of the United States of America 2007;104:3967-72.

[23] Herr HW, Bean MA, Whitmore WF, Jr. Decreased ability of blood leukocytes from patients with tumors of the urinary bladder to act as stimulator cells in mixed leukocyte culture. Cancer Research 1976;36:2754-60.

[24] Loskog A, Ninalga C, Paul-Wetterberg G, et al. Human bladder carcinoma is dominated by T-regulatory cells and Th1 inhibitory cytokines. Journal of Urology 2007;177:353-8.

[25] Mukamel E, Shohat B, Servadio C. Immunological profile of patients with transitional cell carcinoma of the bladder. British journal of urology 1982;54:11-5.

[26] Boorjian SA, Sheinin Y, Crispen PL, et al. T-cell coregulatory molecule expression in urothelial cell carcinoma: clinicopathologic correlations and association with survival. Clin Cancer Res 2008;14:4800-8.

[27] Carthon BC, Wolchok JD, Yuan J, et al. Preoperative CTLA-4 blockade: tolerability and immune monitoring in the setting of a presurgical clinical trial. Clin Cancer Res 2010;16:2861-71.

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

[29] Sharma P, Bono P, Kim JW, et al. Efficacy and safety of nivolumab monotherapy in metastatic urothelial cancer (mUC): Results from the Phase 1/2 CheckMate 032 study [abstract]. J Clin Oncol 2016;34 suppl; abs 4501, oral presentation.

[30] Galsky M, Retz M, Siefker-Radtke A, et al. Efficacy and safety of nivolumab monotherapy in patients with metastatic urothelial cancer (mUC) who have received prior treatment: Results from the Phase 2 CheckMate 275 study. Presented at: 2016 ESMO Congress; October 7-11, 2016; Copenhagen, Denmark. Abstract LBA31

[31] KEYTRUDA (pembrolizumab) US Prescribing Information, Merck & Co., Inc., Whitehouse Station, NJ. June 2018.

[32] TECENTRIQ (atezolizumab) US Prescribing Information, Genentech, Inc, South San Francisco, CA, July 2018.

[33] A phase 1/2, open-label study of nivolumab monotherapy or nivolumab combined with ipilimumab in subjects with advanced or metastatic solid tumors; Interim Clinical Study Report for Study CA209032. Bristol-Myers Squibb Company; 2019. Document Control No. 930133244.

[34] Balar AV, Galsky MD, Rosenberg JE, et al. Atezolizumab as first-line therapy in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. Lancet. 2017; 389(10064): 67–76.

[35] A phase 2 single arm clinical trial of nivolumab (BMS-936558) in subjects with metastatic or unresectable urothelial cancer who have progressed or recurred following treatment with a platinum agent; Final Clinical Study Report for Study CA209-275; Report Addendum 01. Bristol-Myers Squibb Company; 2016. Document Control No. 930107331.

[36] Momtaz P, Park V, Panageas KS, et al. Safety of Infusing Ipilimumab Over 30 Minutes. J Clin Oncol 2015;33(30):3454-3458.

[37] Castillo-Martin M, Domingo-Domenech J, Karni-Schmidt O, Matos T, Cordon-Cardo C. Molecular pathways of urothelial development and bladder tumorigenesis. Urol. Oncol 2010;28(4):401–408.

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

[39] Zitvogel L, Tesniere A, Kroemer G. Cancer despite immunosurveillance: immunoselection and immunosubversion. Nat Rev Immunol 2006; 6:715-27.

[40] Dunn GP, Bruce AT, Ikeda H, et al. Cancer immunoediting: from immunosurveillance to tumor escape. Nat Immunol. 2002; 3:991-8.

[41] Greenwald RJ, Freeman GH, Sharpe AH. The B7 family revisited. Annu Rev Immunol 2004;23:515-48.

[42] Freeman FJ, Long AJ, Iwai Y, et al. Engagement of the PD-1 immunohibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. J Exp Med 2000;192(7):1027-34.

[43] Sharpe AH, Wherry EJ, Ahmed R, et al. The function of programmed cell death 1 and its ligands in regulating autoimmunity and infection. Nature Immunol 2007;8:237-45.

[44] Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 2009;15:7412-20.

[45] Postow MA, Harding J, Wolchok JD. Targeting immune checkpoints: Releasing the restraints on anti-tumor immunity for patients with melanoma. Cancer 2012;18:153-159.

[46] Clinical Study Report: Study No. CA209004. A Phase 1b, Open- Label, Multicenter, Multidose, Dose-Escalation Study of MDX-1106 (BMS-936558) in Combination with Ipilimumab (BMS-734016) in Participants with Unresectable Stage III or Stage IV Malignant Melanoma. Bristol-Myers Squibb Company; 2014. Document Control No. 930082868.

[47] Curran MA, Montalvo W, Yagita H, et al. PD-1 and CTLA-4 combination blockade expands infiltrating T cells and reduces regulatory T and myeloid cells within B16 melanoma tumors. PNAS 2010; 107: 4275-80.

[48] Wolchok J, Kluger H, Callahan MK, et al. Safety and clinical activity of nivolumab (anti-PD-1, BMS-936558, ONO-4538) in combination with ipilimumab in participants (pts) with advanced melanoma (MEL). J Clin Oncol 2013; suppl; abstr 9012.

[49] Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med 2015 Jul 2;373(1):23-34. doi: 10.1056/NEJMoa1504030. Epub 2015 May 31.

[50] CA209016, Data on file.

[51] Nivolumab Investigator Brochure Version 15; June 2016.

[52] Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 2009;15:7412-20.

[53] BMS Clinical Study Report CA209004, December 2014.

[54] Postow MA1, Chesney J, Pavlick AC, Robert C et al.Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. N Engl J Med 2015 May 21;372(21):2006-17. doi: 10.1056/NEJMoa1414428. Epub 2015 Apr 20

[55] Hammers HJ, Plimack ER, Infante JR, et al. Expanded cohort results from CheckMate 016: A phase I study of nivolumab in combination with ipilimumab in metastatic renal cell carcinoma (mRCC). J Clin Oncol 33, 2015 (suppl; abstr 4516)

[56] Hellmann MD, Gettinger SN, Goldman JW et al. CheckMate 012: Safety and efficacy of first-line (1L) nivolumab (nivo; N) and ipilimumab (ipi; I) in advanced (adv) NSCLC. J Clin Oncol 34, 2016 (suppl; abstr 3001)

[57] Antonia SJ, Bendell JC, Taylor MH, et al. Phase 1/2 study of nivolumab with or without ipilimumab for treatment of recurrent small cell lung cancer (SCLC): CA209-032. J Clin Oncol 33, 2015 (suppl; abstr 7503)

[58] Janjigian YY, Bendell JC, Calvo E, et al. CheckMate-032: Phase 1/2, open-label study of safety and activity of nivolumab (nivo) alone or with ipilimumab (ipi) in advanced and metastatic (A/M) gastric cancer (GC). J Clin Oncol 34, 2016 (suppl; abstr 4010)

[59] Ipilimumab Investigator Brochure Version 19; March 2016.

[60] Brahmer J, Reckamo KL, Bass P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med 2015;373(2):123-35.

[61] Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. N. Engl. J. Med. doi:10.1056/NEJMoa1510665

[62] Schadendorf D. et al. 2016 Annual Meeting of the European Association of Dermato-Oncology; August 31-September 3, 2016; Vienna, Austria.

[63] Schadendorf D, Hodi SF, Robert C, et al. Pooled analysis of long-term survival data from phase II and phase III Trials of ipilimumab in unresectable or metastatic melanoma. J Clin Oncol 33:1889-1894.

[64] Sharma P et al. Efficacy and Safety of Nivolumab Plus Ipilimumab in Metastatic Urothelial Carcinoma: First Results From the Phase I/II CheckMate 032 Study. SITC, DC, 2016.

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

[66] Momtaz P, Park V, Panageas KS, et al. Safety of Infusing Ipilimumab Over 30 Minutes. J Clin Oncol 2015;33(30):3454-3458.

[67] BMS-936558: A Phase 2, Randomized, Double Blinded Study of Nivolumab (BM-936558) in Combination with Ipilimumab vs Ipilimumab Alone in Participants with Previously Untreated, Unresectable or metastatic Melanoma). Bristol-Myers Squibb Company; 2013. Document Control No. 930084565.

[68] Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 2009;15:7412-20.

