Official Title of Study:

A Phase 2 Trial of Nivolumab Plus Ipilimumab, Ipilimumab Alone, or Cabazitaxel in Men with Metastatic Castration-Resistant Prostate Cancer

Protocol Number: CA209-650

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CLINICAL PROTOCOL CA209650

A Phase 2 Trial of Nivolumab Plus Ipilimumab, Ipilimumab Alone, or Cabazitaxel in Men with Metastatic Castration-Resistant Prostate Cancer

Protocol Amendment Number: 05

Incorporates Administrative Letter 05

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DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Protocol Amendment 05	01-Dec-2021	• Modified sample size to reflect actual enrollment. • Modified accrual duration for Cohort D to reflect actual time. • Modified timing of dual primary endpoint analyses. • Removed references to Cohort D Part 1 and 2; renamed as simply Cohort D. • [redacted] • Added COVID-19 guidance
Administrative Letter 05	15-Sept-2021	• Study personnel updated.
Administrative Letter 04	01-Apr-2021	• Study personnel updated.
Administrative Letter 03	23-Mar-2021	• Study personnel updated.
Revised Protocol 04	26-Mar-2020	• Modified the maximum tumor sample age from 5 years to 1 year. The study will allow submission of tumor samples obtained more than 1 year prior to enrollment if collected in the metastatic setting and if approved by the BMS Medical Monitor/designee. • Allowed starting dose of cabazitaxel of 20 mg/m^2 to align with cabazitaxel labeling • Clarified the population for analyses in Cohort D Part 1 • Clarified the exclusion criteria for prior pelvic radiotherapy • Incorporated updated nivolumab clinical program protocol standards • Made minor clarifications for consistency throughout document. • Incorporates Administrative Letter 02
Administrative Letter 02	20-Jun-2019	To correct the potency of Cabazitaxel and Prednisone.
Revised Protocol 03	21-Feb-2019	• Added new treatment Cohort D (Arms D1, D2, D3, and D4) • Updated study objectives and endpoints with new study design • Updated outcomes measures and healthcare resource utilization • Allowed reinduction and crossover treatment with new study design • Updated prohibited/restricted treatments • [redacted] • Updated statistical section with new study design
Revised Protocol 02	28-Aug-2017	• [redacted] • Updated eligibility criteria • Updated dose delay and dose discontinuation criteria • Corrected typographical and formatting errors • Incorporates Administrative Letter 01
Administrative Letter 01	24-Apr-2017	This Administrative Letter updates the Medical Monitor for the study, as well as clarify Cohort A.

Document	Date of Issue	Summary of Change
Revised Protocol 01	01-Feb-2017	Incorporates Amendment 01
Amendment 01	01-Feb-2017	This amendment adds planned interim reviews of early toxicities and early disease control as well as stopping rules for safety to the protocol. The amendment also incorporates other minor changes to correct and/or clarify protocol requirements and procedures. This amendment applies to all subjects.
Original Protocol	30-Sep-2016	Not applicable

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 05

Study enrollment closed on 08-Sep-2021. Several enrollment challenges significantly impacted study timelines, notably the coronavirus disease 2019 (COVID-19) pandemic [redacted]. In addition, enrollment of patients with measurable disease at baseline was difficult after reaching the cap on patients with non-measurable disease. Bristol-Myers Squibb Company (BMS) determined that the number of patients enrolled will be sufficient to inform the efficacy and safety for the 4 arms of Cohort D.

Protocol Amendment 05 includes changes to modify the sample size, accrual duration for Cohort D, and timing of dual primary endpoint analyses to reflect actual enrollment and time. Due to prolonged enrollment from Cohort D-Part 1 and BMS reprioritization, Cohort D-Part 2 will no longer be conducted. Additional guidance related to COVID-19 was also added to the amendment.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 05

Section Number & Title	Description of Change	Brief Rationale
Synopsis	Changes to ensure alignment with protocol amendment body.	To ensure alignment with protocol amendment body.
Section 1, Introduction and Study Rationale; Section 1.3.1, Primary Objectives; Section 3.1, Study Design and Duration; Figure 3.1-2, Study Design Schematic for Addition of Cohort D; Section 3.2, Post Study Access to Therapy; Table 5.1-1, Screening Procedural Outline for All Treatment Arms (Cohorts A, B, C, and D); Section 5.5, Efficacy Assessments; Section 8.1, Sample Size Determination; Section 8.1.1, Populations for Analyses; Section 8.2.1, Dual Primary Endpoints; Section 8.2.2, Secondary Endpoint(s); Section 8.2.9, Outcomes Research Analyses; Section 8.2.9.2, Change in Cancer-related Symptoms and Quality of Life; Section 8.2.9.3, Change in Health Status and Health Utility	Removed all text related to Cohort D-Part 2. Changed all references of Cohort D-Part 1 to Cohort D.	Due to prolonged enrollment from Cohort D-Part 1 and BMS reprioritization, Cohort D-Part 2 will no longer be pursued. Cohort D-Part 1 is now referred to simply as Cohort D.
Section 1.1.13, Rationale for Duration of Treatment with Nivolumab plus Ipilimumab; Section 4.5, Selection and Timing of Dose for Each Subject	Added "For subjects in these cohorts who receive immunotherapy treatment beyond 2 years, treatment will be given for a maximum of 5 years from the start of study treatment."	No clinical benefit has been demonstrated after 24 months of immunotherapy. However, for subjects that receive immunotherapy beyond 2 years,

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 05		
Section Number & Title	**Description of Change**	**Brief Rationale**
		a maximum treatment duration was added.
Section 1.3.1, Primary Objectives; Section 8.1, Sample Size Determination; Section 8.1, Populations for Analyses; Section 8.2.1, Dual Primary Endpoints; Section 8.2.5, Efficacy Analyses	Clarified that measurable disease is per investigator assessment (as entered in the interactive web response system [IWRS]).	To clarify language.
[redacted]		
Section 3.1, Study Design and Duration; Section 5.5.1, Primary Efficacy Endpoints	Added "If exceptional circumstances preclude the continued administration of measures using planned modalities, then alternate administration methods may be required after consultation with a sponsor or a sponsor's representative."	To allow for virtual follow up visits and assessments as needed.
[redacted]		

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 05		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 3.1, Study Design and Duration	• Modified the accrual duration of the study for Cohort D to reflect actual accrual time of 24 months instead of previously written 8 months. • Clarified time period for long-term survival analysis. • Analyses for the dual primary endpoints of rPFS and ORR were modified for timing of the analyses from "minimum 9 months" to "approximately 9 months of minimum follow up and from "all" to "90%" subjects • Added "Additional survival analysis may be conducted for up to 5 years from the date of randomization of the last patients following analysis of the primary endpoint."	• Accrual duration was updated to reflect a more accurate accrual time. • [redacted] • To maintain consistency with Cohorts A, B, and C, language has been added to allow possible survival analyses.
Section 3.1, Study Design and Duration; Section 3.3.4, Exclusion Criteria for Crossover Phase for Subjects Originally Randomized to Arm D3 or Arm D4 only; Section 4.5.1, Dose Delay Criteria for Nivolumab and Ipilimumab; Section 4.5.5, Dose Delay, Modification, and Discontinuation for Cabazitaxel; Section 4.5.5.5, Criteria to Resume Study Treatment following SARS-CoV-2 Infection; Table 5.1-1, Screening Procedural Outline for All Treatment Arms (Cohorts A, B, C, and D); Table 5.1-2, On Treatment Part 1: Sequential Treatment with Nivolumab and Ipilimumab Procedural Outline - Cohorts A, B, and C; Table 5.1-3, On Treatment Part 2: Nivolumab Monotherapy Phase Procedural Outline for Cohorts A, B, and C; Table 5.1-4, On Treatment Procedural Outline for Cohort D; Table 5.1-5, Follow-up Assessments for All Treatment Arms (Cohorts A, B, C, and D); Section 6.1.1, Serious Adverse Event Collection and	Added guidance regarding severe acute respiratory syndrome (SARS-CoV-2) infection.	To mitigate chances that SARS-CoV-2 infection sequelae increase toxicity of study drug. To aid in interpretation of study AEs. To offer guidance on when to safely resume study drug in participants with SARS-CoV-2 infection.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 05		
Section Number & Title	**Description of Change**	**Brief Rationale**
Reporting; Section 6.2.1, Nonserious Adverse Event Collection and Reporting		
Section 3.1, Study Design and Duration; Figure 3.1-2, Study Design Schematic for Addition of Cohort D; Section 8.1, Sample Size Determination	Decreased enrollment in Cohort D from 315 to 259 subjects.	Several enrollment challenges significantly impacted study timelines, notably the COVID-19 pandemic [redacted] In addition, enrollment of patients with measurable disease at baseline was difficult after reaching the cap on patients with non-measurable disease. BMS determined that the number of patients enrolled will be sufficient to inform the efficacy and safety for the 4 arms of Cohort D.
Section 3.3.3, Exclusion Criteria	Added exclusion criterion 5) d): "Participation in another clinical trial concurrent with this study."	To align with the current protocol model document (PMD).
Section 4, Study Treatment	Added ipilimumab 50 mg as a study treatment.	Ipilimumab 50 mg will be available starting Q3 2022 and may be used in this study.
Section 4.5, Selection and Timing of Dose for Each Subject	Clarified that dose reductions are only allowed for cabazitaxel.	To clarify language.
Section 4.5.5, Dose Delay, Modification, and Discontinuation for Cabazitaxel	Added "Regardless of whether or not the event is attributed to cabazitaxel, study treatment must be delayed until treatment can resume. Tumor assessments for all subjects should continue as per protocol even if dosing is delayed."	To clarify language.
Section 5.8, Outcomes Research Assessments	Added "If exceptional circumstances preclude the continued administration of measures using planned modalities, then alternate administration methods may be required after consultation with a sponsor or a sponsor's representative."	This allows flexibility to continue data collection when feasible to accommodate subject's changing health or personal circumstances during treatment and in follow-up.
Section 8.1, Sample Size Determination	• Updated accrual duration. • Updated timing of the dual primary endpoint analyses. • Combined database locks. • Updated the 95% confidence interval per new sample size	• Enrollment has now been closed, thus sample size updated more closely reflect final actual sample size • [redacted]

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 05		
Section Number & Title	**Description of Change**	**Brief Rationale**
		• [redacted] • [redacted] • Updated the precision for the response rate per new sample size
Section 8.1.1, Populations for Analyses; Section 8.2.2, Secondary Endpoints; [redacted]	Clarified populations for analyses by cohort.	To clarify language.
Section 8.2.1, Dual Primary Endpoints	• Added "In Cohort D, the radiographic progression-free survival (rPFS) is defined as the time between the date of randomization and the first date of documented progression per BICR (radiographic a-b) or death due to any cause, whichever occurs first." • Added details regarding assessment of best overall response (BOR) for Cohort D.	To clarify language.
[redacted]		
Section 8.2.4, Demographics and Baseline Characteristics	Added "For Cohort D, similar analyses will be repeated by treatment group and total for all randomized subjects."	To specify that analyses in Cohort D are for all "randomized" subjects instead of all "treated" subjects.
Section 8.2.5, Efficacy Analyses; Section 8.2.6, Safety Analyses	Clarified planned efficacy and safety analyses and the populations for analyses.	To clarify language.
Section 8.2.9.1, Change in Pain Intensity	Clarified that the primary analysis will be "pain intensity change over time" rather than "time to deterioration of pain intensity."	To clarify language.
Section 9.1.2, Monitoring	• Removed "BMS 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." • Added "Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and	To align with mandatory updates to the PMD.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 05		
Section Number & Title	**Description of Change**	**Brief Rationale**
	quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan."	
Section 9.3, Dissemination of Clinical Study Data	Added new section: "In order to benefit potential study participants, patients, healthcare providers and researchers, and to help BMS honor its commitments to study participants, BMS will make information about clinical research studies and a summary of their results available to the public as per regulatory and BMS requirements. BMS will post study information on local, national, or regional databases in compliance with national and international standards for disclosure. BMS may also voluntarily disclose information to applicable databases."	To align with mandatory updates to the PMD.

SYNOPSIS

Clinical Protocol CA209650

Protocol Title: A Phase 2 Trial of Nivolumab Plus Ipilimumab, Ipilimumab Alone, or Cabazitaxel in Men with Metastatic Castration-Resistant Prostate Cancer

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s):

Cohorts A, B, and C: nivolumab 1 mg/kg IV combined with ipilimumab 3 mg/kg IV every 3 weeks for 4 doses then flat dose nivolumab 480 mg every 4 weeks until disease progression or unacceptable toxicity.

Cohort D contains the following dose regimens:

- **Arm D1**: Nivolumab 3 mg/kg Q3W + ipilimumab 1 mg/kg Q3W up to 4 cycles, then nivolumab 480 mg Q4W
- **Arm D2:** Nivolumab 1 mg/kg Q3W (8 doses)+ ipilimumab 3 mg/kg Q6W (4 doses), then nivolumab 480 mg Q4W
- **Arm D3:** Ipilimumab 3 mg/kg Q3W up to 4 cycles
- **Arm D4:** Cabazitaxel 20 mg/m^2 or 25 mg/m^2 (at investigator's discretion and according to country-specific label) Q3W + prednisone 10mg PO D1-D21 up to 10 cycles

Study Phase: II

Research Hypothesis: Treatment with nivolumab combined with ipilimumab will have clinical activity in subjects with metastatic castrate resistant prostate cancer (mCRPC).

Objectives:

Primary Objectives:

- Evaluate objective response rate (ORR) by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 assessed by Blinded Independent Central Review (BICR) in subjects with mCRPC and measurable disease at baseline per investigator assessment as entered in the interactive web response system (IWRS).
- Assess Radiographic Progression Free Survival (rPFS) assessed by BICR in all treated subjects with mCRPC in Cohorts B and C, and all randomized subjects with mCRPC in Cohort D using RECIST v1.1 for soft tissue disease progression and PCWG2 for bone disease progression.

Secondary Objectives:

- Assess radiographic/clinical Progression Free Survival (rcPFS) .
- Assess overall survival (OS).
- Evaluate PSA response rate (PSA-RR)
- Determine the safety and tolerability in all treated subjects.
- Estimate changes in pain as measured by the Brief Pain Inventory-Short Form (BPI-SF)
- Estimate changes in cancer-related symptoms and quality of life (QoL) using the FACT-P questionnaire (Cohort D only)
- Estimate changes in health status and health utility as measured by the 3-level EuroQol Five Dimensions questionnaire (EQ-5D-3L)

[redacted]

Study Design for Cohorts A, B, C: This is a Phase 2 open-label study of nivolumab plus ipilimumab in subjects with metastatic castration-resistant prostate cancer (mCRPC).

The trial will include 3 treatment cohorts dosed with nivolumab 1 mg/kg plus ipilimumab 3 mg/kg (see Study Design Schema below). No dose increases or reductions will be allowed for either drug.

Approximately 90 subjects will be treated in 3 cohorts as follows:

Cohort A: Asymptomatic or minimally symptomatic mCRPC subjects who have not been treated with and are unable or unwilling to receive second generation hormone therapies or cytotoxic chemotherapy in mCRPC setting. **Enrollment discontinued per Revised Protocol 02.**

Cohort B: Asymptomatic or minimally symptomatic mCRPC subjects who must have progressed after second generation hormone therapies in mCRPC setting and have not been treated with cytotoxic chemotherapy in mCRPC setting.

Cohort C: Subjects must have progressed after prior taxane-based cytotoxic chemotherapy in the mCRPC setting.

Per Revised Protocol 02, Cohort A enrollment will be discontinued due to slow accrual and to reflect the changing landscape of mCRPC (see Section 1.1.10). Addendum in the protocol). Per Revised Protocol 02, the remainder of planned number of patients for Cohort A will be allocated to Cohorts B and C in order to have more precise efficacy estimates in those arms. In each of the 2 cohorts B and C, at least 30 subjects must have RECIST v1.1 defined measurable disease and no more than 15 subjects will have non-measurable disease by RECIST v1.1.

Subjects will be treated with up to 4 cycles of nivolumab in combination with ipilimumab (Part 1, See Section 4.3.1 of the protocol), followed by monotherapy nivolumab monotherapy (Part 2, Section 4.3.2 of the protocol) until progression of disease, unacceptable toxicity, or subject withdrawal of consent. In Part 1, a minimum of 1 combination cycle of nivolumab and ipilimumab is required.

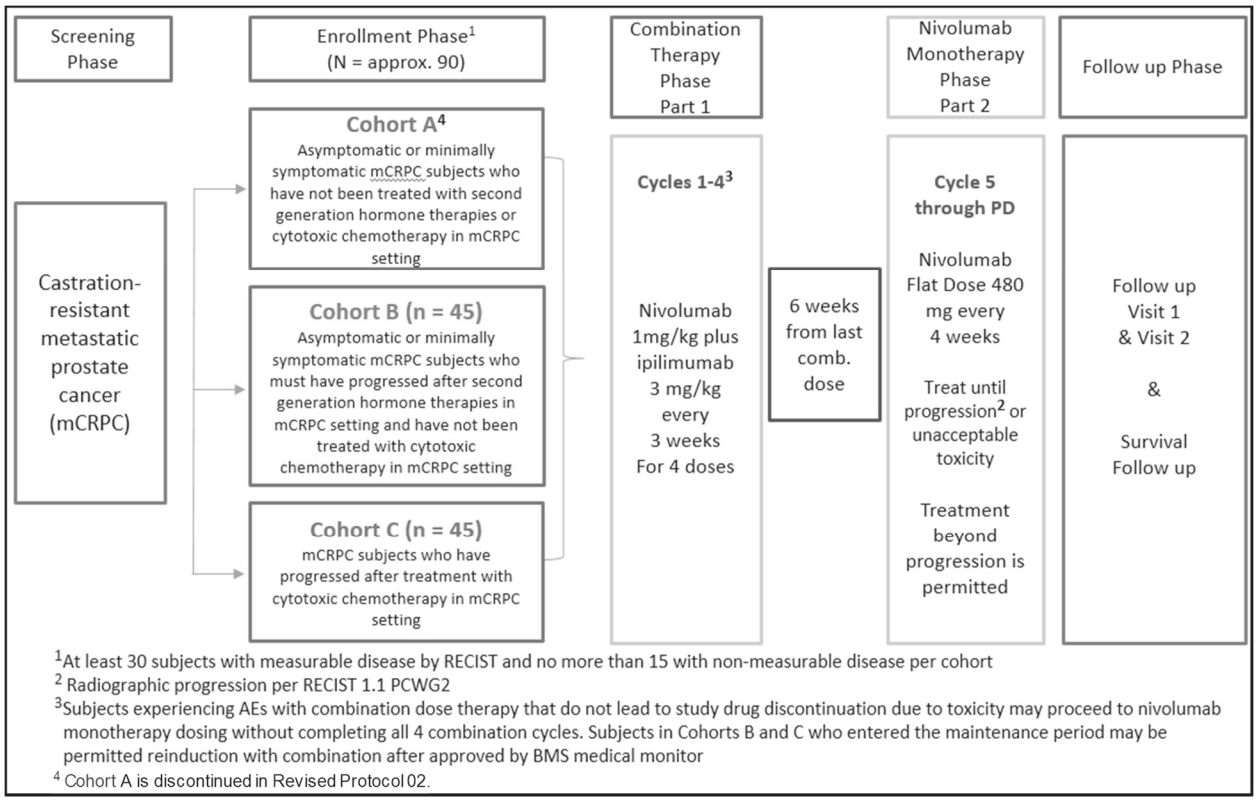
In Part 1, each treatment cycle will be 3 weeks in duration. Nivolumab and ipilimumab will be dosed every 3 weeks for four doses. After completion of the last combination cycle in Part 1 (i.e. 6 weeks after the last dose of nivolumab plus ipilimumab), subjects will then receive nivolumab monotherapy every four weeks in Part 2 until progression of disease, unacceptable toxicity, or subject withdrawal of consent.

Subjects experiencing adverse events (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 Bristol-Myers Squibb (BMS) Medical Monitor, on a case-by-case basis.

Subjects from Cohorts B and C who entered the maintenance period may be permitted re-induction with the combination upon PSA progression or radiographic progression (whichever occurs first) and after approval by the BMS medical monitor.

It is strongly recommended that subjects in Arms A, B, and C limit treatment duration with immunotherapy treatment for up to 2 years. See Section 1.1.13.

Schema for Cohorts A, B, and C



Study Design for Cohort D: This is a phase 2 open-label study evaluating different dosing regimens containing nivolumab plus ipilimumab, ipilimumab alone, or cabazitaxel in subjects with mCRPC who have progressed and have received docetaxel-containing regimen.

The addition of Cohort D to the trial will include 4 treatment arms. For Cohort D, approximately 259 subjects will be randomized in a 2:2:1:2 ratio to one of 4 open-label treatment arms including two new combination arms (Arm D1 and Arm D2) evaluating alternative nivolumab plus ipilimumab doses and schedules, one arm (Arm D3) evaluating ipilimumab monotherapy, and one reference arm (Arm D4) evaluating SOC treatment in this setting cabazitaxel (see study schema below). Randomization will be stratified by the presence or absence of measurable disease (measurable vs non-measurable disease) at study entry to ensure treatment arms are balanced.

Subjects in Arms D1 and D2 experiencing drug-related AEs with combination dose therapy that do not lead to study treatment discontinuation due to toxicity may proceed to nivolumab monotherapy dosing without completing all 4 combination cycles. Subjects must have received at least 1 dose of combination therapy before proceeding to nivolumab monotherapy after consultation with the Medical Monitor, on a case-by-case basis.

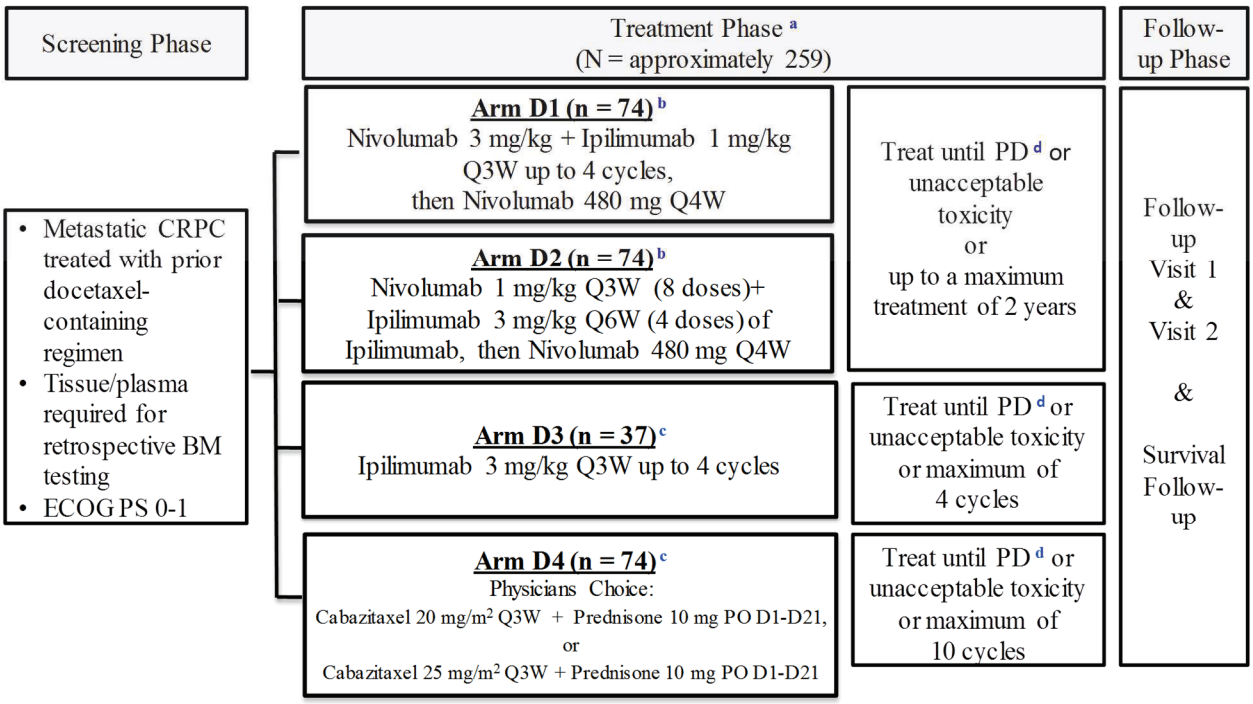
Nivolumab monotherapy in Arms D1 and D2 may continue until progression of disease, unacceptable toxicity, 2 year maximum treatment duration, or subject withdrawal of consent.

Furthermore, subjects from these Arms D1 and D2 who entered the maintenance period may be permitted re-induction with the combination upon PSA progression or radiographic progression (whichever occurs first) and after approval by the BMS medical monitor.

Subjects treated in Arms D3 and D4 who demonstrate radiographic progression on or after treatment may be eligible to receive optional crossover nivolumab in combination with ipilimumab (Arm D1) upon BICR confirmed radiographic progression if their case is reviewed with and approved by the BMS Medical Monitor.

The aim of Cohort D is to select a combination immunotherapy regimen with optimal benefit/risk profile [redacted].

Schema for Cohort D



Randomization 2:2:1:2
Stratification: measurable vs non-measurable disease

NOTES:

a. Subjects with investigator-assessed non-measurable disease at baseline will be capped when approximately 105 subjects are randomized.
b. Subjects in Arms D1 and D2 experiencing drug-related AEs with combination dose therapy that do not lead to study treatment discontinuation due to toxicity may proceed to nivolumab monotherapy dosing without completing all 4 combination cycles. Subjects who entered the maintenance period may be permitted re-induction with the combination after approval by the BMS medical monitor.
c. Subjects in Arms D3 and D4 who have BICR confirmed progression on or after treatment have the option to crossover to Arm D1 after approval by the BMS medical monitor
d. Radiographic progression per RECIST 1.1 or PCWG2 (Section 5.5.3). Treatment beyond investigator-assessed RECIST 1.1-defined progression may be considered for subjects meeting criteria according to Section 4.5.4

In accordance with Revised Protocol 03, additional subjects who have progressed after prior docetaxel-containing regimen will be enrolled into Cohort D.

Interim reviews of safety and efficacy data will be performed on all subjects receiving IO therapy by the Sponsor and participating investigators from the Study Steering Committee for Cohort D after the first 15 treated subjects for each cohort/arm have at least 8 weeks of follow-up after first dose and at least one post-baseline tumor assessment. This interim review will be used to evaluate early severe toxicity events and early disease control at Week 8 in order to provide information regarding safety and futility to make decisions about whether to continue patient accrual onto the study.

Study Population:

Key Inclusion Criteria: (see Protocol Section 3.3.1 for full list of criteria)

- Men, 18 years or older with histologic confirmation of adenocarcinoma of the prostate and current evidence of metastatic disease documented by either bone lesions on radionuclide bone scan and/or soft tissue lesions on CT/MRI. Metastases may be in regional lymph nodes (N1 per AJCC staging criteria, 8th edition) and/or distant metastases (M1 per AJCC staging criteria, 8th edition).
  - Subjects whose disease spread is limited to regional pelvic lymph nodes (N1M0) must have a lymph node measuring at least 2 cm in short axis to be considered eligible.
- Ongoing androgen deprivation therapy (ADT) with a gonadotropin-releasing hormone (GnRH) analogue or bilateral orchiectomy (ie, surgical or medical castration) confirmed by testosterone level ≤ 1.73 nmol/L (50 ng/dL) at the screening visit
- Subjects with castrate levels of testosterone while receiving ADT with evidence of progressive disease within 6 months prior to screening defined by the Prostate Cancer Working Group (PCWG2) criteria (confirmed rise in prostate-specific antigen (PSA) with (i) soft tissue disease progression per RECIST 1.1 or (ii) bone disease progression by PCWG2 criteria or both (i) and (ii) are eligible for the study)
- mCRPC subjects will be enrolled in the following cohorts as follows:
  - **Cohort A**: Subjects with asymptomatic or minimally symptomatic mCPRC who have not been treated with and are unable or unwilling to receive second generation hormone therapies or cytotoxic chemotherapy. **Enrollment discontinued per Revised Protocol 02**.
  - **Cohort B**: Subjects with asymptomatic or minimally symptomatic mCPRC who have progressed after second generation hormone therapies and have not been treated with cytotoxic chemotherapy.
  - **Cohort C**: Subjects must have progressed after prior taxane-based cytotoxic chemotherapy in the mCRPC setting.
  - **Cohort D**: Subjects must have progressed after prior docetaxel-containing regimen. Cohort D will contain 4 treatments arms, as previously described.
- Subjects already on agents for the management of skeletal-related events (SREs) are allowed to continue with anti-bone resorptive therapy that was initiated more than 28 days prior to study treatment
- Sufficient tumor samples from either a fresh biopsy (collected during screening period) or archival tumor tissue in the form of formalin-fixed paraffin-embedded [FFPE] block or a minimum of 15 unstained tumor tissue slides. Archival tumor samples must be obtained within 1 year prior to enrollment date, either from a metastatic tumor lesion (preferred) or from a primary tumor lesion that has not been previously irradiated. Tumor samples collected more than 1 year prior to enrollment date may be acceptable if obtained in the metastatic setting and following discussion with and approval by the BMS Medical Monitor/designee. Tumor sample may be from core biopsy, punch biopsy, excisional biopsy, or surgical specimen). Fine needle aspiration is unacceptable for submission. [redacted] Central laboratory must confirm receipt of tumor samples prior to randomization.

Key Exclusion Criteria: (see Protocol Section 3.3.2 for full list of criteria)

- Visceral metastases in the liver
- Active brain metastases or leptomeningeal metastases
- Ongoing systemic treatment with either corticosteroids or other immunosuppressive medications within 14 days of start of study therapy
- Less than 1 month since resolution of ≥ Grade 2 toxicity related to pelvic-targeted therapy (eg, radiation enteritis)
- 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, superficial bladder cancer, or carcinoma in situ of the breast
- Prior I-O agents (ie, any antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways)
- Prior radiation therapy within 14 days prior to starting study therapy. Any toxicity related to prior radiation therapy must have resolved to Grade ≤ 1 or baseline prior to starting study therapy.

Study Treatment: includes both Investigational [Medicinal] Products (IP/IMP) and Non-investigational [Medicinal] Products (Non-IP/Non-IMP) as listed:

Study Treatment for CA209650		
Medication	**Potency**	**IP/Non-IP**
Nivolumab BMS-936558 Solution for Injection	100 mg (10 mg/mL) or 40 mg (10 mg/mL)	IP
Ipilimumab	200 mg (5 mg/mL)	IP
Ipilimumab	50 mg (5 mg/mL)	IP
Cabazitaxel	60 mg	IP
Prednisone	5 mg	Non-IP

Key Study Assessments:

- Adverse Events will be collected to determine the incidence of drug-related adverse events in each cohort
- Subjects will be assessed by computer tomography (CT) or magnetic resonance imaging (MRI) and radionuclide bone scans at baseline and on-treatment beginning Week 8 (± 7 days) from first dose of study therapy and continuing every 8 weeks (± 7 days) for the first 6 months and then every 12 weeks (± 7 days) weeks until disease progression
- Patient-reported outcomes will be collected using the EQ-5D-3L, FACT-P, and BPI-SF. See Section 5.8 for assessment for Cohorts A, B, C, and D.

Statistical Considerations:

Sample Size:

Study Design (Cohorts A, B, and C) Approximately 90 subjects with mCRPC will be enrolled and treated in 2 cohorts, subjects who must have progressed after second-generation hormone therapies but have not received cytotoxic chemotherapy, and subjects who have progressed following cytotoxic chemotherapy (Cohorts B and C, respectively). Each cohort will consist of 30 or more subjects with measurable disease at baseline per RECIST v1.1 and no more than 15 with non-measurable disease.

This open-label Phase 2 study is not designed to statistically test specific hypotheses. Therefore the sample size is not based on statistical power calculations, but the size in each cohort is calculated using the observed objective response rate among treated subjects with measurable disease at baseline.

Study Design for Cohort D: Approximately 259 subjects with mCRPC, previously treated with docetaxel, will be randomized and treated in Cohort D. These 259 subjects will be randomized between 4 arms in a 2:2:1:2 ratio (74, 74, 37, and 74 subjects in Arms D1, D2, D3, and D4, respectively) and stratified by presence/absence of measurable disease by RECIST v1.1 per investigator assessment at study entry to ensure treatment arms are balanced. Subjects with non-measurable disease at baseline by RECIST v1.1 per investigator assessment will be capped when approximately 105 subjects are randomized so that the remaining 154 subjects (44, 44, 22, and 44 subjects in Arms D1, D2, D3, and D4, respectively) will have measurable disease at baseline.

Cohort D will evaluate the above immunotherapy regimens and the standard of care comparator cabazitaxel in unselected mCRPC patients. [redacted]

Endpoints:

The dual primary endpoints are Objective Response Rate (ORR) and radiographic Progression-Free Survival (rPFS) by BICR (BICR assessment will be performed retrospectively in Cohorts B and C, and prospectively in Cohort D).

The secondary endpoints are Radiographic/Clinical Progression-Free Survival (rcPFS), Overall Survival (OS), PSA response rate (PSA-RR), overall safety and tolerability, changes in pain (measured by BPI-SF), changes in disease-related symptoms and quality of life (measured by the FACT-P), and changes in health status and utility (measured by EQ-5D-3L).

Statistical Analyses:

For Cohorts B and C, all efficacy analyses will be performed by cohort as applicable to either (i) subjects with investigator-assessed measurable disease by RECIST v1.1 and/or (ii) total number of subjects within each cohort. All efficacy data for treated subjects in Cohort A, if any, will be listed. For Cohort D, efficacy analysis will be performed by treatment arm for all randomized subjects.

For the dual primary endpoint of ORR, estimated rates and corresponding 95% exact confidence intervals (CIs) will be calculated using the Clopper-Pearson method for all treated subjects with measurable disease at baseline per RECIST v1.1 in Cohorts B and C and for all randomized subjects with measurable disease at baseline per RECIST v1.1 as entered in IWRS in Cohort D. In Cohorts B and C, estimated odds ratios and differences and corresponding 95% CIs between cohorts will be calculated for descriptive purpose. In Cohort D, sensitivity analysis of ORR may also be performed for all randomized subjects with measurable disease at baseline as entered in the CRF if the discrepancy rate is higher than 5%.

For time to event endpoints (eg, dual primary endpoint of rPFS, and secondary endpoints of rcPFS and OS), medians and rates at months 6 and 12 and corresponding 95% CIs will be estimated for each cohort via the Kaplan-Meier methodology for all treated subjects in Cohorts B and C, and similar analyses will be done for each treatment arm for all randomized subjects in Cohort D. Kaplan-Meier plots will be presented for each cohort for Cohorts B and C; similarly, Kaplan-Meier plots will be displayed by treatment arm for all randomized subjects in Cohort D. Note that these analyses will be stratified by the stratification factor when these are conducted for Cohort D.

Estimate of PSA-RR and corresponding 2-sided exact 95% CI using the Clopper-Pearson method will be performed on all treated subjects with PSA values at baseline and at least one post-baseline assessment for Cohorts B and C; similar analysis will be done for each treatment arm in Cohort D with PSA values at baseline and at least one post-baseline assessment. Note that this analysis will be stratified by the stratification factor when conducted for Cohort D.

For all treated subjects with measurable disease at baseline in Cohorts B and C, [redacted] will be summarized by cohort for subjects with a BOR of PR or CR using the Kaplan-Meier methodology. Median values, along with two-sided 95% CIs will also be calculated. Summary statistics of [redacted] will be provided by cohort for subjects with a BOR of CR or PR. For all randomized subjects with measurable disease at baseline by RECIST v1.1 per investigator assessment as entered in IWRS in Cohort D, similar [redacted] and [redacted] analyses will be repeated by treatment arm.

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1 INTRODUCTION AND STUDY RATIONALE

CA209650 is a Phase 2, open-label study of the evaluation of efficacy, safety and tolerability of same day sequential dosing of nivolumab followed by ipilimumab, in subjects with metastatic castration resistant prostate cancer (mCRPC). Subjects with mCRPC, defined as castrate resistant prostate cancer and M1 metastatic disease on bone, CT and/or MRI scan per NCCN criteria[1], who are either asymptomatic or minimally symptomatic, will be evaluated in 3 cohorts as follows: (A) Subjects who have never received treatment either with cytotoxic chemotherapy or second-generation hormone therapies such as enzalutamide and/or abiraterone, (B) Subjects who have progressed after second-generation hormone therapies such as enzalutamide and/or abiraterone but have not been treated with cytotoxic chemotherapy (C) Subjects who have progressed after treatment with cytotoxic chemotherapy. Cohort A enrollment will be discontinued in Revised Protocol 02 due to slow accrual and to reflect the changing landscape of metastatic castration-resistant prostate cancer (Section 1.1.10, Addendum).

The study aims to demonstrate that treatment with nivolumab combined with ipilimumab will have clinical activity in subjects with mCRPC. Additional objectives of the study include further characterization of efficacy, safety and tolerability, determining changes in patient-reported outcomes for quality of life assessments and pain measures, as well as pharmacokinetics, [redacted].

In accordance with Revised Protocol 03, the study will enroll a new cohort of subjects (Cohort D) who have progressed after prior docetaxel-containing regimen. In Cohort D, subjects will be randomized to one of four open-label treatment arms including two new combination arms evaluating alternative nivolumab plus ipilimumab doses and schedules, one arm evaluating ipilimumab monotherapy, and one reference arm evaluating SOC treatment in this setting (cabazitaxel). The aim of Cohort D is to select a combination immunotherapy regimen with optimal benefit/risk profile [redacted].

1.1 Study Rationale

1.1.1 Disease Background

Prostate cancer is a leading cause of cancer mortality in men worldwide.[2] With an estimated incidence of 220,800 new cases and 27,540 deaths in 2015, prostate cancer is the most frequently diagnosed cancer and second most frequent cause of cancer deaths in US males.[3] In Europe prostate cancer was the third most common cancer in 2012, with 417,000 new cases and 92,000 deaths from prostate cancer being reported in that year.[4]

In 1941, Huggins and Hodges first noted the beneficial effects of castration and injection of estrogens in subjects with metastatic prostate cancer.[5] Over time, androgen deprivation therapy (ADT), defined as medical castration, became the cornerstone of treatment for subjects with metastatic disease, as well as for subjects with localized or locally advanced prostate cancers when administered as neoadjuvant, concomitant or adjuvant therapy in combination with radiation. While ADT results in disease remission in 90% of metastatic prostate cancer subjects evidenced

by a decline in levels of prostate-specific antigen (PSA),[6] most subjects become resistant with disease progression occurring within a median of 18–24 months of continuous hormonal manipulation.[7]

Prostate Cancer Working Group 2 (PCWG2)[8] categorizes the disease continuum of prostate cancer as a rising PSA state as non-castrate or castrate subjects, with either non-measurable disease or with distant metastases, on the basis of (i) whether the serum testosterone level is in the castrate range of ≤ 50 ng/dL by surgical orchiectomy or medical therapy with gonadotropin-releasing hormone analogs and anti-androgens and (ii) presence or absence of metastases detectable clinically or by imaging.[1] Metastatic castration resistant prostate cancer (mCRPC) is defined as subjects with confirmed castrate levels of testosterone following orchiectomy or treatment with ADT, and presence of distant soft tissue or bony metastases by NCCN criteria.[1] Subjects with established metastatic CRPC (mCRPC) have a life expectancy in the range of 27 to 32 months.[9,10,11]

In 1996, mitoxantrone plus prednisone was approved for the treatment of subjects with mCRPC based on improvement in pain palliation.[12] In 2004, 2 Phase 3 studies (TAX327 and SWOG S9916) demonstrated that docetaxel- based regimens can improve overall survival of subjects with mCRPC.[13,14] However, docetaxel-based treatment is associated with clinically significant toxicities that greatly limit its use in the management of lower risk, asymptomatic and minimally symptomatic mCRPC subjects without visceral metastases.

Since 2010, six new therapeutic agents with diverse mechanisms of action have been added to the therapeutic armamentarium, five of which sipuleucel-T, cabazitaxel, abiraterone, enzalutamide, and radium-223, have been approved for the treatment of mCRPC based on improvement in median overall survival. While the availability of these new treatment options allows for tailoring therapy to patient characteristics such as presence or absence of symptoms, prior treatments, patient preferences and life expectancy, it is also recognized that none of these therapies result in durable clinical responses. Despite high initial response rates, remissions following second-generation hormone therapies are temporary[15] due to the occurrence of resistance mechanisms including androgen receptor reactivation.[16] At this time, with judicious sequencing and use of available new therapies, subjects with established metastatic CRPC (ie, without prior chemotherapy) have life expectancy in the range of 27 to 32 months.[9,10,11]Thus mCRPC remains a disease with a lethal outcome with the urgent need for treatment options that will provide durable disease control and long term survival.

1.1.2 Rationale for Immunotherapy in Castrate Resistant Prostate Cancer (CRPC)

Immunotherapy agents represent a promising approach for chemotherapy-free alternatives for the management of asymptomatic and minimally symptomatic CRPC subjects.

1) Like most types of cancer, prostate cancer develops in an immune-competent environment. Immune responses against prostate tumors are noted in the form of intratumoral leukocyte

infiltration and inflammatory pathway activation.[17] Evidence from animal models and human prostate cancer suggests that despite the presence of immune effector cells that recognize tumor antigens, these cells are actively tolerized and become incapable of mediating tumor destruction.[18] The induction of regulatory or suppressor T cells[19] with increased CD4+CD25+ and CD8+Foxp3+ regulatory T cells (Treg) detected both within prostate glands and in the peripheral blood of prostate cancer subjects, suggests the presence of active immune suppression of antitumor immunity.[20,21]

These lines of evidence support targeting the immune system itself via activation of T cells and overcoming T-cell tolerance, to result in durable antitumor activity in prostate cancer.

2) The inherent characteristics of prostate cancer also make it an ideal target for immunotherapy. Prostate cancer is generally considered a slow-growing-tumor, which may allow adequate time for an immunotherapy agent to activate the immune system.