12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AT	aminotransaminases
BCG	Bacillus Calmette-Guerin
BICR	Blinded Independent Central Review Committee
BMI	body mass index
BMS	Bristol-Myers Squibb
BP	blood pressure
BUN	blood urea nitrogen
C	Celsius
Ca^{++}	calcium
Cavg	average concentration
CBC	complete blood count
ccRCC	Clear-cell renal cell carcinoma
CFR	Code of Federal Regulations
CI	confidence interval
CLcr	creatinine clearance
Cmax, CMAX	maximum observed concentration
Cmin, CMIN	minimum observed concentration
CNS	Central nervous system
CRF	Case Report Form, paper or electronic
CR	Complete response
DMC	Data monitoring committee
DOR	Duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture

Term	Definition
EEG	electroencephalogram
eg	exempli gratia (for example)
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire- Core 30
EQ-5D	European Quality of Life 5 Dimension
FDA	Food and Drug Administration
FFPE	Formalin-fixed Paraffin Embedded
FSH	follicle stimulating hormone
g	gram
GCP	Good Clinical Practice
GFR	glomerular filtration rate
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	Human Immunodeficiency Virus
HR	heart rate
HRQoL	Health Related Quality of Life
HRT	hormone replacement therapy
ICD	International Classification of Diseases
ICH	International Conference on Harmonisation
ie	id est (that is)
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IMAE	Immune-mediated adverse event
IMP	investigational medicinal products
IND	Investigational New Drug Exemption
I-O	Immuno-oncology
IRB	Institutional Review Board
IRT	Interactive Response Technology
IU	International Unit

Term	Definition
IV	intravenous
K	slope of the terminal phase of the log concentration-time curve
K^+	potassium
kg	kilogram
KPS	Karnofsky Performance Status
L	liter
LAM	Lactation amenorrhea method
LC	liquid chromatography
LFT	Liver function test
LDH	lactate dehydrogenase
MDSC	Myeloid derived suppressor cells
mg	milligram
Mg^{++}	magnesium
min	minute
mL	milliliter
mmHg	millimeters of mercury
MR	medical research
mRCC	Metastatic Renal Cell Carcinoma
MSKCC	Memorial Sloan Kettering Cancer Center
MTD	maximum tolerated dose
mWHO	Modified World Health Organization
µg	microgram
N	number of subjects or observations
Na^+	sodium
N/A	not applicable
ng	nanogram
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
PBMC	Peripheral blood mononuclear cells

Term	Definition
PD	Progressive diseases
PFS	Progression-free survival
PK	pharmacokinetics
PR	Partial response
RBC	red blood cell
SAE	serious adverse event
SD	standard deviation
SOP	Standard Operating Procedures
UC	Urothelial carcinoma
ULN	Upper limit of normal
VEGF	Vascular epithelial growth factor
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential

APPENDIX 2 PERFORMANCE STATUS SCORES

	SCALES		
STATUS	**KARNOFSKY**	**ZUBROD-ECOG-WHO**	**STATUS**
Normal, no complaints	100	0	Normal activity
Able to carry on normal activities Minor signs or symptoms of disease	90	0	
Normal activity with effort	80	1	Symptoms, but fully ambulatory
Cares for self. Unable to carry on normal activity or to do active work	70	1	
Requires occasional assistance, but able to care for most of his needs	60	2	Symptomatic, but in bed < 50% of the day.
Requires considerable assistance and frequent medical care	50	2	
Disabled. Requires special care and assistance	40	3	Needs to be in bed > 50% of the day, but not bedridden
Severely disabled. Hospitalization indicated though death non imminent	30	3	
Very sick. Hospitalization necessary. Active supportive treatment necessary	20	4	Unable to get out of bed
Moribund	10	4	
Dead	0	5	Dead

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.

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 case report form.

Events Meeting the AE Definition

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

Events NOT Meeting the AE Definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.

Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

DEFINITION OF SAE

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

SERIOUS ADVERSE EVENTS

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
Requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below) NOTE: The following hospitalizations are not considered SAEs in BMS clinical studies: o 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) o elective surgery, planned prior to signing consent o admissions as per protocol for a planned medical/surgical procedure o routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy) o medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases o 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) o 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 drug 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 RECIST 1.1 GUIDELINES (WITH BMS MODIFICATIONS)

1 EVALUATION OF LESIONS

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

1.1 Measurable

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

10 mm by CT/MRI scan (CT scan slice thickness no greater than 5 mm), or ≥2x slice thickness if greater than 5mm.
Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

Note: Lesions on X-Ray are not to be selected as Target or Non-Target Lesions.

1.2 Non-Measurable

All other lesions are considered non-measurable, including small lesions (longest diameter < 10mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Note: Lesions on X-Ray are not to be selected as Target or Non-Target Lesions.

1.3 Special considerations regarding lesion measurability

1.3.1 Bone lesions

- Bone scan, PET scan or plain films are ***not*** considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with *identifiable soft tissue components*, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the *soft tissue component* meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

1.4 Baseline Documentation Of 'Target' And 'Non-Target' Lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded).

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple nontarget lesions involving the same organ as a single item on the case record form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

2 RESPONSE CRITERIA

2.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

2.1.1 Special Notes on the Assessment of Target Lesions

2.1.1.1 Lymph nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

2.1.1.2 Target lesions that become 'too small to measure'

While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

2.1.1.3 Lesions that split or coalesce on treatment

When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each

individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

2.2 Evaluation of Non-Target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (< 10mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

2.2.1 Special Notes on Assessment of Progression of Non-Target Disease

The concept of progression of non-target disease requires additional explanation as follows:

2.2.1.1 When the patient also has measurable disease

In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy (see examples in Appendix 2 and further details below). A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. Pleural effusions, pericardial effusions and ascites will not be followed as target or non-target lesions and will not contribute to response or progression. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

2.2.1.2 When the patient has only non-measurable disease

This circumstance arises in some trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in

lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore the increase must be substantial.

- To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening such that the overall tumor burden has increased sufficiently to merit discontinuation of therapy.
- A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.
- Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are non-measurable) a useful test that can be applied when assessing participants for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include, an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'.
- If 'unequivocal progression' is seen, the subject should be considered to have had overall PD at that point.

2.2.2 New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

NOTE: Fluid collections (pleural effusions, pericardial effusions, ascites) will not be considered new lesions and will not contribute to response or progression. In the event a new fluid collection is seen on a post-baseline imaging exam, a comment may be made, but the appearance of a new fluid collection alone should not result in an assessment of Progressive Disease (PD).A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline. A lesion identified on Chest X-Ray that was not present in prior CT can be considered a new lesion and will result in Progressive Disease (PD).

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan. While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

1. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
2. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

2.3 Response Assessment

2.3.1 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement.

2.3.2 Time Point Response

It is assumed that at each protocol specified time point, a response assessment occurs. Table 2.3.2-1 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline. When patients have non-measurable (therefore non-target) disease only, Table 2.3.2-2 is to be used.

Table 2.3.2-1: Time Point Response: Patients With Target (+/- Non-Target) Disease

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD

Table 2.3.2-1: Time Point Response: Patients With Target (+/- Non-Target) Disease

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease and NE = inevaluable

Table 2.3.2-2: Time Point Response: Patients with Non-target Disease Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD
CR = complete response, PD = progressive disease and NE = inevaluable		

[a] Non-CR/non-PD is preferred over SD for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

2.3.3 Best Overall Response

Best response determination of complete or partial response requires confirmation: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point of ≥ 4 weeks (28 days) later. In this circumstance, the best overall response can be interpreted as in Table 2.3.3-1. When SD is believed to be best response, it must meet the protocol specified minimum time from first treatment.

The minimum time on study for determination of Best Response of SD will be based on the first scheduled follow-up imaging visit minus the permitted imaging time window.

For example, if the first scheduled follow-up imaging visit is Week 9 (minus 7 days) for this protocol, a Best Response of SD can only be made after the subject is on-study for a minimum of 9 weeks (63 days) minus 7 days, for an absolute minimum time on-study of 56 days from the date of first dose (the date of first dose is considered Day 1 on study). If the subject is not on-study for at least this amount of time, any tumor assessment indicating stable disease before this time period will have a Best Response of NE unless PD is identified.

Special note on response assessment: When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a measurement reported

on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (CRF).

Table 2.3.3-1: Best Overall Response (Confirmation of CR&PR Required)

Overall Response First Time Point	Overall Response Subsequent Time Point	BEST Overall Response
CR	CR	CR
CR	PR	SD, PD OR PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE
CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable		

[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

2.3.4 Confirmation Scans

Verification of Response: To be assigned a status of CR or PR, changes in tumor measurements must be confirmed by consecutive repeat assessments that should be performed no less than 28 days after the criteria for response are first met. For this study, the next scheduled tumor assessment can meet this requirement.

Verification of Progression: Progression of disease should be verified in cases where progression is equivocal. If repeat scans confirm PD, then progression should be declared using the date of the initial scan. If repeat scans do not confirm PD, then the subject is considered to not have progressive disease.

APPENDIX 5 MANAGEMENT ALGORITHIMS

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.

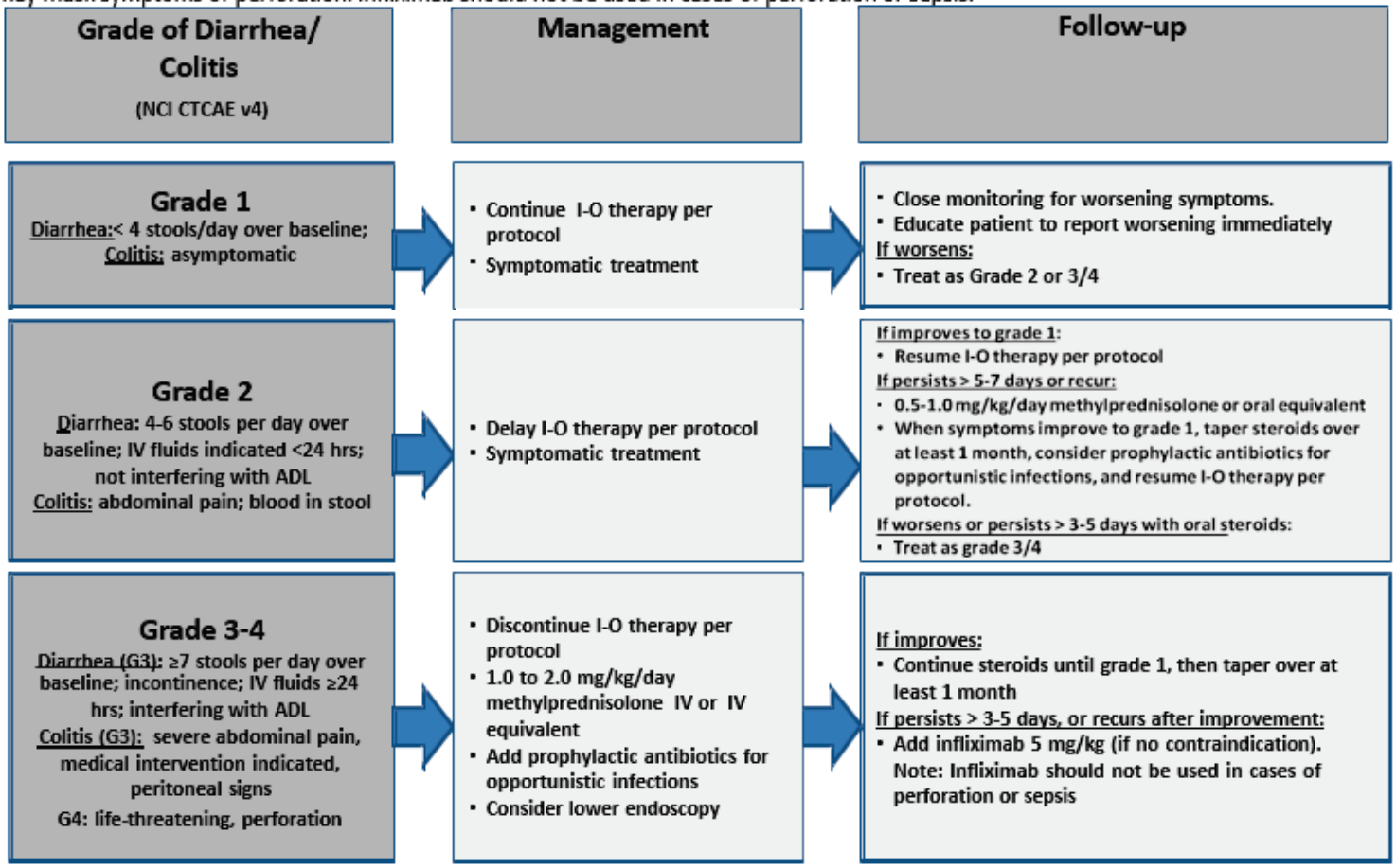
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the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

27-Jun-2019

Renal Adverse Event Management Algorithm

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

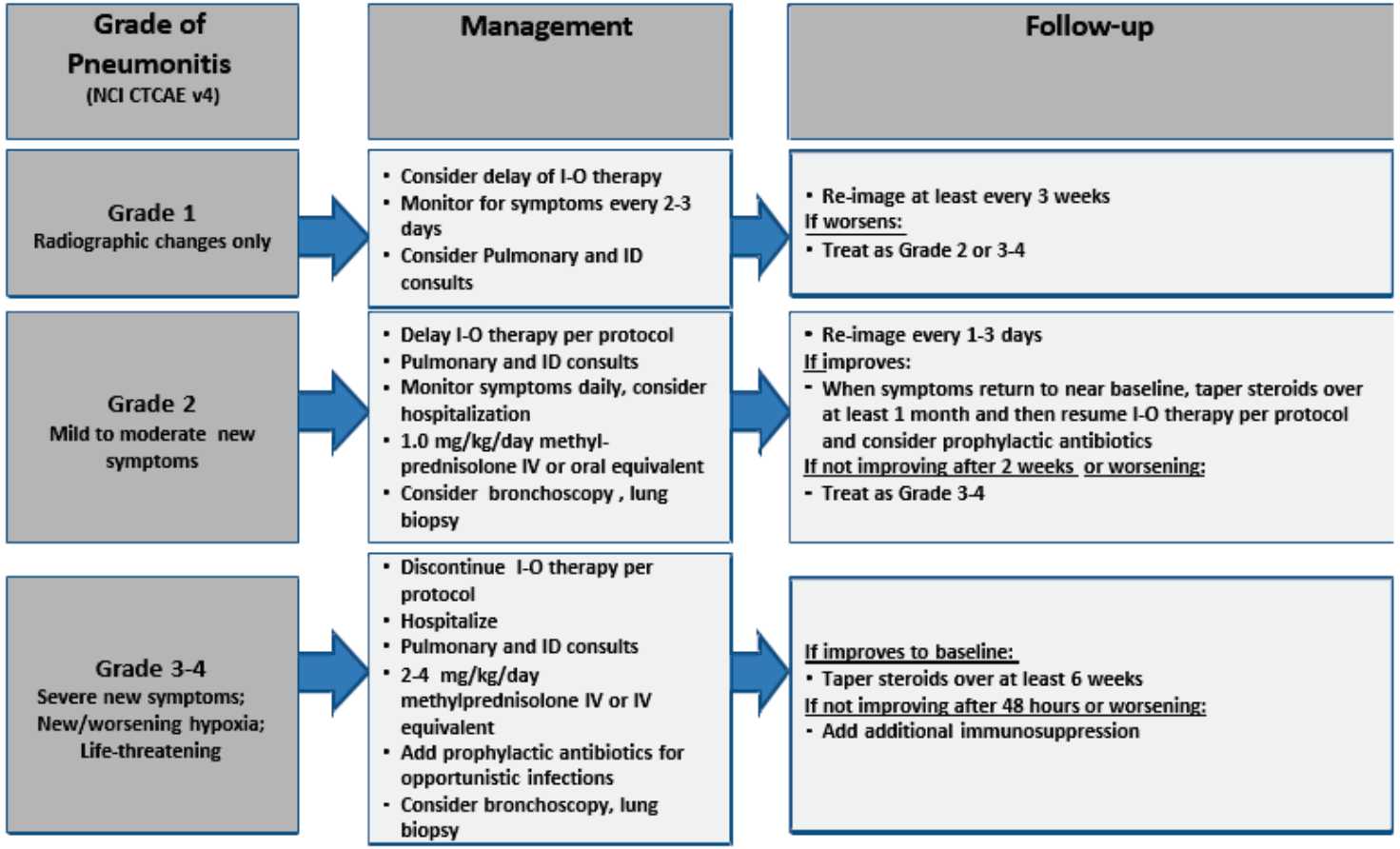
Grade of Creatinine Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 Creatinine > ULN and > than baseline but ≤ 1.5x baseline	• Continue I-O therapy per protocol • Monitor creatinine weekly	If returns to baseline: •Resume routine creatinine monitoring per protocol If worsens: •Treat as Grade 2 or 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.

27-Jun-2019

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.