   Furthermore, prostate cancer has many well-described tumor-associated antigens (TAAs), which may be ideal targets for immunotherapy such as vaccines because they are specific to the cancer. Examples of TAA for prostate cancer include PSA, prostatic acid phosphatase (PAP), and prostate-specific membrane antigen (PSMA). This has led to the evaluation of therapeutic cancer vaccines designed to break immune tolerance[22] being explored in subjects with early CRPC, ie, before chemotherapy, with vaccines of autologous origin,[23] poxvirus,[24] and PSA TRICOM.[25]

   Prostvac (developed by the National Cancer Institute and licensed to BN Immunotherapeutics, Mountain View, CA), is a prostate cancer vaccine consisting of a recombinant vaccinia vector as a primary vaccination, engineered to express prostate-specific antigen (PSA) and a triad of human T-cell costimulatory molecules (designated TRICOM). A multicenter randomized phase II study that randomized minimally symptomatic mCRPC subjects to Prostvac vs placebo showed preliminary evidence of improved overall survival.[26] The IMPACT study evaluated Sipuleucel-T (Dendreon Corp., Seattle, WA) an autologous vaccine vs. placebo in chemotherapy-naïve CRPC subjects and reported a 4.1 month survival improvement in asymptomatic or minimally symptomatic CRPC subjects.[27] While these preliminary data show little overall impact on delaying progression of disease, the reported benefits in overall survival may be considered "proof of concept" that immunotherapeutic agents can play an important role in treating advanced prostate cancer.[28]

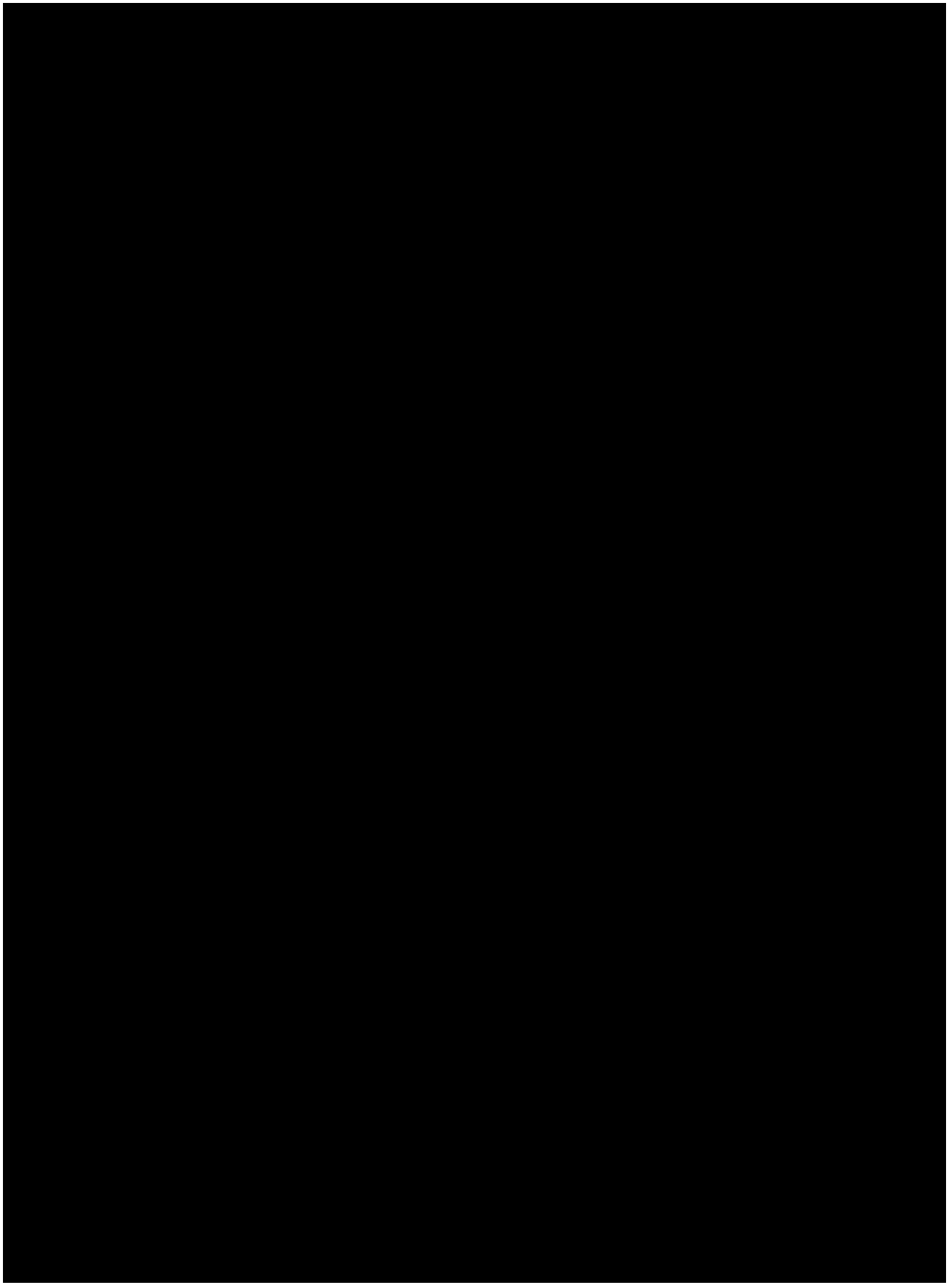
   While antigen-specific therapies such as vaccines have shown evidence of potential for benefit in the clinic, this approach has many limitations,[29,30,31,32] underscoring the need to explore immunotherapy that does not rely mainly on the expression of a specific antigen.

3) Androgen-deprivation therapy (ADT), a mainstay of treatment for both high-risk early prostate cancer and recurrent and/or metastatic disease, has been shown to alter the immune environment in prostate cancer.[33] For example, neoadjuvant ADT of prostate cancer subjects results in increased numbers of infiltrating CD4 T cells, CD8 T cells, natural killer cells, and macrophages in prostate tissues.[34,35] Mouse models have shown that ADT increases the

number of T cells in peripheral lymphoid tissues and prostate glands, enhances T-cell proliferation to antigen, promotes recovery of T- and B-cell populations following chemotherapy[36] and mitigates tolerance of prostate-specific CD4 T cells. Furthermore, ADT has also been shown to reverse age-related thymic atrophy in mice and to restore thymic T-cell output in both mice and prostate cancer subjects.[37]

Immunotherapy agents in conjunction with standard of care therapy ie, ADT could potentially result in increasing immune-mediated anti-tumor activity in subjects with prostate cancer.

Taken together, these lines of evidence strongly support the continued investigation of immunotherapy agents to improve outcomes in mCRPC. Accordingly, alternate approaches aimed at targeting the immune system itself to result in durable antitumor activity, including evaluation of combination checkpoint blockade inhibition, are warranted.



[redacted]

1.1.4 Rationale for Nivolumab and Ipilimumab in Prostate Cancer

(i) Ipilimumab in prostate cancer:

Due to its potentially broad mechanism of action, ipilimumab has been investigated in several other solid tumor settings, including mCRPC. In fact, the first in-human study of ipilimumab was in prostate cancer: an investigation of a single 3 mg/kg dose of ipilimumab in 14 subjects with CRPC.[42] Ipilimumab as a single dose had acceptable pharmacokinetic and safety profiles, but only two of the 14 subjects experienced PSA declines of > 50%. Results have since been reported for six other clinical studies of ipilimumab in mCRPC[42]. Together, these seven trials encompassed 240 subjects across multiple settings of advanced CRPC, roughly 20% of whom had progressed on or relapsed after docetaxel.[43] These studies utilized multiple doses (ranging from 0.5 to 10 mg/kg as either monotherapy or in combination studies) and schedules (ranging from a single dose of ipilimumab to recurring doses every 3 weeks for four cycles) and demonstrated the clinical activity of ipilimumab 3, 5 and 10 mg/kg, defined as PSA response, in the treatment of mCRPC (Table 1.1.4-1) whether used as monotherapy,[42] with ADT [44] or with other interventions such as radiotherapy,[45] or other immunotherapeutics with different mechanisms of action.[46,47,48,49] In 3 studies which included ipilimumab monotherapy at 3 mg/kg in mCRPC, PSA responses were observed in 6 of 44 evaluable patients (13.6%). In one study which included ipilimumab monotherapy at 10 mg/kg, PSA responses were observed in 4 of 16 patients (25%).

Table 1.1.4-1: Phase 1/2 Studies with Ipilimumab in Prostate Cancer

Protocol	Population	Combination	Subjects Treated/Target	PSA Response	PSA Response Rate (%)
MDX010-21 (CA184017)	Docetaxel failure and docetaxel eligible	Monotherapy and single-dose radiation combination	3 mg/kg: 8/6	2	13/70 evaluable (18.6%)
			5 mg/kg: 6/6	1	
			10 mg/kg:16/16	4	
			3 mg/kg + RT: 6/6	2	
			10 mg/kg + RT: 34/34	4	
MDX010-17 (CA184119)	Docetaxel eligible	GVAX (CellGenesys)	< 3 mg/kg: 6/6		5/28 (18%)
			3 mg/kg: 19/19	3	
			5 mg/kg: 3/3	2	
CTEP 7207[a] (CA184066)	Docetaxel failure and docetaxel eligible	Prostavac (fixed dose)	1 mg/kg: 3/3		5/28 (7%)
			3 mg/kg: 6/6	1	
			5 mg/kg: 6/6	3	
			10 mg/kg: 13/16	1	
CTEP 6032 (CA184067)	Docetaxel eligible	GM-CSF (on Days 1-14)	< 3 mg/kg: 15/15 3 mg/kg: 9/9 5 mg/kg: 5/6 10 mg/kg: 1/16	3	3/30 (10%)
MDX010-01 (CA184009)	Metastatic HRPC	Monotherapy	3 mg/kg: 14/14	2	2/14 (14%)
MDX010-07 (CA184019)	Docetaxel eligible	Docetaxel	3 mg/kg alone: 24/20	2	3/42 evaluable (7%)
			3 mg/kg + docetaxel: 20/20	1	
		HRPC (subtotal)	190/225	31	16%
MDX010-06 (CA184118)	Unresectable PC (< 90 days prior hormonal Rx)	3 months androgen ablative therapy	3 mg/kg: 50/108	11	11/50 (22%)
		Total Subjects	240/333	44	17%

[a] Ongoing accrual

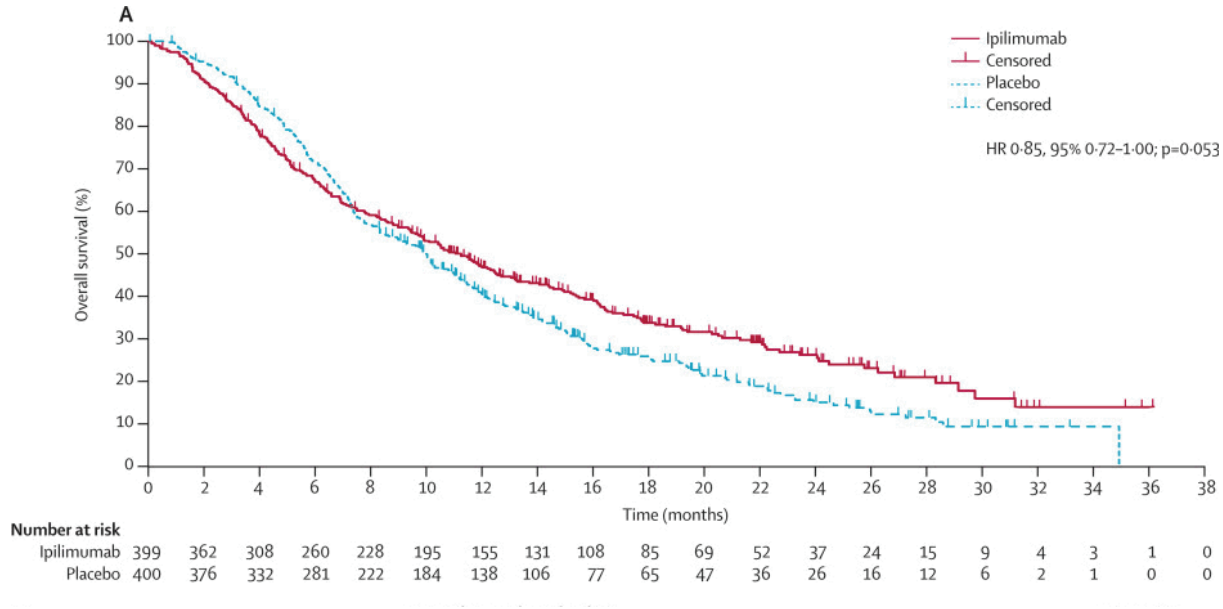
Two Phase 3 Studies (CA184043 and CA184095) carried out subsequently have failed to show a clear-cut survival advantage for ipilimumab (10 mg/kg) over placebo. An updated, double-blind, randomized Phase 3 study in subjects with mCRPC who had received prior treatment with docetaxel for their disease, did not meet its primary endpoint of demonstrating a statistically significant prolongation of survival for the ipilimumab group compared with the placebo group. No difference in overall survival was noted between subjects who received ipilimumab and those who received placebo after bone-directed radiotherapy.[50] However, the assessment of the proportional hazards assumption showed that it was violated (p=0.0031) in the primary analysis. A piecewise hazard model showed that the HR changed over time: the HR for 0–5 months was 1.46 (95% CI 1.10–1.95), for 5–12 months was 0.65 (0.50–0.85), and beyond 12 months was 0.60 (0.43–0.86). Kaplan-Meier (K-M) survival curves show the ipilimumab group to be below the placebo group through approximately Month 8, after which time the K-M survival curves crossed, and the ipilimumab group remained above the placebo group for the remainder of the follow-up phase (See Figure 1.1.4-1). In addition, ipilimumab was associated with reductions in PSA concentration (13.1% [95% CI.9·5–17.5] for ipilimumab and 5.2% [3.0–8.4] for placebo) and an improvement in PFS compared with placebo (median 4.0 [95% CI 3.6–4.3] vs 3.1 [2.9–3.4] months; HR 0.70, 95% CI 0.61–0.82; p<0.0001). PFS was a composite endpoint based on confirmed PSA progression, confirmed radiological progression, clinical deterioration, or death. A long-term survival analysis with 2-years of additional follow-up from the primary analysis of the CA184-043 study showed that survival significantly favored the ipilimumab arm (HR =0.83 (95% CI: 0.71-0.96); p=0.013).[51] Landmark OS rates in the ipilimumab and placebo arms were 15.3% (95% CI: 11.7, 18.9) versus 7.9% (95% CI: 5.2, 10.6) at 3 years, 10.1% (95% CI: 6.9, 13.3) vs. 3.3% (95% CI: 1.3, 5.3) at 4 years, and 7.9% (95% CI: 4.4, 11.4) vs. 2.7% (95% CI: 0.8, 4.7) at 5 years. There were 49/399 long-term survivors in the ipilimumab arm and 29/400 in the placebo arm.

Similarly, study CA184095 a double-blind, randomized Phase 3 study in subjects with asymptomatic or minimally symptomatic, chemotherapy-naïve, mCRPC with no known visceral metastases did not meet its primary endpoint based on intent-to-treat analysis (HR 1.11; 95.87% CI: 0.88, 1.39; P value = 0.3667) for OS. However, treatment with ipilimumab was associated with longer median PFS (defined as time to confirmed PSA or radiological progression, clinical deterioration, or death) in the ipilimumab group (5.6 months) versus the placebo group (3.8 months, HR, 0.67; 95.87% CI, 0.55 to 0.81), longer median time to non-hormonal cytoxic chemotherapy (HR, 0.65; 95.87% CI, 0.52 to 0.83) and to docetaxel therapy (HR, 0.70; 95% CI, 0.55 to 0.88) in the ipilimumab arm versus placebo. In addition, a higher PSA response rate was observed with ipilimumab (23%; 95% CI, 19% to 27%) compared to placebo (8%, 95% CI, 5% to 13%).

Given the improved tolerability of ipilimumab 3 mg/kg compared to 10 mg/kg and the clinical activity observed at the 3 mg/kg dose, the current study will assess ipilimumab 3 mg/kg in Arm D3 [redacted] with the aim of identifying a subset of men with CRPC who may benefit from ipilimumab treatment. Arm D3

also aims to characterize the contribution of ipilimumab to the nivolumab + ipilimumab combinations evaluated in this study.

Figure 1.1.4-1: Kaplan-Meier Plot of Overall Survival -Randomized Subjects



(ii) PD-1/PD-L1 pathway in Prostate cancer

Prostate cancer has been shown to have low tumor expression of PD-L1.[52] However, in a study evaluating human prostate cancer cell lines for PD-L1 expression and loss of phosphatase and tensin homolog (PTEN) by flow cytometry and western blotting, many prostate cancer cell lines upregulated PD-L1 expression in response to inflammatory cytokines in vitro, consistent with adaptive immune resistance. In these cell lines, no association between PTEN loss and PD-L1 expression was apparent. In primary prostate tumors, PD-L1 expression was rare, and was not associated with PTEN loss suggesting that innate immune resistance was not a likely mechanism of immune resistance as a mechanism resulting in decreased antitumor immune responses in prostate cancer (as opposed to an adaptive immune resistance response mechanisms (refer to Section 1.1.2).[53] Furthermore, an analysis of the prognostic significance of PD-1 and/or PD-L1 expression in a cohort of 535 prostate cancer tumors showed that a high density of PD-1+ lymphocytes independently predicted shorter clinical failure-free survival.[54] This may indicate that tumor immune escape, and thus tumor immune elimination, are important mechanisms in prostate cancer, and the association of pathway molecules with poor prognosis makes them attractive targets for inhibition.

Nivolumab monotherapy was evaluated in a cohort of 17 subjects with mCRPC.[55] All subjects with mCRPC were treated with nivolumab 10 mg/kg, and no objective responses were observed. One out of 10 subjects evaluable for PSA response demonstrated a PSA reduction ≥ 50% from

baseline. Prostate tumor samples were available in 2 subjects with mCRPC, and tumor PD-L1 expression was 0% in both subjects.

Other anti-PD-(L)1 inhibitors have also demonstrated limited clinical activity in mCRPC. Atezolizumab monotherapy was evaluated in a phase 1a study, including 15 heavily pretreated subjects with mCRPC.[56] There were no objective responses per RECIST v1.1, although 1 subject had a PR per immune-related response criteria (irRC). Analysis of tumor tissue in this subject revealed no PD-L1 IHC expression at baseline but did demonstrate an ATM mutation, a component of the DNA damage response pathway.

Pembrolizumab was recently evaluated in a phase 2 study of mCRPC patients previously treated with docetaxel.[57] Among those with measurable disease, ORR was 3% and 5% in PD-L1 negative (n=67) and positive (n=131) patients, respectively. PSA responses were observed in 11% of evaluable patients (n = 193). Among 19 patients with somatic aberrations in BRCA1/2 or ATM, ORR was 11%, suggesting that DNA repair defects may be associated with anti-tumor activity. In conclusion, single-agent PD-(L)1 inhibitors appear to have limited anti-tumor activity in mCRPC.

(iii) Role for dual checkpoint blockade inhibition: (anti-CTLA4 and anti-PD-1) in prostate cancer

Consistent with the above pre-clinical data, it has been observed that ipilimumab induces an adaptive immune response within the prostate tumor microenvironment.[58] In a clinical trial, subjects with localized prostate cancer who were treated with ADT plus 2 doses of anti-CTLA4 antibody (ipilimumab) observed an increased frequency of CD4 and CD8 T cell infiltration into tumor tissues. Treatment with ipilimumab also led to increased expression of PD-1 and PD-L1 (on both immune and epithelial cells).[58] Of particular interest was the finding that PD-L1 expression in the tumor microenvironment co-localized with CD8 T cells in prostate tumors after ipilimumab treatment. Since CD8 T cells are the key effector immune cells that mediate tumor rejection, it is possible that increased expression of PD-L1, as well as PD-1, occurs on T cells as a critical mechanism to suppress T cell responses in tissues, resulting in tumor growth. These results are consistent with recent reports that CD8 T cells and PD-L1 expression are co-localized in the melanoma tumor microenvironment.[59,60]

In summary, while treatment with ipilimumab resulted in expected immune augmentation, it was also associated with the induction of immune inhibitory PD-1/PD-L1 pathway, providing perhaps a potential explanation as to why a significant proportion of subjects with prostate cancer did not benefit from treatment with ipilimumab or nivolumab as monotherapy. Accordingly, utilizing a combination checkpoint blockade inhibition approach with anti-CTLA-4 and anti-PD-1 agents may be necessary to boost anti-tumor activity for maximum clinical benefit in prostate cancer.

Combination of nivolumab 1 mg/kg plus ipilimumab 3 mg/kg Q3W for up to 4 doses, followed by nivolumab 480 mg every 4 weeks has been evaluated in Cohorts B and C of this study. A safety and efficacy analysis (Database lock date 03-Jul-2018) was conducted in all treated patients with at least 24 weeks of follow-up in Cohort B (n=33) and Cohort C (n=45). Among patients with baseline measurable disease, ORR was 26% in Cohort B and 10% in Cohort C. Among patients with measurable disease, 33 subjects had tumor samples that underwent whole exome sequencing

for HRD and TMB testing (TMB "high" and "low" represent above and below the median of 74.5 mutations per patient). ORR were higher in HRD positive (67% [2/3] in Cohort B and 50% [1/2] in Cohort C) compared to HRD negative patients (25% [4/16] in Cohort B and 17% [2/12] in Cohort C). Similarly, ORR was higher in TMB-high patients (60% [6/10] in Cohort B and 50% [3/6] in Cohort C) compared to TMB-low patients (0% in both Cohorts B and C). Confirmed/unconfirmed PSA decline ≥ 50% in patients with baseline and ≥ 1 post-baseline PSA result were 21% Cohort B and 15% in Cohort C.

Grade 3–4 treatment-related adverse events occurred in 39% and 51% of pts in cohorts B and C, respectively; one grade 5 event occurred in each cohort (sudden death in Cohort B and septic shock in Cohort C). Although the safety profile was consistent with studies in other malignancies using the same dosing schedule, early toxicity prevented the majority of patients from completing 4 combination doses.

Furthermore, combination of nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every 3 weeks for four doses, then maintenance nivolumab 3 mg/kg every 2 weeks was recently evaluated in 15 patients with AR-V7-positive mCRPC.[61] Overall, the PSA response rate was 2/15 (13%), ORR was 2/8 (25%) in those with measurable disease, median PSA-PFS was 3.0 (95% CI 2.1– NR) months, PFS was 3.7 (95%CI 2.8–7.5) months, and OS was 8.2 (95%CI 5.5– 10.4) months. Outcomes appeared generally better in DNA repair deficiency (DRD) + versus DRD– tumors with respect to PSA responses (33% vs. 0%; P=0.14), ORR (40% vs. 0%; P=0.46), PSA-PFS (HR 0.19; P<0.01), PFS (HR 0.31; p=0.01), and OS (HR 0.41; P=0.11). No new safety concerns were observed and the most common toxicities were fatigue, AST elevation, diarrhea and anorexia. Seventeen grade 3-4 adverse events occurred in 7 of 15 patients (46%). There were no treatment-related deaths.

Given that nivolumab in combination with ipilimumab appears to be active in patients with mCRPC and existing data have shown that anti-CTLA-4 therapy can enhance immune cell infiltration into prostate tumors and increase PD-L1 expression,[62] the addition of Cohort D in this study will explore two different dosing schedules of nivolumab in combination with ipilimumab to identify a dose combination which reduces toxicity and increases the potential clinical benefit from dual checkpoint inhibition. [redacted]

1.1.5 Rationale to Support Nivolumab plus Ipilimumab Dose and Schedule Selection for Cohorts A, B, and C

The nivolumab plus ipilimumab combination dosing regimen selected for evaluation in Cohorts A, B, and C of this study is nivolumab 1 mg/kg combined with ipilimumab 3 mg/kg administered every 3 weeks (Q3W) for 4 doses. The nivolumab plus ipilimumab combination dosing regimen will be followed by 480 mg flat dose of nivolumab every 4 weeks (Q4W) until progression of disease, unacceptable toxicity, or subject withdrawal of consent.

Multiple doses (ranging from 0.5 to 10 mg/kg as either monotherapy or in combination studies) and schedules (ranging from a single dose of ipilimumab to recurring doses every 3 weeks for four cycles) were evaluated in several Phase 1/2 trials of ipilimumab in CRPC.[43] Although efficacy

endpoints varied amongst the studies, ipilimumab showed clinical activity in CRPC with PSA responses (≥ 50% decline) across doses of 3, 5, and 10 mg/kg administered as monotherapy.[43] Declines in PSA were consistently noted (15–20%) at doses of ≥ 3 mg/kg with varying patterns of PSA response including at treatment onset, after a short period of stable disease, late responses after 6 months of treatment), as well as PSA responses observed after an initial PSA rise within 6 months.[43] All trials utilized the Prostate Cancer Working Group 2 (PCWG2) criteria.[63]

Exposure-response analysis of nivolumab monotherapy have been performed across dose ranges of 1 mg/kg to 10 mg/kg and show a relatively flat dose-response relationship for safety and efficacy in most tumor types evaluated (except for non-small cell lung cancer/NSCLC).[64] Minimum serum concentration after first dose (Cmin1) produced by 3 mg/kg nivolumab was not a significant predictor of probability of overall response in treatment refractory squamous non-small cell lung cancer (NSCLC), and advanced melanoma. Nivolumab steady state time-averaged concentration (Cavgss) was not a significant predictor of hazard of death in subjects with advanced RCC after accounting for the effect of nivolumab clearance (CL). Clinical prognostic factors such as sex, baseline Memorial Sloan-Kettering Cancer Center risk score, baseline Karnofsky performance status, and baseline weight, were significant predictors of OS in subjects with advanced RCC. The risk of time to first Grade 3+ drug-related AEs and AEs leading to discontinuation did not increase with Cavgss produced by doses ranging from 0.1 to 10 mg/kg nivolumab, and at 3 mg/kg dose in advanced melanoma. (Subjects with NSCLC appeared to have a higher risk of AEs leading to discontinuation than subjects with other tumor types including melanoma).[64]

Exposure-response relationships of ipilimumab monotherapy for efficacy (ie, overall survival, OS) and safety (ie, immune-related adverse events, irAEs) were characterized using data from 4 Phase 2 studies (CA184004, CA184007, CA184008, and CA184022) and 1 Phase 3 study (CA184024) in subjects with advanced melanoma.[65] In contrast to nivolumab, OS increased with increasing ipilimumab steady state trough concentration (Cminss) over the range of exposures achieved with both the 3- and 10-mg/kg doses.[66] Exposure-response analysis of escalating doses (0.3 mg/kg, 3 mg/kg, and 10 mg/kg) of ipilimumab monotherapy have demonstrated increasing activity with increase in dose in the phase 2 study CA184022.[67] The probability of experiencing Grade ≥ 2 and ≥ 3 irAEs also increased with increasing ipilimumab Cminss.[65]

Hence, to balance the concern of potential toxicity due to the combination of 2 checkpoint inhibitors, the lowest clinically active ipilimumab dose of 3 mg/kg was chosen in combination with nivolumab dose of 1 mg/kg (given the somewhat flat dose-response relationship noted with nivolumab across the dose range of 1 to 10 mg/kg). Accordingly nivolumab 1 mg/kg plus ipilimumab 3 mg/kg will be evaluated within 2 cohorts of metastatic castration-resistant metastatic prostate cancer subjects (mCRPC).

1.1.6 Rationale to Support Dose and Schedule Selection in Cohort D

Three additional immunotherapy arms will be explored in Cohort D including two different nivolumab and ipilimumab combination regimens and ipilimumab monotherapy arm. The combination regimens were selected with the objective to improve the tolerability profile and to

maintain or improve the efficacy observed from preliminary results from Cohorts B and C. The inclusion of the ipilimumab monotherapy arm will support assessment of the contribution of ipilimumab to the nivolumab + ipilimumab combination, particularly in biomarker-defined sub-groups which were not evaluated in prior ipilimumab studies in mCRPC.

1.1.6.1 Arm D1 Rationale for Combination Regimen (nivolumab 3 mg/kg plus ipilimumab 1 mg/kg)

The combination regimen is nivolumab 3mg/kg plus ipilimumab 1 mg/kg given every three weeks (Q3W) (N3I1) for up to 4 cycles, followed by nivolumab 480 mg every four weeks (Q4W) starting three weeks after the last combination dose for up to 2 years or until disease progression. This combination regimen is currently approved in the US to treat 1L RCC and MSI-High or dMMR mCRC.[68] The nivolumab dose is higher and the ipilimumab dose is lower in this regimen compared to the regimen evaluated in Cohorts A, B, and C, and has shown activity in AR-V7 mCRPC,[69] with a manageable safety profile as described in Section 1.1.4. Further support for the N3I1 regimen having an improved safety profile comes from the metastatic RCC setting in study CA209016 [redacted] and the metastatic melanoma setting, where the safety profile of N3I1 Q3W and N1I3 Q3W, followed by 480 mg Q4W nivolumab maintenance were compared in clinical study CA209511.[70] N3I1 demonstrated a reduced rate of drug-related Grade 3-4 AEs compared with N1I3, with rates of 33.3 % (60/180) and 48.3% (86/178), respectively.

1.1.6.2 Arm D2 Rationale for Combination Regimen (nivolumab 1mg/kg Q3W (8 Doses) plus ipilimumab 3 mg/kg Q6W (4 Doses)

The combination regimen is nivolumab 1 mg/kg every 3 weeks plus ipilimumab 3 mg/kg every 2 cycles (ie, every 6 weeks) for up to 4 ipilimumab doses, followed by nivolumab 480 mg every 4 weeks, starting six weeks after the last ipilimumab combination dose for up to 2 years or until disease progression. This combination regimen maintains the nivolumab and ipilimumab dose to that of the regimen in Cohorts A, B, and C, but lowers the ipilimumab time-averaged concentration (Cavgss) by ~ 2-fold by extending the dosing interval from Q3W to Q6W. A prior clinical study in advanced NSCLC (CA209012) supports the rationale to decrease ipilimumab dosing frequency to improve tolerability, while maintaining efficacy. Promising clinical activity with a favorable safety profile was observed in cohort P (nivolumab 3 mg/kg Q2W+ ipilimumab 1 mg/kg Q12W, ORR 47.4 % [18/38]) and cohort Q (nivolumab 3 mg/kg Q2W+ ipilimumab 1 mg/kg Q6W, ORR 38.5 % [15/39]) in CA209-012. A notable improvement in drug-related AEs leading to discontinuation was observed in cohorts P (15.8%, 6/38) and Q (17.9%, 7/39) compared to the combination nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W for 4 cycles, followed by nivolumab 3 mg/kg Q2W (40%, 10/25).[71]

1.1.6.3 Arm D3 Rationale for Ipilimumab 3 mg/kg Q3W

The ipilimumab monotherapy arm will be dosed at 3 mg/kg Q3W for 4 cycles with no maintenance dosing. This is the approved ipilimumab dose for metastatic melanoma and, as described in Section 1.1.4 above, has shown some clinical activity as measured by PSA response in prior studies where ipilimumab monotherapy at this dose was evaluated in mCRPC (CA184009, CA184019, and CA184017). Arm D3 will provide an estimation of the relative benefit of the

combination regimens evaluated in Arms D1 and D2 compared to ipilimumab alone. [redacted]

1.1.6.4 Arm D4 Rationale for Cabazitaxel in Prostate Cancer

Taxanes bind microtubules, promoting their stabilization and preventing cellular mitosis and division. Additionally, taxanes inhibit androgen receptor (AR) signaling by binding cellular microtubules and the microtubule-associated motor protein dynein, and consequently preventing AR nuclear translocation.[72] Docetaxel, a second-generation semisynthetic taxane analog, became the first chemotherapeutic agent to show an OS benefit in mCRPC in two randomized controlled clinical trials (TAX 327[73] and SWOG 99-16[74]), and was approved in combination with prednisone for this indication in the US in 2004.

Cabazitaxel is another taxane-based chemotherapy that was approved by the FDA in 2010 for patients with mCRPC previously treated with docetaxel.[75] Cabazitaxel retains significant cytotoxicity in docetaxel-resistant cell lines due to p-glycoprotein 1 (gp-1) overexpression. Another attractive property of cabazitaxel is its enhanced solubility in water-based solutions compared with other taxanes, enabling better blood–brain barrier penetration, resulting in higher central nervous system drug concentrations with systemic administration in mouse models. In the TROPIC study, 755 men with mCRPC who previously received docetaxel chemotherapy were randomized to receive either cabazitaxel 25 mg/ m^2 (n = 378) or mitoxantrone 12 mg/m^2 (n = 377) every 3 weeks for a maximum of 10 cycles, concurrently with prednisone 10 mg daily.[76] At the first interim analysis, with a median follow up of 12.7 months, median overall survival was 15.1 months for the cabazitaxel group versus 12.7 months for the mitoxantrone group, corresponding to a 30% reduction in relative risk of death (hazard ratio 0.70, 95% confidence interval 0.59–0.83, p < 0·0001). Other clinical endpoints, including PSA response (39.2% v 17.8%, respectively; P < .001), PFS (2.8 v 1.4 months, respectively; P < .001), objective tumor response (14.4% vs 4.4% respectively; P < .001) and pain progression all favored the cabazitaxel treatment arm. The most common toxic effects of cabazitaxel were hematological; the most frequent hematological grade 3 or higher adverse events were neutropenia, leukopenia, and anemia. The most common non-hematological grade 3 or higher adverse event was diarrhea. Overall, peripheral neuropathy (all grades) was reported in 14% of patients, but G3 peripheral neuropathy was uncommon (1%). Peripheral edema (all grades) occurred in 9% of patients treated with cabazitaxel. An updated analysis 2 years after the original TROPIC data cutoff (March 2012) confirmed a sustained survival benefit with longer follow up, with cabazitaxel treatment being predictive of survival over 2 years.[77]

Randomization to a cabazitaxel arm in Cohort D is included as a reference for the immunotherapy arms in the cohort. [redacted].

Dosing of cabazitaxel in this study is based upon doses recommended in the current prescribing information. Please see prescribing information for this agent for more information.

1.1.7 Rationale for Shorter Infusion Times for Nivolumab and Ipilimumab

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 minutes' duration will diminish the burden, provided that there is no change in the safety profile. Previous clinical studies of nivolumab and ipilimumab monotherapies and the combination of nivolumab and ipilimumab have used a 60-minute infusion duration for nivolumab and a 90-minute infusion duration for ipilimumab (1 - 3 mg/kg dosing for both). However, both nivolumab and ipilimumab have been administered at up to 10 mg/kg with the same infusion duration (ie, 60 minutes).

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 subjects 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 subject (1.4%) in the 0.3 mg/kg and in 2 subjects (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 subjects. Administering 3 mg/kg of ipilimumab represents approximately one-third of the 10 mg/kg dose.

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.

1.1.8 Rationale for Flat Dose 480 mg Nivolumab every 4 weeks (Nivolumab Monotherapy Phase)

Nivolumab monotherapy has been extensively studied in a number of tumor types including non-small cell lung cancer (NSCLC), melanoma, renal cell carcinoma (RCC), and colorectal cancer (CRC) with body weight normalized dosing (mg/kg). Nivolumab pharmacokinetics (PK) and exposures of subjects 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 subjects, relative to the exposures in lighter subjects.

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 subjects. A dose of 240 mg nivolumab is identical to a dose of 3 mg/kg for subjects weighing ~ 80 kg, which is the approximate median body weight of subjects 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 subjects 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, subjects will receive flat dose 480 mg nivolumab every 4 weeks (Q4W), which provides a more convenient dosing regimen for subjects. Subjects Arm D1 will start nivolumab monotherapy 3 weeks after the last combination dose, while subjects in Arm D2 will start nivolumab monotherapy 6 weeks after the last combination dose.

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 of this study.

1.1.9 Rationale for Shorter Infusion Times with 480 mg Flat Dosing

Long infusion times place a burden on subjects and treatment centers. Establishing that nivolumab can be safely administered using shorter infusion times of 30 minutes duration in subjects 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 subjects 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-min infusion was assessed in CA209153 in subjects 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 subjects administered nivolumab over a 30 min infusion compared with that reported for subjects with the 60 min infusion. An infusion duration of 30 minutes for 1 mg/kg nivolumab and nivolumab 480 mg 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.

1.1.10 Rationale for Evaluating Chemotherapy-Naive, Second-Generation Hormone Therapy-Naive, Asymptomatic or Minimally Symptomatic Metastatic CPRC Subjects (Cohort A Subjects)

Docetaxel became the first approved therapy to prolong survival for men with mCRPC in 2004.[13,14] Subsequently, since 2010, six novel therapies have been shown to prolong survival in men with mCRPC.[78] The trials have demonstrated prolongation of overall survival as well as trends toward preserved quality of life (QoL), albeit less rigorously assessed and documented.[79] Of note, all these new therapies in mCRPC have distinct mechanisms of action and include unique classes of agents: novel androgen receptor (AR) pathway inhibitors abiraterone acetate (abiraterone) and enzalutamide as well as a bone targeting alpha-emitting radionuclide,

radium-223 chloride (radium-223), taxanes, docetaxel and cabazitaxel, and sipuleucel-T, an immunotherapeutic agent.

Of the six new therapies that have been approved since 2010 for mCRPC, sipuleucel-T has been tested predominantly (~85%) in chemotherapy-naïve men with mCRPC and showed no effect on response rates or progression free survival (PFS).[27] More recently, two second-generation hormone therapies, abiraterone acetate[10] and enzalutamide[9] targeting inhibition of the androgen receptor (AR) signaling pathway have been investigated and shown to prolong overall survival in large phase III trials in minimally symptomatic subjects in the pre- docetaxel states. See Table 1.1.10-1. Enzalutamide also extended time to radiographic progression and death as well as improved overall survival in men with mCRPC prior to receiving chemotherapy.[9] Delay in time to chemotherapy was also reported.[9] Similar to enzalutamide, abiraterone was also shown to delay radiographic progression and time to chemotherapy in men with mCRPC.[10] Despite the success of these second-generation AR-targeted therapies, inherent or acquired resistance remains a major clinical challenge and most subjects will progress.[80] Clinical data from a number of small retrospective cohort studies suggests that once subjects progress response rates to abiraterone after enzalutamide and conversely enzalutamide after abiraterone are low and no robust criteria exist clinically to select one drug rather than the other.[81,82] The presence of androgen receptor splice variants without the ligand-binding domain has been associated with resistance to abiraterone and enzalutamide and could be one explanation for this significant cross-resistance.[83] Docetaxel after one or both of newer AR pathway inhibitors may have less activity than in the pivotal trials.[84] Thus there is still an unmet need in mCRPC for treatment options that will provide durable disease control and long term survival.

Table 1.1.10-1: Summary of key data from sipuleucel-T, abiraterone acetate and enzalutamide registrational trials

Endpoints	Asymptomatic mCRPC (no liver mets) IMPACT trial (Sipuleucel-T)[27]	Asymptomatic or minimally symptomatic mCRPC[9] Enzalutamide pre-chemotherapy	Asymptomatic or minimally symptomatic mCRPC Abiraterone+prednisone pre-chemotherapy[10]
mOS	4.1 months (25.8 vs 21.7 mo, HR=0.78)	2.2 mo (32.4 vs 30.2 mo, HR=0.71)- study was stopped after a planned IA (rPFS/OS co-primary)	NR vs 27.2 mo, HR 0.75
m-rPFS	No difference vs placebo at 3.7 mo (vs3.6 mo)	At 12 mo f/u, rPFS rate= 65% vs 14%, HR=0.19; m-rPFS was not reached, 3.9 mo in placebo arm	16.5 mo vs 8.3 mo, HR =0.53
Objective soft tissue response	No difference vs placebo	59% vs 5%	36% vs 16%

While the successful registration of several drugs for mCRPC provided new options for treatment, they have also led to considerable uncertainty as to the best treatment choices, sequence of treatment options and appropriate patient selection with the achievement of durable, long term responses remaining an elusive goal.

In daily practice, clinicians often face the difficult task of choosing among treatment options with different mechanisms of action, administration and toxicity profiles and the desire to tailor novel treatment options to the specific needs of the individual mCRPC subjects.[85] The first St Gallen Advanced Prostate Cancer Consensus Conference (APCCC) Expert Panel reviewed the available evidence for the ten most important areas of controversy in advanced prostate cancer (APC) management to provide management recommendations based on expert opinion in these situations.[79] Of note, for subjects with mCRPC in the absence of symptoms and imminent complications, two-thirds of the APCCC panel recommended that agents with potential for survival prolongation should be initiated within 4–8 weeks.[79]

Although 2 Phase 3 studies of ipilimumab monotherapy in pre- and post-docetaxel mCRPC (CA184095 and CA184043, respectively) failed to show an overall survival advantage, additional analyses of outcome data from both studies are important to consider (See Section 1.1.10), given the understanding that (i) currently available therapies do not result in durable, long term remissions in mCRPC subjects and (ii) emerging data from other solid tumors that have been studied, notably, melanoma, the use of checkpoint blockade inhibition suggests the potential for prolonged duration of response with immunotherapy in a subset of subjects.[86]

As noted previously in Section 1.1.5, ipilimumab has been shown to induce an adaptive immune response within the prostate tumor microenvironment.[87] In a clinical trial, subjects with localized prostate cancer who were treated with ADT plus 2 doses of anti-CTLA4 antibody (ipilimumab) observed an increased frequency of CD4 and CD8 T cell infiltration into tumor tissues and increased expression of PD-1 and PD-L1 (on both immune and epithelial cells).[87] These findings suggest that while treatment with ipilimumab resulted in expected immune augmentation, it was also associated with the induction of immune inhibitory PD-1/PD-L1 pathway. These preliminary clinical data provide a potential explanation as to why a significant proportion of subjects with prostate cancer did not benefit from treatment with ipilimumab or nivolumab monotherapy. Accordingly, utilizing a combination checkpoint blockade inhibition approach, with anti-CTLA4 and anti-PD-1 antibodies may be necessary to augment T cell responses for greater anti-tumor activity in prostate cancer.

Taken together these data suggest that in mCRPC subjects the activity of ipilimumab monotherapy could potentially be strongly enhanced by the combination with another checkpoint inhibitor to result in durable anti-tumor responses. And asymptomatic or minimally symptomatic mCRPC subjects who are early on in the disease state of mCRPC may in fact be optimal candidates for the evaluation of combination of checkpoint blockade inhibitors, ipilimumab and nivolumab, with the possibility of achieving long term remission from disease.

Addendum:

Cohort A enrollment was discontinued in Revised Protocol 02 due to slow accrual and to reflect the changing landscape of metastatic castration-resistant prostate cancer.

Both enzalutamide and abiraterone are currently approved for the treatment of patients with mCRPC who have not received chemotherapy. These drugs, which have now become the standard of care in this setting, have a well-established safety profile and have demonstrated OS improvement and delay of radiographic disease progression and need for cytotoxic chemotherapy.[9],[10],[88] Furthermore, the addition of abiraterone to first-line ADT resulted in a significant improvement in OS in men with prostate cancer, according to recently reported results from the LATITUDE [89] and STAMPEDE [90] clinical trials. The abiraterone/prednisone/ADT arm had a 38% reduction in risk of death when compared to the control in the LATITUDE trial (OS: not reached vs. 34.7 months, HR: 0.62, 95% CI: 0.51-0.76; P<0.0001). The 3-year OS rate was 66% in the abiraterone arm versus 49% in the placebo arm. Overall survival benefit persisted across all of the pre-specified subgroups. In the Phase 3 STAMPEDE trial, ADT plus abiraterone and prednisolone was associated with significantly higher rates of overall survival (HR: 0.63, 95% CI: 0.52-0.76; P=0.001) and failure-free survival (HR: 0.29; 95% CI, 0.25 to 0.34; P<0.001) than ADT alone among men with locally advanced or metastatic prostate cancer.

Thus, the use of abiraterone is expected to continue expanding in earlier settings of the prostate cancer treatment landscape and eligibility criteria for participation in Cohort A are anticipated to be less relevant in future practice due to changes in standard of care.

This trial will now include 2 cohorts in mCRPC, Cohorts B and C, and the remainder of Cohort A subjects will be allocated to Arms B and C in order to have more precise efficacy estimates in those arms.

1.1.11 Rationale for Treatment Beyond PSA Elevation

For consistency of trial reporting, the PCWG2 defines PSA progression as the date that an increase of 25% or more and an absolute increase of 2 ng/mL or more from the nadir are documented.[8] For subjects who had an initial PSA decline during treatment, this must be confirmed by a second value 3 or more weeks later. However, PSA progression alone is not necessarily an indication to stop treatment, because in some cases, PSA levels may rise slowly or stabilize after an initial rise with no other sign of clinical progression.[91] Because there are cases in which additional years of disease control would not have been realized had therapy been stopped on the basis of PSA change alone, therapy will not be stopped for subjects with apparent PSA progression alone. However, subjects meeting criteria for discontinuation of therapy (Section 3.5) and PSA elevation will come off study.