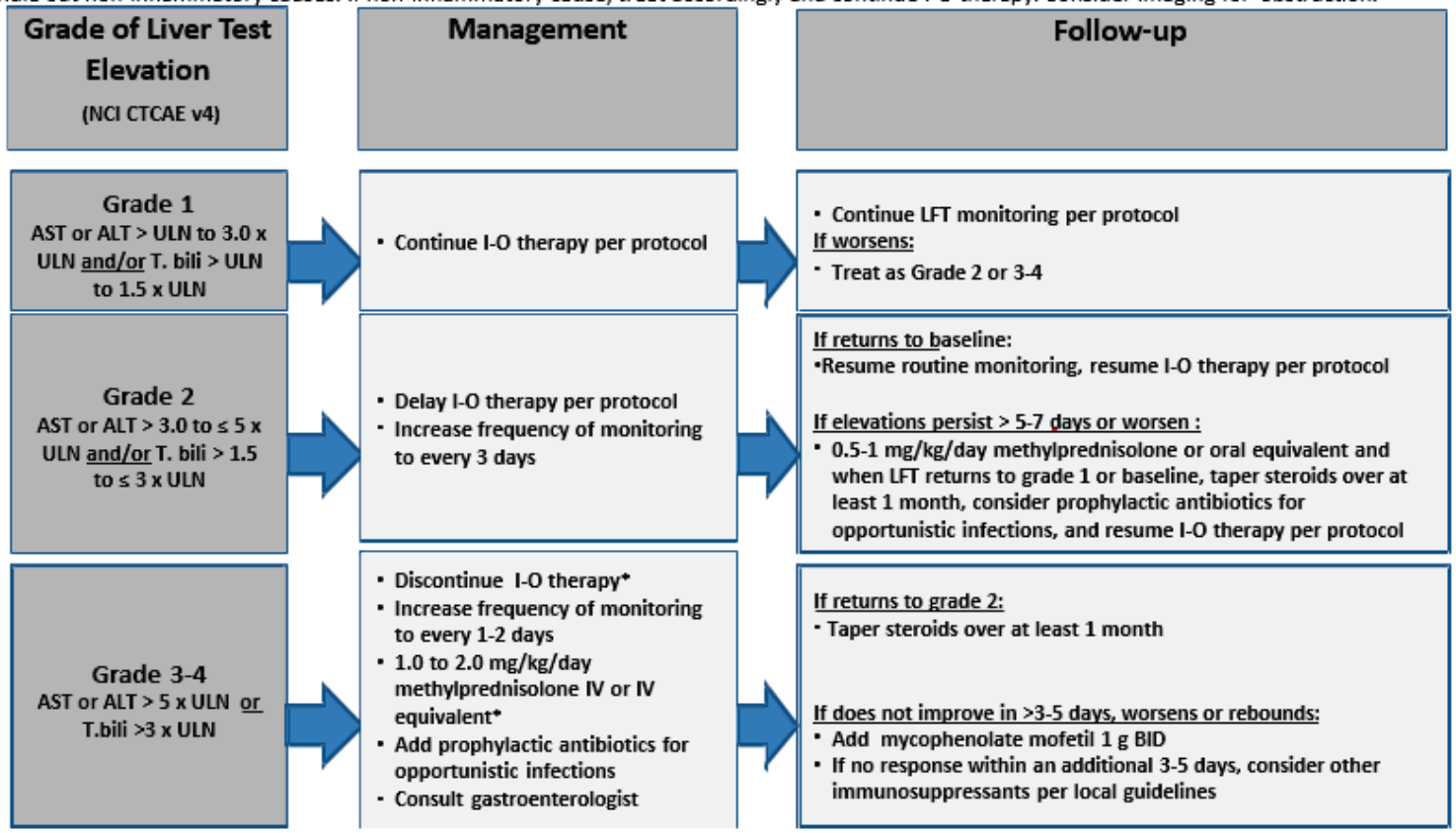


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

27-Jun-2019

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.



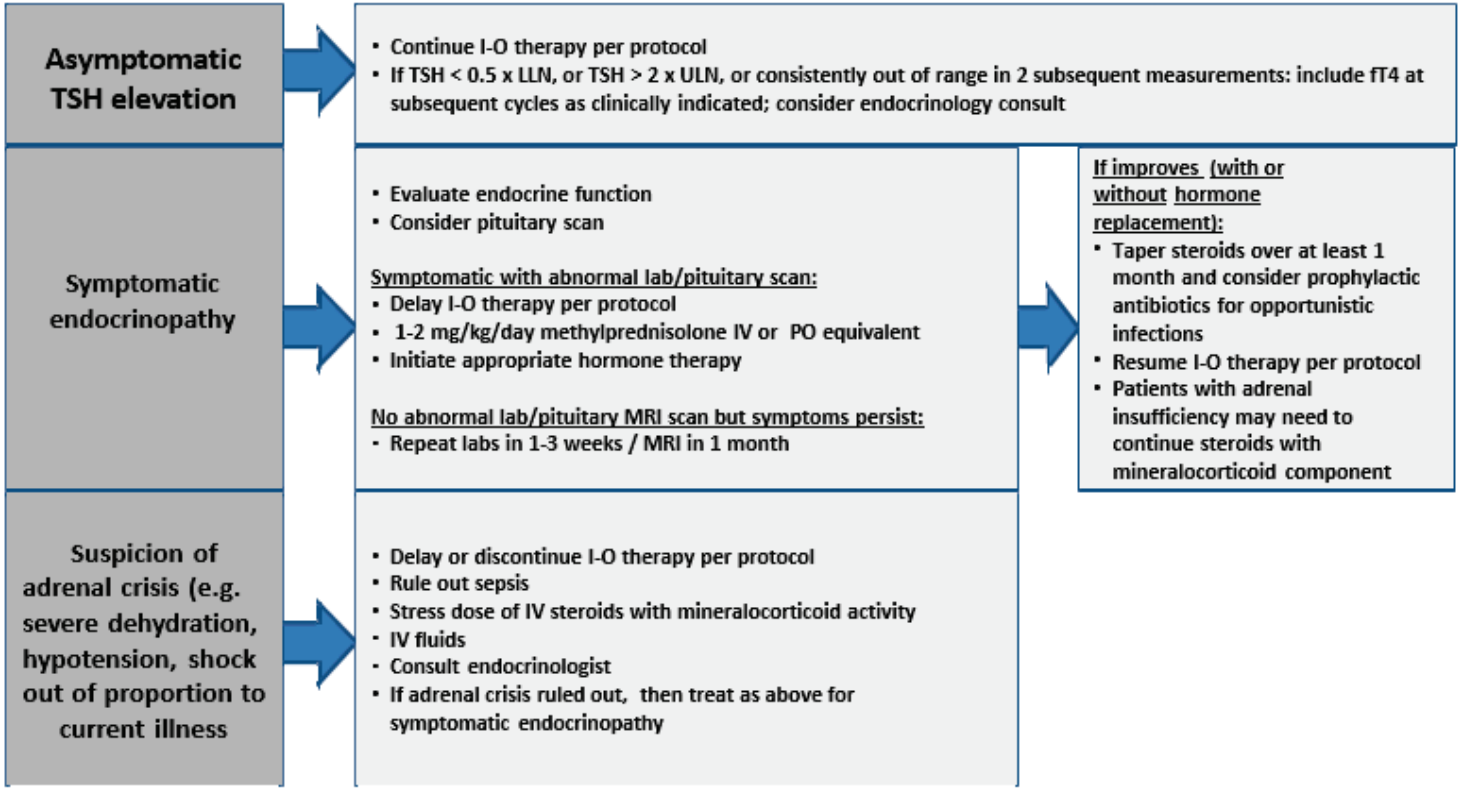
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

27-Jun-2019

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.

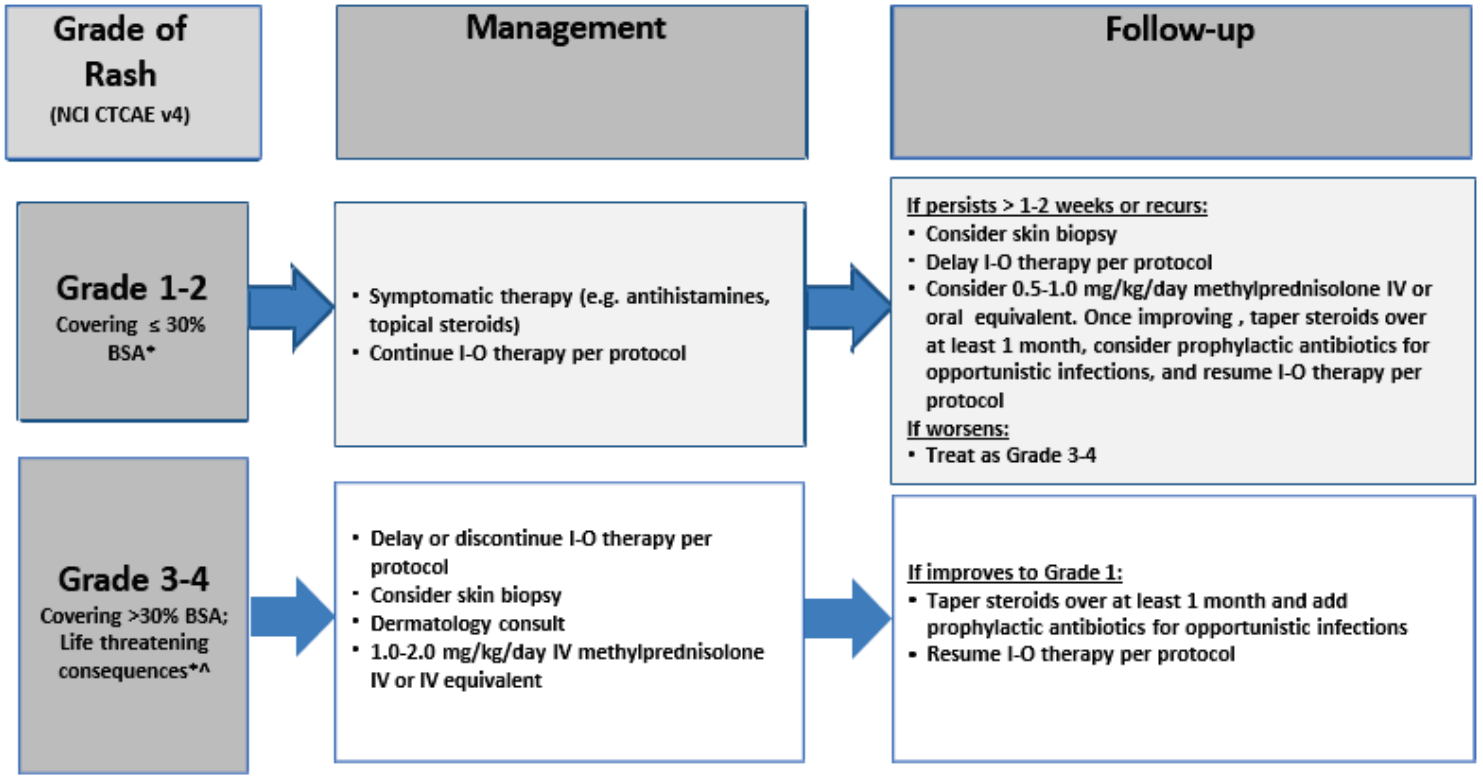


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

27-Jun-2019

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.

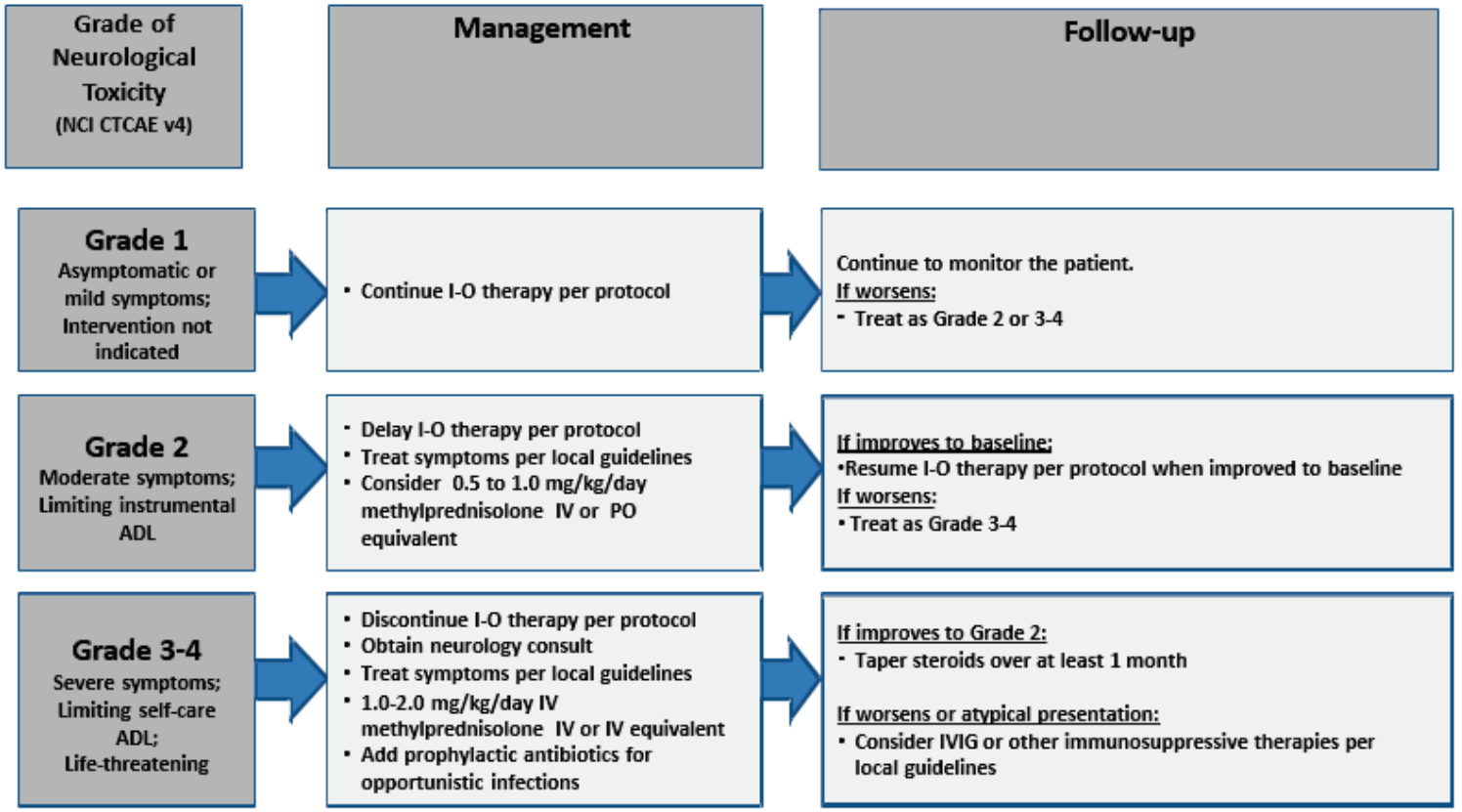
*Refer to NCI CTCAE v4 for term-specific grading criteria.

^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.

27-Jun-2019

Neurological Adverse Event Management Algorithm

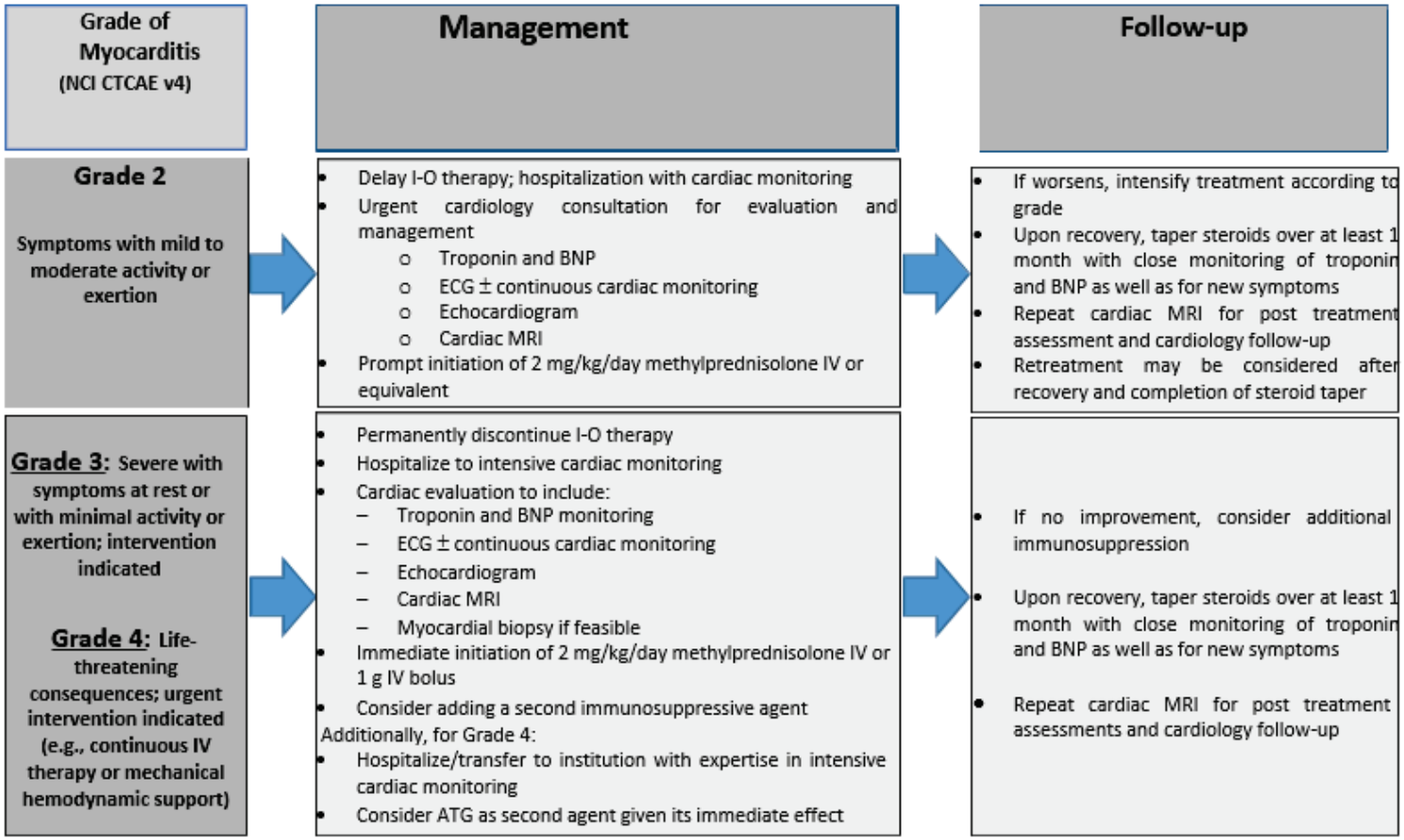
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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.

27-Jun-2019

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

27-Jun-2019

APPENDIX 6 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.*

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal
• Progestogen-only hormonal contraception associated with inhibition of ovulation[b] – oral – injectable

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

Unacceptable Methods of Contraception
• Male or female condom with or without spermicide. *Male and female condoms cannot be used simultaneously • Diaphragm with spermicide • Cervical cap with spermicide • Vaginal Sponge with spermicide • Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action

- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus).
- Spermicide only
- Lactation amenorrhea method (LAM)

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

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

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.

- 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 condom for study duration and until end of relevant systemic exposure defined as 7 months after the end of study treatment.
- 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 7 months 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 condom during each episode of penile penetration during the treatment and until 7 months after the end of study treatment.
- Refrain from donating sperm for the duration of the study treatment and until 7 months 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 7 NYHA FUNCTIONAL CLASSIFICATION

NYHA Class	Patients with Cardiac Disease (Description of HF Related Symptoms)
Class I (Mild)	Patients with cardiac disease but without resulting in limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation (rapid or pounding heart beat), dyspnea (shortness of breath), or anginal pain (chest pain).
Class II (Mild)	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain
Class III (Moderate)	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV (Severe)	Patients with cardiac disease resulting in the inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

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

APPENDIX 8 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.

The investigator is responsible for providing oversight of the conduct of the study at the site and adherence to requirements of the following where applicable:

- ICH guidelines
- United States (US) Code of Federal Regulations, Title 21, Part 50 (21CFR50)
- European Union (EU) Directive 2001/20/EC
- European Regulation 536/2014 for clinical studies (if applicable)
- European Medical Device Regulation 2017/745 for clinical device research (if applicable)
- the IRB/IEC
- all other applicable local regulations

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.

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.
- Explain the nature of the study to the participant or his/her legally acceptable representative and answer all questions regarding the study.
- Inform the participant that his/her participation is voluntary. The participant or his/her legally acceptable representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR Part 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- Include a statement in the participant's medical record that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Re-consent the participant to the most current version of the ICF(s) during his/her participation.
- 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.