1.1.12 Rationale for Optional Crossover Combination for Monotherapy Arms (Arm D3 and D4)

In some cancer types, combined blockade of both PD-1 and CTLA-4 has proven more efficacious than inhibition of either pathway alone. Furthermore, preliminary data with nivolumab in combination with ipilimumab have shown promising clinical activity in mCRPC

(see Section 1.1.4). Based on these data, this study will provide subjects who are randomized to the monotherapy Arms D3 and D4 the option to receive nivolumab in combination with ipilimumab in Arm D1 upon BICR-confirmed radiographic progression and provided that such crossover treatment is discussed with and approved by the BMS Medical Monitor.

1.1.13 Rationale for Duration of Treatment with Nivolumab plus Ipilimumab

The optimal duration of immunotherapy is an important question and continues to be investigated. Clinical trials across different tumors types in the nivolumab and ipilimumab development program indicate that most of the responses occur early, with a median time to response of 2-4 months, and emerging data suggests that benefit can be maintained in the absence of continued treatment. 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.[92] 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 around 2 years after the start of treatment.[93]

Accumulating data suggest that 2 years of PD-1 checkpoint inhibitor treatment may be sufficient for long term benefit. CA209003, a dose-escalation cohort expansion trial evaluating the safety and clinical activity of nivolumab in patients with previously treated advanced solid tumors (including 129 subjects with NSCLC), specified a maximum treatment duration of 2 years. Among 16 subjects with non-small cell lung cancer (NSCLC) who discontinued nivolumab after completing 2 years of treatment, 12 subjects were alive >5 years and remained progression-free without any subsequent therapy. In the CA209003 NSCLC cohort, the overall survival (OS) curve begins to plateau after 2 years, with an OS rate of 25% at 2 years and 18% at 3 years.[94].These survival outcomes are similar to phase 3 studies in previously treated NSCLC, in which nivolumab treatment was continued until progression or unacceptable toxicity (2 year OS rates of 23% and 29%, and 3 year OS rates of 16%-18% for squamous and non-squamous NSCLC respectively).[95]

Similar results have been reported in clinical studies of pembrolizumab, another PD-1 inhibitor. Keynote-010 was a randomized phase 3 trial of pembrolizumab (at either 2 mg/kg or 10 mg/kg every 3 weeks) versus docetaxel in subjects with previously treated, PD-L1-positive, advanced NSCLC which specified a maximum treatment duration of 2 years for pembrolizumab. OS was significantly longer with both pembrolizumab 2 mg/kg (HR 0.72, $p = 0.00017$) and pembrolizumab 10 mg/kg (HR 0.60, $p < 0.00001$) compared to docetaxel, with an OS plateau developing beyond 2 years in both pembrolizumab arms. Among 690 patients who received pembrolizumab, 47 patients completed 2 years of pembrolizumab and stopped treatment. Most were able to maintain their response, including those with stable disease, with only 2 patients (4%) having confirmed progression after stopping at 2 years.[96]

Keynote-006 was a randomized phase 3 study of pembrolizumab versus ipilimumab in patients with advanced melanoma, which also specified a maximum 2 year duration of pembrolizumab treatment. 104 (19%) of 556 patients randomized to pembrolizumab completed 2 years of

treatment. With a median follow-up of 9 months after completion of pembrolizumab, the estimated risk of progression or death was 9% in these patients.[97]

Taken together, these data suggest that treatment beyond 2 years is unlikely to confer additional clinically meaningful benefit and that the risk of progression after discontinuing treatment at 2 years is low.

In contrast, a shorter duration of nivolumab of only 1 year was associated with increased risk of progression in previously treated patients with NSCLC, suggesting that treatment beyond 1 year is likely needed. In CA209153, patients with previously treated advanced NSCLC who completed 1 year of nivolumab therapy were randomized to either continue or stop treatment, with the option of retreatment upon progression. Among 163 patients still on treatment at 1 year and without progression, those who were randomized to continue nivolumab had significant improvement in progression-free survival (PFS) compared to those who were randomized to stop treatment, with median PFS (post-randomization) not reached vs 10.3 months, respectively; HR=0.42 (95% CI, 0.25 to 0.71). With a median follow-up of 14.9 months post-randomization, there also was a trend for patients on continued treatment to live longer (OS HR = 0.63 [95% CI: 0.33, 1.20]). Of note, the PFS curves in both groups plateau approximately 1 year after randomization (i.e., 2 years after treatment initiation), suggesting that there may be minimal benefit in extending treatment beyond a total of 2 years.[98]

Collectively, these data suggest that there is minimal if any benefit derived from continuing I-O treatment beyond two years in advanced tumors. However, even though immunotherapy is well tolerated, patients will be at risk for additional toxicity with longer term treatment. Therefore, in this study, treatment will be given for a maximum of 2 years from the start of study treatment for subjects in Cohort D.

It is strongly recommended that subjects in Cohorts A, B, and C limit treatment duration with immunotherapy treatment for up to 2 years. For subjects in these cohorts who receive immunotherapy treatment beyond 2 years, treatment will be given for a maximum of 5 years from the start of study treatment.

1.2 Research Hypothesis

Treatment with nivolumab combined with ipilimumab will have clinical activity in subjects with metastatic castrate resistant prostate cancer (mCRPC).

1.3 Objectives(s)

1.3.1 Primary Objectives

- Evaluate objective response rate (ORR) by Response Evaluation Criteria in Solid Tumors (RECIST) V1.1 assessed by Blinded Independent Central Review (BICR) in subjects with mCRPC and measurable disease at baseline per investigator assessment as entered in the interactive web response system (IWRS).
- Assess Radiographic Progression Free Survival (rPFS) assessed by BICR in all treated subjects with mCRPC in Cohorts B and C and all randomized subjects with mCRPC in Cohort D using RECIST V1.1 for soft tissue disease progression and PCWG2 for bone disease progression.

1.3.2 Secondary Objectives

- Assess radiographic/clinical Progression Free Survival (rcPFS, as defined in Section 5.5.3).
- Assess overall survival (OS).
- Evaluate PSA response rate (PSA-RR)
- Determine the safety and tolerability in all treated subjects.
- Estimate changes in pain as measured by the Brief Pain Inventory-Short Form (BPI-SF)
- Estimate changes in cancer-related symptoms and quality of life (QoL) using the FACT-P questionnaire (Cohort D only)
- Estimate changes in health status and health utility as measured by the 3-level EQ-5D-3L questionnaire

1.4 Product Development Background

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.[99,100,101] 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.

1.4.1 Mechanism of Action of Nivolumab

PD-1 is a member of the CD28 family of T-cell co-stimulatory receptors that also includes CD28, CTLA 4, ICOS, and BTLA.[102] 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.[103] 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 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). BMS-936558 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 Peripheral Blood Mononuclear cells (PBMC), the effect of nivolumab on antigen specific recall response indicates that nivolumab augmented IFN-γ secretion from CMV specific memory T cells in a dose-dependent manner 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).[104]

Immunotherapeutic approaches recently have demonstrated clinical efficacy in several cancer types, including melanoma, and NSCLC, and RCC.[105,106,107,108] Nivolumab (Opdivo®) is approved in multiple countries including the US for treatment of previously treated, unresectable or metastatic melanoma and previously treated, metastatic NSCLC, and advanced RCC.[109]

1.4.2 Mechanism of Action of Ipilimumab

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.[110,111]

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.

1.4.3 Nivolumab-plus-Ipilimumab Mechanism of Action

Preclinical and clinical 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- to 7-fold over either agent alone in a mixed lymphocyte reaction. 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.[112]

In the Phase 1 dose escalation Study CA209004, the combination of nivolumab and ipilimumab has been studied in subjects with unresectable or metastatic melanoma. In this study, a safe dose level for the combination of ipilimumab and nivolumab was established for the treatment of advanced melanoma. At this dose level, 3 mg/kg ipilimumab plus 1 mg/kg nivolumab, an ORR of 53% was observed. This dose level has been approved in subjects with advanced melanoma in the US based on the Phase 3 Study CA209067.[113]

1.4.4 Overview of Nivolumab and Ipilimumab Clinical Pharmacology

The clinical pharmacology profiling of the combination of nivolumab and ipilimumab together with an overview of the results of these analyses are summarized below. In addition, the Clinical Pharmacology Section of the product labels for ipilimumab and nivolumab, as well as the investigational brochures, have additional details.[114,115,116,117]

1.4.4.1 Population Pharmacokinetics of Nivolumab

The PK, clinical activity, and safety of nivolumab has been assessed in completed and ongoing Phase 1, 2, and 3 studies in adult subjects with non-small cell lung cancer (NSCLC), melanoma, and renal cell carcinoma (RCC) in addition to other tumor types.[118]

The PK of nivolumab as monotherapy was characterized by PPK analysis. Nivolumab clearance increased with baseline body weight, estimated glomerular filtration (eGFR), and Eastern Cooperative Oncology Group (ECOG) performance status > 0. The PPK analysis was performed using data from 1908 subjects who received nivolumab from the following studies: nivolumab monotherapy data from studies MDX-1106-01, ONO-4538-01, ONO-4538-02, MDX-1106-03, CA209010, CA209063, and CA209037. Studies CA209004, CA209069, CA209066, and CA209067 provided PK data of nivolumab monotherapy as well as in combination with ipilimumab in the target population (advanced melanoma) who received the proposed dosing regimens. The data from these studies also allowed for an evaluation of potential drug interactions between nivolumab and ipilimumab and of the effect of immunogenicity on clearance. Thus, for this analysis, the covariates assessed included ADA status, baseline ECOG status, baseline eGFR, baseline body weight (BW), gender and co-administration of ipilimumab.

Co-administration with ipilimumab 3 mg/kg resulted in a modest increase in nivolumab CL of 35% whereas coadministration with ipilimumab 1 mg/kg did not appear to have an effect on nivolumab CL. Presence of anti-nivolumab antibodies increased nivolumab CL by 25%, consistent with prior findings. In subjects with an ECOG performance status of > 0, nivolumab CL was 22%

higher (based on median values). Male subjects had a median of 12% higher volume of distribution of central compartment (VC) than females. Baseline body weight was identified as a significant covariate for both CL and VC and the magnitude of the effect of baseline eGFR on CL was not considered clinically relevant. The geometric mean CL, Vss, and terminal half-life of nivolumab were 9.83 mL/h, 7.62 L, and 24.1 days, respectively. When administered in combination, the CL of nivolumab was increased by 35%, whereas there was no effect on the clearance of ipilimumab.

1.4.4.2 Population Pharmacokinetics of Ipilimumab

The PPK of ipilimumab was evaluated using data from 1345 subjects in 4 Phase 2 studies with ipilimumab monotherapy (CA184004, CA184007, CA184008, and CA184022), as well as one Phase 1 study (CA209004), one Phase 2 study (CA209069) and one Phase 3 study (CA209067) with ipilimumab monotherapy and nivolumab in combination with ipilimumab. The ipilimumab data from CA209004, CA209069, and CA209067 are included as they provide ipilimumab PK samples that were collected in combination with nivolumab in the target population. The data from 4 ipilimumab monotherapy studies (CA184004, CA184007, CA184008, and CA184022) were included in the PPK analysis, to enable the assessment of the potential nivolumab effect on ipilimumab PK.

The co-administration of ipilimumab (3 mg/kg) with nivolumab 0.3 mg/kg and nivolumab 3.0 mg/kg resulted in minimal changes in ipilimumab CL (-7.5% and 11%, respectively); however, sample sizes at these doses were small. The CL of ipilimumab coadministered with 1 mg/kg nivolumab was estimated to be 1% higher (95% CI: 97.8 - 106) relative to the CL of ipilimumab monotherapy, demonstrating that ipilimumab CL is unaffected by co-administration of 1 mg/kg nivolumab. Ipilimumab CL was estimated to increase by 6% (95% CI: 96.5 - 115) in the presence of ipilimumab ADA, as measured by the drug tolerant (2nd generation) assay. This effect is not considered to be statistically significant (95% CI includes 1). Ipilimumab CL and VC increased with increasing baseline body weight, and ipilimumab CL increased with increasing baseline LDH.

1.4.4.3 Pharmacokinetics of Nivolumab and Ipilimumab

The PK of nivolumab and ipilimumab, when administered in combination, were characterized by summary statistics of observed data from CA209004 and by PPK analyses using serum concentration data collected in studies CA209004, CA209069 and CA209067.

A dose-related increase in nivolumab peak and trough concentrations was observed after the first dose in Study CA209004. Peak and trough concentrations after the first dose for 1 mg/kg of nivolumab in combination with 3 mg/kg of ipilimumab Q3W were in the range of 18.1 - 21.5 μg/mL and 3.2 - 4.8 μg/mL, respectively. Ipilimumab peak concentrations at 3 mg/kg in combination with 1 mg/kg nivolumab after the first dose were in the range of 63.5 - 68.5 μg/mL. Ipilimumab trough concentrations at 3 mg/kg in combination with 1 mg/kg nivolumab after the first dose were in the range of 9.8 - 11.9 μg/mL.

1.4.5 Safety Summary

1.4.5.1 Nivolumab Safety Summary

Nivolumab has been studied in over 8,600 subjects and is widely approved in multiple indications.

Overall, the safety profile of nivolumab monotherapy is manageable and generally consistent across completed and ongoing clinical trials, with no maximum tolerated dose (MTD) reached up to 10 mg/kg. Most AEs were low-grade (Grades 1 to 2) with relatively few high-grade (Grades 3 to 4) AEs related to study drug. 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 1. Most high-grade events were manageable with the use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in these algorithms.

For further safety information, please refer to Opdivo® USPI and SmPC.

1.4.5.2 Ipilimumab Safety Summary

A pooled analysis of 14 phase I-III studies evaluating various doses of ipilimumab in advanced melanoma demonstrated that 64.2% of subjects experienced an irAE of any grade.[119]The majority of irAEs were mild-moderate (grade 1-2) with death due to irAEs occurring in <1% of subjects. The skin and GI tract were most frequently affected, while hepatic, endocrine, and neurologic events were less common.[119] In a phase II trial comparing three dose levels of ipilimumab (0.3 mg/kg, 3.0 mg/kg, and 10 mg/kg) in subjects who were pretreated for advanced melanoma—followed by maintenance in subjects achieving an objective response or stable disease—the incidence of irAEs was 26%, 56%, and 70%, with an occurrence of grade 3-4 irAEs in 0%, 7%, and 25% of subjects, respectively suggesting a dose-response for safety.[120]

For further safety information with ipilimumab 3 mg/kg in advanced melanoma, including timing of onset and resolution of events, please refer to Yervoy® USPI and SmPC.

1.4.5.3 Ipilimumab Safety in Prostate Cancer

A summary of safety observed in the completed Phase 1 and 2 CRPC studies, which used ipilimumab as monotherapy or in combination with other therapeutic modalities (ie, docetaxel, GVAX) is shown in Table 1.4.5.3-1. Overall, the safety profile of ipilimumab as monotherapy or in combination with other treatment modalities in CRPC was characterized by irAEs involving skin, GI tract, endocrine tract, and liver, a profile which is consistent with that observed in the clinical development program.

Table 1.4.5.3-1: Overall Summary of Safety in Completed Phase 1 and 2 CRPC Studies of Ipilimumab

	Number of Subjects (%)		
	MDXCTLA4-01[a] (N = 14)	**MDX010-07[b] (N = 44)**	**MDX010-17[c] (N = 28)**
Any Drug-related AE	5 (35.7)	33 (75.0)	28 (100.0)
Grade 3 - 4	NA	26 (59.1)	NA
Most Frequently Reported Drug-related AEs			
Fatigue	0	16 (36.4)	22 (78.6)
Pruritus	2 (14.2)	10 (22.7)	6 (21.4)
Nausea	0	7 (15.9)	8 (28.6)
Rash	2 (14.2)	5 (11.4)	11 (39.3)
Diarrhea	0	3 (6.8)	7 (25.0)
Vomiting	0	3 (6.8)	6 (21.4)
Headache	0	3 (6.8)	7 (25.0)
Anorexia	0	3 (6.8)	6 (21.4)
Pyrexia	--	1 (2.3)	16 (57.1)
Malaise	1 (7.1)	--	6 (21.4)
Influenza-like Illness	0	--	12 (42.9)
Any Serious Adverse Events	6 (42.9)	15 (34.1)	14 (50.0)
Grade 3 - 4	5 (35.7)	15 (34.1)	NA
Any Drug-related Serious Adverse Events	1 (7.1)	7 (15.9)	7 (25.0)
Grade 3 - 4	1 (7.1)	7 (15.9)	NA
Any irAE	1 (7.1)[d]	24 (54.6)[d]	5 (17.9)[d]
Grade 3 - 4	1 (7.1)	7 (15.9)	NA
Any Serious irAE	1 (7.1)	4 (9.1)	NA
Grade 3 - 4	1 (7.1)	NA	NA

Source: CSRs for MDXCTLA4-01,MDX010-07, and preliminary data from MDX010-17

NA = not available

[a] Ipilimumab monotherapy

[b] Data pooled for ipilimumab monotherapy and ipilimumab in combination with docetaxel

[c] Ipilimumab in combination with GVAX

[d] Referred to as immune breakthrough events in CSR

The safety profile based on the preliminary data from MDX010-21, A Phase 1/2, Open-label, Dose-escalation Study of MDX-010 Administered Every 3 Weeks for 4 Doses in Subjects with Metastatic Hormone-Refractory Prostate Cancer is presented in Table 1.4.5.3-2.[121] The safety

profile in this study was characterized by irAEs involving skin, GI tract, endocrine tract, and liver, which is consistent with that observed in the clinical development program.

Table 1.4.5.3-2: MDX010-21 - Overall Summary of Safety

Parameter	Number (%) of Subjects					
	3 mg/kg N=8	5 mg/kg N=6	10 mg/kg N=16	3 mg/kg + XRT N=7	10 mg/kg + XRT N=34	Total N = 71
Deaths	5 (62.5)	4 (66.7)	7 (43.8)	3 (42.9)	18 (52.9)	37 (52.1)
≤ 70 days after last dose	0	0	0	0	6 (17.6)	6 (8.5)
SAE	3 (37.5)	2 (33.3)	9 (56.3)	2 (28.6)	19 (55.9)	35 (49.3)
Related	2 (25.0)	1 (16.7)	7 (43.8)	2 (28.6)	7 (20.6)	19 (26.8)
AE to DC	2 (25.0)	2 (33.3)	7 (43.8)	3 (42.9)	13 (38.2)	27 (38.0)
Related	2 (25.0)	2 (33.3)	6 (37.5)	3 (42.9)	8 (23.5)	21 (29.6)
AE	8 (100)	6 (100)	16 (100)	6 (85.7)	34 (100)	70 (98.6)
Grade 3-4	2 (25.0)	5 (83.3)	12 (75.0)	3 (42.9)	20 (58.8)	42 (59.2)
Related AE	8 (100)	5 (83.3)	16 (100)	6 (85.7)	29 (85.3)	64 (90.1)
Grade 3-4	2 (25.0)	3 (50.0)	10 (62.5)	3 (42.9)	13 (38.2)	31 (43.7)
irAE	6 (75.0)	5 (83.3)	16 (100)	4 (57.1)	24 (70.6)	55 (77.5)
Grade 3-4	1 (12.5)	3 (50.0)	10 (62.5)	3 (42.9)	6 (17.6)	23 (32.4)

Abbreviations: SAE = serious adverse event; AE = adverse event; DC = discontinuation; irAE = immune-related AE

Ipilimumab, at escalating doses of 3, 5, and 10 mg/kg with and without a single dose of XRT administered every 3 weeks up to 4 times was tolerable with a safety profile consistent with that demonstrated in previous studies of ipilimumab. Although no DLTs were observed and no MTD was reached during the course of the study, rate of AEs showed increase from 3 mg/kg to 10 mg/kg.[121]

The phase 3 Study CA184043 evaluated ipilimumab 10 mg/kg monotherapy dose vs. placebo in mCRPC.[50] The overall safety profile for ipilimumab in these studies was generally consistent with the previous Phase 1 and 2 studies of ipilimumab 10 mg/kg monotherapy in prostate cancer. The most frequently reported on-study immune-related adverse events of any grade in the ipilimumab group were diarrhea, pruritus, rash, colitis, increased aspartate aminotransferase, and increased alanine aminotransferase. While less than 2% of fatal adverse events in either treatment group were regarded as drug-related, more on-study deaths occurred overall and in the first 5 months in the ipilimumab 10 mg/kg group than in the placebo group.

1.4.5.4 Nivolumab-plus-Ipilimumab Safety Summary

In the Phase 1b, open-label, multi-center, multi-dose, dose-escalation study of nivolumab in combination with ipilimumab, study drugs were administered either concurrently (Cohorts 1 through 3, and Cohort 8) or in a sequenced regimen (Cohorts 6 and 7) in subjects with advanced melanoma.[38] Each arm in this multi-arm study had an induction phase (ipilimumab dosed Q3 weeks x4; nivolumab dosed Q3 weeks x8) and a maintenance phase (ipilimumab dosed

Q12 weeks x8; nivolumab dosed Q12 weeks x8). Initial 3 dose-escalation cohorts consisted of Cohort 1 (nivolumab 0.3 mg/kg plus ipilimumab 3 mg/kg; n = 14), Cohort 2 (nivolumab 1.0 mg/kg plus ipilimumab 3 mg/kg; n = 16) and Cohort 3 (nivolumab 3.0 mg/kg plus ipilimumab 3 mg/kg; n = 6).[38]

Unlike single-agent nivolumab, a dose relationship with toxicity was observed with the combination of nivolumab and ipilimumab[38]. The lowest dose of nivolumab (Cohort 1, 0.3 mg/kg with 3 mg/kg ipilimumab) resulted in a lower incidence of Grade 3-4 AEs, SAEs, and AEs leading to treatment discontinuation compared with the higher dose cohorts. Treatment with 3 mg/kg nivolumab and 3 mg/kg ipilimumab (Cohort 3) resulted in 3 of 6 subjects experiencing DLTs that exceeded the protocol-defined MTD. No subjects were enrolled in Cohorts 4 and 5 because the maximum tolerated dose (MTD) was exceeded in Cohort 3 and the protocol was amended to evaluate a lower dose of ipilimumab (1 mg/kg) in combination with 3 mg/kg nivolumab (Cohort 2a). Both Cohort 2 (1 mg/kg nivolumab and 3 mg/kg ipilimumab) and Cohort 2a (3 mg/kg nivolumab and 1 mg/kg ipilimumab) were deemed tolerable establishing both dose combinations as MTD (2 of 17 and 0 of 16 subjects had DLTs in Cohort 2 and 2a, respectively).[38]

Treatment with nivolumab in combination with ipilimumab generally resulted in greater frequencies of Grade > 3 AEs, SAEs, AEs leading to discontinuation and select AEs than that observed with either agent alone; however, no new types of AEs were observed. The overall frequency in the pooled Cohorts 1-3 and in Cohort 8 of skin, GI, hepatic and endocrine select AEs were greater than either agent alone and the frequency of Grade 3-4 select skin, GI, and hepatic AEs was higher than that observed with nivolumab or ipilimumab monotherapy in melanoma subjects.[38] In contrast, pulmonary and renal select AEs were only slightly higher than observed with single-agent nivolumab .The frequency of some Grade 3-4 AEs, notably those related to GI, hepatic, and skin, were also increased with combination treatment relative to ipilimumab.[38]

In study CA209-067, a randomized, double-blind, multicenter, phase 3 trial that was conducted to evaluate the safety and efficacy of nivolumab alone or nivolumab combined with ipilimumab in comparison with ipilimumab alone in subjects with previously untreated metastatic melanoma, treatment-related adverse events of any grade occurred in 82.1% of the subjects in the nivolumab group, 95.5% of those in the nivolumab plus ipilimumab group, and 86.2% of those in the ipilimumab group.[122] The most common adverse events in the nivolumab-plus-ipilimumab group were diarrhea (in 44.1% of subjects), fatigue (in 35.1%), and pruritus (in 33.2%).[122] The incidence of treatment-related adverse events of grade 3 or 4 was also higher in the nivolumab-plus-ipilimumab group (55.0%) than in the nivolumab group (16.3%) or the ipilimumab group (27.3%).[122] Treatment-related adverse events of any grade that led to discontinuation of the study drug occurred in 7.7% of the subjects in the nivolumab group, 36.4% of those in the nivolumab plus ipilimumab group, and 14.8% of those in the ipilimumab group, with the most common events being diarrhea (in 1.9%, 8.3%, and 4.5%, respectively) and colitis (in 0.6%, 8.3%, and 7.7%, respectively).[122] Grade 3 or 4 diarrhea were higher in the combination cohort (2.2% in nivolumab group vs. 9.3% in the nivolumab-plus-ipilimumab group, and 6.1% in the ipilimumab group). Similarly colitis (in 0.6%, 7.7%, and 8.7%, respectively), and increased

alanine aminotransferase level (in 1.3%, 8.3%, and 1.6%, respectively) were higher in the nivolumab-plus-ipilimumab combination arms.[122]

1.5 Overall Risk/Benefit Assessment

New therapeutic options with the potential to provide durable, long term responses across the disease states spectrum of mCRPC are needed. Several lines of evidence, as outlined in Section 1.1.2, strongly support the investigation of immunotherapy agents to improve outcomes in mCRPC.

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.[123,122] 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)[124], non-small cell lung cancer (NSCLC)[125], Small Cell Lung Cancer (SCLC)[126] and gastric cancer[127].

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.

The current melanoma label supports sequential administration of nivolumab and then ipilimumab, one administered soon after the other. The recommended dose and schedule is nivolumab 1 mg/kg administered as an intravenous infusion over 30 minutes, followed by ipilimumab 3mg/kg administered over 90 minutes on the same day, every 3 weeks for four doses. The time in between infusions is expected to be approximately 30 minutes but may be more or less depending on the situation. The recommended maintenance dose given after the combination has been completed is nivolumab, as a single agent, 3 mg/kg, as an intravenous infusion every 2 weeks, until disease progression or unacceptable toxicity. However, in this study after completion of the combination portion of the study, subjects will receive flat dose 480 mg nivolumab every 4 weeks (Q4W), which provides a more convenient dosing regimen for subjects. 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 subjects 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.

1.5.1 *Based on these data, nivolumab 480 mg Q4W is expected to have similar efficacy and safety profiles to nivolumab 3 mg/kg Q2W.Overall Risk/Benefit Assessment for Additional Cohort D*

As outlined in Section 1.1, the recent data from Cohorts B and C in CA209650 suggest that nivolumab in combination with ipilimumab is an active regimen in patients with mCRPC, with potentially greater activity in patients with HRD mutations or higher TMB, but early toxicity was the factor which limited the number of combination doses received. Mitigation of severe toxicities through alternative combination schedules may help to further improve outcomes, and this approach will be explored in the following two arms:

- Arm D1 will evaluate the combination using a lower dose of ipilimumab (1 mg/kg), but at the same frequency used in Part 1 (Q3W). As described earlier, the safety profile and clinical activity of Nivolumab 3 mg/kg combined with ipilimumab 1 mg/kg was demonstrated by the approval of this regimen in other cancer types. This combination has also shown acceptable safety and encouraging efficacy in men with AR-V7-expressing advanced prostate cancer who harbor DNA-repair alterations.
- Since ipilimumab dose of 3 mg/kg may be critical to enhance immune cell infiltration into tumors and driving the anti-tumor response, arm D2 will explore the same dose of ipilimumab used in Cohorts B and C (3 mg/kg), but at a reduced frequency (Q6W), As described earlier, CA209012 supports the rationale to decrease ipilimumab dosing frequency to improve tolerability, while maintaining efficacy.

Furthermore, as outlined in Sections 1.1.4 and 1.4.5, ipilimumab monotherapy has demonstrated clinical activity and an acceptable safety profile, and previous trials in mCRPC highlight the need to identify [redacted] patients most likely to benefit. Ipilimumab will be evaluated in Arm D3 to assess its contribution to the activity of the combination in the chosen population.

Arm D4 will evaluate the standard of care cabazitaxel in the target population and allow for comparison with the immunotherapy regimens, [redacted] Cabazitaxel has a well-characterized AE profile as a cytotoxic chemotherapy, including the potential of neutropenia, anemia, thrombocytopenia, diarrhea, nausea and vomiting.

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

- Early interim reviews of safety and efficacy data will be performed by the Sponsor and participating investigators from the Study Steering Committee for Cohort D after the first 15 treated subjects for each arm have at least 8 weeks of follow-up after first dose and at least

one post-baseline tumor assessment in subjects receiving immunotherapy in Arms D1, D2, and D3.

- Rigorous safety monitoring by BMS to ensure participants' safety including regular and systematic review of safety data, close follow-up of reported safety events, and intensive site and study investigator training/education on the implementation of the nivolumab and ipilimumab toxicity management algorithms
- Open-label drug administration of study treatments to allow for prompt and accurate assessment of the unique toxicities associated with study treatments

In conclusion, the overall risk-benefit of the proposed study arms is deemed acceptable.

2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Council for Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50) and applicable local requirements.

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion 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).

2.2 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, subject recruitment materials (eg, advertisements), and any other written information to be provided to subjects. 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 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.

2.3 Informed Consent

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

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

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

Investigators must:

- Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood
- Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study
- Obtain an informed consent signed and personally dated by the subject or the subject'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, prior to the beginning of the study, and after any revisions are completed for new information

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

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

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

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

Subjects unable to give their written consent (eg, subjects with stroke) may only be enrolled in the study with the consent of a legally acceptable representative. The subject must also be informed about the nature of the study to the extent compatible with his or her understanding, and should

this subject become capable, he or she should personally sign and date the consent form as soon as possible. The explicit wish of a subject 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 are the most important considerations and should prevail over interests of science and society.

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

This is a Phase 2 open-label study of nivolumab plus ipilimumab in subjects with metastatic castration-resistant prostate cancer (mCRPC). The trial will include 3 treatment cohorts:

Cohort A: Asymptomatic or minimally symptomatic mCRPC subjects who have not been treated with and are unable or unwilling to receive second generation hormone therapies or cytotoxic chemotherapy in mCRPC setting.

Addendum: Per Revised Protocol 02, Cohort A was discontinued for further enrollment. The remainder of Cohort A participants will be allocated to Cohorts B and C in order to have more precise efficacy estimates in those arms.

Cohort B: Asymptomatic or minimally symptomatic mCRPC subjects who must have progressed after second generation hormone therapies in mCRPC setting and have not been treated with cytotoxic chemotherapy in mCRPC setting.

Cohort C: Subjects must have progressed after prior taxane-based cytotoxic chemotherapy in the mCRPC setting.

In accordance with Revised Protocol 02, 45 subjects will be treated per treatment Cohorts B and C. At least 30 subjects with measurable disease by RECIST V1.1 criteria will be enrolled in each cohort. No more than 15 subjects will have non-measurable disease by RECIST V1.1 in each cohort.

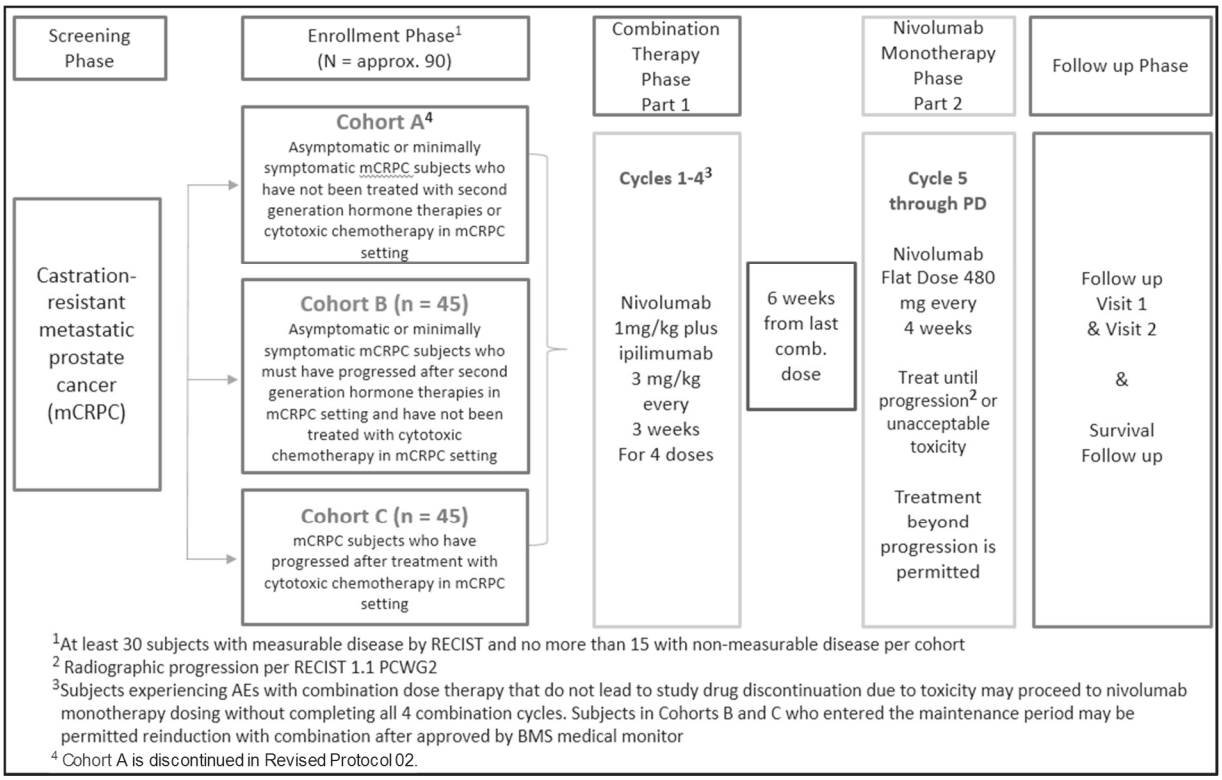
Subjects will be treated with up to 4 cycles of nivolumab in combination with ipilimumab (Part 1, See Section 4.3.1), followed by nivolumab monotherapy (Part 2, Section 4.3.2) until progression of disease, unacceptable toxicity, or subject withdrawal of consent. In Part 1, a minimum of 1 combination cycle of nivolumab and ipilimumab is required. Subjects 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.

Each treatment cycle will be 3 weeks in duration for Part 1. Nivolumab and ipilimumab will be dosed every 3 weeks for four doses. After completion of the last combination cycle in Part 1 (ie, 6 weeks after the last dose of nivolumab plus ipilimumab), subjects will then receive nivolumab monotherapy every four weeks for Part 2 until progression of disease, unacceptable toxicity, or subject withdrawal of consent.

No dose increases or reductions will be allowed for either drug during both the combination therapy phase and the nivolumab monotherapy phase.

The study design schematic is presented in Figure 3.1-1.

Figure 3.1-1: Study Design Schematic Cohorts A, B, and C



In accordance with Revised Protocol 03, additional subjects who have progressed after prior docetaxel-containing regimen will be enrolled into Cohort D.

For Cohort D, approximately 259 subjects will be randomized in a 2:2:1:2 ratio to one of the following open-label treatment arms:

- Arm D1: nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg every 3 weeks for up to 4 doses (Cycles 1 to 4), followed by nivolumab 480 mg administered every 4 weeks (Cycle 5 and beyond). Subjects who are receiving maintenance nivolumab with ongoing disease control (ongoing CR, PR, or SD) or with radiographic progression per RECIST v1.1/PCWG2 may be permitted re-induction with the combination of ipilimumab and nivolumab at their original combination dose upon PSA progression or radiographic progression (whichever occurs first), as specified in Section 4.3.5. Treatment will continue until disease progression, unacceptable toxicity, withdrawal of consent, 2 year maximum treatment duration, or the study ends, whichever occurs first.
- Arm D2: nivolumab 1 mg/kg every 3 weeks plus ipilimumab 3 mg/kg every 2 cycles (ie, every 6 weeks) for up to 4 ipilimumab doses, followed by nivolumab 480 mg every 4 weeks. Subjects who are receiving maintenance nivolumab with ongoing disease control (ongoing CR, PR, or

SD) or with radiographic progression per RECIST v1.1/PCWG2 may be permitted re-induction with the combination of ipilimumab and nivolumab at their original combination dose upon PSA progression or radiographic progression (whichever occurs first), as specified in Section 4.3.5. Treatment will continue until disease progression, unacceptable toxicity, withdrawal of consent, 2 year maximum treatment duration, or the study ends, whichever occurs first.

- Arm D3: ipilimumab 3 mg/kg every 3 weeks for up to 4 doses. Treatment will continue until disease progression, unacceptable toxicity, withdrawal of consent, completion of 4 cycles, or the study ends, whichever occurs first.
- Arm D4: Cabazitaxel 20 mg/m^2 or 25 mg/m^2 (at investigator's discretion and according to country-specific label) every 3 weeks in combination with oral prednisone or prednisolone 10 mg daily for up to 10 cycles. Treatment will continue until disease progression, unacceptable toxicity, withdrawal of consent, completion of 10 cycles of treatment, or the study ends, whichever occurs first.

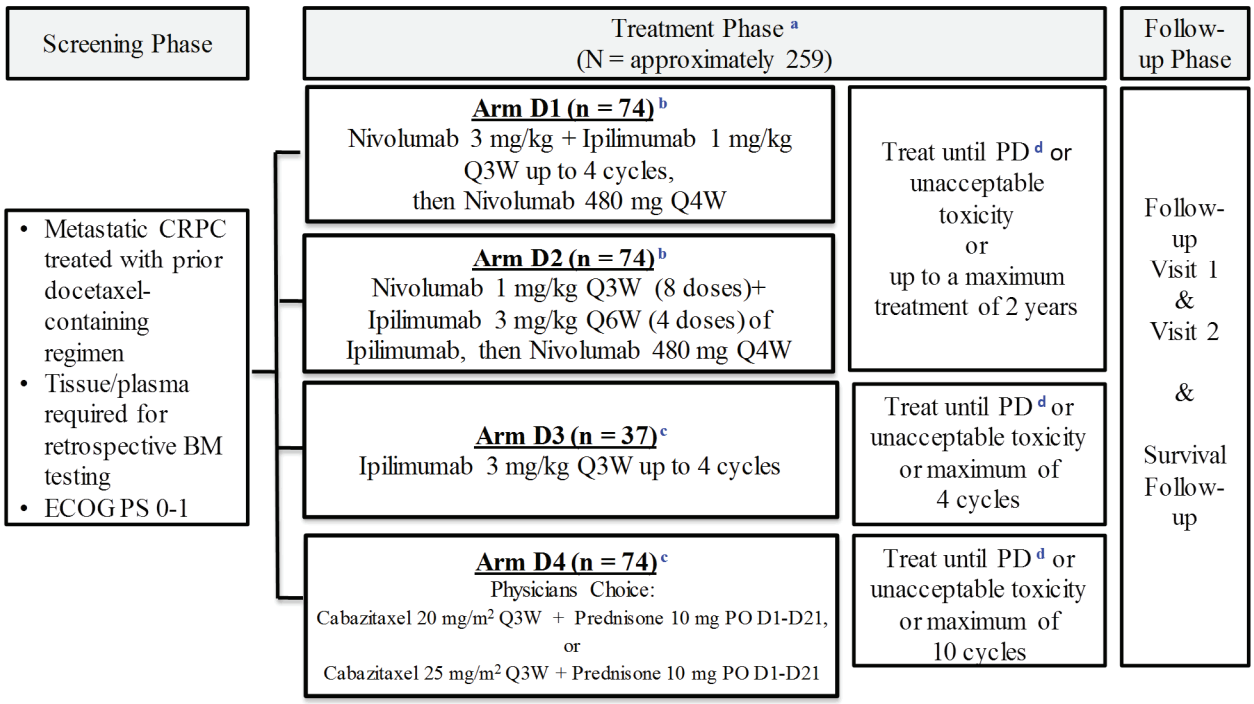
Randomization will be stratified by the presence or absence of measurable disease per investigator assessment (measurable disease vs only non-measurable disease) at study entry to ensure treatment arms are balanced.

Note: Subjects treated in Arms D3 and D4 who progress on or after treatment may be eligible to crossover to Arm D1.

Cohort D will evaluate the above immunotherapy regimens and the standard of care comparator cabazitaxel in unselected mCRPC patients. [redacted]

The study design schematic for the addition of Cohort D is presented in Figure 3.1-2:

Figure 3.1-2: Study Design Schematic for Addition of Cohort D



Notes:

[a] Subjects with investigator-assessed non-measurable disease at baseline will be capped when approximately 105 subjects are randomized.

[b] Subjects in Arms D1 and D2 experiencing drug-related AEs with combination dose therapy that do not lead to study treatment discontinuation due to toxicity may proceed to nivolumab monotherapy dosing without completing all 4 combination cycles. Subjects who entered the maintenance period may be permitted re-induction with the combination after approval by the BMS medical monitor

[c] Subjects in Arms D3 and D4 who have progressed on or after treatment have the option to crossover to Arm D1 at BICR confirmed disease progression after approval by the BMS medical monitor

[d] Radiographic progression per RECIST v1.1 or PCWG2 (Section 5.5.3). Treatment beyond investigator-assessed RECIST v1.1-defined progression may be considered for subjects meeting criteria according to Section 4.5.4

The study will consist of the following three phases:

Screening Phase:

- Begins by establishing the subject's initial eligibility and signing of the informed consent form (ICF).
- Subject is enrolled using the IWRS.

Treatment Phase:

- Begins with the cohort assignment call to the IWRS
- Within 3 calendar days from cohort assignment the subject must receive the first dose of study medication (Day 1 of Cycle 1)
- On-study laboratory assessments (Cycle 2 and beyond) should be drawn within 72 hours prior to dosing
- Adverse event assessments should be documented at each clinic visit
- [redacted]
- Study treatment dosing may be delayed for toxicity as described in section 4.5.1

Cohort D : The treatment phase consists of 4 open-label treatment arms (Arm D1, D2, D3, and D4):

- Arm D1: nivolumab and ipilimumab are administered every 3 weeks for up to 4 doses, followed by nivolumab administered every 4 weeks (Cycle 5 and beyond). The first nivolumab dose of 480 mg will be administered 3 weeks after the last combination dose of nivolumab/ipilimumab
- Arm D2: nivolumab is administered every three weeks up to 8 doses. Ipilimumab is administered every 6 weeks for up to 4 doses followed by nivolumab administered every 4 weeks (Cycle 9 and beyond). The first flat dose 480 mg nivolumab will be administered 3 weeks after the last nivolumab 1 mg/kg dose (and 6 weeks after the last combination dose).
- Arm D3: ipilimumab is administered every 3 weeks for up to 4 doses
- Arm D4: Cabazitaxel will be administered every 3 weeks in combination with oral prednisone or prednisolone up to 10 cycles.

For Cohorts B and C, tumor assessments are scheduled to be performed every 8 weeks for 6 months following treatment initiation and thereafter every 12 weeks until radiographic progression or withdrawal of consent.

For Arms D1, D2, D3, and D4, tumor assessments are scheduled to be performed every 8 weeks (± 7 days) for 6 months following treatment initiation and thereafter every 12 weeks (± 7 days) until radiographic progression has been assessed by the investigator and confirmed by BICR (see Section 5.5.3) or withdrawal of consent.

This treatment phase ends when the subject is discontinued from study therapy.