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

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.

Participants unable to give their written consent (eg, stroke or subjects/participants with or severe dementia) may only be enrolled in the study with the consent of a legally acceptable representative. The participant must also be informed about the nature of the study to the extent compatible with his or her understanding, and should this participant become capable, he or she should personally sign and date the consent form as soon as possible. The explicit wish of a participant who is unable to give his or her written consent, but who is capable of forming an opinion and assessing information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

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.

BMS COMMITMENT TO DIVERSITY IN CLINICAL TRIALS

The mission of BMS is to transform patients' lives through science by discovering, developing, and delivering innovative medicines that help them prevail over serious diseases.

BMS is committed to doing its part to ensure that patients have a fair and just opportunity to achieve optimal health outcomes.

BMS is working to improve the recruitment of a diverse participant population with the goal that the clinical trial becomes more reflective of the real-world population and the people impacted by the diseases studied.

DATA PROTECTION, DATA PRIVACY, AND DATA SECURITY

BMS collects and processes personal data of study participants, patients, health care providers, and researchers for biopharmaceutical research and development to advance innovative, high-quality medicines that address the medical needs of patients. BMS ensures the privacy, protection, and confidentiality of such personal data to comply with applicable laws. To achieve these goals, BMS has internal policies that indicate measures and controls for processing personal data. BMS adheres to these standards to ensure that collection and processing of personal data are limited and proportionate to the purpose for which BMS collects such personal data. This purpose is clearly and unambiguously notified to the individual at the time of collection of personal data. In the true spirit of science, BMS is dedicated to sharing clinical trial information and data with participants,

medical/research communities, the media, policy makers, and the general public. This is done in a manner that safeguards participant privacy and informed consent while respecting the integrity of national regulatory systems. Clinical trial data, health-related research, and pharmacovigilance activities on key-coded health data transferred by BMS across national borders is done in compliance with the relevant data protection laws in the country and GCP requirements.

BMS protects Personal Information with adequate and appropriate security controls as indicated under the data protection laws. To align with the recommended security standards, BMS has adopted internal security standards and policies to protect personal data at every stage of its processing.

To supplement these standards, BMS enters into Clinical Trial Agreements (CTAgs) with confidentiality obligations to ensure proper handling and protection of personal data by third parties accessing and handling personal data.

BMS takes unauthorized access and disclosure of Personal Information very seriously. BMS has adopted the security standards that include National Institute of Standards and Technology Cybersecurity Framework for studies in the US. BMS aligns with these standards to continuously assess and improve its ability to protect, detect, and respond to cyberattacks and other unauthorized attempts to access personal data. These standards also aid in mitigating possible adverse effects. Furthermore, BMS Information Technology has defined 6 principles to protect our digital resources and information:

1) Responsibilities of IT Personnel
2) Securing the BMS Digital Infrastructure
3) Identity and Access Management
4) External Partner Connections
5) Cyber Threat Detection and Response
6) Internal Cyber Incident Investigation

SOURCE DOCUMENTS

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the electronic Case Report Form (eCRF) that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained.

- The investigator may need to request previous medical records or transfer records depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data and its origin can be found in the source data location list/map or equivalent document.

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	The investigator or designee accepts responsibility for documenting traceability and study treatment

If	Then
sourced from the sites stock or commercial supply, or a specialty pharmacy)	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

The terms "participant" and "subject" refer to a person who has consented to participate in the clinical research study. Typically, the term "participant" is used in the protocol and the term "subject" is used in the Case Report Form (CRF).

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 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 non-compliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

Sponsor or designee representatives will review data centrally to identify potential issues to determine a schedule of on-site visits for targeted review of study records.

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. Certain CRF pages and/or electronic files may serve as the source documents:

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.

Records collected throughout the study will be stored in the BMS clinical data management system for a duration of the life of the product plus 25 years.

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). Partially used study interventions and/or empty containers may be destroyed after proper reconciliation and documentation. However, unused Investigational Medicinal Product must be reconciled by the site monitor/clinical research associate prior to destruction. 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.

STUDY AND SITE CLOSURE

The Sponsor/designee reserves the right to close the study site or to terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include, but are not limited to, the following:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local Health Authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should ensure appropriate participant therapy and/or follow-up.

DISSEMINATION OF CLINICAL STUDY DATA

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

CLINICAL STUDY REPORT

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

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

- External Principal Investigator designated at protocol development
- National Coordinating Investigator
- Study Steering Committee chair or their designee
- Participant recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design
- Regional representation (eg, among top quartile of enrollers from a specified region or country)

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 9 COUNTRY SPECIFIC REQUIREMENTS

Criteria for exclusion of HIV-positive subjects in Germany:

	Country-specific language
Section 6.2 Exclusion Criteria, Exclusion criterion 2k	"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 2 Flow Chart/Time and Events Schedule, Table 2-1: Screening Assessments- Laboratory Tests	Add "HIV" to the list of laboratory tests
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 10 REVISED PROTOCOL SUMMARY OF CHANGE HISTORY

Overall Rationale for Revised Protocol 04, 20-Mar-2020

Overall Survival (OS) is the most unambiguous, unbiased and patient-relevant endpoint for oncology randomized trials. In particular, in the setting of newly diagnosed, metastatic urinary bladder cancer, there was recently a randomized phase III study reported, assessing the addition of a PD-L1 inhibitor to cytotoxic, platinum-based doublet chemotherapy (IMvigor 130). In the cisplatin-based treated cohort (n=273), the addition of the PD-L1 inhibitor to cisplatin/gemcitabine chemotherapy, led to a statistically significant PFS prolongation (HR = 0.73, 95% CI 0.55-0.97), corresponding to an absolute improvement of 2.4 months. In terms of OS, the experimental regimen resulted in a numerically higher mOS (HR = 0.66, 95% CI 0.47 – 0.94), with an absolute OS prolongation that reached 8.4 months. The afore-mentioned results indicate that OS is better fitted to capture the potential benefit of the addition of nivolumab, a PD-1 inhibitor, to cisplatin-gemcitabine chemotherapy for patients with newly diagnosed, previously untreated metastatic bladder cancer.

On the basis of these considerations, this revision incorporates the following changes in the CA209-901 protocol:

- OS elevation to become a primary endpoint, together with PFS
- Increase in the sample size of the CA209-901 sub-study by 300 cisplatin-eligible subjects, to ensure sufficient power for assessment of the primary endpoints OS and PFS
- Removal of the interim PFS analysis, in accordance with scientific advice received previously by the regulatory authorities, and
- Addition of an interim analysis for OS

Summary of Key Changes for Revised Protocol 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Synopsis, Table 2	Changed substudy secondary objective and endpoint comparing OS of nivolumab combined with SOC chemotherapy versus SOC chemotherapy to substudy primary objectives and endpoints.	See Overall Rationale above.
Synopsis, Figure 1	Study schematic has been updated.	See Overall Rationale above.
Synopsis, Substudy	Deleted text stating that the substudy will not stop enrolling participants before the primary study completes enrollment.	See Overall Rationale above.

Summary of Key Changes for Revised Protocol 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Synopsis, Number of Participants	Increased number of participants enrolled from 1375 to 1792. Increased number of participants randomized from 990 to 1290. Increased number of cisplatin-eligible participants in the substudy from 300 to 600. Increased number of cisplatin-eligible participants to be randomized from 545 to 845. Monthly participant accrual rate decreased from 21 to 18 once enrollment in the primary study is closed.	See Overall Rationale above.
Section 4 Objectives and Endpoints, Table 4-2	Changed substudy secondary objective and endpoint comparing OS of nivolumab combined with SOC chemotherapy versus SOC chemotherapy to substudy primary objectives and endpoints.	See Overall Rationale above.
Section 5.1, Overall Design, Figure 5.1-1	Study schematic has been updated. Deleted text stating that the substudy will not stop enrolling participants before the primary study completes enrollment. Edited figure note to reflect inclusion of OS as a primary objective in the substudy rather than a secondary endpoint.	See Overall Rationale above.
Section 5.2 Number of Participants	Increased number of participants enrolled from 1375 to 1792. Increased number of participants randomized from 990 to 1290. Increased number of cisplatin-eligible participants in the substudy from 300 to 600. Added text stating that randomization to the substudy is increased by 300 cisplatin eligible participants to ensure adequate power of primary endpoints OS and PFS. Deleted text referencing changes in revised protocol version 03. Updated the number of months expected to randomize 600 cisplatin-eligible participants in the substudy. Deleted text stating that the substudy will not stop enrolling participants before the primary study completes enrollment. Monthly participant accrual rate decreased from 21 to 18 once enrollment in the primary study is closed.	See Overall Rationale above.
Section 7.4.4 Management Algorithms for Immuno-Oncology Agents	Added myocarditis to list of management algorithms.	To meet current standards.
Section 9.8 biomarkers, Table 9.8-1	Corrected footnote c.	To accurately reflect countries for which PBMC sampling will occur.