Optional Re-induction Combination for Cohorts B, C, Arms D1, and D2

Subjects with PSA progression or with radiographic progression per RECIST v1.1/PCWG2 (whichever occurs first) during or after nivolumab monotherapy maintenance may receive nivolumab and ipilimumab combination at the same dose levels as assigned at study start and follow the same Time and Events schedule, as specified in Section 5.

Optional Crossover Combination for Arms D3 and D4

Subjects treated in Arms D3 and D4 who demonstrate radiographic progression assessed by the investigator and confirmed by BICR during or after treatment may be eligible to receive optional crossover nivolumab in combination with ipilimumab (Arm D1) if their case is reviewed with and approved by the BMS Medical Monitor:

Subjects must continue to meet all inclusion criteria and all exclusion criteria specified in Section 3.3, including criteria related to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

Nivolumab 3 mg/kg plus ipilimumab 1 mg/kg Q3W for up to 4 cycles, followed by nivolumab 480 mg mg/kg Q4W is administered every 4 weeks until disease progression, unacceptable toxicity, withdrawal of consent, completion of 2 years of treatment, or the study ends, whichever occurs first. At least a 3 week period from last dose of study treatment (ipilimumab or cabazitaxel) is required prior to first dose of crossover treatment.

Study assessments are to be collected as outlined in Section 5. A tumor assessment within 28 days prior to the first crossover dose is recommended, which can serve as the new baseline by which to assess response to nivolumab and ipilimumab. Imaging tumor assessments performed during crossover nivolumab should be submitted to the central imaging vendor.

Nivolumab treatment beyond initial radiographic progression defined by RECIST v1.1 (for soft tissue lesions) and PCWG2 (for bone lesions) is permitted if the subject has investigator assessed clinical benefit and is tolerating the treatment, as specified in Section 4.5.4.

Upon discontinuation of crossover treatment subjects will enter the Follow-Up Phase.

Follow-Up Phase:

- Begins when the decision to discontinue a subject from study therapy is made (no further treatment with study therapy)
- [redacted]
- Subjects who discontinue treatment for reasons other than disease progression or consent withdrawal will continue to have tumor assessments (if clinically feasible) according to the schedule in Table 5.1-5 until progression
- Subjects enrolled in Arms D1, D2, D3, or D4 who discontinue treatment without BICR-confirmed progression or consent withdrawal will continue to have tumor assessments (if clinically feasible) according to the schedule in Table 5.1-5 until radiographic progression has been assessed by the investigator and confirmed by BICR.
- Subjects will be followed for drug-related toxicities until these toxicities resolve, return to baseline or are deemed irreversible. All adverse events will be documented for a minimum of 100 days after last dose

- After completion of the first two follow-up visits, subjects will be followed every 3 months for survival
- BMS may request that survival data be collected on all treated subjects in Cohorts B and C, and all randomized subjects in Cohort D outside of the protocol defined window as detailed in the Time and Events Table (Section 5). At the time of this request, each subject will be contacted to determine their survival status unless the subject has withdrawn consent for all contact.
- If exceptional circumstances preclude the continued administration of measures using planned modalities, then alternate administration methods may be required after consultation with a sponsor or a sponsor's representative.

Duration of Study for Cohorts A, B, and C: It is expected that the trial will be open to accrual for 9 months, with a planned enrollment of 90 subjects. Survival follow-up will continue until BMS informs sites to end the study.

The accrual duration is approximately 9 months, assuming a monthly rate of 10 subjects. The analysis of the dual primary endpoint of ORR will occur after all the subjects have been followed for a total period of approximately 24 weeks, ie, after treatment with a maximum of 4 cycles of combination treatment and at least 2 cycles of nivolumab monotherapy treatment. Subjects who receive less than 4 cycles of (ie, between 1-3 cycles), will also be included in the analysis after they complete 24 weeks of follow-up.

This will allow sufficient follow up for a stable estimate of best overall response and adequate safety follow up. The primary analysis of ORR is expected to occur approximately 15 months after the first subject is treated. The analysis of the dual primary endpoint of rPFS will occur after all the subjects have been followed up for approximately 12 months since treatment initiation to have a stable estimate of one year rPFS.

Additional survival analysis may be conducted for up to 5 years after treatment initiation following analysis of the primary endpoint.

Duration of Study for Cohort D: The accrual duration is approximately 24 months for this period. The analyses of the dual primary endpoints of rPFS and ORR per BICR will occur when around 90% of all randomized subjects have approximately 9 months of minimum follow up, which will be a sufficient duration of follow-up for a stable estimate of rPFS and best overall response, as well as adequate safety follow up.

Additional long-term survival analysis may be conducted for up to 5 years from the date of randomization of the last patient following analysis of the primary endpoint.

3.2 Post Study Access to Therapy

At the conclusion of the study, subjects 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 marketing application is rejected by responsible health authority; b) the study is terminated due to safety concerns; c) the subject can obtain medication from a government sponsored or private health program; or d) therapeutic alternatives become available in the local market.

BMS may request that survival data be collected on all treated subjects in Cohorts B and C and all randomized subjects in Cohort D outside of the protocol defined window. At the time of this request, each subject will be contacted to determine their survival status unless the subject has withdrawn consent for all contacts or is lost to follow-up.

At the conclusion of the study, participants who continue to demonstrate clinical benefit will be eligible to receive BMS supplied study treatment **for the maximum treatment duration specified in protocol Section 1.1.13.** 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

3.3 Study Population

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

3.3.1 Inclusion Criteria

1) Signed Written Informed Consent

a) Willing and able to provide informed consent.

2) Target Population

a) Men, 18 years or older

b) ECOG performance status 0-1

c) Histologic confirmation of adenocarcinoma of the prostate

d) Current evidence of metastatic disease documented by either bone lesions on radionuclide bone scan and/or soft tissue lesions on CT/MRI. Metastases may be in regional lymph nodes (N1 per AJCC staging criteria, 8th edition)[128] and/or distant metastases (M1 per AJCC staging criteria, 8th edition).

i) Subjects whose disease spread is limited to regional pelvic lymph nodes (N1M0) must have a lymph node measuring at least 2 cm in short axis to be considered eligible.

e) Ongoing androgen deprivation therapy (ADT) with a GnRH analogue or bilateral orchiectomy (ie, surgical or medical castration) confirmed by testosterone level ≤ 1.73 nmol/L (50 ng/dL) at the screening visit. Castrate levels of testosterone must be maintained by surgical or medical means (LHRH/GnRH analogues) throughout the conduct of the study

f) Tumor progression while receiving ADT per PCWG2 criteria and within 6 months prior to screening, with at least one of the following:

i) PSA progression* defined by a minimum of two rising PSA levels with an interval of ≥ 1 week between each determination. The PSA value at the Screening visit should be ≥ 2 ug/L (2 ng/mL).

*Subjects who received an anti-androgen must have progression after withdrawal (≥ 4 weeks since last flutamide or ≥ 6 weeks since last bicalutamide or nilutamide).

ii) Soft tissue disease progression defined by RECIST V1.1.

iii) Bone disease progression defined by PCWG2 with two or more new lesions on bone scan

g) mCRPC subjects will be enrolled into separate cohorts as follows:

i) **Cohort A**: Asymptomatic or minimally symptomatic mCRPC subjects. Prior treatment with second-generation hormone therapies (eg, enzalutamide, abiraterone) or cytotoxic chemotherapy (eg, docetaxel, mitoxantrone) in the mCRPC setting is not allowed. Subject's refusal of or inability to receive treatment with second-generation hormone therapies or cytotoxic chemotherapy must be appropriately documented. Prior prostate cancer vaccine therapy, radiation therapy, radium 223, anti-androgens (eg, flutamide, bicalutamide), ketoconazole and DES or other estrogens, are allowed up to 28 days prior to study treatment. Note: bicalumatamide or nilutamide must be discontinued within 6 weeks of study treatment. **Enrollment discontinued per Revised Protocol 02.**

ii) **Cohort B**: Asymptomatic or minimally symptomatic mCRPC subjects who have progressed following treatment with at least one second-generation hormone therapies (eg, enzalutamide or abiraterone) in the mCRPC setting. Prior cytotoxic chemotherapy (eg, docetaxel, mitoxantrone) in the mCRPC setting is not allowed. Prior prostate cancer vaccine therapy, radiation therapy, radium-223, anti-androgens (eg, flutamide), ketoconazole, and DES or other estrogens, are allowed up to 28 days prior to study treatment. Note: bicalutamide or nilutamide must be discontinued within 6 weeks of study treatment.

Note: Asymptomatic or minimally symptomatic:

(1) Asymptomatic is defined as BPI-SF item #3 score of 0 to 1

(2) Minimally symptomatic is defined as BPI-SF item #3 score of 2 to 4

Note: Any cancer related pain must not require any opiate analgesics (including codeine and dextropropoxyphene) over the 5 day assessment period prior to treatment initiation.

iii) **Cohort C**: Subjects must have progressed after prior taxane-based cytotoxic chemotherapy in the mCRPC setting. Ketoconazole, abiraterone, enzalutamide, prostate cancer vaccine therapy, radiation therapy, radium-223, anti-androgens (eg, flutamide), and DES or other estrogens, are allowed up to 28 days prior to study treatment. Note: bicalutamide or nilutamide must be discontinued within 6 weeks of study treatment.

iv) **Cohort D:** Subjects must have progressed after a prior docetaxel-containing regimen and received no more than 2 prior chemotherapy regimens in the metastatic setting. If docetaxel was only given in the metastatic castration-sensitive setting, subjects must also have progressed following prior treatment with a second generation hormonal therapy. Prior second-generation hormonal manipulations (eg, abiraterone acetate, enzalutamide, apalutamide), ketoconazole, prostate cancer vaccine therapy, radium-223, anti-androgens (eg, flutamide), chemotherapy and DES or other estrogens, are allowed up to 28 days prior to study treatment.

Note: bicalutamide or nilutamide must be discontinued at least 6 weeks prior to study treatment.

h) Not applicable per Revised Protocol 02.

i) Anti-androgens (bicalutamide, flutamide, nilutamide) or adrenal androgen production inhibitors (aminoglutethamide or ketoconazole) should be discontinued prior to starting study therapy:

   i) Subjects with a history of response to an anti-androgen or adrenal androgen production inhibitor and subsequent progression while on that anti-androgen should be assessed for anti-androgen withdrawal response for 4 weeks (6 weeks for bicalutamide or nilutamide), and must demonstrate progression, as described in Inclusion Criterion 2) f), off anti-androgen prior to enrollment;

   ii) For subjects that have never responded to anti-androgens, observation for anti-androgen withdrawal response is not necessary; however, a 2 week washout period is required prior to start of study therapy

j) Subjects already on agents for the management of skeletal-related events (SREs) are allowed to continue with anti-bone resorptive therapy that was initiated more than 28 days prior to study treatment.

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

l) Sufficient tumor samples from either a fresh biopsy (collected during screening period) or archival tumor tissue in the form of formalin-fixed paraffin-embedded (FFPE) block or a minimum of 15 unstained tumor tissue slides. Archival tumor samples must be obtained within 1 year prior to enrollment date, either from a metastatic tumor lesion (preferred) or from a primary tumor lesion that has not been previously irradiated. Tumor samples collected more than 1 year prior to enrollment date may be acceptable if obtained in the metastatic setting and following discussion with and approval by the BMS Medical Monitor/designee. Tumor sample may be from core biopsy, punch biopsy, excisional biopsy, or surgical specimen. Fine needle aspiration is unacceptable for submission. [redacted] Central laboratory must confirm receipt of tumor samples prior to randomization.

3) Age and Reproductive Status

a) Men ≥ 18 years of age or minimum age of consent per local regulations

b) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug(s) for a total of 7 months post-treatment completion

c) Azoospermic males are exempt from contraceptive requirements

Investigators shall counsel male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise male subjects who are sexually active with WOCBP on the use of highly effective methods of contraception (see Appendix 3). Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly.

3.3.2 *Inclusion Criteria for Crossover Phase for Subjects Originally Randomized to Arm D3 or Arm D4 only*

1) Signed Written Informed Consent

a) Subjects must have signed and dated an IRB/IC approved written informed consent form for crossover combination treatment

2) Target Population

a) Subjects previously randomized to Arm D3 or D4 who had histologic confirmation of adenocarcinoma of the prostate and evidence of Stage IV disease (as defined by AJCC criteria) prior to randomization

b) ECOG performance status 0-1

c) Ongoing androgen deprivation therapy (ADT) with a GnRH analogue or bilateral orchiectomy (ie, surgical or medical castration) confirmed by testosterone level ≤ 1.73 nmol/L (50 ng/dL) at the screening visit. Castrate levels of testosterone must be maintained by surgical or medical means (LHRH/GnRH analogues) throughout the conduct of the study

d) Tumor progression per PCWG2 criteria with at least one of the following assessed by the investigator and confirmed by BICR:

i) Soft tissue disease progression defined by RECIST V1.1. Subjects whose disease spread is limited to regional pelvic lymph nodes measuring at least 2 cm in short axis will be considered eligible

ii) Bone disease progression defined by PCWG2 with two or more new lesions on bone scan

e) At least a 3 week period from last dose of study treatment (ipilimumab or cabazitaxel) is required prior to first dose of crossover treatment.

f) Subjects already on agents for the management of skeletal-related events (SREs) are allowed to continue with anti-bone resorptive therapy that was initiated more than 28 days prior to study treatment.

3) Age and Reproductive Status

a) Men ≥ 18 years of age or minimum age of consent per local regulations

b) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug(s) for a total of 7 months post-treatment completion

c) Azoospermic males are exempt from contraceptive requirements

Investigators shall counsel male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise male subjects who are sexually active with WOCBP on the use of highly effective methods of contraception (see Appendix 3). Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly.

3.3.3 Exclusion Criteria

1) Target Disease Exceptions

a) Presence of visceral metastases in liver.

b) Active brain metastases or leptomeningeal metastases. Subjects 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. 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, Concurrent Diseases and Prior Therapies

a) Subjects 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.

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

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

d) Less than 1 month since resolution of ≥ Grade 2 toxicity related to pelvic-targeted therapy (eg, radiation enteritis).

e) Prior radiation therapy within 14 days prior to starting study therapy. Any toxicity related to prior radiation therapy must have resolved to Grade ≤ 1 or baseline prior to starting study therapy.

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

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

h) Subjects with serious or uncontrolled medical disorders that in the opinion of the investigator, would impair the ability of the subject to receive protocol therapy or obscure the interpretation of AEs, such as a condition associated with frequent diarrhea

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. Subjects 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. <u>For Cohort D: Subjects with symptomatic peripheral neuropathy grade > 2 are excluded</u>

j) 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

k) 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, superficial bladder cancer, or carcinoma in situ of the breast

l) Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, history of congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements

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

o) For Cohort D: previous treatment with cabazitaxel in the metastatic setting

p) Participants with superscan on Technecium-99m radionuclide bone scans are not eligible for the study. Superscan is defined as a bone scan which demonstrates markedly increased skeletal radioisotope uptake relative to soft tissues in association with absent or faint renal activity (absent kidney sign).

3) Physical and Laboratory Test Findings

a) WBC < 2000/μL

b) Neutrophils < 1500/μL

c) Platelets < 100 x 10^3/μL

d) Hemoglobin < 9.0 g/dL

e) Serum creatinine >1.5 x ULN or calculated creatinine clearance < 40 mL/min (using the Cockcroft-Gault formula)

f) AST/ALT: > 3.0 x ULN

g) Total bilirubin > 1.5 x ULN

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

4) Allergies and Adverse Drug Reaction

a) History of allergy or hypersensitivity to study drug components.

b) Cohort D: History of severe (> grade 2) hypersensitivity to docetaxel, or polysorbate 80.

5) Other Exclusion Criteria

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

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

c) Sexually active fertile men not using effective birth control if their partners are women of child-bearing potential (WOCBP).

d) Participation in another clinical trial concurrent with this study.

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

3.3.4 Exclusion Criteria for Crossover Phase for Subjects Originally Randomized to Arm D3 or Arm D4 only

1) Target Disease Exceptions

a) Active brain metastases or leptomeningeal metastases. Subjects 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. 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, Concurrent Diseases and Prior Therapies

a) Subjects must have recovered from the effects of major surgery requiring general anesthetic or significant traumatic injury at least 14 days before first dose of nivolumab combined with ipilimumab.

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

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

d) Less than 1 month since resolution of ≥ Grade 2 toxicity related to pelvic-targeted therapy (eg, radiation enteritis).

e) Prior radiation therapy within 14 days prior to first dose of nivolumab combined with ipilimumab. Any toxicity related to prior radiation therapy must have resolved to Grade ≤ 1 or baseline prior to first dose of nivolumab combined with ipilimumab.

f) For subjects previously randomized to Arm D4, prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways are not allowed.

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

h) Subjects with serious or uncontrolled medical disorders that in the opinion of the investigator, would impair the ability of the subject to receive protocol therapy or obscure the interpretation of AEs, such as a condition associated with frequent diarrhea

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 nivolumab combined with ipilimumab. Subjects 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) 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

k) Any positive test for hepatitis B virus or hepatitis C virus indicating acute or chronic infection, and/or detectable virus

l) History of allergy or hypersensitivity to study drug components

m) 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, superficial bladder cancer, or carcinoma in situ of the breast

n) Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, history of congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements

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

p) Subjects who have received systemic anti-cancer therapy after the last dose of study treatment (ipilimumab or cabazitaxel)

q) If participant has a current or recent SARS-CoV-2 infection, they may be considered eligible after meeting all of the following criteria:

1) At least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared or positive reverse transcription polymerase chain reaction (RT-PCR) or viral antigen test result, and

2) At least 24 hours have passed since last fever without the use of fever-reducing medications, and

3) Acute symptoms (eg, cough, shortness of breath) have resolved and

4) In the opinion of the investigator, there are no coronavirus disease 2019 (COVID-19)-related sequelae that may place the participant at a higher risk of receiving investigational treatment, and

5) Negative follow-up SARS-CoV-2 RT-PCR or viral antigen test based on institutional, local, or regional guidelines

3) Physical and Laboratory Test Findings

a) WBC < 2000/μL

b) Neutrophils < 1500/μL

c) Platelets < 100 x 10^3/μL

d) Hemoglobin < 9.0 g/dL

e) Serum creatinine >1.5 x ULN or calculated creatinine clearance < 40 mL/min (using the Cockcroft-Gault formula)

f) AST/ALT: > 3.0 x ULN

g) Total bilirubin > 1.5 x ULN

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

4) Other Exclusion Criteria

a) Prisoners or subjects who are involuntarily incarcerated. (Note: under certain specific circumstances and only in countries where local permissions permit, a person who has been imprisoned may be included or permitted to continue as a subject. Strict conditions apply and Bristol-Myers Squibb approval is required.)

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

c) Sexually active fertile men not using effective birth control if their partners are women of child-bearing potential (WOCBP).

3.3.5 Women of Childbearing Potential

Not Applicable.

3.4 Concomitant Treatments

3.4.1 Prohibited and/or Restricted Treatments for All Arms

Treatment with any of the following medications are prohibited during the study:

- Any concurrent non-protocol-specified anti-neoplastic therapy (ie, chemotherapy, hormonal therapy other than ADT, immunotherapy, extensive, non-palliative radiation therapy, standard or investigational agents for treatment of mCRPC)
- 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.

3.4.1.1 Prohibited and/or Restricted Treatments on Nivolumab and Ipilimumab

Treatment with any of the following medications are prohibited during treatment with nivolumab and/or ipilimumab:

- Immunosuppressive agents (except to treat a drug-related adverse event)
- Systemic corticosteroids > 10 mg daily prednisone equivalent (except as stated in Section 3.4.3 below or to treat a drug-related adverse event).
- Any live/attenuated vaccine (eg varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella (MMR)) during treatment and until 100 days post last dose.

3.4.1.2 Prohibited and/or Restricted Treatments on Cabazitaxel

Treatment with any of the following medications are prohibited during treatment with cabazitaxel (Arm D4)

- Concomitant administration of strong CYP3A inhibitors (eg, ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) should be avoided as an increase of plasma concentrations of cabazitaxel may occur.
- Concomitant administration of strong CYP3A inducers (eg, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital) should be avoided as a decrease of plasma concentrations of cabazitaxel may occur. In addition, patients should also refrain from taking St. John's Wort.
- Concomitant administration of transport proteins of the Organic Anion Transport Polypeptides OATP1B1: In vitro, cabazitaxel has also been shown to inhibit the transport proteins of the Organic Anion Transport Polypeptides OATP1B1. The risk of interaction with OATP1B1 substrates (eg, statins, valsartan, repaglinide) is possible, notably during the infusion duration (1 hour) and up to 20 minutes after the end of the infusion. A time interval of 12 hours is recommended before the infusion and at least 3 hours after the end of infusion before administering the OATP1B1 substrates.

Additional information can be found in the cabazitaxel prescribing information.

3.4.2 Other Restrictions and Precautions

Palliative (limited-field) radiation therapy and palliative surgical resection are permitted, if the case is discussed with the BMS Medical Monitor or Study Director.

If palliative radiation therapy involves more than one site or if surgery of kyphoplasty to any neoplastic lesion is performed, the date of initiation of radiation therapy or date of surgery should be reported as the date of clinical progression (Section 5.5.3).

Participants requiring palliative local therapy should be evaluated (by CT/MRI and bone scan if clinically indicated) for objective evidence of disease progression prior to the initiation of such therapy, particularly if the most recent tumor assessment was more than 4 weeks prior to the planned start of local therapy. If progression per PCWG2 is identified prior to the initiation of palliative local therapy, then participants must either discontinue study treatment or they must meet criteria to continue treatment beyond progression (Section 4.5.4) in order to resume study treatment after the completion of palliative local therapy

In cases where palliative radiotherapy is required, nivolumab and ipilimumab dosing should be withheld for at least 1 week before, during, and 1 week after radiotherapy. Participants should be closely monitored for any potential toxicity during and after receiving radiotherapy, and AEs should resolved to Grade ≤ 1 prior to resuming nivolumab.

3.4.3 Permitted Therapy

Castrate status must be maintained on study; therefore, subjects who have not had an orchiectomy must continue on LHRH/GnRH agonist therapy.

Subjects 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.

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

3.4.4 Other Restrictions and Precautions

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

Specific to MRI, subjects 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 subject population. In addition, subjects are excluded from MRI if they have tattoos, metallic implants, pacemakers, etc.

The ultimate decision to perform MRI in an individual subject in this study rests with the site radiologist, the investigator and the standard set by the local Ethics Committee.

3.5 Discontinuation of Subjects following any Treatment with Study Drug

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.

If a subject meets the criteria for discontinuation of ipilimumab but not nivolumab, treatment with nivolumab may not resume until the AE has fully resolved and the subject has discontinued steroids, if they were required for treatment of the AE. The relationship to ipilimumab should be well documented in the source documents. Nivolumab should be resumed at 480 mg every 4 weeks starting 6 weeks after the last co-administered dose.

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

- Subject's request to stop study treatment
- 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 subject
- 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. Note: Under specific circumstances and only in countries where local regulations permit, a participant who has been imprisoned may be permitted to continue as a participant. Strict conditions apply and BMS approval is required.
- Additional protocol specified reasons for discontinuation (see Sections 4.5.3 and 4.5.4)
- Subject meets criteria for radiographic progression by PCWG2 or RECIST v1.1 criteria[7]

All subjects who discontinue study treatment should comply with protocol specified follow-up procedures as outlined in Table 5.1-5.The only exception to this requirement is when a subject 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 subject's completion of the study, the reason for the discontinuation must be documented in the subject's medical records and entered on the appropriate case report form (CRF) page.

3.6 Follow up after discontinuation of study drug

In this study, overall survival is a key endpoint of the study. Post treatment follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects 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 3.1 until death or the conclusion of the study.

3.6.1 Withdrawal of Consent

Subjects 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 subject specifically withdraws consent for any further contact with him/her or persons previously authorized by subject to provide this information. Subjects should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, if 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. As vital status (whether the subject 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.

3.6.2 Lost to Follow-Up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of three documented phone calls, faxes, or emails as well as lack of response by subject to one registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the 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 subject's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining subject'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 subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

4 STUDY TREATMENT

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

Table 4-1: Study Treatment for CA209650

Product Description / Class and Dosage Form	Potency	Primary Packaging (Volume)/ Label Type	Secondary Packaging (Qty) /Label Type	Packaging/ Appearance	Storage Conditions (per label)
Nivolumab Solution for Injection[a]	100 mg (10 mg/mL) or 40 mg (10 mg/mL)	10 mL per vial/Open label Or 4 mL vial/Open label	5 or 10 vials per carton/ Open-label Or 240 mg kits (2-100 mg vials & 1-40 mg vial)	Clear to opalescent colorless to pale yellow liquid. May contain particles	2° to 8°C. Protect from light and freezing
Ipilimumab	200 mg (5 mg/mL)	40 mL per vial/Open-label	4 vials per carton/Open-label	Clear to opalescent colorless to pale yellow liquid. May contain particles	2° to 8°C. Protect from light and freezing
Ipilimumab[b]	50 mg (5 mg/mL)	10 mL per vial/Open label	6 vials per carton/Open-label	Clear to opalescent colorless to pale yellow liquid. May contain particles	2° to 8°C. Protect from light and freezing
Prednisone[c]	5 mg tablets	Wallet/blister card/bottle containing tablets/open-label	Wallet card or outer carton/open-label	Tablets (appearance may vary)	Refer to storage conditions on container label.
Cabazitaxel concentrate and solvent for solution for infusion[c]	60 mg	Vial/Open-label	Vials in a carton/Open-label	Vial (various configurations possible)	Refer to storage conditions on container label.

[a] Nivolumab is labeled as BMS-936558-01 Solution for Injection.

[b] Ipilimumab 50 mg will be available starting Q3 2022 and may be used in this study.

[c] Cabazitaxel and prednisone may be obtained by the investigational sites in certain countries as local commercial product (which may be available as a different potency/package configuration). Prednisone or prednisolone can be used according to local standards.

Pre-medications or medications used to treat in infusion reactions should be sourced by the investigative sites if available and permitted by local regulations.

4.1 Investigational Product

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.

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 subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

In this protocol, investigational products are:

- Nivolumab
- Ipilimumab
- Cabazitaxel

4.2 Non-investigational Product

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. In this protocol, non-investigational product is:

- Prednisone

4.3 Storage and Dispensing

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 BMS must be contacted immediately.

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

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

4.3.1 Arms A, B, and C Part 1 Study Treatment Administration - Nivolumab and Ipilimumab Combination Phase (Cycles 1-4)

In the nivolumab plus ipilimumab combination portion, nivolumab is to be administered first. Subjects 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 4 doses (Cycles 1-4). In Part 1, a minimum of 1 combination cycle of nivolumab and ipilimumab is required. Subjects 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 the Medical Monitor, on a case-by-case basis.

During Part 1, subjects 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.

The nivolumab infusion must be promptly followed by a flush of diluent 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 subject 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. Subjects 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 subject 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 subjects and treatment centers. Establishing that these agents can be safely administered using shorter infusion times will diminish some of this burden. Previous clinical studies of nivolumab have used a 60-minute infusion duration, and for ipilimumab 90-minutes. 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.[129]

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.[130]

Subjects should be carefully monitored for infusion reactions during nivolumab/ipilimumab administration. If an acute infusion reaction is noted, subjects should be managed according to Section 4.5.7.

4.3.2 Arms A, B, and C Part 2 Study Treatment Administration - Nivolumab Monotherapy Phase (Cycle 5 and beyond)

Starting 6 weeks after the last co-administered dose in Part 1, subjects will be administered a flat dose of 480 mg nivolumab on Day 1 of each 4 week treatment cycle given IV given over approximately 30 minutes every 4 weeks (Q4W) until unacceptable toxicity or disease progression.

Subjects 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. 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 subject 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 monotherapy.

Subjects from Cohorts B and C who entered the maintenance period may be permitted re-induction with the combination after approval by the BMS medical monitor (see Section 4.3.5).

4.3.3 Arm D1 Study Treatment Administration - Nivolumab and Ipilimumab

Subjects randomized to Arm D1 should receive nivolumab 3 mg/kg administered IV over 30 minutes followed by ipilimumab 1 mg/kg administered IV over 30 minutes on Day 1 of each treatment cycle every 3 weeks for 4 doses (Cycles 1 to 4), followed by nivolumab 480 mg administered IV over 30 minutes on Day 1 of each treatment cycle every 4 weeks (±3 days) until progression, unacceptable toxicity, withdrawal of consent, completion of 2 years of treatment, or the study ends, whichever occurs first. The first flat dose 480 mg nivolumab will be administered 3 weeks after the last combination dose.

Participants should begin study treatment within 3 calendar days of randomization. During the combination portion, subjects 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.

When study treatments (nivolumab and ipilimumab) are to be administered on the same day, nivolumab is to be administered first. Nivolumab infusion must be promptly followed by a flush of diluent to clear the line of nivolumab before starting the ipilimumab infusion. The second infusion will always be the ipilimumab study treatment and will start after the infusion line has been flushed, filters changed and patient has been observed to ensure no infusion reaction has occurred.

During the combination phase, a minimum of 1 combination cycle of nivolumab and ipilimumab is required. Subjects experiencing AEs related to combination dose therapy that do not meet dose discontinuation criteria, may proceed to nivolumab monotherapy dosing without completing all 4 combination doses, after consultation with the Medical Monitor, on a case-by-case basis.

Dosing calculations for the combination phase should be based on the body weight assessed at baseline. 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 up or to the nearest milligram per institutional standard.

Premedication for Arm D1 is not recommended for the first dose of nivolumab and ipilimumab.

4.3.4 Arm D2 Study Treatment Administration for Nivolumab and Ipilimumab

Subjects randomized to Arm D2 will 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 8 cycles (on weeks 1, 4, 7, 10, 13, 16, 19 and 22) and ipilimumab 3 mg/kg administered IV over 30 minutes every 2 cycles (ie, every 6 weeks on weeks 1, 7, 13 and 19) for 4 ipilimumab doses, followed by nivolumab 480 mg administered IV over 30 minutes on Day 1 of each treatment cycle every 4 weeks (± 3 days) starting from cycle 9 (week 25). Treatment will be administered until progression, unacceptable toxicity, withdrawal of consent, completion of 2 years of treatment, or the study ends, whichever occurs first. The first flat dose 480 mg nivolumab will be administered 3 weeks after the last nivolumab 1 mg/kg dose (and 6 weeks after the last combination dose).

Participants should begin study treatment within 3 calendar days of randomization. During the combination phase, subjects may be dosed with nivolumab no less than 19 days from the previous dose of nivolumab and may be dosed with ipilimumab no less than 37 days from the previous dose of ipilimumab.

When study treatments (nivolumab and ipilimumab) are to be administered on the same day, nivolumab is to be administered first. Nivolumab infusion must be promptly followed by a flush of diluent to clear the line of nivolumab before starting the ipilimumab infusion. The second infusion will always be the ipilimumab study treatment and will start after the infusion line has been flushed, filters changed and patient has been observed to ensure no infusion reaction has occurred.

During the combination phase, a minimum of 1 combination cycle of nivolumab and ipilimumab is required. Subjects experiencing AEs related to combination dose therapy that do not meet dose discontinuation criteria, may proceed to nivolumab monotherapy dosing without completing all 4 doses of ipilimumab, after consultation with the Medical Monitor, on a case-by-case basis.

Dosing calculations for the combination phase should be based on the body weight assessed at baseline. 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 up or to the nearest milligram per institutional standard.

Premedication for Arm D2is not recommended for the first dose of nivolumab and ipilimumab.

4.3.5 Re-Induction of Study Therapy For Subjects in Cohorts B, C, Arms D1 and D2

Subjects in Cohorts B, C and in Arms D1 and D2 who are receiving maintenance nivolumab with ongoing disease control (ongoing CR, PR, or SD) or with radiographic progression per RECIST v1.1/PCWG2 may be permitted re-induction with the combination of ipilimumab and nivolumab at their original combination dose upon PSA progression or radiographic progression per

RECIST v1.1/PCWG2 (whichever occurs first; see Section 5.5.3), and after discussion and agreement with BMS Medical Monitor.

For subjects in Arm D1, the first re-induction combination dosing can start no sooner than 4 weeks after the last nivolumab 480 mg dose and no sooner than 12 weeks after the last ipilimumab dose.

For subjects in Arm D2, the first re-induction combination dosing can start no sooner than 8 weeks after the last nivolumab 480 mg dose and no sooner than 12 weeks after the last ipilimumab dose. Pausing nivolumab maintenance dosing is permitted in patients who are planning to receive re-induction in Arm D2.

Subjects entering this phase will follow the same Time and Events schedule as outlined in Table 5.1-2 and Table 5.1-4.

Subjects undergoing re-induction of study therapy should continue to meet eligibility criteria at the time study treatment resumes and should not have experienced a toxicity that would require permanent discontinuation of study therapy. Subjects will continue to receive study therapy at the same dose levels as assigned at study start.

Additional, separate, safety and efficacy summaries will be presented for those subjects who reinitiated study therapy.

4.3.6 Arm D3 Study Treatment Administration

Participants should receive ipilimumab at a dose of 3 mg/kg administered IV over 30 minutes on Day 1 of each treatment cycle every 3 weeks for 4 doses. Treatment will continue until disease progression, unacceptable toxicity, withdrawal of consent, completion of 4 cycles of treatment, or the study ends, whichever occurs first.

Participants should begin study treatment within 3 calendar days of randomization. Subjects may be dosed with ipilimumab no less than 19 days from the previous dose of ipilimumab.

Dosing calculations should be based on the body weight assessed at baseline. 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 up or to the nearest milligram per institutional standard.

Premedication for Arm D3 is not recommended for the first dose of ipilimumab.

4.3.7 Arm D4 Study treatment administration - cabazitaxel plus prednisone

The recommended dose of cabazitaxel is 20 mg/m^2 or 25 mg/m^2 at investigator's discretion and according to country-specific label, administered as a 1 hour intravenous infusion every 3 weeks in combination with oral prednisone or prednisolone 10 mg administered daily throughout treatment. Since cabazitaxel is extensively metabolized by the liver, patients with mild hepatic impairment (total bilirubin >1 to ≤ 1.5 × ULN or AST >1.5 × ULN) must start cabazitaxel at the dose of 20 mg/m^2.

Dosing of cabazitaxel will continue for a maximum of 10 cycles every 3 weeks (± 3 days), until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first. Participants should begin study treatment within 3 calendar days of randomization.

Dosing calculations of cabazitaxel should be based on the body weight assessed at baseline. 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 up or to the nearest milligram per institutional standard.

Premedication for cabazitaxel

The recommended premedication regimen should be performed at least 30 minutes prior to each administration of cabazitaxel with the following intravenous medicinal products to mitigate the risk and severity of hypersensitivity:

- antihistamine (dexchlorpheniramine 5 mg or diphenhydramine 25 mg or equivalent),
- corticosteroid (dexamethasone 8 mg or equivalent), and
- H2 antagonist (ranitidine or equivalent)

The above prophylaxis can be adjusted according to local standards in patients who have experienced hypersensitivity reactions not requiring discontinuation.

Antiemetic prophylaxis is recommended and can be given orally or intravenously as per local guidelines.

4.3.8 Study Treatment Preparation and Infusion

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

For details on prepared study treatment storage, preparation, and administration, please refer to the current nivolumab and ipilimumab IBs and/or pharmacy manual.

4.4 Method of Assigning Treatment

CA209650 is an open-label study. After the subject's initial eligibility is established and informed consent has been obtained, the subject must be enrolled into the study by accessing an Interactive Response Technologies web-based system (IWRS) to obtain the subject number. Every subject that signs the informed consent form must be assigned a subject number in IWRS. Specific instructions for using IWRS will be provided to the investigational site in a separate document. All participants in Cohort D will be centrally randomized using IWRS. Before the study is initiated, each user will receive log in information and directions on how to access the IWRS. The following information is required for enrollment:

- Date that informed consent was obtained
- Date of birth

Once enrolled in IWRS, enrolled subjects that have met all eligibility criteria will be ready to be assigned treatment through the IWRS. The following information is required for subject first treatment:

- Subject number
- Date of birth
- Presence or absence of measureable disease as per RECIST v1.1 at screening

The exact procedures for using the IWRS will be detailed in the IWRS manual.

4.5 Selection and Timing of Dose for Each Subject

The dosing regimen and schedule for Cohorts A, B, and C are detailed in Table 4.5-1 and Table 4.5-2, respectively. The dosing regimen and schedule for Cohort D is shown in Table 4.5-3.

Table 4.5-1: Cohorts A, B, and C Dosing Schedule for Part 1 (Cycles 1 through 4)[a]

Every 3 weeks dosing 1 cycle = 3 weeks				
	Cycle 1	**Cycle 2**	**Cycle 3**	**Cycle 4**
All Subjects	Nivolumab 1 mg/kg Ipilimumab 3 mg/kg	Nivolumab 1 mg/kg Ipilimumab 3 mg/kg	Nivolumab 1 mg/kg Ipilimumab 3 mg/kg	Nivolumab 1 mg/kg Ipilimumab 3 mg/kg

[a] Minimum of 1 cycle, maximum of 4 combination cycles

The first flat dose 480 mg nivolumab in Part 2 will be administered 6 weeks after the last combination dose in Part 1.

Table 4.5-2: Cohorts A, B, and C Dosing Schedule for Part 2 (Cycles 5 through PD)

Every 4 weeks dosing 1 cycle = 4 weeks, Cycle 5 to begin 6 weeks after Cycle 4	
	Cycle 5 and beyond[a]
All Subjects	Flat dose 480 mg nivolumab

[a] Cycle 6, 7, 8, 9, etc. until disease progression or unacceptable toxicity. In some instances, Part 2 may start after Cycle 1, 2 or 3 of Part 1.

Table 4.5-3: Cohort D Dosing Schedule		
	Induction	**Maintenance**
Arm D1	Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg Q3W up to 4 cycles,	Nivolumab 480 mg Q4W
Arm D2	Nivolumab 1 mg/kg Q3W (up to 8 doses)+ Ipilimumab 3 mg/kg Q6W (up to 4 doses)	Nivolumab 480 mg Q4W
Arm D3	Ipilimumab 3 mg/kg Q3W up to 4 cycles	Not applicable
Arm D4	Cabazitaxel 20 mg/m^2 or 25mg/m^2 (at investigator's discretion and according to country-specific label) Q3W + Prednisone 10 mg PO D1-D21* for up to 10 cycles	

* Starting dose of cabazitaxel is 20 mg/m2 in patients with mild hepatic impairment (total bilirubin >1 to ≤ 1.5 × ULN or AST >1.5 × ULN)

There will be no dose escalations of study treatment allowed. Dose reductions are only allowed for cabazitaxel.

Doses may be interrupted, delayed, or discontinued depending on how well the subject tolerates the treatment. Dosing visits are not skipped, only delayed. The maximum duration of treatment of 2 years includes any dose interruptions or delays in Cohort D. It is strongly recommended that subjects in Cohorts A, B, and C limit treatment duration with immunotherapy treatment for up to 2 years. For subjects in these cohorts who receive immunotherapy treatment beyond 2 years, treatment will be given for a maximum of 5 years from the start of study treatment.

When subjects are treated Q3W, subjects 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.

During nivolumab monotherapy, subjects may be dosed within a ± 3 day window.

Subjects experiencing AEs related to combination dose therapy that do not meet dose discontinuation criteria, may proceed to nivolumab monotherapy dosing without completing all 4 combination doses, after consultation with BMS Medical Monitor, on a case-by-case basis (Section 4.5.3).

4.5.1 Dose Delay Criteria for Nivolumab and Ipilimumab

Regardless of whether or not the event is attributed to nivolumab or ipilimumab, both study treatments must be delayed until treatment can resume. Tumor assessments for all subjects should continue as per protocol even if dosing is delayed. During Part 1, both nivolumab and ipilimumab should be delayed at the same time.

Nivolumab and ipilimumab administration should be delayed for the following:

- Any Grade ≥ 2 non-skin, drug-related adverse event, with the following exception:
  - Grade 2 drug-related fatigue does not require a treatment delay
- Grade 2 drug-related creatinine, AST, ALT or Total Bilirubin abnormalities
- Any Grade 3 skin, drug-related adverse event

- Any Grade 3 drug-related laboratory abnormality (excluding AST, ALT or Total Bilirubin), 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
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication
- SARS-CoV-2 infection either confirmed or suspected

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

4.5.2 Criteria to Resume Treatment for Nivolumab and Ipilimumab

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

- Subjects may resume treatment in the presence of Grade 2 fatigue
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- For subjects with Grade 2 AST, ALT, or TBILI elevations, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, is complete
- Subjects with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (Section 4.5.3) should have treatment permanently discontinued
- Drug-related pulmonary toxicity, diarrhea or colitis must have resolved to baseline before treatment is resumed. Subjects 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

Subjects 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.

4.5.3 Dose Discontinuation for Nivolumab and Ipilimumab

Study treatment (nivolumab or ipilimumab) 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 reactions, 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 requires discontinuation:
    - Grade ≥ 3 drug-related AST, ALT or Total Bilirubin requires discontinuation*
    - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2x ULN

*In most cases of Grade 3 AST or ALT elevation, study treatment(s) will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment(s), a discussion between the investigator and the BMS Medical Monitor/designee must occur.

- Any Grade 4 drug-related 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. Grade 4 drug-related adrenal insufficiency or hypophysitis requires discontinuation regardless of control with hormone replacement.
- Any event that leads to delay in dosing lasting > 8 weeks from the previous dose for Q3W dosing cycles , and >10 weeks for Q4W dosing cycles requires discontinuation, with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a subject with a dosing delay lasting > 8 weeks from the previous dose for Q3W dosing cycles and >10 weeks for Q4W dosing cycles , the BMS Medical Monitor must be consulted.

- Subjects experiencing AEs related to combination dose therapy that do not meet dose discontinuation criteria, may proceed to nivolumab monotherapy dosing without completing all 4 combination doses, after consultation with BMS Medical Monitor, on a case-by-case basis.
- 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.
- Dosing delays lasting > 8 weeks from the previous dose for Q3W dosing cycles and >10 weeks for Q4W dosing cycles that occur for nondrug-related reasons may be allowed if approved by the BMS Medical Monitor. Prior to reinitiating treatment in a subject with a dosing delay lasting > 8 weeks for Q3W dosing cycles and >10 weeks for Q4W dosing cycles, the BMS Medical Monitor must be consulted.

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

4.5.4 Treatment Beyond Disease Progression

Accumulating evidence indicates that some subjects treated with immunotherapy may derive clinical benefit despite initial evidence of PD.

Subjects treated with immunotherapy study treatment(s) will be permitted to continue treatment beyond initial radiographic progression defined by RECIST v1.1 (for soft tissue lesions) and PCWG2 (for bone lesions) as described in Section 5.5.3. Subjects in Arm D4 may not receive treatment beyond progression. Subjects who meet PD criteria as assessed by the investigator may continue with study therapy as long as they meet the following criteria (following consultation with BMS Medical Monitor):

- Investigator-assessed clinical benefit
- Tolerance of study treatment
- Stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases)
- Subject provides written informed consent prior to receiving additional nivolumab and ipilimumab combination or nivolumab monotherapy 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 5 Schedule of Activities for the duration of the treatment beyond progression and should be submitted to the central imaging vendor. The assessment of clinical benefit should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive any benefit from continued treatment with nivolumab.

If the investigator feels that the subject continues to achieve clinical benefit by continuing treatment, the subject should remain on the trial and continue to receive monitoring according to the Time and Events Schedule (Section 5).