Summary of Key Changes for Revised Protocol 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 10.1 Sample Size Determination	Updated description of sample size and alpha level determination for the substudy to reflect inclusion of 2 primary efficacy endpoints PFS and OS. Updated description of sample size to reflect an increase to 845 cisplatin-eligible participants, with 245 randomized in the primary study and 600 randomized in the substudy. Added text stating that cisplatin-eligible participants randomized following the end of enrollment into the primary study will be randomized into the substudy.	See Overall Rationale above.
Section 10.1.3 Sample Size Justification for the Dual Primary Endpoints of Progression Free Survival and Overall Survival in Cisplatin-eligible Randomized Participants in the Substudy	Section heading updated. Updated text to reflect inclusion of primary endpoints PFS and OS.	See Overall Rationale above.
Section 10.1.3.1 Progression Free Survival	Updated text describing justification for sample size in analysis of PFS. Added text stating that if OS superiority is demonstrated in interim analysis for the substudy, formal testing of PFS will be performed. Deleted text regarding inclusion of an interim analysis of PFS. Updated assumption underlying the time needed to observe the required number of PFS events for the interim analysis (if performed).	See Overall Rationale above.
Section 10.1.3.2 Overall Survival	Added section describing sample size justification for OS as a primary endpoint for the substudy.	See Overall Rationale above.
Section 10.1.4 Analysis Timing Projections Table 10.1.4-1	Increased the number of participants with previously untreated, unresectable or metastatic UC to be randomized from 990 to 1290. Updated table to reflect that the PFS interim analysis will only be performed if OS interim analysis is significant in the substudy, updated analysis criteria and projected timing.	See Overall Rationale above.
Section 10.3.1 Efficacy Analyses	Updated description of the substudy analyses to reflect inclusion of OS and PFS as primary endpoints for primary objective. Deleted paragraph referencing OS as a secondary objective. Added paragraph describing secondary objective of whether PD-L1 expression is a predictive biomarker of efficacy.	See Overall Rationale above.
Section 10.3.1.1 Primary Endpoints	Updated description of the substudy analyses to reflect inclusion of OS and PFS as primary endpoints for primary objectives.	See Overall Rationale above.

Summary of Key Changes for Revised Protocol 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
	Added paragraph describing details of the testing strategy between the PFS and OS endpoints for the substudy.	
Section 10.3.1.2 Secondary Endpoints	Deleted text describing analysis of OS as a secondary endpoints. Added text describing PD-L1 expression as a predictive biomarker of efficacy.	See Overall Rationale above.
Section 10.3.3.3 Biomarker Analyses	Deleted PD-L1 from the list of exploratory biomarker analyses to be conducted in the substudy.	See Overall Rationale above.
Section 10.3.4 Interim Analyses	Revised text to reflect inclusion of an interim analysis of OS and hierarchical testing of interim analysis of PFS if OS interim analysis is significant.	See Overall Rationale above.
Appendix 5 Management Algorithms	Updated appendix.	To meet current standards.
Appendix 8 Study Governance Considerations	Updated appendix.	To meet current standards.

Overall Rationale for the Revised Protocol 03, 09-Apr-2019

This revision removes PFS as a co-primary objective and endpoint and adds OS in PD-L1 positive (≥ 1%) as a primary population, adds 100 cisplatin-ineligible participants ineligible and a corresponding number of cisplatin-eligible to the primary study, and revises the timing of the OS interim analysis for the primary study. The timing of the interim analysis for the substudy is revised as well.

This protocol is revised to react to the dynamic changes of cancer treatment options and rapidly emerging scientific evidence. Accumulated evidence indicates that PFS would not be clinically meaningful and is not comparable in immunotherapy with chemotherapy in cisplatin-ineligible participants, thus it is removed. Growing data point to the benefit of immunotherapy in PD-L1 positive patients and, supported by regulatory approval for the application of pembrolizumab and atezolizumab in PD-L1 positive cisplatin-ineligible patients, adding OS in PD-L1 positive metastatic UC patients is reasonable. To ensure sufficient power for the two (amended) primary populations for the endpoint of OS in cisplatin ineligible and OS in PD-L1 positive metastatic UC, 100 cisplatin-ineligible participants will be added to the primary study and the number of cisplatin eligible participants will be increased accordingly. After removing the co-primary endpoint PFS, the timing for the interim OS analysis was revised, similarly, the timing for the substudy interim analysis was revised to align with the primary study interim analysis.

Summary of key changes of Revised Protocol 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title page	Study director changed to Shengting Li	To update information
Synopsis, Key Inclusion/Exclusion, Inclusion	Corrected fourth bullet to allow for fresh biopsy within 2 years prior to enrollment period	To align with Section 6.1 and Table 2-1
Synopsis, Key Inclusion/Exclusion, Exclusion 6.2 Exclusion Criteria (6 c, d)	Added exclusion for vaccine Added exclusion for treatment with botanical preparations	For consistency with program standards
Synopsis, Table 1, Objectives and Endpoints: Primary Study 3.1.1.1 Research Hypothesis for Primary Study 3.1.4 Rationale for PD-L1 Subpopulation being Co-primary Analysis Population Table 4-1 Objectives and Endpoints: Primary Study 5.4 Scientific Rationale for Study Design 10.1 Sample Size Determination 10.2 Population for Analyses 10.3.1.2 Secondary Endpoints	Removed PFS as co-primary objective and endpoint Added comparison of OS in PD-L1 positive (PD-L1 ≥ 1%) participants and OS endpoint as primary objective Added new rationale subsection 3.1.4 Removed PFS in all randomized participants as secondary objective In Secondary Objectives, changed PFS analysis to the cisplatin-ineligible and PD-L1 populations as well as all randomized participants Removed PD-L1 as secondary objective Removed PFS as exploratory objective	See Overall Rationale above
Synopsis Table 2 Objectives and Endpoints: Substudy Table 4-2 Objectives and Endpoints: Substudy	Inserted “cisplatin-eligible” before participant Changed ipilimumab to “SOC chemotherapy” Changed PPK to PK parameters	To correct typographical errors
Synopsis, Figure 1 Study Design Schematic Figure 5.1-1 Study Design Schematic	Updated Figure, Footnotes, and Notes Changed stratification (ii) from “cisplatin-ineligibility” to “cisplatin-eligibility” and removed Primary Study prior to substudy start In the notes, the first sentence of the section was revised to clarify that “all participants” will be randomized 1:1 to Arms A or B during the primary study; the primary study secondary endpoint language was revised to clarify “all randomized participants;” and the substudy secondary endpoint language was revised to add reference to “hierarchical testing procedure”	For greater clarity and for consistency with changes made through-out protocol
Synopsis, Figure 1 Study Design Schematic Table 2-2 On Treatment Procedural Outline for Arm A, Part 1: Ipilimumab/Nivolumab Combination Treatment	Added 1 week window for week 9 assessments	For consistency

Summary of key changes of Revised Protocol 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-3 On Treatment Procedural Outline for Arms A and C, Part 2 Nivolumab Monotherapy Treatment Table 2-4 On Study Assessments Treatment Arm B and Arm D (Cisplatin-Eligible) Doublet Gemcitabine-Cisplatin Chemotherapy Table 2-5 On Study Assessments Treatment Arm B (Cisplatin-Ineligible) Doublet Gemcitabine/Carboplatin Chemotherapy Table 2-6 On Study Assessments Treatment Substudy: (Arm C, Part 1) Nivolumab + Doublet Gemcitabine-Cisplatin Chemotherapy Table 2-7 Follow-Up Period Figure 5.1-1 Study Design Schematic		
Synopsis, Number of Participants 5.2 Number of Participants 10.1 Sample Size Determination	Revised screen failure rate, sample size numbers, added PD-L1 population, revised accrual enrollment numbers Added 100 cisplatin-ineligible and adjusted cisplatin eligible participants to primary study to ensure adequate power in both primary populations	See Overall Rationale above
Table 2-1 Screening Procedural Outline for All Participants Table 2-2 On Treatment Procedural Outline for Arm A, Part 1: Ipilimumab/Nivolumab Combination Treatment Table 2-3 On Treatment Procedural Outline for Arms A and C, Part 2 Nivolumab Monotherapy Treatment Table 2-6 On Study Assessments Treatment Substudy: (Arm C, Part 1) Nivolumab + Doublet Gemcitabine-Cisplatin Chemotherapy Table 2-7 Follow-Up Period 9.4 Safety	Specified that total T3 and T4 are acceptable if free T3 and T4 are not available	To allow for differences in lab testing globally
Table 2-1 Screening Procedural Outline for All Participants 6.1 Inclusion Criteria (2j)	Added details regarding palliative radiotherapy	For consistency with program standards
Table 2-1 Screening Procedural Outline for All Participants Table 2-2 On Treatment Procedural Outline for Arm A, Part 1: Ipilimumab/Nivolumab Combination Treatment	Specified that CT with or without contrast is acceptable if MRI prohibited for medical reasons	Permit image submission of alternate modality