For the subjects who continue study therapy beyond progression, further progression is defined as follows:

Further disease progression of soft tissue 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.

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.

Further bone disease progression is defined as additional two or more new bone lesions noted on bone scans compared to the time of PCWG2-defined progression of bone disease.

Nivolumab-plus-ipilimumab or nivolumab treatment should be discontinued permanently upon documentation of further progression.

Confirmed PSA progression alone is not an indication to stop treatment.

4.5.5 Dose Delay, Modification, and Discontinuation for Cabazitaxel

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

Cabazitaxel administration should be delayed for the following:

- SARS-CoV-2 infection either confirmed or suspected

The cabazitaxel dose will be modified in case of toxicity. Dose modifications are summarized in Table 4.5.5-1.

Table 4.5.5-1: Dose Modification* and Dose Delay for Cabazitaxel			
Toxicity	**Grade 2**	**Grade 3**	**Grade 4**
Neutropenia	If not recovered on D21, delay** next infusion until recovery to grade ≤ 1 (neutrophil ≥ 1.5 x 109/L). • 1st episode: No dose reduction required. • 2nd episode; reduce by 1dose level	No dose reduction if isolated and duration ≤ 7 days. If duration more than 7 days or not recovered on D21 Delay** next infusion until ANC ≥ 1.5 x 109/L and: • 1st episode: Administer prophylactic G-CSF treatment in subsequent cycles. • 2nd episode or 1st episode despite prophylactic G-CSF: Reduce dose by 1 dose level. • 3rd episode or 2nd episode despite prophylactic G-CSF: Withdraw from study treatment	
Febrile neutropenia or neutropenic infection	Not applicable	Delay** next infusion until recovery and ANC ≥ 1.5 x 109/L and: • 1st episode: reduce the dose and administer prophylactic G-CSF treatment in subsequent cycles. • 2nd episode: Withdraw from study treatment	
Thrombocytopenia	Delay** next infusion until recovery to grade ≤ 1 (platelets ≥ 75 x 109/L). No dose reduction required.	Delay** infusion until platelets ≥ 75 x 109/L: If grade 3 without delay, no dose reduction required. If grade 4 , or grade 3 with delay • 1st episode: reduce dose by 1 dose level. • 2nd episode: reduce dose by 1 more dose level. • 3rd episode: Withdraw from study treatment in case of recurrence	
Diarrhea	Delay** next infusion until recovery (grade ≤1) No dose reduction required.	• 1st episode: Reduce dose by 1 dose level. • 2nd episode: Reduce dose by 1 more dose level. • 3rd episode: Withdraw from study treatment.	
Stomatitis	Delay** next infusion until recovery (grade ≤1) No dose reduction required.	• 1st episode: Reduce dose by 1 dose level. • 2nd episode: Reduce dose by 1 more dose level. • 3rd episode: Withdraw from study treatment.	

Table 4.5.5-1: Dose Modification* and Dose Delay for Cabazitaxel			
Toxicity	**Grade 2**	**Grade 3**	**Grade 4**
Cutaneous Reactions	Delay** next infusion until recovery (grade ≤1) No dose reduction required.	**Grade 3** Delay** next infusion until recovery (grade ≤1): • 1st episode: Reduce dose by 1 dose level. • 2nd episode: Withdraw from study treatment.	**Grade 4** Withdraw from study treatment.
Creatinine increase/ Creatinine clearance decrease	No delay, in case of creatinine > 1 x ULN calculate creatinine clearance on D21: • if ≥ 60 ml/min, no dose modification • if clearance ≥40 ml/min and < 60 ml/min, reduce dose by one dose level • if clearance <40 ml/min, Withdraw from study treatment.		
Neurological toxicity***	No delay Reduce dose by 1 dose level	Stop study treatment.	
Bilirubin Elevation	Delay** until recovery to bilirubin ≤ 1.0 x UNL and reduce dose by 1 dose level	Withdraw from study treatment	
Transaminases Elevation	Delay** until recovery to AST/ALT ≤ 1.5 x UNL and reduce dose by 1 dose level	Withdraw from study treatment	
Hypersensitivity	No dose reduction. Follow local guidelines for management of hypersensitivity due to study treatment. Withdraw from study treatment in case of 2nd grade 3 episode.	Withdraw from study treatment	

*Dose reduction levels provided in Section 4.5.5.2

**maximum of 2 weeks delay, otherwise the patient will be withdrawn from study treatment, unless otherwise agreed between the investigator and the Sponsor on a case-by-case basis

***Including hearing disorders

§Delay infusion by maximum of 2 weeks until recovery to grade ≤ 1 and apply dose reduction according to worst grade observed

4.5.5.1 Other Toxicities for Cabazitaxel

For ≥ Grade 3 drug-related AEs except fatigue, local reaction, fluid retention, anemia and other toxicities that in the opinion of the investigator are not clinically significant, chemotherapy should be held for a maximum of two weeks from the planned date of reinfusion until resolution to ≤ Grade 1, then reinstituted, if medically appropriate. In case of treatment delay greater than 2 weeks, patient should discontinue study treatment, unless there is strong evidence of clinical benefit to justify continuation of dosing with study treatment, and the investigator must discuss the rationale with the Sponsor before a decision is taken. A dose reduction of subsequent doses

will be left to the investigator's judgment. These patients will be withdrawn from study treatment if >2 dose reductions are needed.

4.5.5.2 Dose Reduction for cabazitaxel

Cabazitaxel dose can be reduced when necessary as described in following sections. The dose, which has been reduced for toxicity, must not be re-escalated. Up to a maximum of 2 dose reductions will be allowed per patient. If a third dose reduction is required per the modifications below, the patient should discontinue study treatment.

Table 4.5.5.2-1: Dose reduction levels for cabazitaxel

Dose reduction levels for cabazitaxel			
	Starting dose (mg/m²)	**1st Dose Reduction**	**2nd Dose Reduction**
Cabazitaxel	20	15	12
Cabazitaxel	25	20	15

Note: Starting dose is 20 mg/m2 or 25 mg/m2 at investigator's discretion and according to country-specific label; participants with hepatic impairment must start cabazitaxel at the dose of 20 mg/m2).

4.5.5.3 Special Precautions for Cabazitaxel

1) Risk of neutropenia: Neutropenia is the most common adverse reaction of cabazitaxel. Monitoring of complete blood counts is essential on a weekly basis during cycle 1 and before each treatment cycle thereafter so that the dose can be adjusted, if needed. Patients treated with cabazitaxel may receive prophylactic G-CSF as per current institutional guidelines, to reduce the risk or manage neutropenia complications.
2) Primary prophylaxis with G-CSF should be considered in patients with high-risk clinical features (age >65 years, poor performance status, previous episodes of febrile neutropenia, extensive prior radiation ports, poor nutritional status, or other serious comorbidities) that predispose them to increased complications from prolonged neutropenia.
3) Gastrointestinal disorders: Symptoms such as abdominal pain and tenderness, fever, persistent constipation, diarrhea, with or without neutropenia, may be early manifestations of serious gastrointestinal toxicity and should be evaluated and treated promptly.
4) Nausea, vomiting and severe diarrhea, at times, may occur. Deaths related to diarrhea and electrolyte imbalance occurred in the randomized clinical trials. Intensive measures may be required for severe diarrhea and electrolyte imbalance. Antiemetic prophylaxis is recommended. Treat patients with rehydration, antidiarrheal or antiemetic medications as needed.

4.5.5.4 Prednisone Dose Modifications and Dose Delays

Prednisone or prednisolone doses should not be delayed or modified or stopped (unless there is a contraindication to continue, the decision will be left to the investigator's discretion). If prednisone or prednisolone is stopped, the patient will continue cabazitaxel treatment in the absence of major toxicity, disease progression, or any other discontinuation criteria as defined in Section 4.5.5.

4.5.5.5 Criteria to Resume Study Treatment following SARS-CoV-2 Infection

Participants with SARS-CoV-2 infection (either confirmed or suspected) may resume treatment after **all of the following**:

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

4.5.6 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 the Appendix 1 of this protocol.

4.5.7 Treatment of Related Infusion Reactions

4.5.7.1 Nivolumab and Ipilimumab Treatment of Related Infusion Reactions

Since nivolumab and ipilimumab contain only human immunoglobulin protein sequences, they are 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 study medical monitor and reported as an SAE if it meets the criteria. Infusion reactions should be graded according to NCI CTCAE (Version 4.0) guidelines.

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

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

- Remain at bedside and monitor subject 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 and/or ipilimumab administrations.

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

- Stop the study treatment infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor subject 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 subject closely. If symptoms recur, then no further study treatment will be administered at that visit
- For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg should be administered at least 30 minutes before nivolumab and/or ipilimumab 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 study treatment. Begin an IV infusion of normal saline and treat the subject 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. Subject should be monitored until the Investigator is comfortable that the symptoms will not recur. Study treatment will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject 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).

4.5.7.2 Hypersensitivity Reactions for Cabazitaxel

All patients should be pre-medicated prior to the initiation of the infusion of cabazitaxel (see Section 4.5.5).

Patients should be observed closely for hypersensitivity reactions especially during the first and second infusions. Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of cabazitaxel, thus facilities and equipment for the treatment of hypotension and bronchospasm should be available. Severe reactions can occur and may include generalized rash/erythema, hypotension and bronchospasm. Severe hypersensitivity reactions require immediate discontinuation of cabazitaxel and appropriate therapy.

4.6 Blinding/Unblinding

This is an Open-label study, blinding procedures are not applicable.

4.7 Treatment Compliance

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

4.8 Return of Study Treatment

For this study, IP (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.

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 IP provided by BMS (or its vendors).

4.9 Retained Samples for Bioavailability/Bioequivalence

At the time of receipt of the investigational product by the investigator or designee's, BMS will specify the appropriate number of containers or units to select for retention, the conditions of sample storage, required duration of sample retention, and provisions for returning or disposing of the investigational product. When samples are selected, containers or units should be placed in packaging with a tamper evident seal provided by BMS. Package labeling should clearly identify the contents as bioavailability/bioequivalence (BA/BE) samples and state that the investigational product should be stored in the restricted area with limited access.

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1-1: Screening Procedural Outline (CA209650) for All Treatment Arms (Cohorts A, B, C, and D)

Procedure	Screening Visit	Notes
Eligibility Assessments		
Informed Consent	X	Prior to any screening procedures. Contact IWRS to obtain study subject number. Study allows for re-enrollment of a subject that has discontinued the study as a pre-treatment failure. If re-enrolled, the subject must be re-consented and assigned a new subject number from IWRS.
Inclusion/Exclusion Criteria	X	All inclusion/exclusion criteria should be assessed at screening and confirmed prior to first treatment. See Section 3.3.
BPI-SF	X	Within 14 days prior to first dose. To be completed for all participants and must be performed to establish eligibility in Cohort B participants. (See Section 3.3.1)
FACT-P (Cohort D only)	X	Within 14 days prior to first dose.
EQ-5D-3L	X	Within 14 days prior to first dose.
Medical History	X	Includes clinical stage and Gleason score at diagnosis
Prior Cancer Therapy	X	Details and dates of prior therapy including all hormonal therapies.
ECOG Performance Score	X	Within 14 days prior to first dose. See Appendix 2 for ECOG Performance Status scale
Safety Assessments		
Physical Examination	X	Within 14 days prior to first dose
Vital Signs	X	Including BP, HR, and temperature. Obtain vital signs at screening visit and within 72 hours prior to first dose.
Physical Measurements	X	Height and Weight
Assessment of Signs and Symptoms	X	Within 14 days prior to first dose
ECG	X	Within 14 days prior to first dose
Adverse Events Assessment	X	All SAEs, including SAEs associated with SARS-CoV-2 infection collected from time of consent. Non-serious AEs associated with SARS-CoV-2 infection, collected from time of consent.

Table 5.1-1: Screening Procedural Outline (CA209650) for All Treatment Arms (Cohorts A, B, C, and D)

Procedure	Screening Visit	Notes
Concomitant Medication Collection	X	Within 14 days prior to first dose
Laboratory Tests	X	On site/local complete blood count (CBC) w/differential, Chemistry panel including: LDH, AST, ALT, ALP, T-Bili, blood urea nitrogen (BUN) or serum urea level, creatinine, phosphate, Ca, Na, K, Cl, glucose, albumin, amylase, lipase, PTT, PT, and INR within 14 days prior to randomization (Cohort D) and first dose for other Cohorts. Endocrine panel (TSH, Free T4, Free T3), Hep B/C (HBV HBsAG, HCV antibody or HCV RNA), within 28 days prior to randomization (Cohort D) and first dose for other Cohorts.
PSA	X	To be performed by local lab up to 6 weeks prior to randomization (Cohort D) and first dose for other Cohorts.
Testosterone	X	To be performed by local lab up to 6 weeks prior to randomization (Cohort D) and first dose for other Cohorts.
Efficacy Assessment		
Screening/Baseline Tumor Assessment	X	Contrast enhanced CT of the Chest, CT/MRI scan of the abdomen, pelvis, and any clinically indicated sites, and radionuclide bone scan within 28 days prior to first dose. MRI of the brain without and with contrast is required for participants with known or suspected brain metastases, unless participant has completed an imaging study of the brain within 30 days of study treatment administration. CT of the brain without and with contrast can be performed if MRI is contraindicated. For the assessment of bone lesions, a Technecium99m (Tech99m) bone scan is the preferred imaging modality. If Tech99m is unavailable, a full body CT/MRI should be performed as described in Section 5.5.2 Images will be collected and held centrally for potential future independent review. See Section 5.5.
[redacted]		

Table 5.1-1: Screening Procedural Outline (CA209650) for All Treatment Arms (Cohorts A, B, C, and D)

Procedure	Screening Visit	Notes
IWRS		
IWRS call or website entry	X	Website entry must be made to IWRS for subject number assignment at the time informed consent is obtained.
Cohort Assignment	X	Website entry to IWRS prior to first dose for cohort assignment.
IWRS Drug Vial Assignment	X	Within 3 working days from vial assignment, the subject must receive the dose of study medication.

Table 5.1-2: On Treatment Part 1: Sequential Treatment with Nivolumab and Ipilimumab Procedural Outline (CA209650) - Cohorts A, B, and C

Procedure	For Part 1, Study Treatment Every 3 Weeks for Cycles 1-4 (Cohorts A, B and C)	Notes
	Cycle 1, 2, 3, 4 (Day 1)	
Safety Assessments		
Targeted Physical Examination	X	To be performed only as clinically indicated within 72 hours prior to dosing
Vital Signs	X	Including BP, HR, and Temperature
Physical Measurements	X	Weight within 72 hours prior to dosing
Adverse Event Assessment	Continuously	Assessed using NCI CTCAE v. 4. All AEs, including those associated with SARS-CoV-2 infection, must be collected continuously during the treatment period.
SAE Assessment	Continuously	Assessed using NCI CTCAE v. 4. All SAEs, including those associated with SARS-CoV-2 infection, must be collected continuously during the treatment period.
Review of Concomitant Medication	X	
Laboratory Tests	X	Within 72 hours prior to each dose. All safety labs to be performed also at the conclusion of Part 1 (~week 12). On site/local CBC w/differential, ALT, AST, ALP T-Bili, BUN or serum urea level, creatinine, calcium, phosphate, Na, K, Cl, LDH, glucose, albumin, amylase, lipase; PTT, PT, and INR Thyroid function testing (TSH with reflexive fT3 and fT4) is to be done every 3 weeks (following each sequential combination dose infusion) for on-treatment Part 1 phase (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 subjects receiving nivolumab at 480 mg q4w Note: Safety Laboratory tests do not need to be repeated on C1D1 if screening labs were performed within 14 days prior to first dose.

Table 5.1-2: On Treatment Part 1: Sequential Treatment with Nivolumab and Ipilimumab Procedural Outline (CA209650) - Cohorts A, B, and C

Procedure	For Part 1, Study Treatment Every 3 Weeks for Cycles 1-4 (Cohorts A, B and C)	Notes
	Cycle 1, 2, 3, 4 (Day 1)	
ECOG Performance Status	X	Refer to Appendix 2
PSA	X	Performed locally D1 (prior to treatment) and every 6 weeks (± 3 calendar days) thereafter. Can be performed at conclusion of Part 1~ week 12.
[redacted]		
Efficacy Assessment		
Body Imaging	X	Contrast enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease should occur every 8 weeks (±7 days) from first dose regardless of treatment schedule for first 6 months.

Table 5.1-2: On Treatment Part 1: Sequential Treatment with Nivolumab and Ipilimumab Procedural Outline (CA209650) - Cohorts A, B, and C

Procedure	For Part 1, Study Treatment Every 3 Weeks for Cycles 1-4 (Cohorts A, B and C) Cycle 1, 2, 3, 4 (Day 1)	Notes
		After that, it will switch to every 12 weeks (±7 days) regardless of treatment schedule until disease progression is documented or treatment is discontinued (whichever occurs later). See Section 5.5.3. Use same imaging method as was used at screening/baseline. Images will be collected and held centrally for retrospective independent review. See Section 5.5.
Brain Imaging	X	Participants with a history of brain metastasis or symptoms should have a surveillance MRI study per standard of care (approximately every 12 weeks), or sooner if clinically indicated. CT of the brain without and with contrast can be performed if MRI is contraindicated.
Tc99m based radionuclide bone scan	X	Every 8 weeks (±7 days) from first dose regardless of treatment schedule for first 6 months. After that, it will switch to every 12 weeks (±7 days) regardless of treatment schedule until disease progression is documented (and confirmed if needed) or treatment is discontinued (whichever occurs later). Evidence of progressive disease as per PCWG2. See Section 5.5.3. Use same imaging method as was used at screening baseline or as described in Section 5.5.2. Images will be collected and held centrally for retrospective independent review. (See Section 5.5).
Outcomes Research Assessments		
BPI-SF	X	Subject must be informed of treatment assignment prior to first post-randomization assessment. Each assessment should be completed at the start of the clinic visit prior to dosing and other study assessments.
EQ-5D-3L	X	

Table 5.1-2: On Treatment Part 1: Sequential Treatment with Nivolumab and Ipilimumab Procedural Outline (CA209650) - Cohorts A, B, and C

Procedure	For Part 1, Study Treatment Every 3 Weeks for Cycles 1-4 (Cohorts A, B and C)	Notes
	Cycle 1, 2, 3, 4 (Day 1)	
Clinical Drug Supplies		
IWRS Drug Vial Assignment	X	Within 72 hours prior to dosing
Administer Study Treatment	X	A minimum of one combination cycle is required.

Table 5.1-3: On Treatment Part 2: Nivolumab Monotherapy Phase Procedural Outline for Cohorts A, B, and C (CA209650)

Procedure	For Part 2, Study Treatment is Administered Every 4 Weeks (Cohorts A, B and C) Cycle 5 and beyond (Day 1)	Notes Cycle 5 will begin 6 weeks after Cycle 4 starts
Safety Assessments		
Targeted Physical Examination	X	To be performed only as clinically indicated within 72 hours prior to dosing
Vital Signs	X	Including BP, HR, and Temperature
Adverse Event Assessment	Continuously	Assessed using NCI CTCAE v. 4. All SAEs, including those associated with SARS-CoV-2 infection, must be collected continuously during the treatment period.
SAE Assessment	Continuously	Assessed using NCI CTCAE v. 4. All SAEs, including those associated with SARS-CoV-2 infection, must be collected continuously during the treatment period.
Review of Concomitant Medication	X	
Laboratory Tests	X	On site/local complete blood count (CBC) w/differential, Chemistry panel including: LDH, AST, ALT, ALP, T-Bili, blood urea nitrogen (BUN) or serum urea level, creatinine, calcium, phosphate, Na, K, Cl, glucose, albumin, amylase lipase; PTT, PT, and INR. Thyroid function testing (TSH with reflexive fT3 and fT4) is to be performed every 8 weeks (start at Cycle 5, ~week 16) for subjects receiving nivolumab maintenance therapy.
Physical measurements (including ECOG Performance Status)	X	Weight and ECOG Performance status within 72 hours prior to dosing

Table 5.1-3: On Treatment Part 2: Nivolumab Monotherapy Phase Procedural Outline for Cohorts A, B, and C (CA209650)

Procedure	For Part 2, Study Treatment is Administered Every 4 Weeks (Cohorts A, B and C) Cycle 5 and beyond (Day 1)	Notes Cycle 5 will begin 6 weeks after Cycle 4 starts
PSA	X	Performed locally at start of Cycle 6 (~week 20) and then every 8 weeks (± 3 calendar days) thereafter until radiographic progression or the start of subsequent systemic cancer therapy, whichever occurs later. PSA evaluation beyond radiographic progression or the start of subsequent systemic cancer therapy to confirm PSA response or PSA progression should be performed as needed.
Testosterone	X	Performed locally at start of Cycle 7 (~week 24), followed by Cycle 10 (~week 36) and then every 12 weeks thereafter to correspond with nivolumab monotherapy dosing.
[redacted]		

Table 5.1-3: On Treatment Part 2: Nivolumab Monotherapy Phase Procedural Outline for Cohorts A, B, and C (CA209650)

Procedure	For Part 2, Study Treatment is Administered Every 4 Weeks (Cohorts A, B and C) Cycle 5 and beyond (Day 1)	Notes Cycle 5 will begin 6 weeks after Cycle 4 starts
Efficacy Assessment		
Body Imaging	X	Contrast enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease should occur every 8 weeks (±7 days) from first dose regardless of treatment schedule for first 6 months. After that, it will switch to every 12 weeks (±7 days) regardless of treatment schedule until disease progression assessed by investigator or treatment is discontinued (whichever occurs later). Evidence of progressive disease as per PCWG2.See Section 5.5.3. Use same imaging method as was used at screening baseline or as described in Section 5.5.2. Images will be collected and held centrally for retrospective independent review. (See Section 5.5.)
Brain Imaging	X	Participants with a history of brain metastasis or symptoms should have surveillance MRIs per standard of care (approximately every 12 weeks) or sooner if clinically indicated. CT of the brain without and with contrast can be performed if MRI is contraindicated
Tc99m based radionuclide bone scan	X	Every 8 weeks (±7 days) from first dose regardless of treatment schedule for first 6 months. After that, it will switch to every 12 weeks (±7 days) regardless of treatment schedule until disease progression is documented (and confirmed if needed) or treatment is discontinued (whichever occurs later). Evidence of progressive disease as per PCWG2. See Section 5.5.3. Use same imaging method as was used at screening baseline or as described in Section 5.5.2 Images will be collected and held centrally for retrospective independent review. (See Section 5.5.)

Table 5.1-3: On Treatment Part 2: Nivolumab Monotherapy Phase Procedural Outline for Cohorts A, B, and C (CA209650)

Procedure	For Part 2, Study Treatment is Administered Every 4 Weeks (Cohorts A, B and C) Cycle 5 and beyond (Day 1)	Notes Cycle 5 will begin 6 weeks after Cycle 4 starts
Clinical Drug Supplies		
IWRS Drug Vial Assignment	X	Within 72 hours prior to dosing
Administer Study Treatment	X	See Section 4.3.2.
Outcomes Research Assessments		
BPI-SF	X	Each assessment should be completed at the start of the clinic visit prior to dosing and other study assessments.
EQ-5D-3L	X	

Table 5.1-4: On Treatment Procedural Outline (CA209650) for Cohort D

Procedure	Cycle 1 Day 1 and each subsequent cycle (C1D1)	Notes
Safety Assessments		
Targeted Physical Examination	X	To be performed only as clinically indicated within 72 hours prior to dosing
Vital Signs	X	Including BP, HR, and Temperature
Physical Measurements	X	Weight within 72 hours prior to dosing
Adverse Event Assessment	Continuously	Assessed using NCI CTCAE v. 4. All AEs, including those associated with SARS-CoV-2 infection, must be collected continuously during the treatment period.
SAE Assessment	Continuously	Assessed using NCI CTCAE v. 4. All SAEs, including those associated with SARS-CoV-2 infection, must be collected continuously during the treatment period.
Review of Concomitant Medication	X	
Laboratory Tests	X	Within 72 hours prior to each dose. On site/local CBC w/differential, ALT, AST, ALP T-Bili, BUN or serum urea level, creatinine, calcium, phosphate, Na, K, Cl, LDH, glucose, albumin, amylase and, lipase. Subjects receiving cabazitaxel must have weekly on site/local CBC w/differential during first cycle. Thyroid function testing (TSH with reflexive fT3 and fT4) is to be done every 3 weeks for Q3W dosing cycles, then every 8 weeks for subjects receiving nivolumab at 480 mg q4w dosing cycles. Note: Safety Laboratory tests do not need to be repeated on C1D1 if screening labs were performed within 14 days prior to first dose.

Table 5.1-4: On Treatment Procedural Outline (CA209650) for Cohort D

Procedure	Cycle 1 Day 1 and each subsequent cycle (C1D1)	Notes
ECOG Performance Status	X	Refer to Appendix 2
PSA	X	Performed locally Day 1 of C1 to C5 (within 72 hours prior to treatment), then Day1 of every odd-numbered cycle (C7, C9, C11, etc) [within 72 hours prior to treatment]. Participants who discontinue study treatment without documented radiographic progression will continue to have PSA performed every 8 weeks (± 7 days) until radiographic progression or the start of subsequent systemic cancer therapy, whichever occurs later. PSA evaluation beyond radiographic progression or the start of subsequent systemic cancer therapy to confirm PSA response or PSA progression should be performed as needed
[redacted]		

Table 5.1-4: On Treatment Procedural Outline (CA209650) for Cohort D

Procedure	Cycle 1 Day 1 and each subsequent cycle (C1D1)	Notes
Efficacy Assessment		
Body Imaging	X	Contrast enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease should occur every 8 weeks (±7 days) from first dose regardless of treatment schedule for first 6 months. After that, it will switch to every 12 weeks (±7 days) regardless of treatment schedule until disease progression is assessed by investigator and confirmed by BICR or treatment is discontinued (whichever occurs later). See Section 5.5.3. Use same imaging method as was used at screening/baseline.
Brain Imaging	X	Participants with a history of brain metastasis or symptoms should have surveillance MRIs per standard of care (approximately every 12 weeks) or sooner if clinically indicated. CT of the brain without and with contrast can be performed if MRI is contraindicated
Tc99m based radionuclide bone scan	X	Every 8 weeks (±7 days) from first dose regardless of treatment schedule for first 6 months. After that, it will switch to every 12 weeks (±7 days) regardless of treatment schedule until disease progression is assessed by the investigator and confirmed by BICR or treatment is discontinued (whichever occurs later). Evidence of progressive disease as per PCWG2. See Section 5.5.3. Use same imaging method as was used at screening baseline or as described in Section 5.5.2.
Outcomes Research Assessments		
BPI-SF	X	Subject must be informed of treatment assignment prior to first post-randomization assessment. Each assessment should be completed at the start of the clinic visit prior to dosing and other study assessments.
FACT-P	X	
EQ-5D-3L	X	
Healthcare Utilization	X	Healthcare resource utilization data will be collected at each visit by study site staff using the case report form (CRF).

Table 5.1-4: On Treatment Procedural Outline (CA209650) for Cohort D

Procedure	Cycle 1 Day 1 and each subsequent cycle (C1D1)	Notes
Clinical Drug Supplies		
IWRS Drug Vial Assignment	X	Within 72 hours prior to dosing
Administer Study Treatment	X	See Section 3.1 for Crossover Treatment. See Section 4.3.5 for Re-induction Treatment. • For subjects in Arm D1, the first re-induction combination dosing can start no sooner than 4 weeks after the last nivolumab 480 mg dose and no sooner than 12 weeks after the last ipilimumab dose. • For subjects in Arm D1, the first re-induction combination dosing can start no sooner than 8 weeks after the last nivolumab 480 mg dose and no sooner than 12 weeks after the last ipilimumab dose. Pausing nivolumab maintenance dosing is permitted in patients who are planning to receive re-induction in Arm D2.

Table 5.1-5: Follow-up Assessments (CA209650) for All Treatment Arms (Cohorts A, B, C, and D)

Procedure	Follow Up[a], Visits X1 and X2	Survival[b], Follow-up Visits	Notes
Safety Assessments			
Targeted Physical Examination	X		To assess for potential late emergent study treatment related issues.
Adverse Event Assessments	X	X	Assessed using NCI CTCAE v. 4. All AEs, including those associated with SARS-CoV-2 infection, must be collected continuously during the treatment period and for a minimum of 100 days following discontinuation of study treatment. Participants will be followed for all SAEs, non-serious AEs of special interest, and all AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection until resolution, the condition stabilizes, the event is otherwise explained, the event is deemed irreversible, the participant is lost to follow-up (as defined in Section 3.6.2), or for suspected cases, until SARS-CoV-2 infection is ruled-out.
SAE Assessment	X	X	Assessed using NCI CTCAE v. 4. All SAEs, including those associated with SARS-CoV-2 infection, must be collected continuously during the treatment period and for a minimum of 100 days following discontinuation of study treatment. Participants will be followed for all SAEs, non-serious AEs of special interest, and all AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection until resolution, the condition stabilizes, the event is otherwise explained, the event is deemed irreversible, the participant is lost to follow-up (as defined in Section 3.6.2), or for suspected cases, until SARS-CoV-2 infection is ruled-out.
Laboratory Tests	X		On site/local CBC w/differential, LFTs, BUN, creatinine, amylase, lipase and TSH (+ reflex Free T4 and Free T3) for X1, repeat at X2 if study treatment related toxicity persists.
PSA	X		PSA to be collected every 8 weeks (± 7 days) in follow up until radiographic disease progression or the start of subsequent systemic cancer therapy, whichever occurs later. PSA evaluation beyond radiographic progression or the start of subsequent systemic cancer therapy to confirm PSA response or PSA progression should be performed as needed.

Table 5.1-5: Follow-up Assessments (CA209650) for All Treatment Arms (Cohorts A, B, C, and D)

Procedure	Follow Up[a], Visits X1 and X2	Survival[b], Follow-up Visits	Notes
Review of Concomitant Medications	X		
[redacted]			
Survival Status			
Collection of Subject Status and Subsequent Therapy Information	X	X	Every 3 months, Survival Follow up Visits may be accomplished by visit or phone contact, or email to include subsequent anti-cancer therapy and OS status. Additional subsequent cancer therapy details such as regimen, setting of the regimen, line of therapy, start date and end date of each regimen, best response to the regimen and date of progression after second line therapy will be collected.
Efficacy Assessments			
Body Imaging	See Notes		Only for subjects without radiographic progression on study therapy. If progression is not recorded during the treatment phase (ie, subjects who discontinue for toxicity), contrast enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease should occur every 8 weeks (± 7 days) for the first 6 months and then every 12 weeks (± 7 days) thereafter until disease progression is documented. Use same imaging method as was used at screening/baseline.

Table 5.1-5: Follow-up Assessments (CA209650) for All Treatment Arms (Cohorts A, B, C, and D)

Procedure	Follow Up[a], Visits X1 and X2	Survival[b], Follow-up Visits	Notes
			For Cohorts A, B, and C, images will be collected and held centrally for retrospective independent review. (See Section 5.5). For Cohort D, images will be collected and reviewed by BICR prospectively on a rolling basis and must continue until radiographic progression has been assessed by investigator and confirmed by BICR.
Brain Imaging	See Notes		Participants with a history of brain metastasis or symptoms should have surveillance MRIs per standard of care (approximately every 12 weeks) or sooner if clinically indicated. CT of the brain without and with contrast can be performed if MRI is contraindicated.
Tc99mm based radionuclide bone Scan	See Notes		If progression is not recorded during the treatment phase (ie, subjects who discontinue for toxicity), bone scan should be completed every 8 weeks (± 7 days) for the first 6 months and then every 12 weeks (± 7 days) thereafter until disease progression is documented (and confirmed if needed). For Cohorts A, B, and C: Images will be collected and held centrally for retrospective independent review. (See Section 5.5). For Cohort D, Images will be collected and reviewed by BICR prospectively on a rolling basis and must continue until radiographic progression has been assessed by investigator and confirmed by BICR.
Outcomes Research Assessments			
BPI-SF	X		Follow-up visits 1 and 2 only
FACT-P (Cohort D only)	X		Follow-up visits 1 and 2 only
FACT-P PCS (Cohort D only)		X	For survival follow-up visits, only the Prostate Cancer Subscale (PCS) portion of the FACT-P should be administered. Can be administered by telephone if needed.

Table 5.1-5: Follow-up Assessments (CA209650) for All Treatment Arms (Cohorts A, B, C, and D)

Procedure	Follow Up[a], Visits X1 and X2	Survival[b], Follow-up Visits	Notes
EQ-5D-3L	X	X	Follow-up visits 1 and 2 and every 3 months for the first 12 months then every 6 months thereafter for the survival follow-up visits. For survival visits, can be administered by telephone if needed.
Healthcare Utilization (Cohort D only)	X	X	Healthcare resource utilization data will be collected at each visit by study site staff using the case report form (CRF).

[a] X visits occur as follows - X1 = 30 days from the last dose (± 7 days) or coincide with the date of discontinuation (± 7 days) if date of discontinuation is greater than 37 days after last dose, X2 = 84 days (± 7 days) from follow-up visit 1. Follow up visits X1 and X2 will occur only after patient completes all study treatment.

[b] Y Survival visits = every 3 months from X2 (± 7 days).

5.2 Re-Testing During Screening or Lead-in Period

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).

Any new result will override the previous result (ie, the most current result prior to treatment) and is the value by which study inclusion will be assessed, as it represents the subject's most current, clinical state.

5.3 Study Materials

- NCI CTCAE version 4
- BMS-936558 (nivolumab) IB
- Ipilimumab IB
- Pharmacy Manual
- Laboratory manuals for collection [redacted]
- Site manual for operation of IWRS, including enrollment worksheets
- Manual for entry of local laboratory data
- Pregnancy surveillance forms (for WOCBP partners of study subjects)
- RECIST v1.1 pocket guide
- Patient reported outcomes questionnaires: BPI-SF, FACT-P, and EQ-5D-3L

5.4 Safety Assessments

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), and temperature. Screening assessments should be performed within 28 calendar days prior to first treatment or as indicated in Schedule of Assessments Table.

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, phosphate, LDH, glucose, albumin, amylase, lipase, PTT, PT, and INR.

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 and Hepatitis B and C testing (HBV sAg and HCV Ab or HCV RNA).

While on-study the following local laboratory assessments are to be done within 72 hours prior to each dose: CBC with differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Na, K, Cl, phosphate, LDH, glucose, albumin, amylase, and lipase.

For Cohorts A, B, and C; PTT, PT, and INR are to be done within 72 hours prior to each dose; and thyroid function testing (TSH with reflexive fT3 and fT4) is to be done every 3 weeks (following

each sequential combination dose infusion) for on-treatment Part 1 phase (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 subjects receiving nivolumab at 480 mg q4w.

For Cohort D, thyroid function testing (TSH with reflexive fT3 and fT4) is to be done every 3 weeks for Q3W dosing cycles, then every 8 weeks for subjects receiving nivolumab at 480 mg q4w dosing cycles.

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

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

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.

On treatment local laboratory assessments are to be completed within 3 calendar days prior to dosing.

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 treatment related toxicities resolve, return to baseline, or are deemed irreversible.

If a subject shows pulmonary-related signs (hypoxia, fever) or symptoms (eg, dyspnea, cough, fever) consistent with possible pulmonary adverse events, the subject 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 1 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.

5.4.1 Imaging Assessment for the Study

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. Images will be submitted to a central imaging vendor and may undergo BICR at any time during the study. Prior to scanning first participant, sites should be

qualified and understand the image acquisition guidelines and submission process as outlined in the CA209650 Imaging Manual provided by the central imaging vendor.

Tumor assessments at other timepoints may be performed if clinically indicated and should be submitted to the central imaging vendor as soon as possible. Unscheduled CT/MRI should be submitted to central imaging vendor. X-rays that clearly demonstrate interval progression of disease (for example, unequivocal lesions that are unmistakably new since the prior CT/MRI) should be submitted to central imaging vendor. Otherwise, X-rays do not need to be submitted centrally.

5.5 Efficacy Assessments

Study evaluations will take place in accordance with the flow charts in Section 5.1. Baseline assessments should be performed within 28 calendar days prior to first treatment utilizing CT or MRI and radionuclide bone scan. In addition to chest, abdomen, pelvis, and brain, all known sites of disease should be assessed at baseline.

Subjects who cannot receive CT IV contrast 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 should use the same imaging method as was used at baseline.

Subjects who cannot receive either CT or MRI contrast can be monitored by CT of chest, abdomen, and pelvis without IV contrast.

To ensure a uniform tumor assessment (TA) schedule, regular radiological imaging (eg, MRI/CT of chest, abdomen, pelvis, plus other nodal disease as applicable, and bone scans) will be performed for all subjects at Screening, and thereafter for tumor response beginning 8 weeks (± 7 days) from first treatment and continuing every 8 weeks (± 7 days) for the first 6 months from first treatment, and every 12 weeks (± 7 days) thereafter. Cohorts A, B, and C will continue scans until radiographic disease progression is documented by the investigator or treatment is discontinued (whichever occurs later). Cohort D will have scans performed until radiographic progression has been assessed by the investigator and is confirmed by BICR or treatment is discontinued (whichever occurs later).

All disease progression should be evaluated per Table 5.5.3-1.

Subjects that enter Follow-up phase without documented PD will have tumor assessments as specified in Table 5.1-5.

For all treated subjects in Cohorts A, B, C, and for all randomized subjects in Cohort D, scans will be collected and held by a centralized imaging core laboratory for review by independent radiologists using RECIST v1.1 and PCWG2 (for bone disease progression) criteria. Scans will be centrally reviewed by BICR retrospectively for Cohorts A, B, and C, and prospectively on a rolling basis for Cohort D.

For subjects with measurable disease, tumor assessments for ongoing study treatment decisions will be completed by the investigator using RECIST v1.1 criteria.

5.5.1 Primary Efficacy Endpoints

The dual primary endpoints are overall response rate (ORR) by RECIST v1.1 for subjects with measurable disease and radiographic progression-free survival (rPFS) assessed by BICR for all subjects as detailed in Table 5.5.3-1. BICR assessment will be performed retrospectively in Cohorts A, B, and C, and prospectively in Cohort D.

Objective response rate (ORR) is defined as the proportion of subjects who had confirmed complete or partial best overall response (BOR) among treated subjects with measurable disease at baseline In all subjects, radiographic progression-free survival (rPFS) is defined as the time between the date of first treatment and the first date of documented radiographic progression or death due to any cause, whichever occurs first.

The consensus guidelines of the Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1) and the Prostate Cancer Clinical Trials Working Group 2 (PCWG2) have been taken into consideration for the determination of radiographic disease progression assessment. Radiographic disease progression is defined by RECIST v1.1 for soft tissue disease, or by PCWG2 for bone lesions demonstrated on Tc99m based radionuclide bone scans.

If exceptional circumstances preclude the continued administration of measures using planned modalities, then alternate administration methods may be required after consultation with a sponsor or a sponsor's representative.

5.5.2 Method of Tumor Response Assessment

All target and non-target sites of disease identified on the baseline bone scan, CT or MRI studies should be reassessed with the same imaging modality at subsequent assessments. If, due to a radioisotope shortage, your imaging facility is unable to perform a Technetium-99m (Tech-99m) bone scan at a protocol-specified time point, then the following scanning options may be used:

- Full body CT
- Full body MRI

If an alternate imaging modality must be used, the following guidelines should be followed:

- If a methodology other than a Tech-99m bone scan is used for a baseline or post-baseline assessment, then that same methodology must be used at all subsequent assessment time points, regardless of the availability of Tech-99m.
- If a Tech-99m bone scan assessment reveals an unconfirmed progression and your imaging facility indicates that Tech-99m may not be available 6 or more weeks later for the confirmatory follow-up scan, then an additional full body scan using an alternate methodology should be performed at first progression in order to ensure that the same scanning methodology will be available at both time points.

5.5.3 Disease Progression Criteria

At each disease assessment, progression (PD) will be determined using the criteria in Table 5.5.3-1 and Table 5.5.3-2. These criteria are based on RECIST v1.1 for soft tissue lesions and PCWG2 for bone lesions and PSA measurements.

For Cohort D participants, sites should submit all scans to the central imaging vendor on a rolling basis, throughout the duration of the study. BICR of scans will occur on a rolling basis, blinded to treatment arm, clinical data, and investigator assessment of submitted scans. When progression per RECIST v1.1 criteria for soft tissue lesions and PCWG2 for bone lesions is assessed by the investigator, the site will inform the central imaging vendor, in order for BICR assessment of progression to be performed. The BICR will be completed and the results provided to the site as specified in the imaging vendor documents, provided there are no pending imaging queries to the site. All details on the timelines and associated process requirements will be outlined in the CA209650 Imaging Manual.

Cohort D 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. Also, if Cohort D participants discontinue treatment without radiographic progression, tumor assessments will continue according to the protocol−specified schedule, as noted in the Schedule of Activities, until progression has been confirmed by BICR or treatment is discontinued, whichever occurs later.

All study treatment decisions will be based on the investigator's assessment of tumor images and not on the BICR assessment.

Radiographic Progression in soft tissue lesions (Target lesions, Non-target (non-bone) lesions) **and Bone lesions** are described in Table 5.5.3-1 below:

Table 5.5.3-1: Definition of Radiographic Progression per protocol

Parameter	Unconfirmed Progression	Confirmed Progression	Date of Progression
Soft tissue lesions (target, non-target) measurements per RECIST v1.1 (CT or MRI)	Progression of soft tissue lesions (target, non-target, new lesions) per RECIST v1.1 (CT or MRI)	Not applicable. RECIST v1.1 does not require confirmation	Date of progression per RECIST v1.1
Bone lesions on radionuclide bone scan per PCWG2	Appearance of ≥ 2 new lesions at the week 8 bone scan* as compared to baseline bone scan	Persistence of the 2 lesions noted on week 8 bone scan* AND Appearance of ≥ 2 new lesions on the next bone scan obtained at least 6 weeks after unconfirmed progression identified (≥ week 14)	Date of unconfirmed progression

Table 5.5.3-1: Definition of Radiographic Progression per protocol

Parameter	Unconfirmed Progression	Confirmed Progression	Date of Progression
	If week 8 bone scan* does not demonstrate ≥ 2 new lesions as compared to baseline bone scan, appearance of ≥ 2 new lesions on any bone scan performed after week 8 bone scan* as compared to the week 8 bone scan*	Not Applicable	Date of unconfirmed progression

*If the bone scan at Week 8 was not performed, use the first post-baseline bone scan performed after Week 8 instead

PSA progression: For participants with an initial PSA decline from baseline, the date of PSA progression is the date that an increase of 25% or more and an absolute increase of 2 ng/mL or more from the nadir are documented and confirmed by a second consecutive PSA value at least 3 weeks later. For participants with no PSA decline from baseline, the date of PSA progression is the date that an increase of 25% or more and an absolute increase of 2 ng/mL or more from baseline are documented at or beyond Week 13.

PSA progression alone is not an indication to stop treatment. Rather, subjects must discontinue treatment upon radiographic progression per RECIST v1.1 criteria for soft tissue disease and/or PCWG2 criteria for bone disease (see Table 5.5.3-1 above).

Participant who discontinue treatment without documented radiographic progression will continue to have PSA performed every 8weeks (± 7 days) until radiographic progression or the start of subsequent systemic cancer therapy, whichever occurs last. PSA evaluation beyond radiographic progression or the start of subsequent systemic cancer therapy to confirm PSA response or PSA progression should be performed as needed.

Table 5.5.3-2: Definition of Disease Progression by PSA (per PCWG2) and Clinical Progression

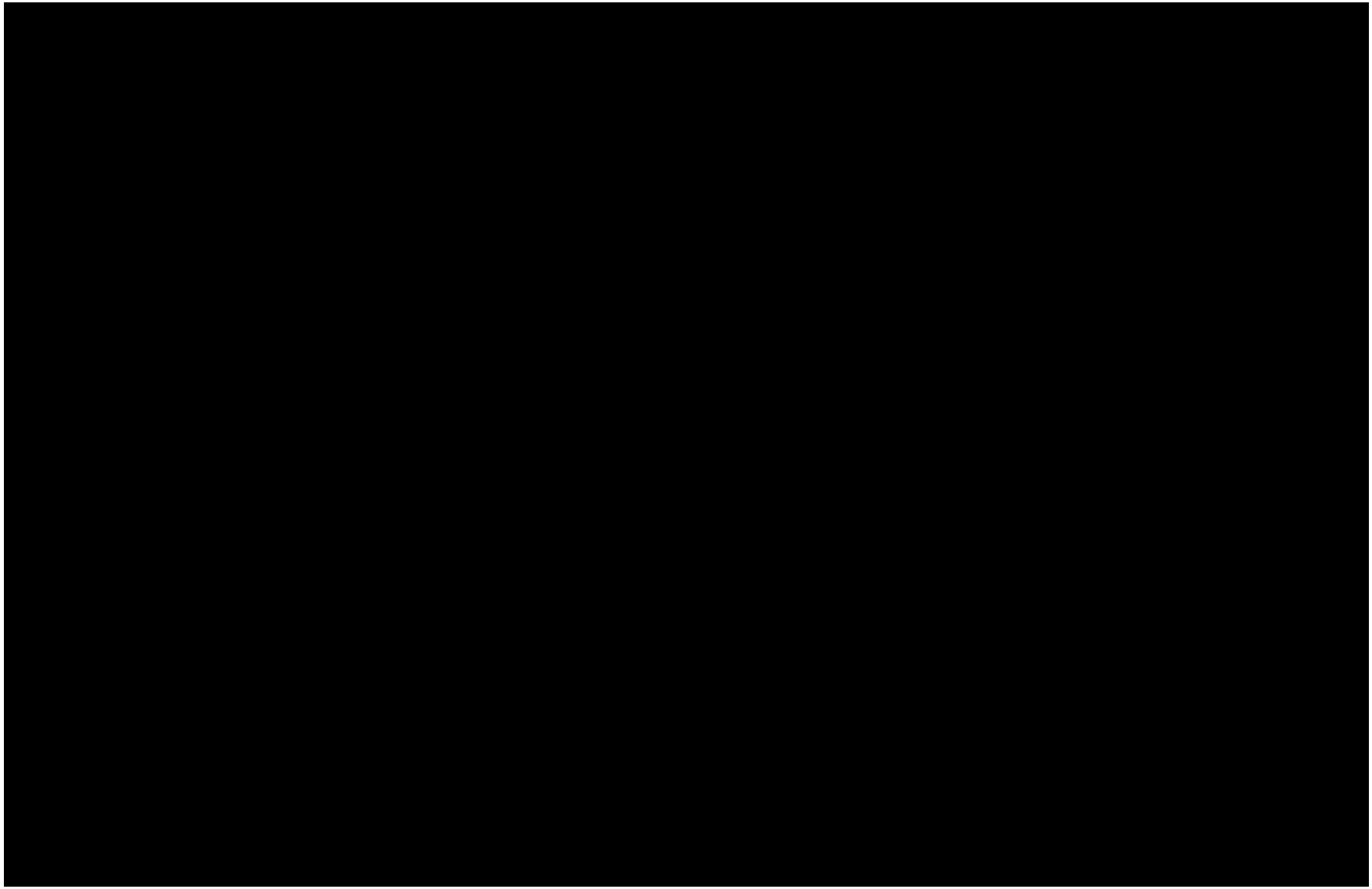
Parameter	Unconfirmed Progression	Confirmed Progression	Date of Progression
PSA	Initial PSA decline from baseline: ≥ 25% increase and ≥ 2 ng/ml increase above the nadir ≥ week 13	Confirmed by a second consecutive PSA value at least 3 weeks later	Date of unconfirmed progression
	No PSA decline from baseline: ≥ 25% increase and ≥ 2 ng/ml increase above the baseline ≥ week 13	Not applicable	Date of unconfirmed progression
Clinical Progression	Need for palliative radiation therapy involving more than one site, OR		Date of palliative radiation therapy,

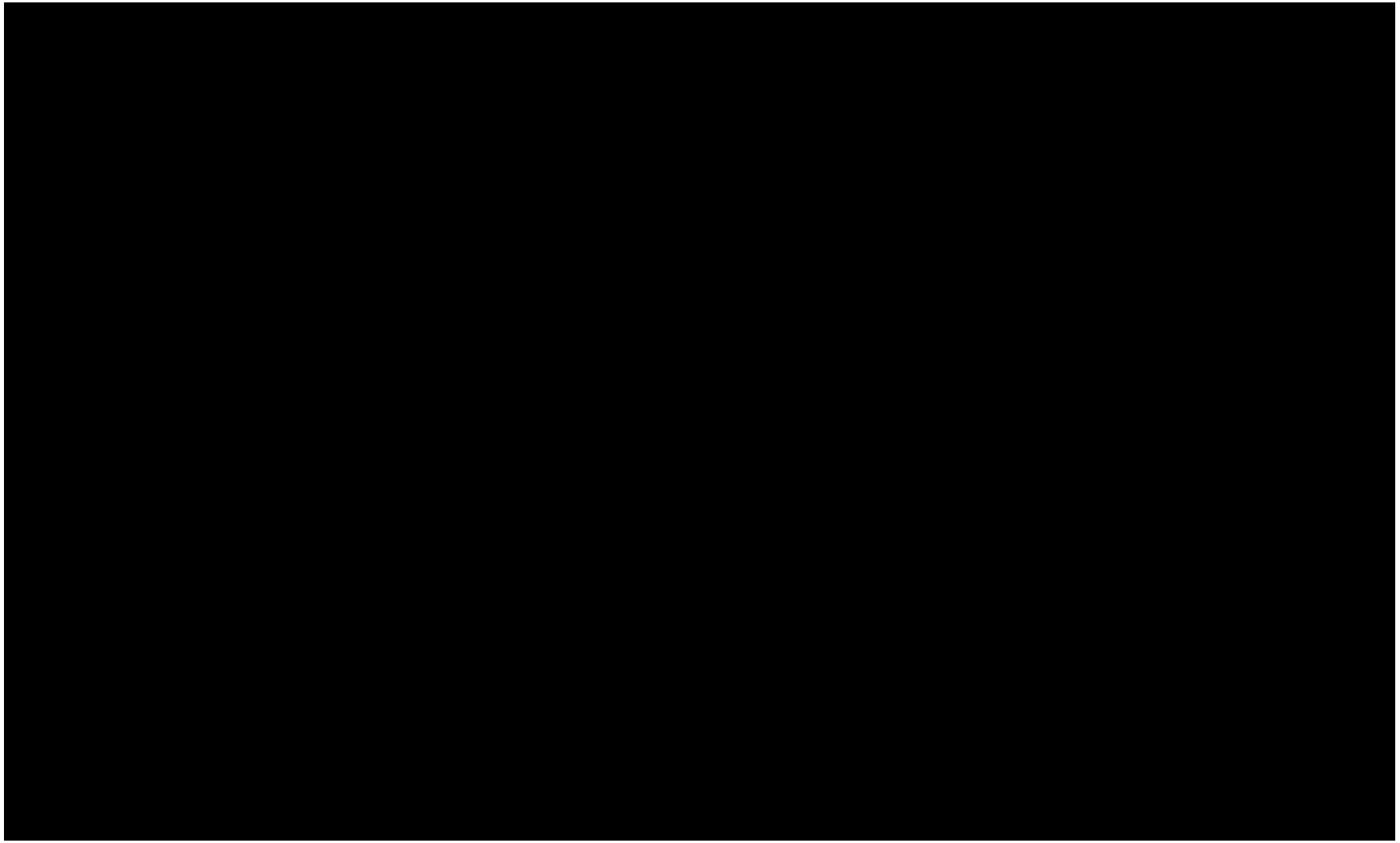
Table 5.5.3-2: Definition of Disease Progression by PSA (per PCWG2) and Clinical Progression

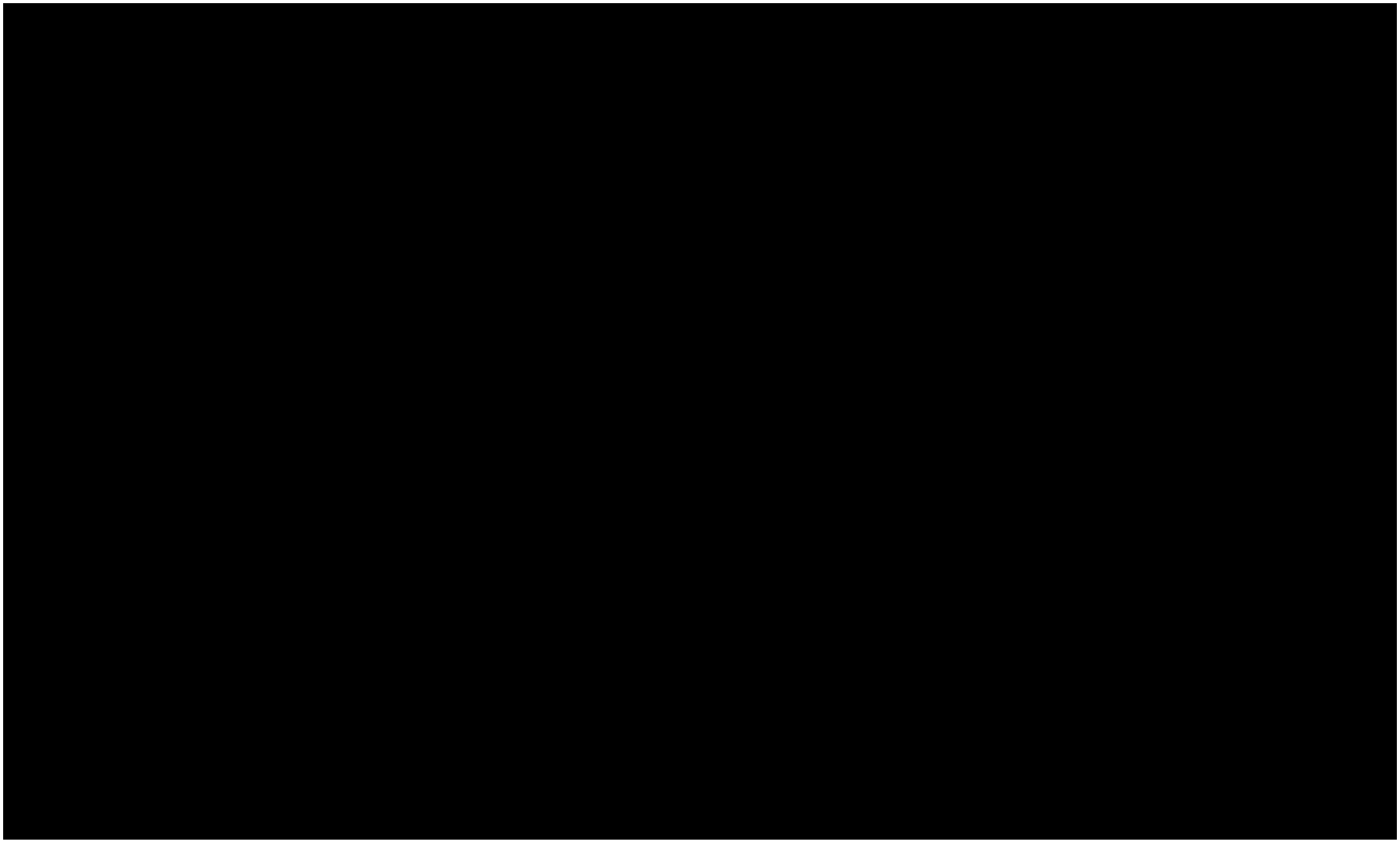
Parameter	Unconfirmed Progression	Confirmed Progression	Date of Progression
	Surgery of kyphoplasty to any neoplastic lesion, OR Cancer-associated clinical deterioration as determined by the treating physician		surgery or clinical deterioration

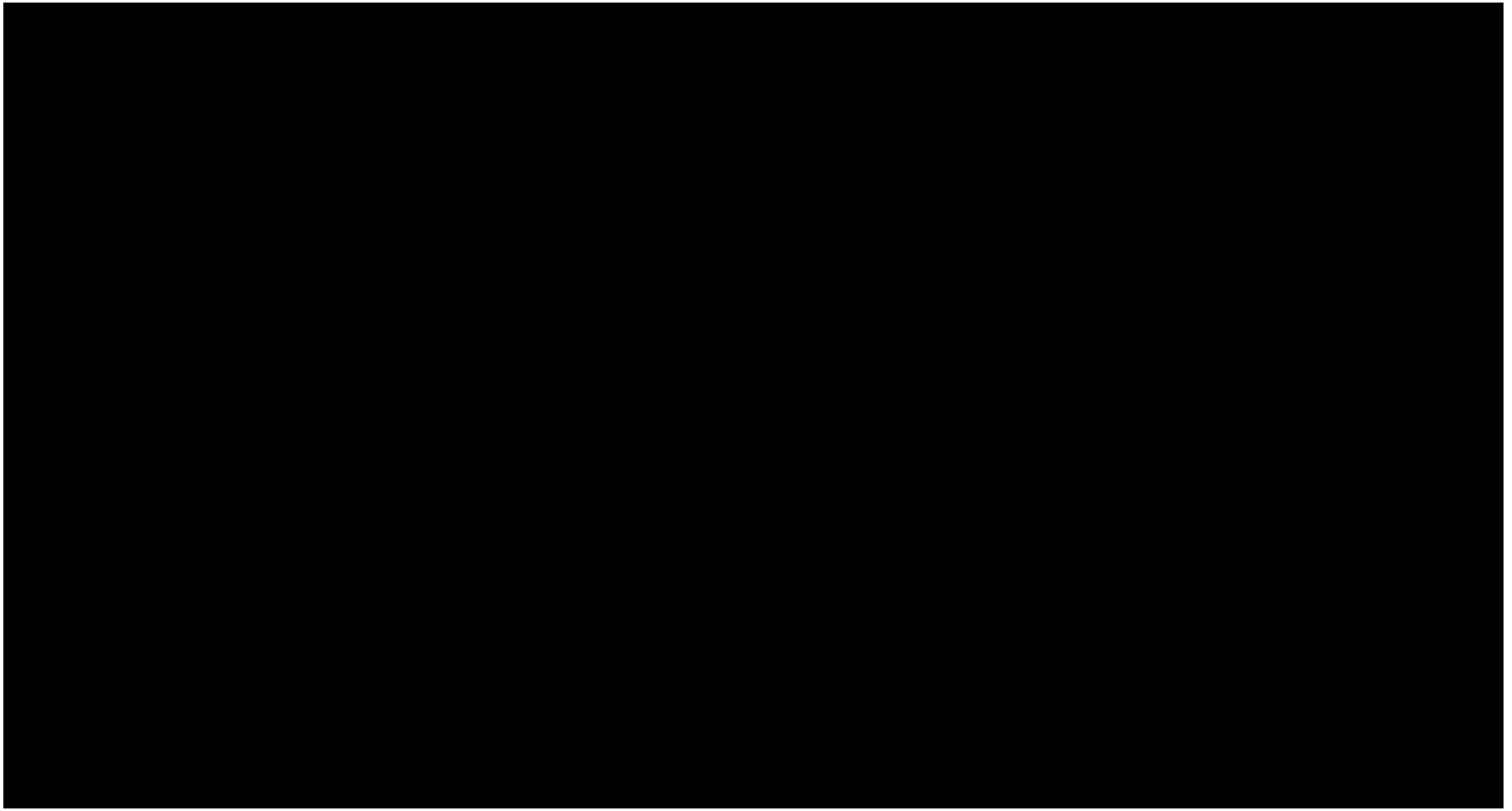
[redacted]

[redacted]









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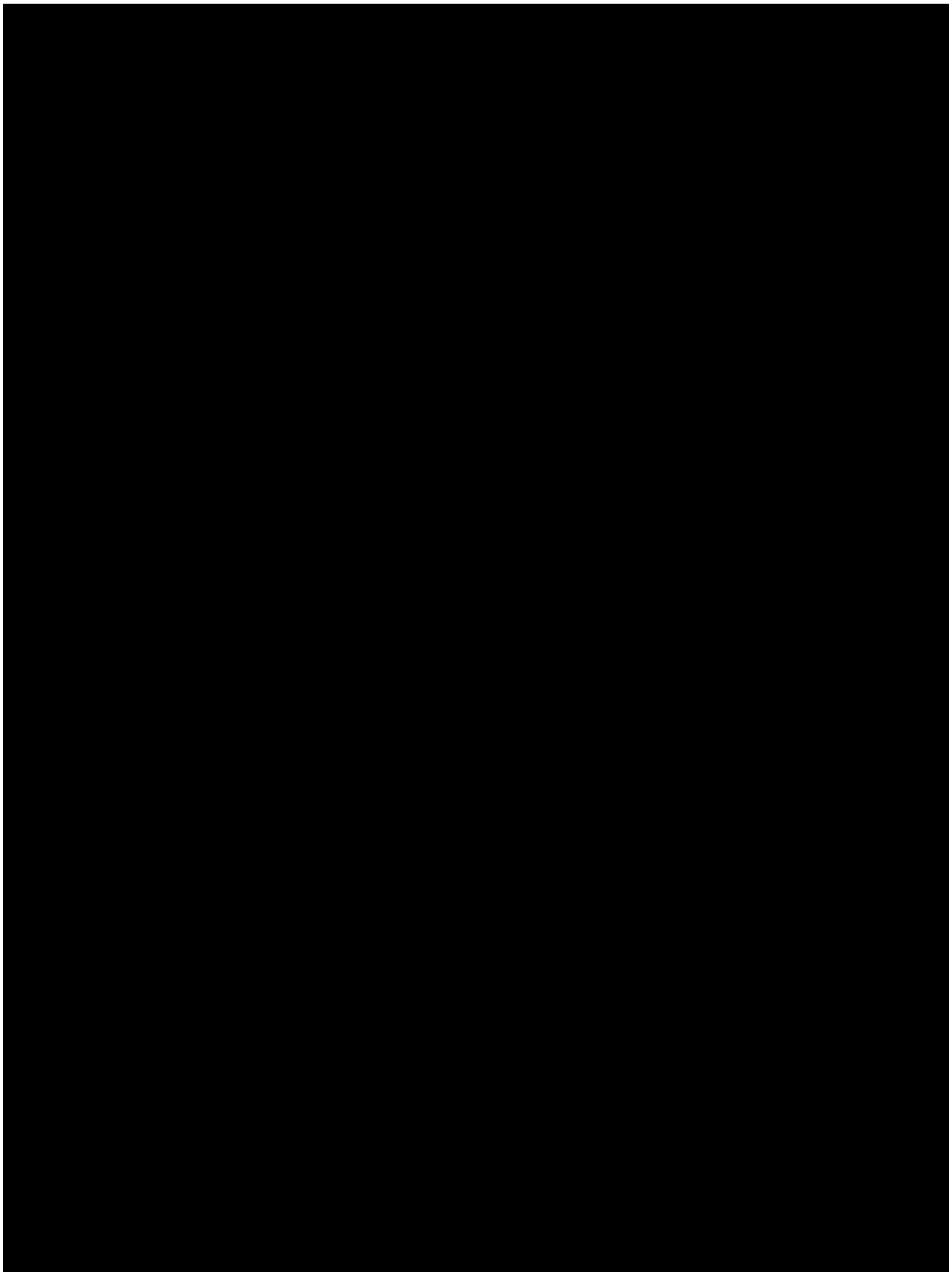
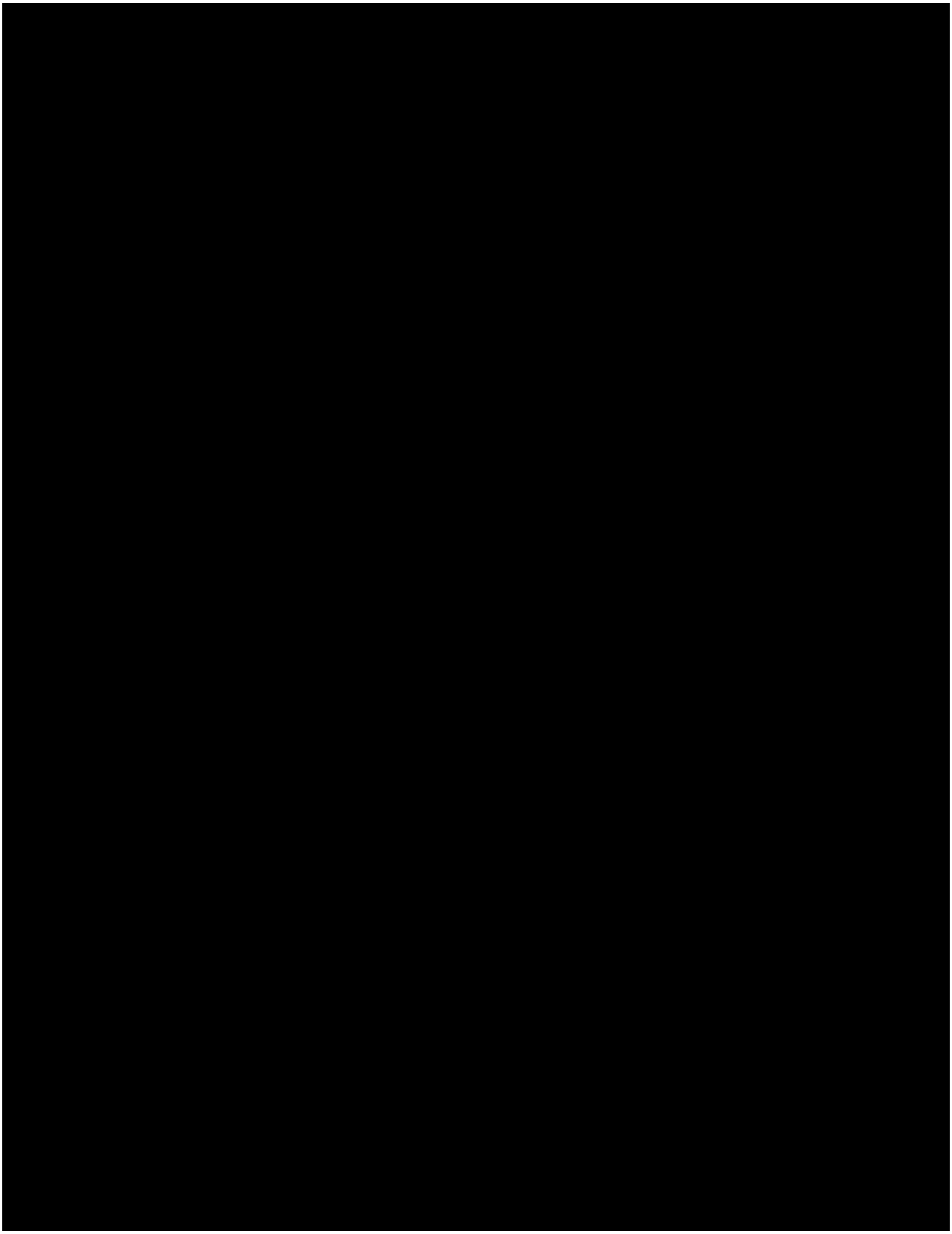
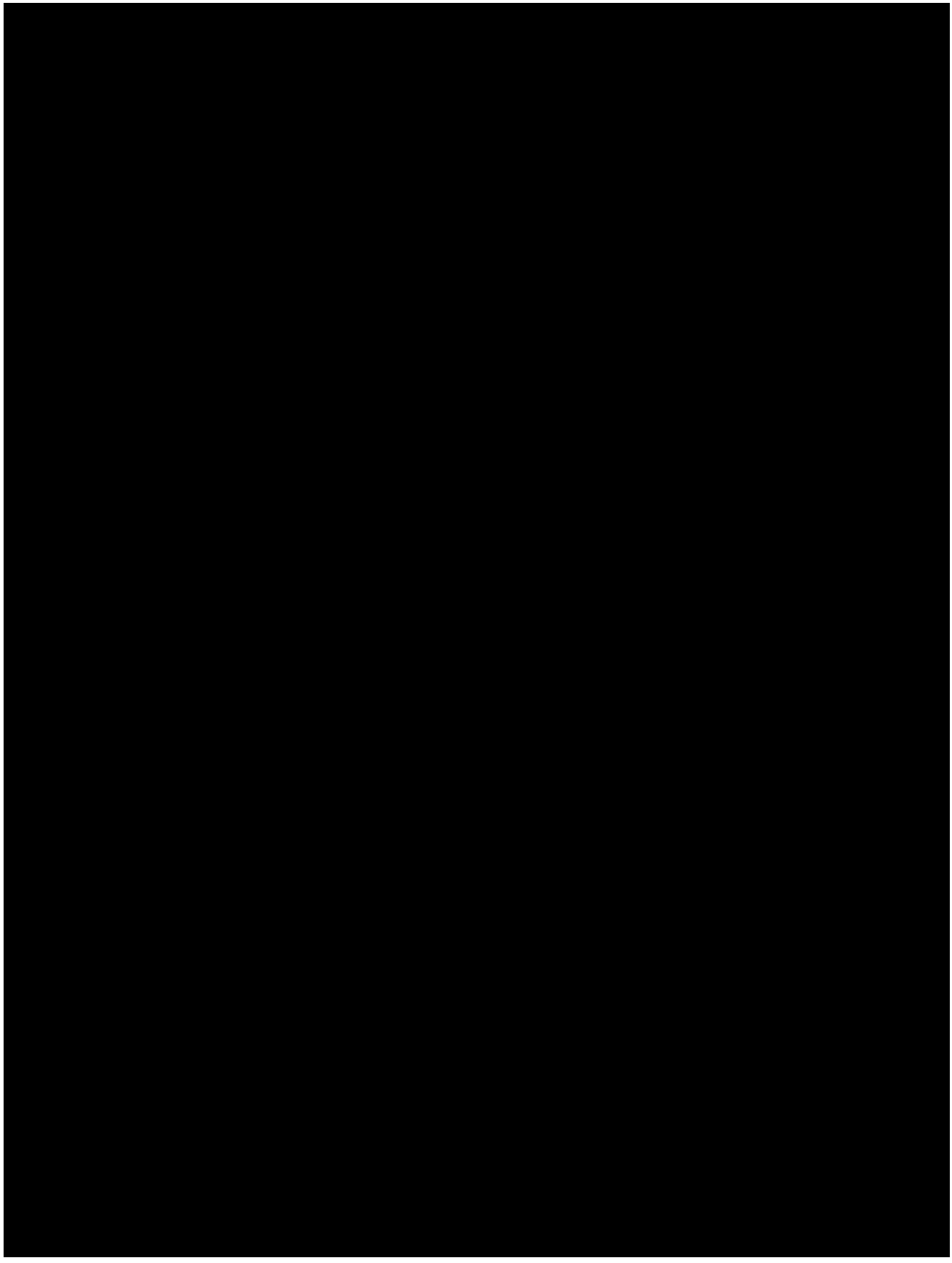






5.8 Outcomes Research Assessments

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

For Cohort D, participants will be asked to complete the Brief Pain Inventory - Short Form (BPI-SF), The Functional Assessment Of Cancer Therapy - Prostate Cancer (FACT-P), and the 3-level version of the EuroQol Group's EQ-5D (EQ-5D-3L) in the participant's preferred language when available. The assessments will be given at screening, before any clinical activities are performed during on-study clinic visits, and at designated visits during the follow-up phase. For Cohorts A, B, and C, the FACT-P will not be administered at any timepoint. Before administering the first patient-reported assessment after randomization, the Investigator should confirm that the participant is aware of their treatment assignment. If exceptional circumstances preclude the continued administration of measures using planned modalities, then alternate administration methods may be required after consultation with a sponsor or a sponsor's representative.

5.8.1 The Brief Pain Inventory - Short Form

The BPI-SF[133] measures both pain severity and functional interference caused by pain through the use of a numerical rating scale. Subjects rate the severity of their pain at its ''worst,'' ''least,'' and ''average'' in the last 24 hours using an 11-point numerical rating scale with anchors of ''no pain'' and ''pain as bad as you can imagine.'' They are also asked to rate their pain at the time they complete the BPI-SF. Using an 11-point numerical rating scale with anchors of ''does not interfere'' and ''completely interferes,'' the BPI-SF similarly assesses to what extent pain interferes with mood, walking, general activity, work, relations with others, sleep, and enjoyment of life. The BPI-SF also asks subjects to mark the location of their pain on a body drawing and includes additional questions regarding pain treatment and the extent of pain relief. The original instrument on which the BPI-SF is based, The Wisconsin Brief Pain Questionnaire, was developed and validated in oncology subjects with the following four tumor types: breast, prostate, colorectal, and gynecological.[134] The BPI-SF has been validated in cancer subjects in several countries with psychometrically validated translations in over 25 countries.

5.8.2 The Functional Assessment Of Cancer Therapy - Prostate Cancer (FACT-P)

The FACT-P is a multidimensional, self-report QoL instrument specifically designed for use with prostate cancer patients.[135] It consists of 27 core items, the Functional Assessment of Cancer Therapy - General (FACT-G) questionnaire, which assesses patient function in 4 domains: Physical, Social/Family, Emotional, and Functional well-being, which is further supplemented by the Prostate Cancer Subscale (PCS), 12 disease-specific items to assess for prostate-related symptoms. Each item is rated on a 0 (Not at all) to 4 (Very much) Likert type scale, and then combined to produce subscale scores for each domain, a Trial Outcome Index (TOI) which is based on the Physical and Functional well-being scales and the PCS as well as a total score which ranges from 0 to 156. Higher scores represent better QoL.

5.8.3 The 3-level EQ-5D-3L

The EQ-5D-3L[136] is a standardized instrument used to measure self-reports of health status and functioning. The instrument's descriptive system consists of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels, reflecting "no health problems," "moderate health problems," and "extreme health problems." A dimension for which there are no problems is said to be at level 1, while a dimension for which there are extreme problems is said to be at level 3. Thus, the vectors 11111 and 33333 represent the best health state and the worst health state, respectively, described by the EQ-5D-3L. Altogether, the instrument describes $3^5 = 243$ health states. Empirically derived weights can be applied to an individual's responses to the EQ-5D-3L descriptive system to generate an index measuring the value to society of his or her current health. Such preference-weighting systems have been developed for Japan, UK, US, Spain, Germany, and numerous other populations. In addition, the EQ-5D-3L includes a visual analog scale (VAS) that allows respondents to rate their own current health on a 100-point scale ranging from "best imaginable" to "worst imaginable" health.

5.9 Additional Research Collection

Additional research collections are mandatory for all participants, except where prohibited by local laws or regulations, ethics committees or where a waiver is provided by the BMS Study Director. Where one or more of these exceptions occurs, participation in the additional research collection should be encouraged but will not be a condition of overall study participation, and subjects may opt out of the collection. This protocol will include residual sample storage for additional research (AR).

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 subjects. 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 to ensure the research supports appropriate and well-defined scientific research activities.

- Additionally, residual blood and tissue collections will also be retained by the BMS Biorepository [redacted] at a BMS approved third party storage management facility for additional research purposes
- Additional research samples will be retained for 15 years or the maximum allowed by applicable law. No additional sampling is required for residual collections

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

5.10 Health Economics OR Medical Resource Utilization and Health Economics

Healthcare resource utilization data will be collected for all randomized participants in Cohort D using an internal CRF developed for use in previous trials. The form, which is completed by study staff, records information about hospital admissions, including the number of days spent in various wards and discharge diagnosis, and non-protocol specified visits related to study therapy, including date of visit, reason for visit, and type of visit. The healthcare resource utilization data will be used to support subsequent economic evaluations.

6 ADVERSE EVENTS

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject 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.

The causal relationship to study treatment is determined by a physician and should be used to assess all adverse events (AE). The causal relationship can be one of the following:

- Related: There is a reasonable causal relationship between study treatment administration and the AE.
- Not related: There is not a reasonable causal relationship between study treatment administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

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.

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.

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).

6.1 Serious Adverse Events

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.

A S***erious 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 subject 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)
- 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 subject or may require intervention [eg, 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 6.6 for the definition of potential DILI.)

Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study treatment is an SAE.

Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 6.1.1 for reporting pregnancies).

Any component of a study endpoint that is considered related to study therapy should be reported as SAE (eg, death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported) (see Section 6.1.1 for reporting details).

NOTE:

The following hospitalizations are not considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason)
- Admission for administration of anticancer therapy in the absence of any other SAEs

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.

6.1.1 Serious Adverse Event Collection and Reporting

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 subject's written consent to participate in the study, all SAEs, whether related or not related to study treatment, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 100 days of the last dose of study treatment.

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.

An SAE report must be completed for any event where doubt exists regarding its seriousness.

If the investigator believes that an SAE is not related to study treatment, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship must be specified in the narrative section of the SAE Report Form.

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

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

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

For studies capturing SAEs through electronic data capture (EDC), electronic submission is the required method for reporting. In the event the electronic system is unavailable for transmission, paper forms must be used and submitted immediately. When paper forms are used, the original paper forms are to remain on site.

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

Follow-up of AEs and SAEs

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

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, non-serious AEs of special interest, and AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection will be followed until resolution, the condition stabilizes, the event is otherwise explained, the event is deemed irreversible, the participant is lost to follow-up (as defined in Section 3.6.2) or for suspected cases, until SARS-CoV-2 infection is ruled-out.

All SAEs must be followed to resolution or stabilization.

BMS 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.

6.2 Nonserious Adverse Events

A ***nonserious adverse event*** is an AE not classified as serious.

6.2.1 Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information (with the exception of non-serious AEs related to SARS-CoV-2 infection) should begin at initiation of study treatment. Nonserious 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 subjects.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 6.1.1). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study treatment and for those present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic).

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

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

All non-serious AEs associated with confirmed or suspected SARS-CoV-2 infection must be collected from the date of the participant's written consent until 100 days following discontinuation of dosing. Every adverse event must be assessed by the investigator with regard to whether it is considered immune-mediated. For events which are potentially immune-mediated, additional information will be collected on the subject's case report form.

6.3 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form 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 subject to have study treatment discontinued or interrupted
- Any laboratory test result abnormality that required the subject 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).

6.4 Pregnancy

Not applicable.

Any pregnancy that occurs in a female partner of a male study participant should be reported to Sponsor or designee. In order for BMS 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.

6.5 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered of both excessive and specifically important.

All occurrences of overdose must be reported as SAEs (see Section 6.1.1 for reporting details).

6.6 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 6.1.1 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

6.7 Other Safety Considerations

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

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

No Data Monitoring Committee is planned

A Study Steering Committee (consisting of selected participating investigators) will meet regularly to advise BMS regarding study-related issues, including safety concerns.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

Sample size determination for Cohorts B and C:

Approximately 90 subjects with mCRPC will be enrolled and treated in 2 cohorts, subjects who must have progressed after second-generation hormone therapies but have not received cytotoxic chemotherapy, and subjects who have progressed following cytotoxic chemotherapy (Cohorts B and C, respectively). Each cohort will consist of 30 or more subjects with measurable disease at baseline per RECIST v1.1 and no more than 15 with non-measurable disease.

This open-label Phase 2 study is not designed to statistically test specific hypotheses. Therefore, the sample size is not based on statistical power calculations, but the size in each cohort is calculated using the observed objective response rate among treated subjects with measurable disease at baseline.

[redacted]

Sample size determination for Cohort D:

Approximately 259 subjects with mCRPC, previously treated with docetaxel, will be randomized and treated in Cohort D. These 259 subjects will be randomized between 4 arms in a 2:2:1:2 ratio (74, 74, 37, and 74 subjects in Arm D1, D2, D3, and D4, respectively) and stratified by presence/absence of measurable disease by RECIST v1.1 per investigator assessment. Subjects with non-measurable disease at baseline by RECIST v1.1 per investigator assessment will be capped when approximately 105 subjects are randomized so that the remaining 154 subjects (44, 44, 22, and 44 subjects in Arm D1, D2, D3, and D4, respectively) will be with measurable disease at baseline.

Because this open-label phase 2 study is not designed to statistically test specific hypotheses, the sample size of Cohort D is not based on statistical power calculations. [redacted]

- [redacted]

[redacted]

8.1.1 Populations for Analyses

- **Enrolled Subjects**: All subjects who signed an informed consent form and were registered into the IWRS.
- **Treated Subjects**: All enrolled subjects who received any dose of study therapy (nivolumab or ipilimumab). This is primary dataset for analysis of study conduct, study population, efficacy, exposure, safety, and outcome research analysis for Cohorts A, B, and C.
- **Treated Subjects in Part 2**: All treated subjects who received at least one dose of study medication in the nivolumab flat dose monotherapy phase (Part 2) for Cohorts A, B, and C.
- **Randomized Subjects**: All subjects who are randomized to any treatment group in Cohort D. This is the population for the analysis of demography, protocol deviations, baseline characteristics, efficacy analysis, and outcome research analysis.
- **Treated Subjects in Cohort D**: All enrolled subjects who received any dose of study therapy in Cohort D. This is the primary population for exposure and safety analyses.
- **Response Evaluable Subjects:** For Cohorts B and C, all treated subjects who had measurable disease at baseline per RECIST v1.1.

[redacted]

8.2 Endpoints

8.2.1 Dual Primary Endpoints

Objective Response Rate (ORR)

In Cohorts B and C, objective response rate (ORR) is defined as the proportion of subjects who had confirmed complete or partial best overall response (BOR) among treated subjects with measurable disease at baseline. In Cohort D, ORR is defined as the proportion of subjects who had confirmed complete or partial BOR among randomized subjects with measurable disease at baseline by RECIST v1.1 per investigator assessment as entered in IWRS. For Cohorts B and C, the BOR is assessed by BICR (BICR assessment will be performed retrospectively in Cohorts A, B, and C, and prospectively in Cohort D) and is recorded between the date of treatment initiation and the date of objectively documented progression per RECIST v1.1 or the date of subsequent systemic anti-cancer therapy, whichever occurs first. For Cohort D, the BOR is assessed by BICR and is recorded between the date of randomization and the date of objectively documented progression per RECIST v1.1 or the date of subsequent systemic anti-cancer therapy, whichever occurs first. For subjects without documented progression or subsequent therapy, all available response assessments will contribute to the BOR assessment. Tumor assessments are scheduled to be performed every 8 weeks (± 7 days) for 6 months since treatment initiation and thereafter every 12 weeks (± 7 days). In Cohorts A, B, and C, tumor assessments continue until radiographic disease progression is documented by the investigator or treatment is discontinued (whichever occurs later). In Cohort D, tumor assessments continue until radiographic progression is documented by the investigator and confirmed by BICR or treatment is discontinued (whichever occurs later).

Radiographic Progression-Free Survival

The following progressive diseases will be collected and documented as assessed as noted below:

- Radiographic progression per BICR assessment

1) Bone disease progression by PCWG2
2) Non-bone soft tissue disease progression by RECIST v1.1

- Clinical progression per investigator assessment

1) Need for palliative radiation therapy involving more than one site, OR
2) Surgery of kyphoplasty to any neoplastic lesion, OR
3) Cancer-associated clinical deterioration as determined by the treating physician.

The following censoring rules will be used to define PFS endpoints for analysis.

i. Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment (ie, bone scan, CT, MRI).

ii. Subjects who did not have any on study tumor assessments and did not die will be censored on their date of first treatment if they are in Cohorts B and C, and will be censored on their date of randomization if they are in Cohort D.

iii. Subjects who receive subsequent systemic anti-cancer therapy prior to progression (or death) will be censored.

In Cohorts B and C, the radiographic progression-free survival (rPFS) is defined as the time between the date of first treatment and the first date of documented progression per BICR (radiographic a-b) or death due to any cause, whichever occurs first. In Cohort D, the radiographic progression-free survival (rPFS) is defined as the time between the date of randomization and the first date of documented progression per BICR (radiographic a-b) or death due to any cause, whichever occurs first. The censoring rules (i-ii) will be applied for primary analyses; as shown above in type of progressive disease and censoring rule. In addition, rPFS with censoring subsequent therapy will also be defined for a sensitivity analysis, ie, the censoring rules (i-iii) will be applied.

8.2.2 Secondary Endpoint(s)

Radiographic/Clinical Progression-Free Survival

In Cohorts B and C, the radiographic/clinical progression-free survival (rcPFS) is defined as the time between the date of first treatment and the first date of documented progression (radiographic a-b; clinical c-e) or death due to any cause, whichever occurs first. In Cohort D, rcPFS is defined as the time between the date of randomization and the first date of documented progression (radiographic a-b; clinical c-e) or death due to any cause, whichever occurs first. The censoring rules (i-ii) and (i-iii) will be applied, respectively (ie, without and with censoring for subsequent therapy); see type of progressive disease and censoring rule in Section 8.2.1.

Overall Survival

In Cohorts B and C, , overall survival (OS) is defined as the time from first treatment to the date of death from any cause. In Cohort D, overall survival (OS) is defined as the time from randomization to the date of death from any cause. For subjects who are alive, their survival time will be censored at the last known alive date. Overall survival will be censored for subjects at the date of first treatment if they had no follow-up.

Safety and Tolerability

Overall safety and tolerability will be measured by the incidence of adverse events, serious adverse events, adverse events leading to discontinuation, immune mediated adverse events, deaths, laboratory abnormalities and changes from baseline.