Summary of key changes of Revised Protocol 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-3 On Treatment Procedural Outline for Arms A and C, Part 2 Nivolumab Monotherapy Treatment Table 2-4 On Study Assessments Treatment Arm B and Arm D (Cisplatin-Eligible) Doublet Gemcitabine-Cisplatin Chemotherapy Table 2-5 On Study Assessments Treatment Arm B (Cisplatin-Ineligible) Doublet Gemcitabine/Carboplatin Chemotherapy Table 2-6 On Study Assessments Treatment Substudy: (Arm C, Part 1) Nivolumab + Doublet Gemcitabine-Cisplatin Chemotherapy Table 2-7 Follow-Up Period		
Table 2-2 On Treatment Procedural Outline for Arm A, Part 1: Ipilimumab/Nivolumab Combination Treatment Table 2-3 On Treatment Procedural Outline for Arms A and C, Part 2 Nivolumab Monotherapy Treatment Table 2-4 On Study Assessments Treatment Arm B and Arm D (Cisplatin-Eligible) Doublet Gemcitabine-Cisplatin Chemotherapy Table 2-5 On Study Assessments Treatment Arm B (Cisplatin-Ineligible) Doublet Gemcitabine/Carboplatin Chemotherapy Table 2-6 On Study Assessments Treatment Substudy: (Arm C, Part 1) Nivolumab + Doublet Gemcitabine-Cisplatin Chemotherapy	For PRO assessments, removed reference to phone administration	Assessment will be done at time of visit
Table 2-2 On Treatment Procedural Outline for Arm A, Part 1: Ipilimumab/Nivolumab Combination Treatment Table 2-3 On Treatment Procedural Outline for Arms A and C, Part 2 Nivolumab Monotherapy Treatment Table 2-3 On Treatment Procedural Outline for Arms A and C, Part 2 Nivolumab Monotherapy Treatment Table 2-4 On Study Assessments Treatment Arm B and Arm D (Cisplatin-Eligible) Doublet Gemcitabine-Cisplatin Chemotherapy Table 2-5 On Study Assessments Treatment Arm B (Cisplatin-Ineligible) Doublet Gemcitabine/Carboplatin Chemotherapy	In 2-2, clarified tumor tissue collection upon disease progression “and” at C2D15 in Procedure column Changed “or” to “and” after progression in Notes column In Table 2-6 inserted the individual biomarkers assessments	To collect biopsy at both times Table 2-6 was revised to align with Table 9.8-1

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Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-6 On Study Assessments Treatment Substudy: (Arm C, Part 1) Nivolumab + Doublet Gemcitabine-Cisplatin Chemotherapy		
Table 2-2 On Treatment Procedural Outline for Arm A, Part 1: Ipilimumab/Nivolumab Combination Treatment Table 2-3 On Treatment Procedural Outline for Arms A and C, Part 2 Nivolumab Monotherapy Treatment Table 2-7 Follow-Up Period	Added Table 9.5-2 to PK/Immunogenicity Assessments	For completeness
Table 2-3 On Treatment Procedural Outline for Arms A and C, Part 2 Nivolumab Monotherapy Treatment	Footnote a - revised text to distinguish different delay periods for Arms A and C In 2-3, Drug Supply, removed "± 2 days" for nivolumab	For greater clarity For consistency with 7.1.1.2
Table 2-4 On Study Assessments Treatment Arm B and Arm D (Cisplatin-Eligible) Doublet Gemcitabine-Cisplatin Chemotherapy Table 2-5 On Study Assessments Treatment Arm B (Cisplatin-Ineligible) Doublet Gemcitabine/Carboplatin Chemotherapy Table 2-6 On Study Assessments Treatment Substudy: (Arm C, Part 1) Nivolumab + Doublet Gemcitabine-Cisplatin Chemotherapy	Removed Performance Status at D8	Mid-cycle performance status assessment not required
Table 2-4 On Study Assessments Treatment Arm B and Arm D (Cisplatin-Eligible) Doublet Gemcitabine-Cisplatin Chemotherapy Table 2-5 On Study Assessments Treatment Arm B (Cisplatin-Ineligible) Doublet Gemcitabine/Carboplatin Chemotherapy	For PRO, added timing in the event of additional cycles as per local guidelines	For consistent data collection across various local guidelines
Table 2-7 Follow-Up Period	Added detail to the physical examine Clarified that serum collection should occur at both Follow-Up Visit 1 and Follow Up Visit 2	For clarity To align with Table 9.8-1
3 Introduction 6.1 Inclusion Criteria (2c)	Revised description of eligible prior treatment	For greater clarity
5.1 Study Design	Revised text on number of cycles for Arm B and D	For compliance with local guidelines
6.4.1 Retesting During Screening or Lead-in Period	Clarified definition of pre-treatment failure	For consistency with program standards

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Section Number & Title	**Description of Change**	**Brief Rationale**
Table 7-1 Study Treatment for CA209901	Added row for China sourcing of a study treatment	For completeness
Table 7.1-1 Treatment Administration 7.1.2 Study Drug Preparation and Infusion 7.1.4 Arm C: Nivolumab plus Platinum-Doublet Chemotherapy 7.1.5 Arm D: Platinum-Doublet Chemotherapy (Cisplatin-Eligible) 7.5 Preparation/Handling/Storage/Accountability	Added footnote that information only applies to chemotherapy and that infusion durations and premedications may follow local guidelines	For compliance with local guidelines
7.1.1.1 Arm A: Part 1 Study Drug Administration - Nivolumab and Ipilimumab Combination Therapy (Cycles 1-4)	Added text regarding participants who experience AEs on combination dose therapy proceeding to nivolumab monotherapy without completing all 4 combination doses	For consistency with program standards
7.1.2 Study Drug Preparation and Infusion	Deleted some study drug description and referred instead to pharmacy manual or IB Removed forward slash in first sentence of the last paragraph of the section to read, “Doses of nivolumab and/or ipilimumab”	For consistency with program standards
7.1.3.1 Gemcitabine/Cisplatin	Added that additional cycles may be permitted	For completeness
7.4.2.1 Nivolumab or Ipilimumab Dose Delay Criteria	Deleted text that during Part 1, nivolumab and ipilimumab should be discontinued together	For consistency with program standards
7.4.5 Treatment Beyond Progression	Removed approval by Medical Monitor Revised radiographic assessment timing language so that it accords with Section 2	For consistency with program standards For clinical and operational ease
7.7.1. Prohibited and/or Restricted Treatments (4 d,e)	Added prohibitions for live/attenuated vaccines and for botanical preparations	For consistency with program standards
7.7.3.1. Imaging Restriction and Precautions	Added text should brain MRI not be available	Permit image submission of alternate modality
8.1.1.1 Discontinuation of Nivolumab or Ipilimumab	Added text specifying that discontinuation assessment should be made separately for each drug Added myocarditis to Grade 3 section	For consistency with program standards
8.1.2.2 Criteria to Resume Treatment with Platinum Doublet Chemotherapy	In the first bullet, ≥ symbol for ANC was corrected to > symbol	To correct typographical error

Summary of key changes of Revised Protocol 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
9.1.1. Overall Survival	Reordered study evaluations	For consistency with changes to protocol
9.1.4.1 BICR Assessment of Progression	Changed "performed" to "expedited" regarding timing of BICR assessment	Corrected to align with the imaging manual
9.4 Safety	Corrected arms for on-treatment monitoring of amylase and lipase	To correct misstatement
9.8 Biomarkers	Revised arm descriptions	To clarify treatment arms
9.8-1 Biomarker Sampling Schedule (All Participants)	Added 2 footnotes with country-specific collection information for MDSCs and Whole Blood (Gene Expression)	For operational ease
10.1 Sample Size Determination	Removed accrual assumptions and referred to Section 5.2 Revised alpha for the primary study Changed from 2 to 1 formal interim analysis for substudy	See Overall Rationale above
10.1.1 Sample Size Justification for the Primary OS in the Primary Study 10.1.1.1 Overall Survival in Cisplatin-ineligible participants 10.1.1.2 Overall Survival in PD-L1 positive (≥ 1%) participants	Revised titles Add new subsection on PD-LI population Moved cisplastin-ineligible participants subsection up and revised event, power, cure fraction, HR calculations, and interim analysis details	See Overall Rationale above
10.1.2 Sample Size Justification for the Secondary OS Endpoint in All Randomized Participants in the Primary Study 10.3.4 Interim Analyses	Removed PFS section Revised numbers and event, power, cure fraction, HR calculations, and interim analysis details for OS in all randomized participants	See Overall Rationale above
10.1.3.1 Progression Free Survival 10.3.4 Interim Analyses	Revised event, power, and accrual assumptions Changed from 2 to 1 formal interim analysis and revised details	See Overall Rationale above
10.1.4 Analysis Timing Projections 10.1.4-1 Populations and Projected Timing for Analysis of Primary Endpoints: Primary Study and Substudy	Revised text, removed 4 bullets, and revised table Added paragraph with rule for timing of interim analysis	See Overall Rationale above

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Section Number & Title	**Description of Change**	**Brief Rationale**
10.2 Population for Analyses	Added row on PD-LI positive patients Revised text in row on PD-LI from "primary study" to "substudy" Deleted paragraph regarding ITT under the table	For consistency with changes to the protocol Any participant randomized will be included in the efficacy analysis and ITT is not a defined study population
10.3.1 Efficacy Analyses 10.3.1.1 Primary Endpoints 10.3.1.2 Secondary Endpoints	Revised text for primary study, including revisions for testing to control for Type 1 error, and substudy Added details on significance levels	For consistency with changes through-out the protocol To outline technical changes
Appendix 2 Performance Status Scores	Updated with revisions in Status Column	For clarity
Appendix 3 AE and SAE Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Updated	For consistency with program standards
Appendix 5 Management Algorithms	Updated to 2018 version	For consistency with program standards
Appendix 6 WOCBP Definitions and Methods of Contraception	Removed hormonal methods of contraception from User Independent Section	For consistency with program standards