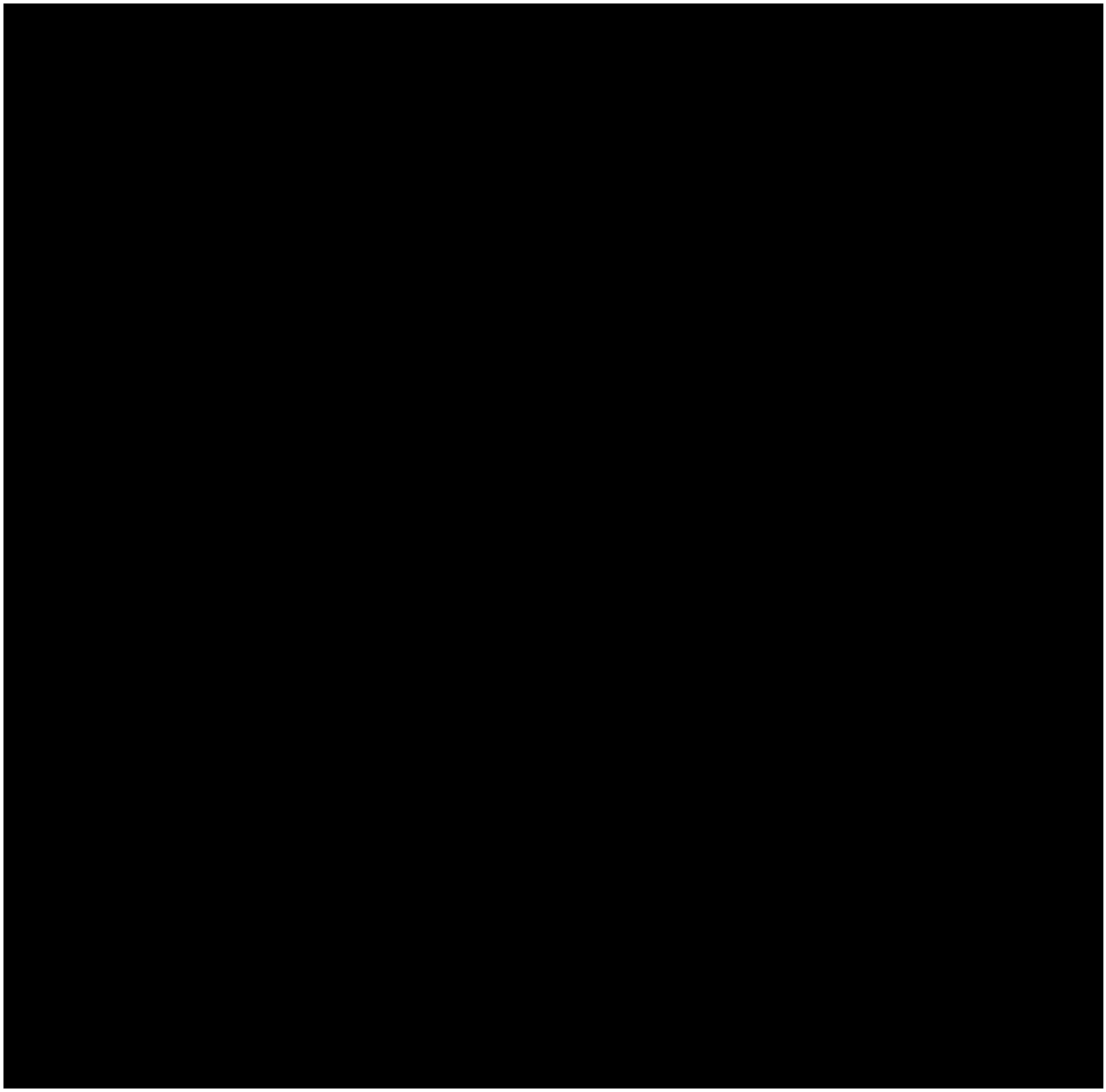
Outcomes Research Assessments

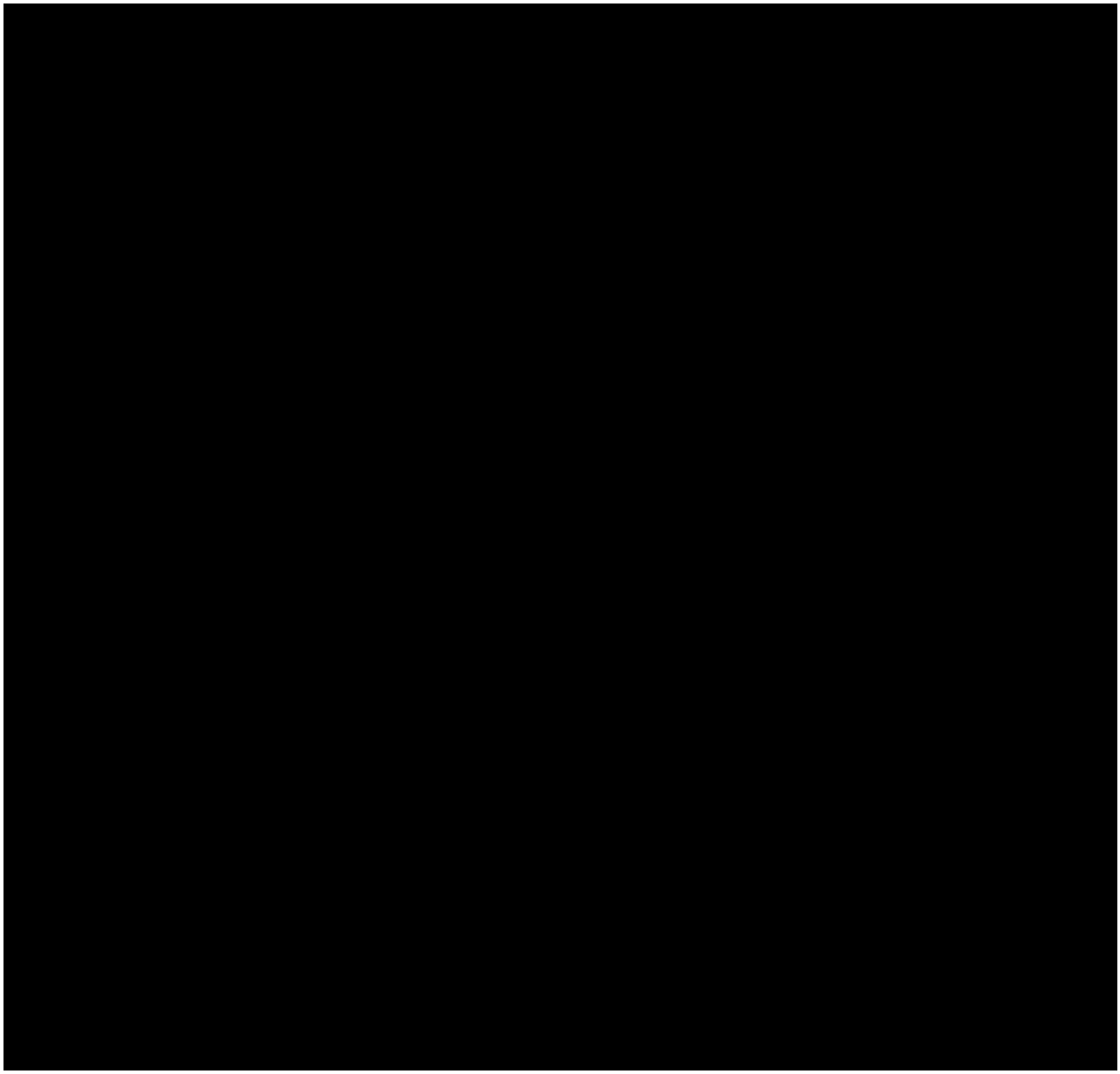
The endpoints of changes pain as measured by BPI-SF, changes in cancer-related symptoms and quality of life (QoL) using the FACT-P questionnaire, and changes in health status and health utility as measured by the EQ-5D-3L questionnaire are described in Section 8.2.9. The analysis of

QoL will be based on all treated subjects for Cohorts B and C and on all randomized subjects for Cohort D.

PSA response rate

PSA response rate (PSA-RR) is the proportion of participants with a 50% or greater decrease in PSA from baseline to the lowest post-baseline PSA result. A second consecutive value obtained 3 or more weeks later is required to confirm the PSA response. PSA response will be calculated for all participants with PSA values at baseline and at least one post baseline assessment. The analysis of PSA-RR will be based on all treated subjects with PSA values at baseline and at least one post-baseline assessment for Cohorts B and C, and on all randomized subjects for Cohort D with PSA values at baseline and at least one post-baseline assessment.





8.2.4 Demographics and Baseline Characteristics

For Cohorts A, B and C, demographics and baseline characteristics will be summarized by cohort and total for all treated subjects, using descriptive statistics. For Cohort D, similar analyes will be repeated by treatment group and total for all randomized subjects.

8.2.5 Efficacy Analyses

For Cohorts B and C, all efficacy analyses will be performed by cohort (ie, Cohorts B and C) as applicable to either (i) subjects with investigator-assessed measurable disease by RECIST v1.1 and/or (ii) total number of subjects within each cohort. All efficacy data for treated subjects in Cohort A, if any, will be listed. For Cohort D, efficacy analysis will be performed by treatment arm for all randomized subjects.

For the dual primary endpoint of ORR, estimated rates and corresponding 95% exact CIs will be calculated using the Clopper-Pearson method for all treated subjects with measurable disease at baseline per RECIST v1.1 in Cohorts B and C and for all randomized subjects with measurable disease at baseline per RECIST v1.1 per investigator assessment as entered in IWRS in Cohort D. In Cohorts B and C, estimated odds ratios and differences and corresponding 95% CIs between cohorts will be calculated for descriptive purpose. In Cohort D, sensitivity analysis of ORR may also be performed for all randomized subjects with measurable disease at baseline as entered in the CRF if the discrepancy rate is higher than 5%.

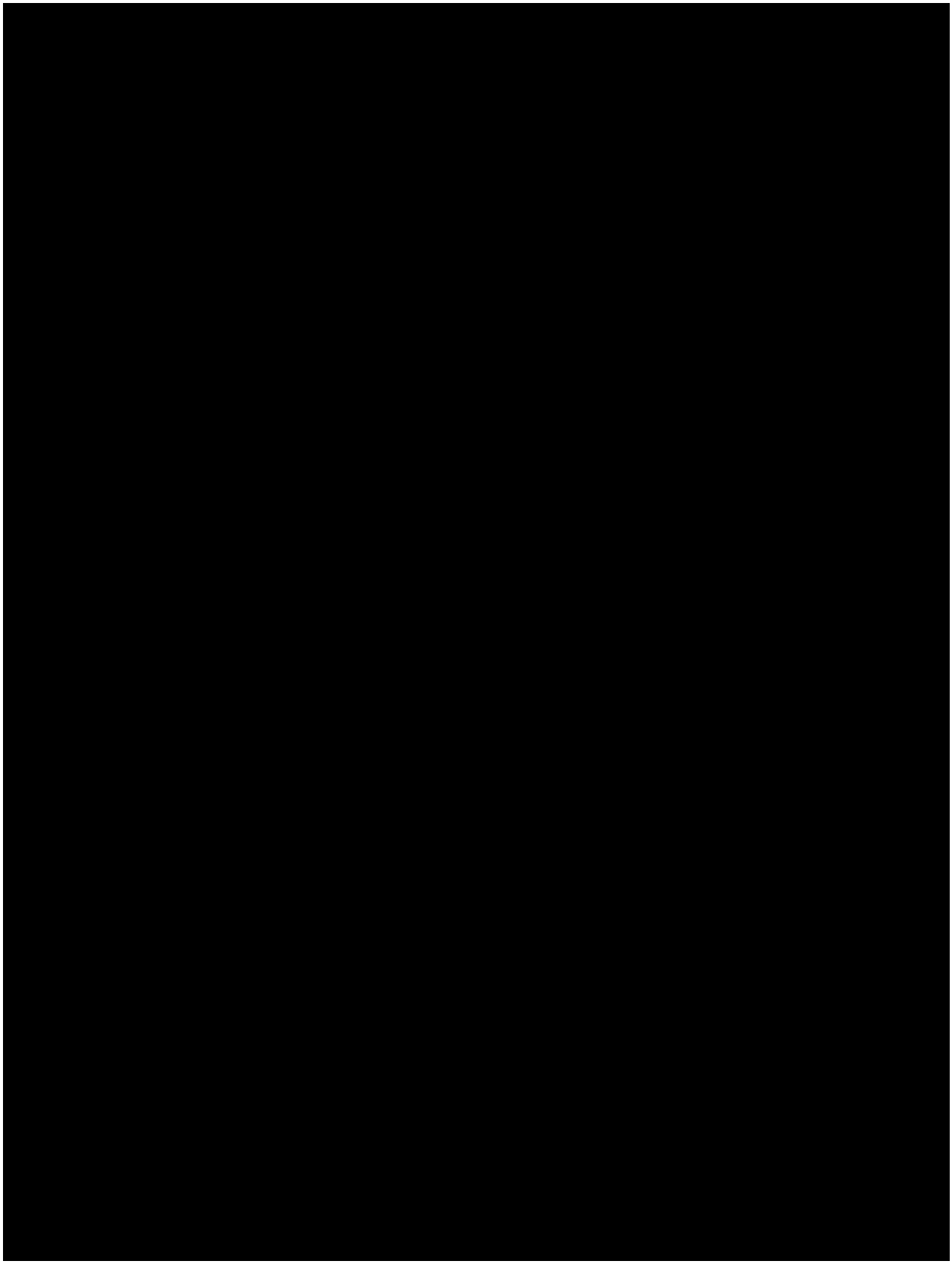
For time to event endpoints (eg, rPFS, rcPFS, and OS), medians and rates at months 6 and 12 and corresponding 95% CIs will be estimated for each cohort via the Kaplan-Meier methodology for all treated subjects in Cohorts B and C, and similar analyses will be done for each treatment arm for all randomized subjects in Cohort D. Kaplan-Meier plots will be presented for each cohort for Cohorts B and C; similarly, Kaplan-Meier plots will be displayed by treatment arm for all randomized subjects in Cohort D. Note that these analyses will be stratified by the stratification factor when these are conducted for Cohort D.

Estimate of PSA-RR and corresponding 2-sided exact 95% CI using the Clopper-Pearson method will be performed on all treated subjects with PSA values at baseline and at least one post-baseline assessment for Cohorts B and C; similar analysis will be done for each treatment arm in Cohort D with PSA values at baseline and at least one post-baseline assessment. Note that this analysis will be stratified by the stratification factor when conducted for Cohort D.

For all treated subjects with measurable disease at baseline in Cohorts B and C, [redacted] will be summarized by cohort for subjects with a BOR of PR or CR using the Kaplan-Meier methodology. Median values, along with two-sided 95% CIs will also be calculated. Summary statistics of [redacted] will be provided by cohort for subjects with a BOR of CR or PR. For all randomized subjects with measurable disease at baseline by RECIST v1.1 per investigator assessment as entered in IWRS in Cohort D, similar [redacted] and [redacted] analyses will be repeated by treatment arm.

8.2.6 Safety Analyses

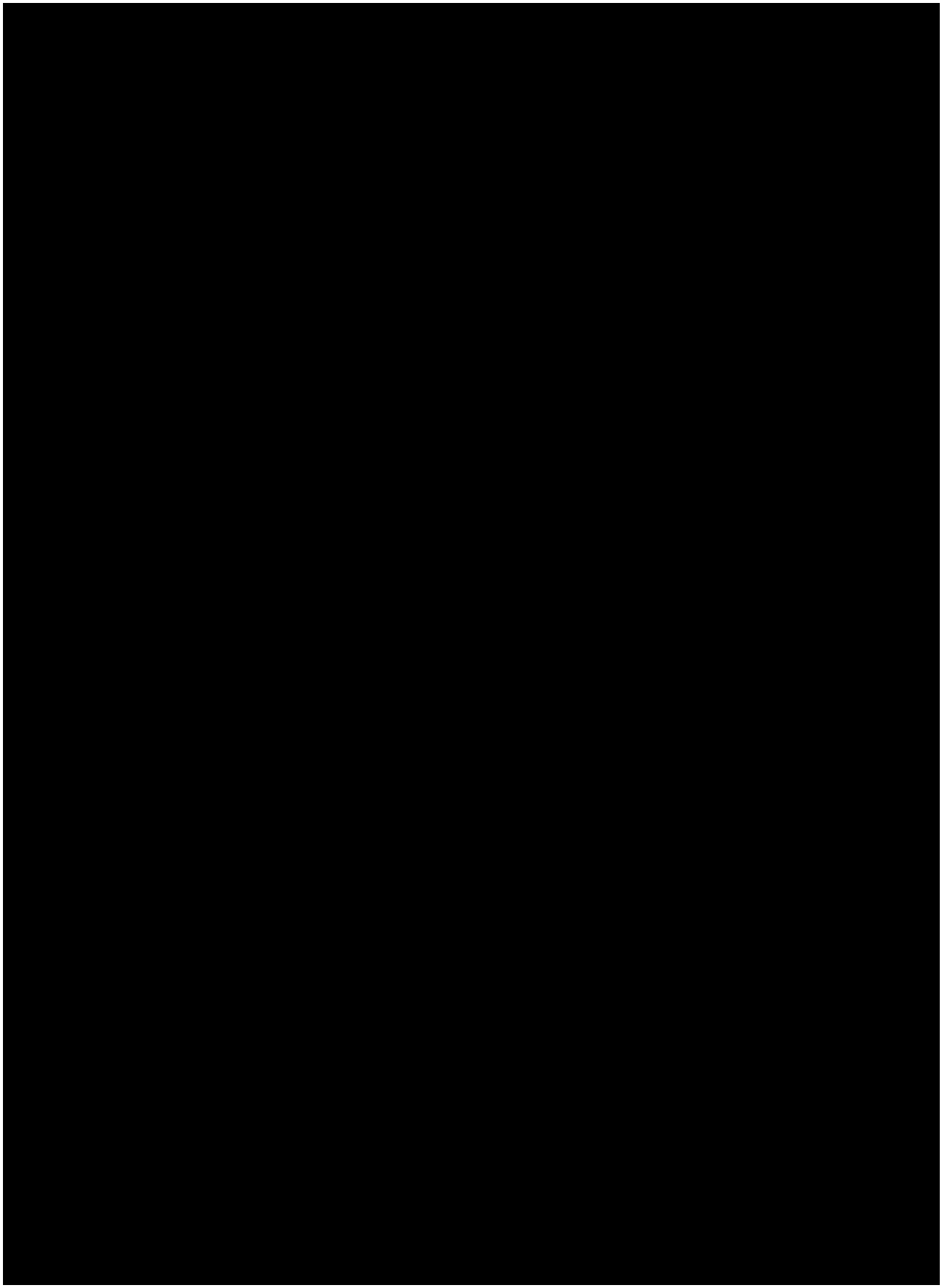
For Cohorts A, B, and C, all the safety analyses will be performed by cohort and total (including treated subjects in Cohort A) for all treated subjects. Descriptive statistics of safety will be presented using the NCI CTCAE v4 by cohort and total. All AEs, drug-related AEs, SAEs and drug-related SAEs will be tabulated using the worst grade per NCI CTCAE v 4 by system organ class and preferred term. On-study lab parameters including hematology, coagulation, chemistry, liver function, thyroid, adrenal and renal function will be summarized using worse grade by NCI CTCAE v 4. In addition, immune mediated adverse events incident rate is defined as the proportion subjects with any grade adverse events among subjects treated by each cohort and total. Events reported from the first dose and up to and including 100 days following the last dose of study treatment could be included in estimating this incidence rate. For Cohort D, similar safety analyses will be repeated by treatment arm for all treated subjects.

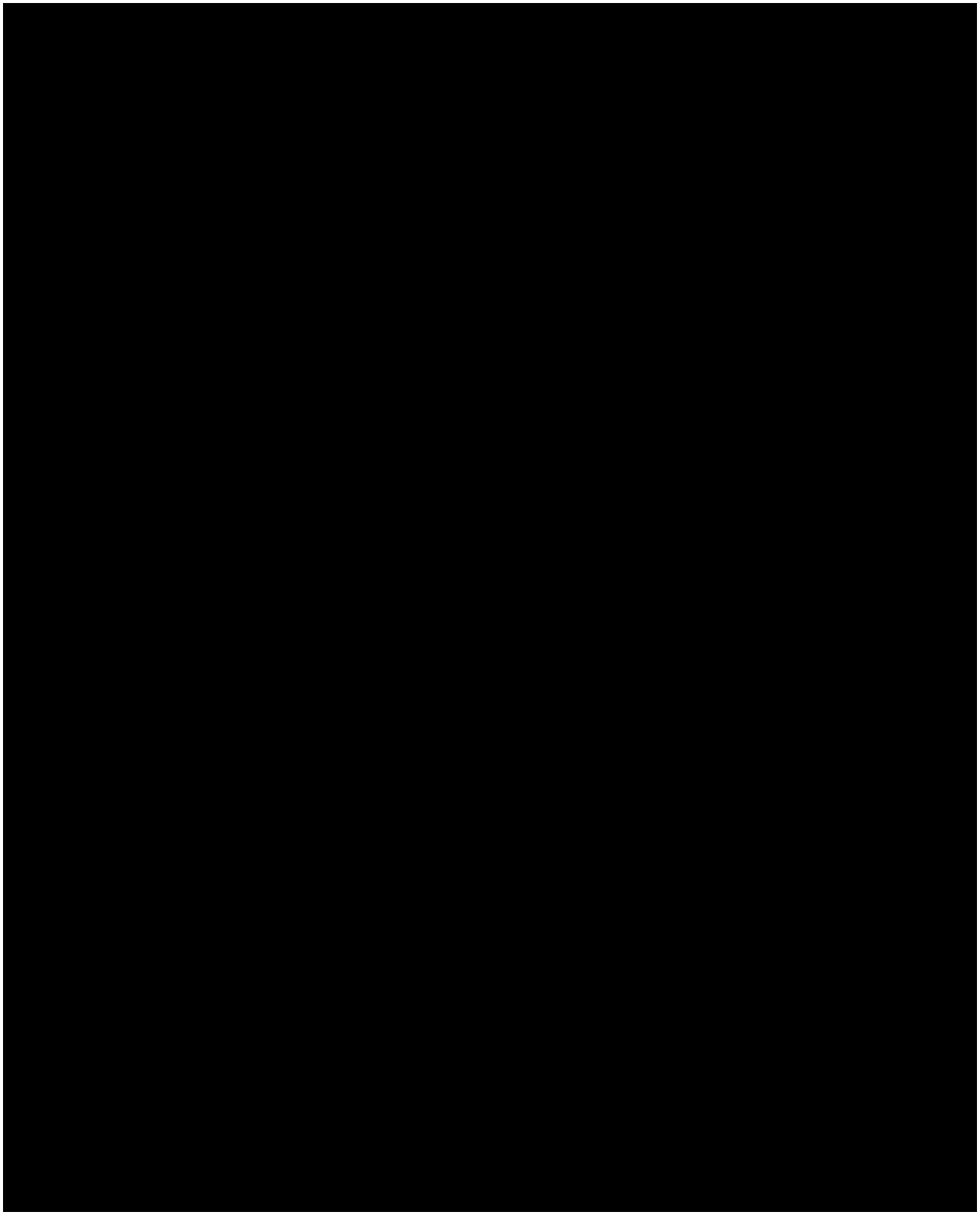


[redacted]

8.2.10 Other Analyses

Methodology for other analyses including [redacted] summary of other questionnaires will be described in the statistical analysis plan.





9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 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. 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 subject: (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 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 prior to enrollment.

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

9.1.2 Monitoring

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

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

In addition, the study may be evaluated by BMS 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 BMS or designee.

9.1.2.1 Source Documentation

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.

9.2 Records

9.2.1 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 or designee 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.

9.2.2 Study Treatment Records

Records for IP (whether supplied by BMS, its vendors, or the site) must substantiate IP 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):	• 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 subject, including unique subject 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, if applicable • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.
Sourced by site, and not supplied by BMS or its vendors (examples include IP sourced from the sites stock or commercial supply, or a specialty pharmacy)	The investigator or designee accepts responsibility for documenting traceability and study treatment integrity in accordance with requirements applicable under law and the SOPs/standards of the sourcing pharmacy. These records should include: • label identification number or batch number • amount dispensed to and returned by each subject, including unique subject identifiers • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

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

9.2.3 Case Report Forms

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

For sites using the Sponsor or designee electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the electronic SAE form and Pregnancy Surveillance form, respectively. If electronic SAE form is not available, a paper SAE form can be used. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by Sponsor of designee.

The confidentiality of records that could identify subjects 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. For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. 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.

9.3 Dissemination of Clinical Study Data

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

9.4 Clinical Study Report

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

For this protocol, the Signatory Investigator will be selected as appropriate based on the following criteria:

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

9.5 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.

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

10 GLOSSARY OF TERMS

Term	Definition
Complete Abstinence	Complete Abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. This also means that abstinence is the preferred and usual lifestyle of the patient. This does not mean periodic abstinence (eg, calendar, ovulation, symptothermal, profession of abstinence for entry into a clinical trial, post-ovulation methods) and withdrawal, which are not acceptable methods of contraception. Women must continue to have pregnancy tests. Acceptable alternate methods of highly or less effective contraception's must be discussed in the event that the subject chooses to forego complete abstinence.

11 LIST OF ABBREVIATIONS

Term	Definition
ADT	androgen deprivation therapy
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AT	aminotransaminases
BA/BE	bioavailability/bioequivalence
BICR	Blinded Independent Central Review
BID, bid	bis in die, twice daily
BMS	Bristol-Myers Squibb
BOR	best overall response
BP	blood pressure
BPI-SF	Brief Pain Inventory-Short Form
BUN	blood urea nitrogen
C	Celsius
Cavgss	average concentration
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
C1-	chloride
cm	centimeter
Cmaxss, CMAX	maximum observed concentration
Cmin1,Cminss	trough observed concentration
CNS	Central nervous system
COVID-19	coronavirus disease 2019
CRC	Colorectal cancer
CrCL	Creatinine clearance
CR	Complete response
CRF	Case Report Form, paper or electronic

Term	Definition
CRPC	castration resistant prostate cancer
CSR	clinical study report
CT	computerized tomography
CTA	Clinical trial agreement
CTCAE	Common Terminology Criteria for Adverse Events
D/C	discontinue
[redacted]	
DES	diethylstilbestrol
DILI	drug induced liver injury
dL	deciliter
DLT	Dose Limiting Toxicity
[redacted]	
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eg	exempli gratia (for example)
eGFR	estimated glomerular filtration
EQ-5D-3L	3-level EuroQol Five Dimensions questionnaire
EMR/EHR	electronic medical/health records
FDA	Food and Drug Administration
g	Gram
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GI	gastrointestinal
GnRH/LHRH	gonadotropin-releasing hormone/luteinizing hormone-releasing hormone
h	hour
HA	Health Authority
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus

Term	Definition
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	Human Immunodeficiency Virus
HR	heart rate
HRPC	hormone-refractory prostate cancer
IB	Investigator Brochure
ICF	Informed consent form
ICH	International Council of Harmonisation
Ie	id est (that is)
IEC	Independent Ethics Committee
IMAE	Immune-mediated adverse events
IMP/IP	investigational medicinal products/investigational product
IND	Investigational New Drug Exemption
INR	international normalized ratio
I-O	Immuno-oncology
IRB	Institutional Review Board
IWRS	Interactive Web Response System
IV	Intravenous
kg	kilogram
L	liter
LDH	lactate dehydrogenase
mAb	monoclonal antibody
mCRPC	metastatic castration-resistant prostate cancer
[redacted]	
mg	milligram
Mg++	Magnesium
min	Minute
mL	Milliliter
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
µg	Microgram

Term	Definition
N	number of subjects or observations
Na+	Sodium
N/A	not applicable
NCCN	National Comprehensive Cancer Network
ng	Nanogram
NSCLC	Non small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PAP	Prostatic acid phosphatase
PBMC	Peripheral Blood Mononuclear Cells
PCWG2	Prostate Cancer Working Group
PD	Pharmacodynamics; progressive disease
PD-1/PD-L1	Programmed cell death protein 1/Programmed death-ligand 1
PFS	Progression free survival
PK	Pharmacokinetics
PO	per os (by mouth route of administration)
PPK	population pharmacokinetic
PR	Partial response
PSA	prostate-specific antigen
PSA-RR	prostate-specific antigen response rate
PSMA	prostate-specific membrane antigen
PT	prothrombin time
PTT	partial thromboplastin time
QC	quality control
QD, qd	quaque die, once daily
QoL	quality of life
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
rPFS	radiographic Progression Free Survival
RT	radiation therapy

Term	Definition
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SCLC	Small cell lung cancer
SD	stable disease
SmPC	Summary of Product Characteristics
[redacted]	
SOC	Standard of care
SOP	Standard Operating Procedures
SRE	skeletal-related events
Subj	Subject
SUSAR	Suspected, Unexpected Serious Adverse Reaction
t	Temperature
T	Time
TAA	tumor-associated antigens
Treg	Regulatory t-cells
[redacted]	
USPI	United States Packaging Insert
VAS	Visual analogue scale
Vss/F (or Vss)	apparent volume of distribution at steady state
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential

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APPENDIX 1 MANAGEMENT ALGORITHMS

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

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

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

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

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

GI Adverse Event Management Algorithm

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

Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea:< 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat as Grade 2 or 3/4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hrs; not interfering with ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recur: • 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as grade 3/4
Grade 3-4 Diarrhea (G3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with ADL Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs G4: life-threatening, perforation	• Discontinue I-O therapy per protocol • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication). Note: 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.

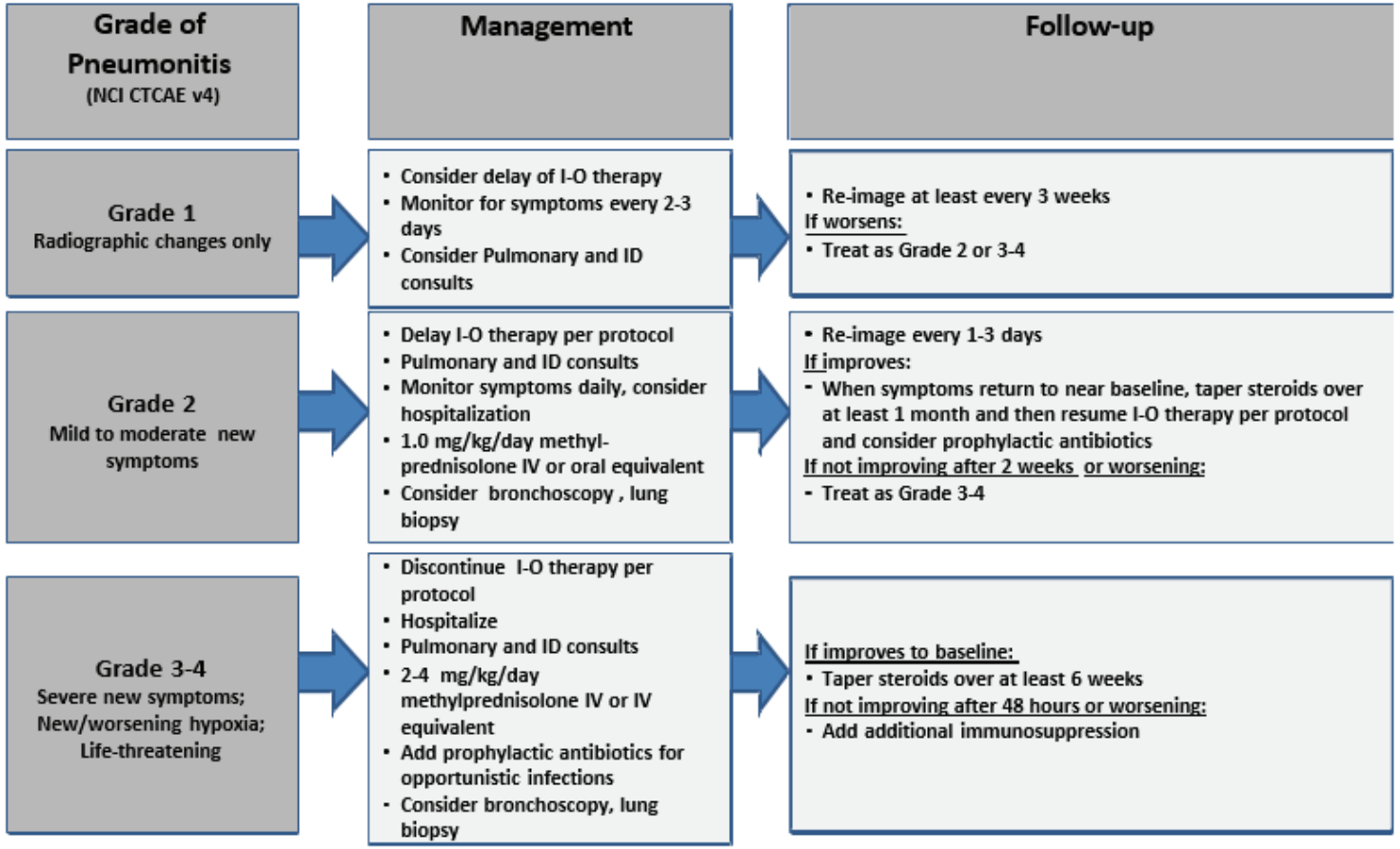
Grade of Creatinine Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 Creatinine > ULN and > than baseline but ≤ 1.5x baseline	• Continue I-O therapy per protocol • Monitor creatinine weekly	If returns to baseline: •Resume routine creatinine monitoring per protocol If worsens: •Treat as Grade 2 or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

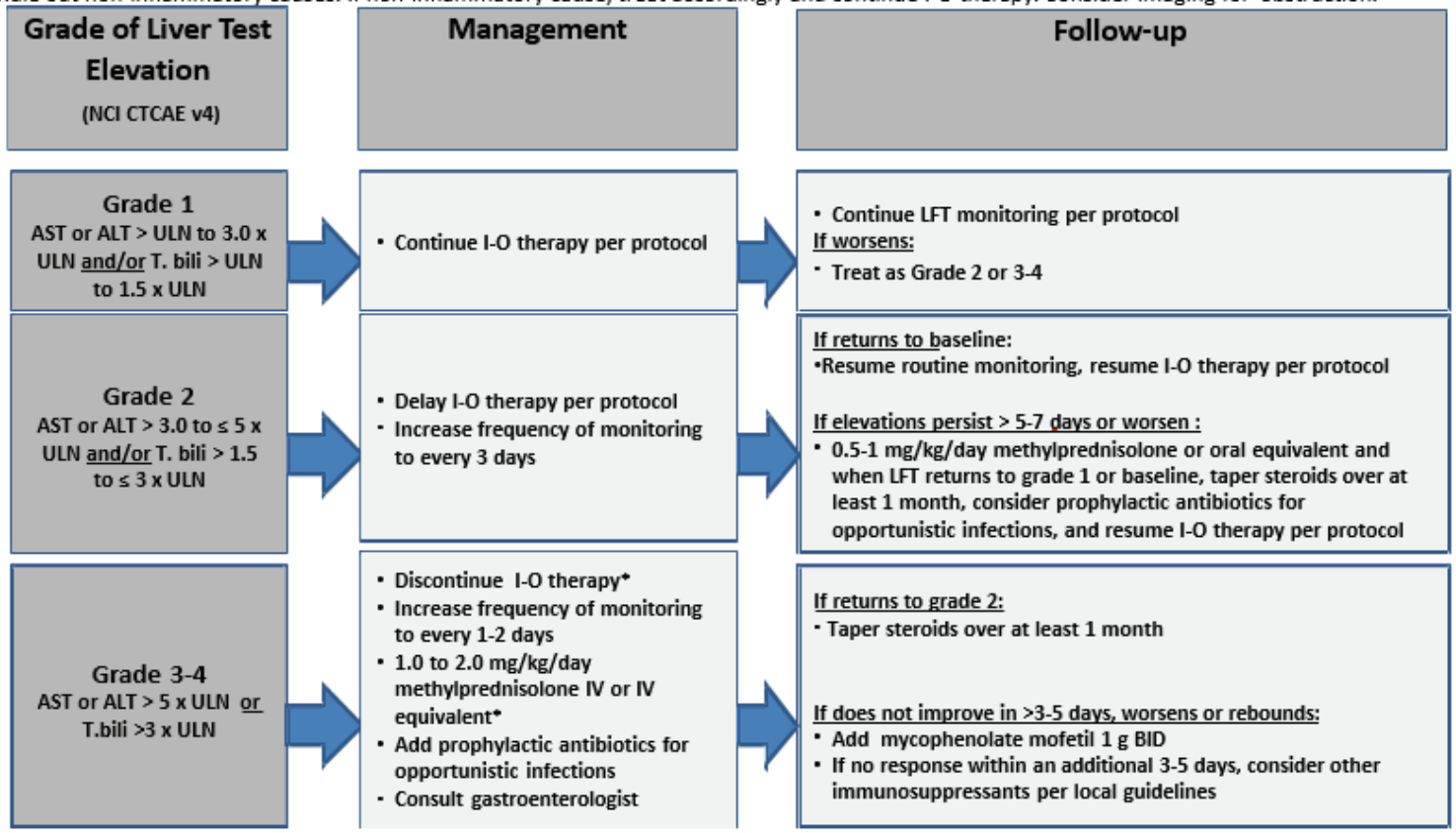


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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



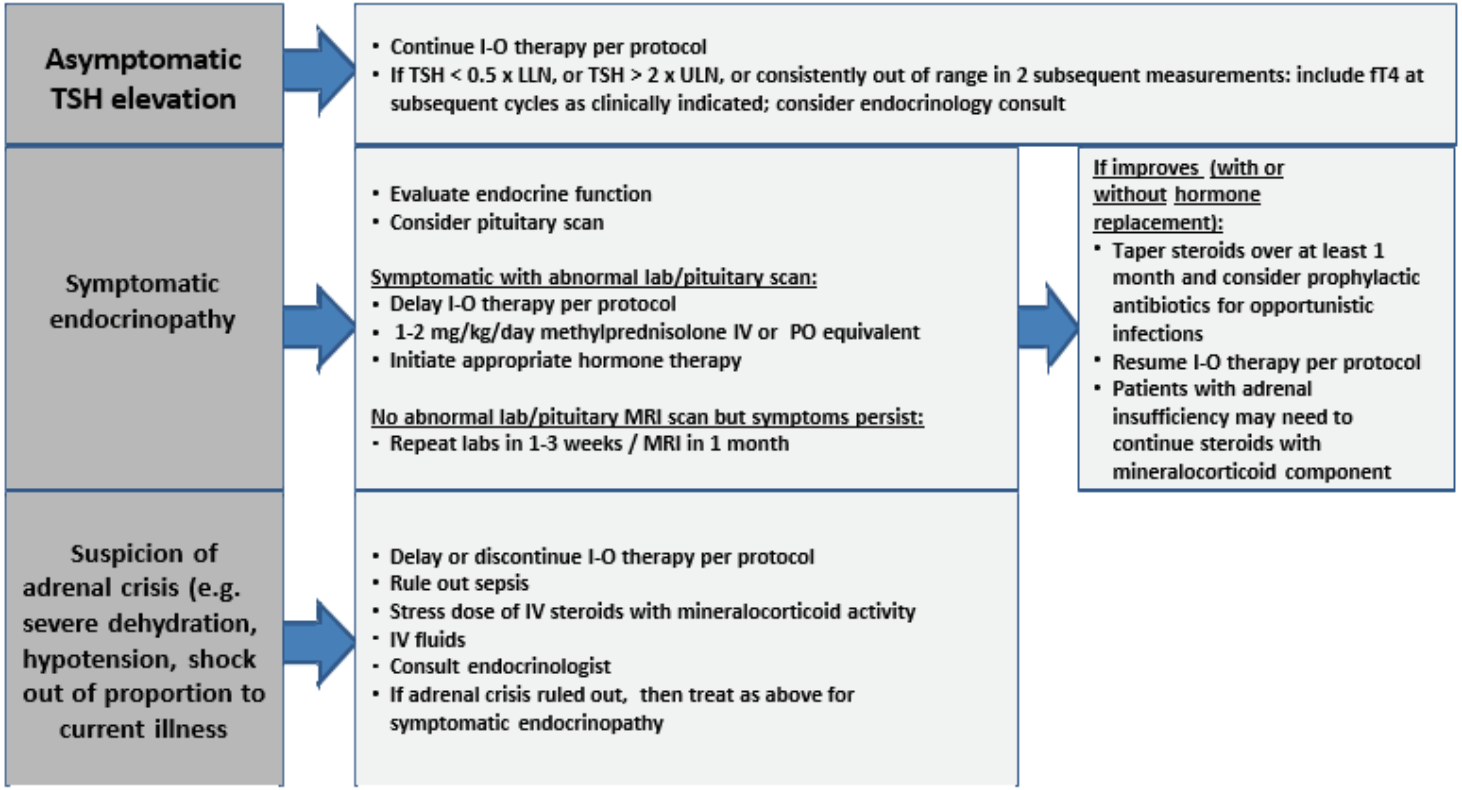
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

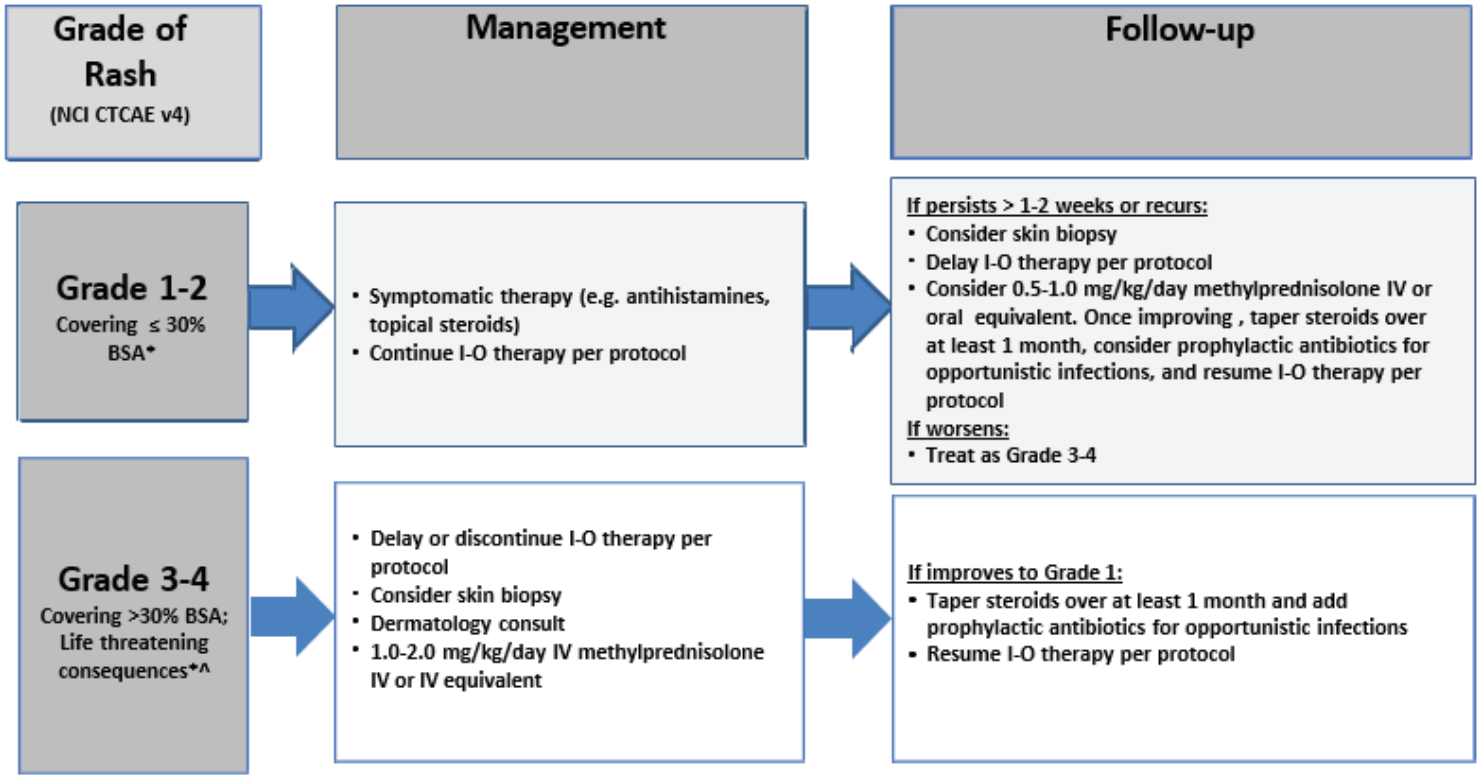


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

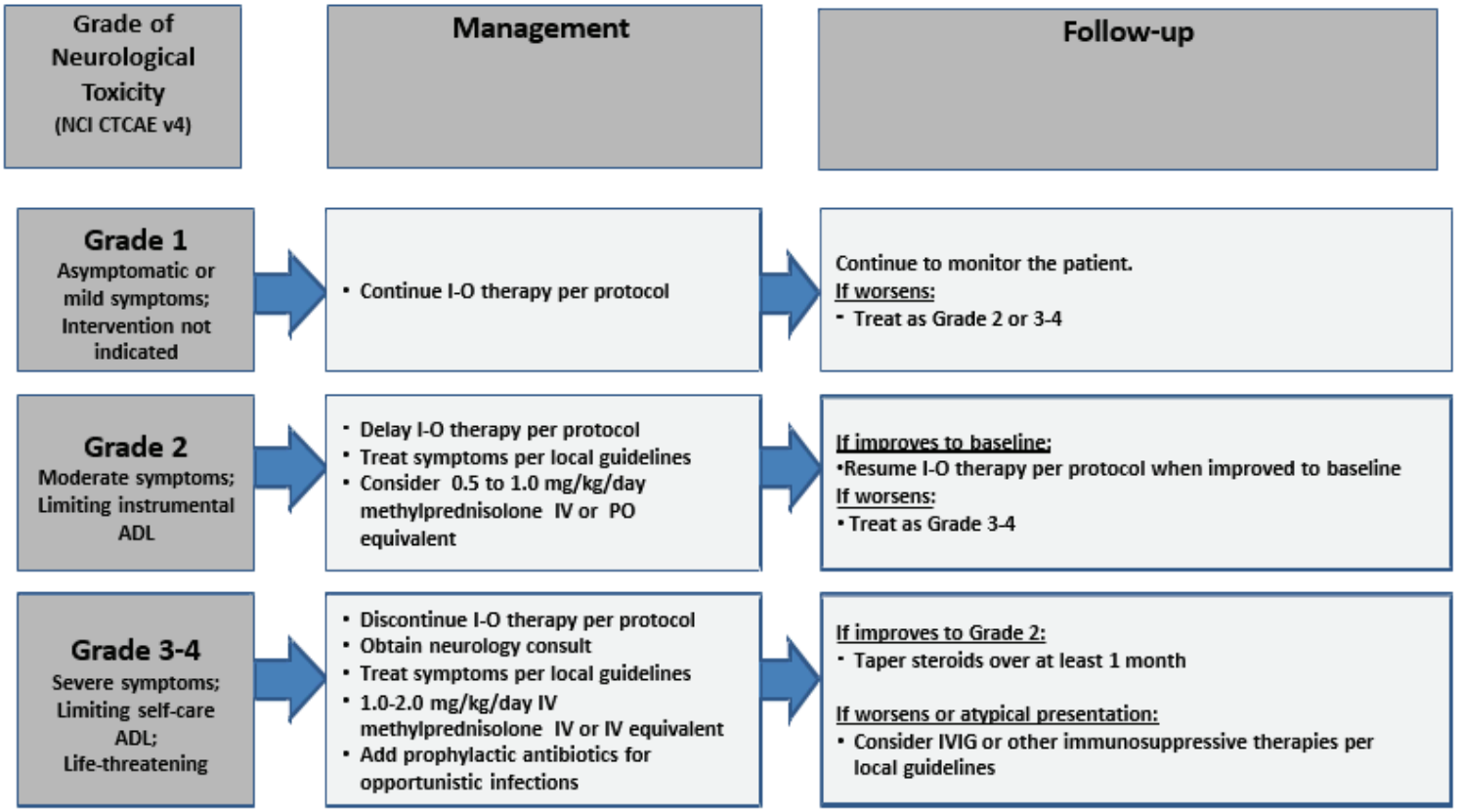
*Refer to NCI CTCAE v4 for term-specific grading criteria.

^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

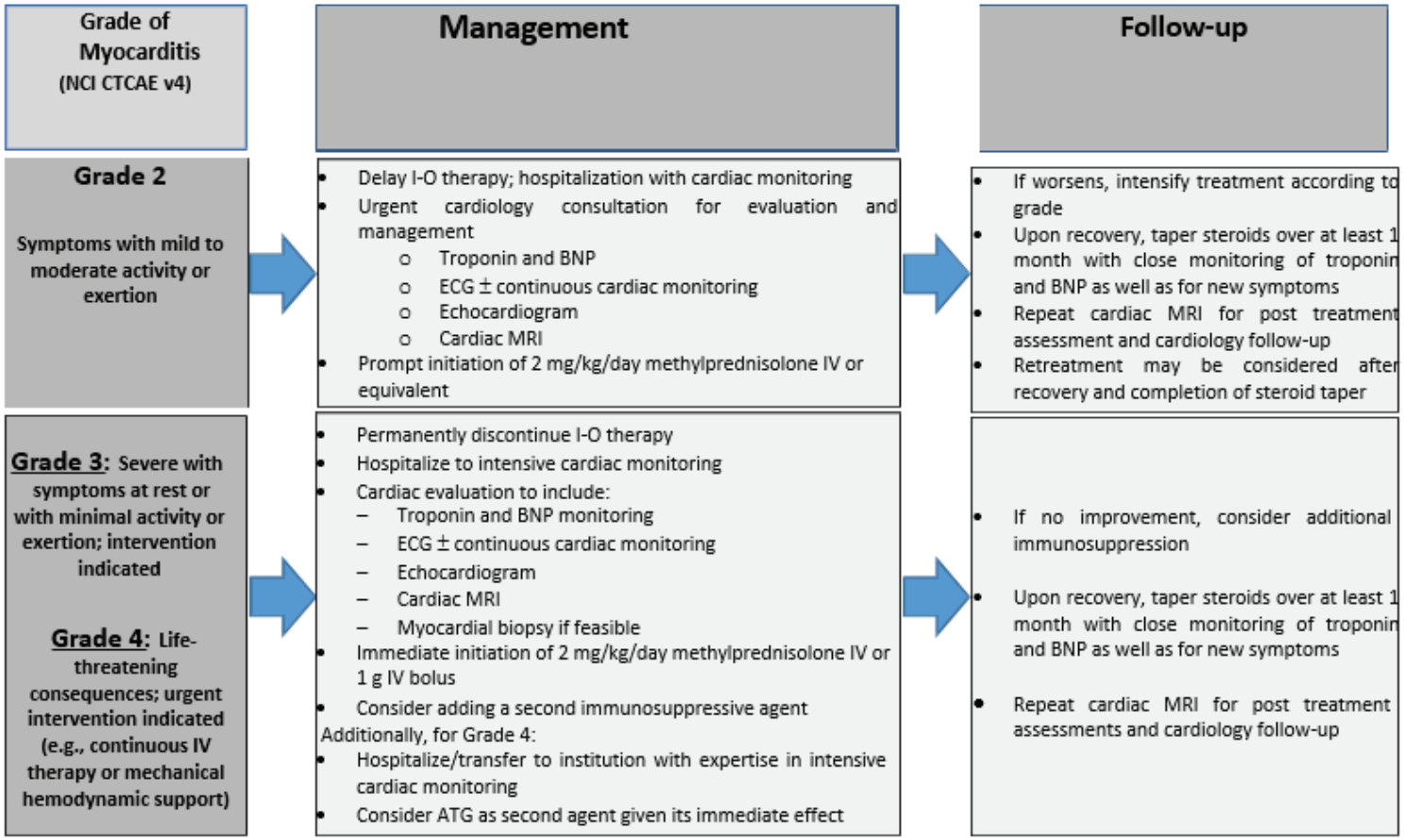
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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 2 PERFORMANCE STATUS SCALES - ECOG

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

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

APPENDIX 3 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] • Hormonal methods of contraception including oral contraceptive pills containing a combination of estrogen and progesterone, vaginal ring, injectables, implants and intrauterine hormone-releasing system (IUS)[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 6.4 and the Appendix for Adverse Events and Serious Adverse Events Definitions and procedures for Evaluating, Follow-up and Reporting.

APPENDIX 4 COUNTRY SPECIFIC REQUIREMENTS

1 COUNTRY SPECIFIC REQUIREMENTS

1.1 Germany

Original language	Country-specific language
Section 5 Schedule of Activities Table 5.1-1 Screening Procedural Outline, Laboratory Tests	Add “HIV” to the list of laboratory tests
Section 3.3.3 Exclusion Criteria, Exclusion criterion 2 j)	“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 5.4 Safety Assessments	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 and Hepatitis B and C testing (HBV sAg and HCV Ab or HCV RNA), and HIV..

APPENDIX 5 REVISED PROTOCOL SUMMARY OF CHANGE HISTORY

Overall Rationale for the Revised Protocol 04, 26-Mar-2020

The purpose of this revision is to modify the maximum tumor sample age from 5 years to 1 year. The study will allow submission of tumor samples obtained more than 1 year prior to enrollment if collected in the metastatic setting and if approved by the BMS Medical Monitor/designee. Recent prostate cancer studies evaluating tumor biology across different settings have found that the frequencies of individual genetic alterations increase as the disease progresses, suggesting that tumor samples collected in the localized disease setting may not reflect the tumor biology at the time of study treatment. In addition, Revised Protocol 04 allows starting dose of cabazitaxel of 20 mg/m^2 to align with cabazitaxel labeling, clarifies the population for analyses in Cohort D-Part 1, clarifies the exclusion criteria for prior pelvic radiotherapy, incorporates updated nivolumab clinical program protocol standards, and makes minor clarifications for consistency throughout the document. Where applicable, sections in the synopsis have been updated to align with the protocol section changes listed below.

Summary of key changes of Revised Protocol 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Global changes	Replaced 'Amendment 02' with 'Revised Protocol 02'.	The mention of Amendment 02 was an error and was corrected to reference Revised Protocol 02
	Where applicable "study drug" was updated to "study treatment".	Revised to align with the most recent language for BMS studies
	Where applicable "co-primary endpoint(s)" was changed to "dual primary endpoint(s)".	To comply with HA's guidance on the definition of multiple endpoints
Section 1.3.1, Primary Objectives, bullet item 2	*Revised bullet item 2. (Text changes are underlined).* • Assess Radiographic Progression Free Survival (rPFS) assessed by BICR in all treated subjects with mCRPC <u>in Cohort B, C, D - Part 2 period and all randomized subjects with mCRPC in Cohort D - Part 1 period</u> using RECIST V1.1 for soft tissue disease progression and PCWG2 for bone disease progression.	To clarify that the population for analyses in Cohort D-Part 1 are all 'randomized subjects' since the study design is randomized.
Section 1.5.1, Overall Risk/Benefit Assessment for Additional Cohort D, bullet item 3	*Revised bullet item 3. (Text changes are underlined).* • Early interim reviews of safety and efficacy data will be performed by the Sponsor and participating investigators <u>from the Study Steering Committee for Cohort D</u> after the first 15 treated subjects for each arm have at least 8 weeks of follow-up after first dose and at least one post-baseline tumor assessment in subjects	To add the Study Steering Committee for Cohort D.

Summary of key changes of Revised Protocol 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
	receiving immunotherapy in Arms D1, D2, and D3.	
Section 2.1, Good Clinical Practice	*Revised paragraph 3 regarding potential breaches.*	Revised to align with the most recent language for BMS studies.
Section 3.1, Study Design and Duration, bullet items 1 and 2 were revised	*Bullet items 1 and 2 were revised. (Text changes are underlined).* • Arm D1: nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg every 3 weeks for up to 4 doses (Cycles 1 to 4), followed by nivolumab 480 mg administered every 4 weeks (Cycle 5 and beyond). Subjects who are receiving maintenance nivolumab with ongoing disease control (ongoing CR, PR, or SD) or with radiographic progression per RECIST 1.1/PCWG2 may be permitted re-induction with the combination of ipilimumab and nivolumab at their original combination dose upon PSA progression or radiographic progression (whichever occurs first), as specified in Section 4.3.5. Treatment will continue until disease progression, unacceptable toxicity, withdrawal of consent, 2 year maximum treatment duration, or the study ends, whichever occurs first. • Arm D2: nivolumab 1 mg/kg every 3 weeks plus ipilimumab 3 mg/kg every 2 cycles (ie, every 6 weeks) for up to 4 ipilimumab doses, followed by nivolumab 480 mg every 4 weeks. Subjects who are receiving maintenance nivolumab with ongoing disease control (ongoing CR, PR, or SD) or with radiographic progression per RECIST 1.1/PCWG2 may be permitted re-induction with the combination of ipilimumab and nivolumab at their original combination dose upon PSA progression or radiographic progression (whichever occurs first), as specified in Section 4.3.5. Treatment will continue until disease progression, unacceptable toxicity, withdrawal of consent, 2 year maximum treatment duration, or the study ends, whichever occurs first.	To allow re-induction in patients with radiographic progression before PSA progression

Summary of key changes of Revised Protocol 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 3.1, Study Design and Duration, bullet item 4	*Bullet item4 was revised. (Text changes are underlined).* • Arm D4: Cabazitaxel 20 mg/m^2 or 25 mg/m^2 (at investigator's discretion and according to country-specific label) every 3 weeks in combination with oral prednisone or prednisolone 10 mg daily for up to 10 cycles. Treatment will continue until disease progression, unacceptable toxicity, withdrawal of consent, completion of 10 cycles of treatment, or the study ends, whichever occurs first.	To align with cabazitaxel product label.
Section 3.1, Study Design and Duration, third paragraph below bulleted list	*The third paragraph below bulleted list was revised. (Text changes are underlined):* Cohort D-Part 1 will evaluate the above immunotherapy regimens and the standard of care comparator cabazitaxel in unselected mCRPC patients. [redacted]	
Figure 3.1-2, Study Design Schematic addition of Cohort D-Part 1	*Revised cabazitaxel dose for Arm D4.*	To align with cabazitaxel product label.

Summary of key changes of Revised Protocol 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 3.1, Study Design and Duration, Treatment Phase	**Previously:** For Arms D1, D2, D3, and D4, tumor assessments are scheduled to be performed every 8 weeks for 6 months following treatment initiation and thereafter every 12 weeks until radiographic progression has been assessed by the investigator and confirmed by BICR (see Section 5.5.3) or withdrawal of consent. **Revised**: For Arms D1, D2, D3, and D4, tumor assessments are scheduled to be performed every 8 weeks (±7 days) for 6 months following treatment initiation and thereafter every 12 weeks (± 7 days) until radiographic progression has been assessed by the investigator and confirmed by BICR (see Section 5.5.3) or withdrawal of consent.	Specify window for tumor assessments.
Section 3.1, Study Design and Duration, Optional Re-induction Combination for Cohorts B, C, Arms D1, and D2	*Revised first paragraph. (Text changes are underlined):* Subjects with PSA progression or with radiographic progression per RECIST 1.1/PCWG2 (whichever occurs first) during or after nivolumab monotherapy maintenance may receive nivolumab and ipilimumab combination at the same dose levels as assigned at study start and follow the same Time and Events schedule, as specified in Section 5.	To allow re-induction in patients with radiographic progression before PSA progression
Section 3.1, Study Design and Duration, Follow-Up Phase, Bullet item 7, sentence 1	*Revised bullet item 7, sentence 1 (Text changes are underlined).* • BMS may request that survival data be collected on all treated subjects in Cohort B, C, D - Part 2 period and all randomized subjects in Cohort D - Part 1 period outside of the protocol defined window as detailed in the Time and Events Table (Section 5). At the time of this request, each subject will be contacted to determine their survival status unless the subject has withdrawn consent for all contact.	To clarify that the population for analyses in Cohort D-Part 1 are all 'randomized subjects' since the study design is randomized.

Summary of key changes of Revised Protocol 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 3.2, Post Study Access to Therapy, paragraph 2, sentence 1.	*Revised paragraph 2, sentence 1 (Text changes are underlined).* BMS may request that survival data be collected on all treated subjects <u>in Cohort B, C, D - Part 2 period and all randomized subjects in Cohort D - Part 1 period</u> outside of the protocol defined window.	To clarify that the population for analyses in Cohort D-Part 1 are all 'randomized subjects' since the study design is randomized.
Section 3.3.1, Inclusion Criteria Criterion 2) Target Population, item d)	**Previously:** d) Evidence of Stage IV disease (as defined by AJCC criteria) on previous bone, CT, and/or MRI scan **Revised:** d) <u>Current evidence of metastatic disease documented by either bone lesions on radionuclide bone scan and/or soft tissue lesions on CT/MRI. Metastases may be in regional lymph nodes (N1 per AJCC staging criteria, 8th edition) and/or distant metastases (M1 per AJCC staging criteria, 8th edition).</u> <u>i) Subjects whose disease spread is limited to regional pelvic lymph nodes (N1M0) must have a lymph node measuring at least 2 cm in short axis to be considered eligible.</u>	Clarified patient eligibility.
Section 3.3.1, Inclusion Criteria Criterion 2) Target Population, f)	*Revised criterion 2) Target Population, f) (Text changes are underlined)* f) Tumor progression while receiving ADT per PCWG2 criteria <u>and within 6 months prior to screening,</u> with at least one of the following:	Clarified patient eligibility.
Section 3.3.1, Inclusion Criteria Criterion 2) Target Population, f), ii)	*Revised this item to remove the sentence*: "Subjects whose disease spread is limited to regional pelvic lymph nodes (N1M0) must have a lymph node measuring at least 2 cm in short axis to be considered eligible."	This sentence was moved to item d), i).
Section 3.3.1, Inclusion Criteria Criterion 2) Target Population, criterion g) iv)	*Revised criterion g) iv). (Text changes are shown as strike through or underlined).* iv) **Cohort D:** Subjects must have progressed after a prior docetaxel-containing regimen and received no more than 2 prior chemotherapy regimens in the metastatic setting. If docetaxel was only given in the metastatic castration-sensitive setting, subjects must also have progressed following prior treatment with a second generation hormonal therapy. Prior second-generation hormonal manipulations (eg,	Revised to clarify washout period for prior chemotherapy.

Summary of key changes of Revised Protocol 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
	abiraterone acetate, enzalutamide, apalutamide), ketoconazole, prostate cancer vaccine therapy, ~~radiation therapy~~, radium-223, anti-androgens (eg, flutamide), chemotherapy and DES or other estrogens, are allowed up to 28 days prior to study treatment.	
Section 3.3.1, Inclusion Criteria Criterion 2) Target Population, criterion l	*Revised criterion l). (Text changes are underlined):* l) Sufficient tumor samples from either a fresh biopsy (collected during screening period) or archival tumor tissue in the form of formalin-fixed paraffin-embedded (FFPE) block or a minimum of 15 unstained tumor tissue slides. Archival tumor samples must be obtained within 1 year prior to enrollment date, either from a metastatic tumor lesion (preferred) or from a primary tumor lesion that has not been previously irradiated. Tumor samples collected more than 1 year prior to enrollment date may be acceptable if obtained in the metastatic setting and following discussion with and approval by the BMS Medical Monitor/designee. Tumor sample may be from core biopsy, punch biopsy, excisional biopsy, or surgical specimen. Fine needle aspiration is unacceptable for submission. [redacted] Central laboratory must confirm receipt of tumor samples prior to randomization.	Revised to restrict the age of tumor samples to 1 year, but to allow submission of tumor samples obtained more than 1 year prior to enrollment if collected in the metastatic setting and if approved by the Sponsor.
Section 3.3.3, Exclusion Criteria, Criterion 2, Medical History, Concurrent Diseases and Prior Therapies	*Criterion d) was revised. (Text changes are underlined).* d) Less than 1 month since resolution of ≥Grade 2 toxicity related to pelvic-targeted therapy (eg, radiation enteritis).	Revised to exclude participants who are less than 1 month since resolution of ≥ Grade 2 toxicity related to pelvic-targeted therapy
Section 3.3.3, Exclusion Criteria, Criterion 2, Medical History, Concurrent Diseases and Prior Therapies	*Criterion e) was revised. (Text changes are underlined).* e) Prior radiation therapy within 14 days prior to starting study therapy. Any toxicity related to prior radiation therapy must have resolved to Grade ≤ 1 or baseline prior to starting study therapy.	Revised to clarify washout from prior radiation therapy (RT) and exclusion of subjects based on resolution of RT-related toxicities.
Section 3.3.3, Exclusion Criteria, Criterion 2, Medical History, Concurrent Diseases and Prior Therapies	*Revised criterion o). (Text changes are underlined).* o) For Cohort D: previous treatment with cabazitaxel in the metastatic setting	To clarify that previous treatment with cabazitaxel is an exclusion criteria only if it was received in the metastatic setting.

Summary of key changes of Revised Protocol 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 3.3.3, Exclusion Criteria, Criterion 5) Other Exclusion Criteria	*Revised criterion a). (Text changes are underlined).* a) Prisoners or subjects who are involuntarily incarcerated. (Note: under certain specific circumstances, and only in countries where local regulations permit, a person who has been imprisoned may be included or permitted to continue as a subject. Strict conditions apply and Bristol-Myers Squibb approval is required.)	Revised to align with the most recent language for BMS studies.
Section 3.3.4, Exclusion Criteria for Crossover Phase for Subjects Originally Randomized to Arm D3 or Arm D4 only, 7) Medical History, Concurrent Diseases and Prior Therapies	*Revised criterion d). (Text changes are underlined).* d) Less than 1 month since resolution of ≥ Grade 2 toxicity related to pelvic-targeted therapy (eg, radiation enteritis).	Revised to exclude participants who are less than 1 month since resolution of ≥ Grade 2 toxicity related to pelvic-targeted therapy.
Section 3.3.4, Exclusion Criteria for Crossover Phase for Subjects Originally Randomized to Arm D3 or Arm D4 only, 7) Medical History, Concurrent Diseases and Prior Therapies; item e)	*Revised criterion e). (Text changes are underlined).* e) Prior radiation therapy within 14 days prior to first dose of nivolumab combined with ipilimumab. Any toxicity related to prior radiation therapy must have resolved to Grade ≤ 1 or baseline prior to first dose of nivolumab combined with ipilimumab.	Revised to clarify washout from prior radiation therapy (RT) and exclusion of subjects based on resolution of RT-related toxicities.
Section 3.3.4, Exclusion Criteria for Crossover Phase for Subjects Originally Randomized to Arm D3 or Arm D4 only, 7) Medical History, Concurrent Diseases and Prior Therapies; item p	*Added criterion p)* p) Subjects who have received systemic anti-cancer therapy after the last dose of study treatment (ipilimumab or cabazitaxel)	To clarify that no systemic anti-cancer therapy is allowed between main treatment and crossover treatment
Section 3.4.2, Other Restrictions and Precautions Revised first paragraph.	**Previously:** Palliative (limited-field) radiation therapy and palliative surgical resection are permitted, if the following criteria are met: 1) The subject will be considered to have progressed at the time of palliative therapy and must meet criteria to continue with treatment beyond progression (Section 4.5.4). 2) The case is discussed with the BMS Medical Monitor or Study Director. **Revised:** Palliative (limited-field) radiation therapy and palliative surgical resection are	To align with Table 5.5.3-2: on when local therapy is considered clinical progression.

Summary of key changes of Revised Protocol 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
	permitted, if the case is discussed with the BMS Medical Monitor or Study Director.	
Section 3.5, Discontinuation of Subjects following any Treatment with Study Drug Added a note to bullet item 4.	*Added a note to bullet item 4. (Text changes are underlined).* Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness. Note: Under specific circumstances and only in countries where local regulations permit, a participant who has been imprisoned may be permitted to continue as a participant. Strict conditions apply and BMS approval is required.	Alignment with current BMS standards for studies using nivolumab.
Section 3.5, Discontinuation of Subjects following any Treatment with Study Drug Revised last bullet item.	**Previously:** • Subject meets criteria for confirmed progression (radiographic and/or clinical) by PCWG2 or RECIST 1.1 criteria. **Revised:** • Subject meets criteria for radiographic progression by PCWG2 or RECIST 1.1 criteria.	To clarify that patients with radiographic progression by PCWG2 or RECIST 1.1 must discontinue treatment. Requirement to discontinue for clinical progression was removed.
Section 4, Study Treatment, Table 4-1, Study Treatment for CA209650	*Corrected potency for prednisone and cabazitaxel.*	Per Administrative Letter 02.
Section 4.3.1, Arms A, B, and C Part 1 Study Treatment Administration - Nivolumab and Ipilimumab Combination Phase (Cycles 1-4)	In paragraph 3, the text “saline flush” was revised to “flush of diluent.”	Alignment with current BMS standards for studies using nivolumab.
Section 4.3.5, Re-Induction of Study Therapy For Subjects in Cohorts B, C, Arms D1 and D2	*Revised first paragraph and added 2 paragraphs. (Text changes are shown as strike through or underlined).* Subjects in Cohorts B, C and in Arms D1 and D2 who are receiving maintenance nivolumab ~~and achieved initial~~ with ongoing disease control (ongoing CR, PR, or SD) ~~during the combination period~~ or with radiographic progression per RECIST 1.1/PCWG2 may be permitted re-induction with the combination of ipilimumab and nivolumab at their original combination dose upon PSA progression ~~as~~ or radiographic progression per RECIST 1.1/PCWG2 (whichever occurs first; see Section 5.5.3), and after discussion and agreement with BMS Medical Monitor.	To allow re-induction in patients with radiographic progression before PSA progression and define timing of starting the first re-induction combination dosing

Summary of key changes of Revised Protocol 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
	For subjects in Arm D1, the first re-induction combination dosing can start no sooner than 4 weeks after the last nivolumab 480 mg dose and no sooner than 12 weeks after the last ipilimumab dose. For subjects in Arm D2, the first re-induction combination dosing can start no sooner than 8 weeks after the last nivolumab 480 mg dose and no sooner than 12 weeks after the last ipilimumab dose. Pausing nivolumab maintenance dosing is permitted in patients who are planning to receive re-induction in Arm D2,	
Section 4.3.7, Arm D4 Study treatment administration - cabazitaxel plus prednisone; and Table 4.5-3, Cohort D Dosing Schedule, row Arm D4	Revised dose of cabazitaxel to include "or 20 mg/m^2 at investigator's discretion and according to country-specific label".	To align with cabazitaxel product label.
Section 4.4, Method of Assigning Treatment	Removed bullet item requiring "M Stage at screening" from the second bulleted list.	To align with IWRS
Table 4.5-3, Cohort D Dosing Schedule, footnote	Revised footnote for starting dose of cabazitaxel for patients with mild hepatic impairment.	To align with cabazitaxel product label.
Section 4.5.3 Dose Discontinuation for Nivolumab and Ipilimumab	Revised first dashed item under bullet 2 to include 'myocarditis."	Alignment with current BMS standards for studies using nivolumab.
Section 4.5.3 Dose Discontinuation for Nivolumab and Ipilimumab	Revised fourth dashed item under bullet 3 to add statement regarding adrenal insufficiency requiring discontinuation.	To align with section 4.5.2 mandating discontinuation for adrenal insufficiency.
Section 4.5.4, Treatment Beyond Disease Progression	Revised Paragraph 5 and 6. Replaced "by RECIST 1.1" with "of soft tissue".	To clarify that the rules for determining further progression do not follow RECIST 1.1 for soft tissue.
Section 4.5.5.1, Other Toxicities for Cabazitaxel	*Added the following sentence.* In case of treatment delay greater than 2 weeks, patient should discontinue study treatment, unless there is strong evidence of clinical benefit to justify continuation of dosing with study treatment, and the investigator must discuss the rationale with the Sponsor before a decision is taken.	To allow more flexibility in case a dose delay > 2 weeks is needed for cabazitaxel.

Summary of key changes of Revised Protocol 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 4.5.5.2-1: Dose reduction levels for cabazitaxel	Revised the table footnote to include "20 mg/m^2 or" for the starting dose of cabazitaxel for subjects with mild hepatic impairment.	To align with cabazitaxel product label.
Section 4.5.6, Management Algorithms for Immuno-Oncology Agents	Added myocarditis to the bullet list of management algorithms.	Alignment with most recent nivolumab IB.
Table 5.1-1, Screening Procedural Outline (CA209650) for All Treatment Arms (Cohorts A, B, C, and D)	Updated table notes for laboratory, PSA, and Testosterone tests.	For consistency with study assessments.
[redacted]		
Table 5.1-4, On Treatment Procedural Outline (CA209650) for Cohort D, Safety Assessments	Laboratory Test row, Notes column, deleted statement regarding all safety labs, deleted PTT, PT, and INR assessments, and revised language for thyroid function testing.	Removed inclusion of tests specific to Cohorts A, B, and C, and clarified laboratory tests specific to Cohort D.
Table 5.1-4, On Treatment Procedural Outline (CA209650) for Cohort D, Safety Assessments	PSA row. Clarified that PSA testing should be performed within 72 hours.	Specify window for PSA testing.
[redacted]		
Table 5.1-4, On Treatment Procedural Outline (CA209650) for Cohort D, Clinical Drug Supplies	*Administer Study Treatment row, Notes column: Added the following bullet items under Re-Induction Treatment:* • For subjects in Arm D1, the first re-induction combination dosing can start no sooner than 4 weeks after the last nivolumab 480 mg dose and no sooner than 12 weeks after the last ipilimumab dose. • For subjects in Arm D1, the first re-induction combination dosing can start no sooner than 8 weeks after the last nivolumab 480 mg dose and no sooner than 12 weeks after the last ipilimumab dose. Pausing nivolumab maintenance dosing is permitted in patients who are planning to receive re-induction in Arm D2	To define the timing of starting the first re-induction combination dosing.

Summary of key changes of Revised Protocol 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 5.1-5, Follow-up Assessments (CA209650) for All Treatment Arms (Cohorts A, B, C, and D)	PSA row. Provided ±7 day window for PSA collection.	Specify window for PSA testing.
	Body Imaging row: Provided ±7 day window for body imaging.	Specify window for body imaging.
	Tc99mm based radionuclide bone Scan row: Provided ±7 day window for bone scan.	Specify window for bone scan.
Section 5.4, Safety Assessments	Updated to text reflect Safety Assessment and Procedures tables.	Align with Flow Chart/Time and Events Schedule.
Section 5.5, Efficacy Assessments, paragraph 8	*Revised paragraph 8. (Text changes are underlined).* For all treated subjects <u>in Cohorts A, B, C, and Cohort D-Part 2 period and for all randomized subjects in Cohort D-Part 1 period</u>, scans will be collected and held by a centralized imaging core laboratory for review by independent radiologists using RECIST 1.1 and PCWG2 (for bone disease progression) criteria. Scans will be centrally reviewed by BICR retrospectively for Cohorts A, B, and C, and prospectively on a rolling basis for Cohort D.	To clarify that scans will be collected and reviewed for all 'randomized subjects' in Cohort D-Part 1.
Section 5.5.3, Disease Progression Criteria	*Revised paragraph 2. (Text changes are shown as strike through or underlined).* PSA progression alone is not an indication to stop treatment. ~~In addition~~ <u>Rather</u>, subjects must ~~also meet~~ <u>discontinue treatment upon radiographic</u> progression ~~by~~ <u>per</u> RECIST 1.1 criteria for ~~measurable~~ <u>soft tissue</u> disease and/or PCWG2 criteria for bone disease (see Table 5.5.3-1 above) ~~and/or criteria for clinical progression (see below).~~	For consistency with the protocol where discontinuation is only mandated for radiographic progression.
[redacted]		

Summary of key changes of Revised Protocol 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		

Summary of key changes of Revised Protocol 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 6, Adverse Events	Added criteria for meeting or not meeting AE definition.	Revised to align with the most recent language for BMS studies.

Summary of key changes of Revised Protocol 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 6.1, Serious Adverse Events	Added definition of an SAE and text for evaluating AEs and SAEs.	Revised to align with the most recent language for BMS studies.
Section 6.1.1, Serious Adverse Event Collection and Reporting	Revised text regarding SAE collection, and reporting, and follow-up of AEs and SAEs.	Revised to align with the most recent language for BMS studies.
Section 7, Data Monitoring Committee and Other External Committees	Revised to include a Study Steering Committee.	To advise BMS regarding study-related issues.
[redacted]		
Section 8.2, Endpoints	Revised this section.	To clarify that the population for analyses in Cohort D-Part 1 are all 'randomized subjects' since the study design is randomized.
Section 8.2.5, Efficacy Analyses, revised second paragraph	*Revised second paragraph. (Text changes are underlined).* For the dual primary endpoint of ORR, estimated rates and corresponding 95% exact CIs will be calculated using the Clopper-Pearson method for all treated subjects with measurable disease at baseline per RECIST 1.1 in Cohort B, C, D - Part 2 period and all randomized subjects with measurable disease at baseline per RECIST 1.1 in Cohort D - Part 1 period. Estimated odds ratios and differences and corresponding 95% CIs between cohorts will be calculated for descriptive purpose.	To comply with HA's guidance on the definition of multiple endpoints
Section 8.2.9, Outcomes Research Analyses	*Updated this section. (Text changes are underlined).* Analyses of BPI-SF, FACT-P, and EQ-5D-3L data will be performed by cohort in all treated subjects in Cohort A, B, C, (BPI-SF and EQ-5D-3L only) and Cohort D-Part 2 period and in all randomized subjects in Cohort D-Part 1 period who have an assessment at baseline (Day 1, assessment	To clarify analyses for each cohort.

Summary of key changes of Revised Protocol 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
	prior to administration of drug on day of first dose) and at least 1 other assessment while on treatment. Questionnaire completion rate, defined as the proportion of questionnaires actually received out of the expected number, will be calculated and summarized at each assessment point.	
Section 8.2.9.2, Change in Cancer-Related Symptoms and Quality of Life	*Revised paragraph 1. (Text changes are shown as underline or strike-through).* Unless otherwise specified, the analysis of FACT-P will be performed in all treated subjects <u>in Cohort D-Part 2 period and in all randomized subjects in Cohort D-Part 1 period</u> who have an assessment at baseline and at least one or more post-baseline assessments. The following descriptive analyses will be conducted: performed in all treated subjects	To clarify that FACT-P is only implemented with Cohort D.
Section 8.2.9.3, Change in Health Status and Health Utility	*Revised paragraph 1. (Text changes are underlined).* EQ-5D-3L data will be described by cohort for all treated subjects in <u>Cohort A, B, C, and Cohort D-Part 2 period and for all randomized subjects in Cohort D-Part 1 period in</u> the following ways*:*	To clarify analyses for each cohort.
[redacted]		
Section 9.3, Clinical Study Report and Publications	Split this section into 2 sections. Revised text regarding Signatory Investigator for the Clinical Study Report. Added content regarding Scientific Publications.	Revised to align with the most recent language for BMS studies.
Section 9.4, Scientific Publications	New Section.	Revised to align with the most recent language for BMS studies.

Summary of key changes of Revised Protocol 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Appendix 1, Management Algorithms	Management algorithms have been updated including new algorithm for myocarditis	Alignment with current BMS standards for studies using nivolumab.
All	Minor formatting and typographical/editorial corrections.	Minor, therefore not summarized.

Overall Rationale for the Revised Protocol 03, 21-Feb-2019

Recent data from Cohorts B and C in CA209650 suggest that nivolumab in combination with ipilimumab is an active regimen in patients with mCRPC, with potentially greater activity in patients with HRD mutations or higher TMB, but early toxicity limited the number of combination doses received. This global Revised Protocol 03 introduces the addition of Cohort D containing 4 open-label treatment arms. These arms (Arm D1 and D2) include 2 different dosing schedules of nivolumab in combination with ipilimumab to identify a dose combination which reduces toxicity and increases the potential clinical benefit from the dual checkpoint inhibition. The 3rd arm (Arm D3) evaluates ipilimumab monotherapy to assess its contribution to the activity of the combination, and the 4th arm (D4) reference arm evaluates SOC cabazitaxel to allow for comparison with the immunotherapy regimens, [redacted]

In addition, this revised protocol introduces optional re-induction for subjects entered the maintenance period, incorporates language to define PSA response and progression according to PCWG2, incorporates updated nivolumab clinical program protocol standards, and makes minor clarifications for consistency throughout the protocol document.

Summary of key changes of Revised Protocol 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Synopsis Section 1.3.1 Primary Objectives Section 3.1 Study Design and Duration	Blinded independent central review (BICR) was added for retrospective analysis for Cohorts A, B, and C and prospective analysis for Cohort D	Tumor assessments generally will be verified by central reviewers blinded to study treatments to minimize assessment bias.

Summary of key changes of Revised Protocol 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 5.5.3 Disease Progression Criteria		
Synopsis, Secondary Objectives Section 1.3.2 Secondary Objectives [redacted] Section 5.5.3 Disease Progression Criteria Table 5.5.3-2 Definition of Disease Progression by PSA (per PCWG2) and Clinical Progression	Objective added to evaluate PSA response rate (PSA-RR) [redacted]	To assess PSA response rate which is an important measure of efficacy outcomes in prostate cancer clinical trials as recommended by PCWG2.
[redacted]		
Synopsis, Secondary Objectives Section 1.3.2 Secondary Objectives	Objective added to estimate changes in cancer-related symptoms and quality of life (QoL) using the FACT-P questionnaire (Cohort D only)	Patient-reported outcomes will provide a better understanding of the clinical efficacy and the impact of treatment from the participant's perspective.
Synopsis Study Design for Cohort D Section 3.1 Study Design and Duration Section 4.3.2 Arms A, B, and C Part 2 Study Drug Administration - Nivolumab Monotherapy Phase (Cycle 5 and beyond) Section 4.3.5 Re-Induction of Study Therapy For Subjects in Cohorts B, C, Arms D1 and D2	Subjects from Cohorts B and C who entered the maintenance period may be permitted re-induction with the combination upon PSA progression and after approval by the BMS medical monitor.	As a result of the recent data from Cohorts B and C showing promising clinical activity in mCRPC, subjects from Arms D3 and D4 have the option to receive nivolumab in combination with ipilimumab upon documented radiographic progression.
Synopsis Study Design for Cohort D Section 1.1.12 Rationale for Optional Crossover Combination for Monotherapy Arms (Arm D3 and D4) Section 3.1.1 Crossover Phase for Subjects Originally Randomized to Arm D3 or Arm D4only	Additional design information and rationale for crossover during treatment phase were added.	Combined blockade of both PD-1 and CTLA-4 has proven more efficacious than inhibition of either pathway alone. Preliminary data with nivolumab in combination with ipilimumab have shown promising clinical activity in mCRPC. Therefore, participants on monotherapy Arms D3 and D4 may receive nivolumab in combination with ipilimumab upon BICR progression and medical monitor approval.

Summary of key changes of Revised Protocol 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Synopsis Section 3.1 Study Design and Duration Section 4.3.5 Re-Induction of Study Therapy For Subjects in Cohorts B, C, Arms D1 and D2	Subjects in Arm D1 and D2 may be permitted re-induction with the combination of ipilimumab and nivolumab at their original combination dose upon PSA progression.	Subjects who entered the maintenance period may be permitted re-induction with the combination after approval by the BMS medical monitor.
Synopsis Section 1.1.13 Rationale for Duration of Treatment with Nivolumab plus Ipilimumab	A treatment duration with immunotherapy treatment limit of 2 years is strongly recommended that subjects in Arms A, B, and C.	Accumulating data suggest that 2 years of PD-1 checkpoint inhibitor treatment may be sufficient for long term benefit.
[redacted]		
Synopsis Study Drug Table Table 4-1 Study Drugs for CA209650 Section 4.1 Investigational Product Section 4.2 Non Investigational Product	Sections and tables were updated with new study drugs, cabazitaxel and prednisone.	Updated language aligns with new study design
[redacted]		
Section 1.1.6 Rationale to Support Dose and Schedule Selection in Cohort D	Supportive data for safety and clinical activity of Cohort D were added.	Provides safety and clinical activity of study drugs in Cohort D
Section 1.5.1 Overall Risk/Benefit Assessment for Additional Cohort D	Section added to provide overall risk/benefit assessment for additional Cohort D	Section added to provide overall risk/benefit assessment of new study design.

Summary of key changes of Revised Protocol 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 3.4.1 Prohibited and/or Restricted Treatments for All Arms Section 3.4.1.1 Prohibited and/or Restricted Treatments on Nivolumab and Ipilimumab	Updated language for prohibited botanical preparations was added. Updated language for prohibited vaccines was added.	Updated language added to align with program standards for safety.
Section 3.4.1.2 Prohibited and/or Restricted Treatments on Cabazitaxel	Updated language for prohibited treatments	Updated language for prohibited treatments with change of study design
Section 3.4.2 Other Restrictions and Precautions	Additional information for the use of palliative radiation therapy was added	Updated language provides clarity
Section 4.3.3 Arm D1 Study Drug Administration - Nivolumab and Ipilimumab Section 4.3.4 Arm D2 Study Drug Administration for Nivolumab and Ipilimumab Section 4.3.5 Re-Induction of Study Therapy For Subjects in Cohorts B, C, Arms D1 and D2 Section 4.3.6 Arm D3 Study Drug Administration Section 4.3.7 Arm D4 Study drug administration - cabazitaxel plus prednisone	Storage and dispensing information for investigational drugs and non-investigational drugs added	Storage and dispensing information added with change of study design
Section 4.5.5 Dose delay, modification, and discontinuation for cabazitaxel Section 4.5.5.1 Other Toxicities for Cabazitaxel Section 4.5.5.2 Dose Reduction for cabazitaxel Section 4.5.5.3 Special Precautions for Cabazitaxel ection 4.5. Hypersensitivity reactions for cabazitaxel	Dose delay, modification, discontinuation, toxicities, dose reductions, and precautions for cabazitaxel added	Sections for cabazitaxel added with change in study design
Section 4.5.5.4 Prednisone Dose Modifications and Dose Delays	Prednisone dose modifications and dose delays added	Sections for prednisone added with change in study design

Summary of key changes of Revised Protocol 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 5.1-1: Screening Procedural Outline (CA209650) for All Treatment Arms (Cohorts A, B, C, and D) Table 5.1-2: On Treatment Part I: Sequential Treatment with Nivolumab and Ipilimumab Procedural Outline (CA209650) - Arms A, B, and C Table 5.1-5: Follow-up Assessments (CA209650) for All Treatment Arms (Cohorts A, B, C, and D)	Updated BPI-SF, FACT-P and EQ-5D-3L schedule in time and events schedule.	PRO instruments added to study to assess patient's symptoms, signs, or an aspect of functioning directly related to disease status.
Table 5.1-2: On Treatment Part I: Sequential Treatment with Nivolumab and Ipilimumab Procedural Outline (CA209650) - Arms A, B, and C	BPI-SF and EQ-5D-3L added to time and events schedule.	PRO instruments added to study to assess patient's symptoms, signs, or an aspect of functioning directly related to disease status.
Table 5.1-1 Screening Procedural Outline (CA209650) for All Treatment Arms (Cohorts A, B, C, and D) Table 5.1-2 On Treatment Part I: Sequential Treatment with Nivolumab and Ipilimumab Procedural Outline (CA209650) - Arms A, B, and C Table 5.1-3 On Treatment Part 2: Nivolumab Monotherapy Phase Procedural Outline (CA209650) Table 5.1-5 Follow-up Assessments (CA209650) for All Treatment Arms (Cohorts A, B, C, and D) Section 5.4.1 Imaging Assessment for the Study	Updated imaging language	Aligns with standard imaging language
Table 5.1-3:On Treatment Part 2: Nivolumab Monotherapy Phase Procedural Outline (CA209650) Table 5.1-5: Follow-up Assessments (CA209650) for All Treatment Arms (Cohorts A, B, C, and D)	Updated PSA collection and response assessment	To assess PSA response rate which is an important measure of efficacy outcomes in prostate cancer clinical trials as recommended by PCWG2.
Table 5.1-4:On Treatment Procedural Outline (CA209650) for Cohort D	Cohort D table added with change in study design	Cohort D table added with change in study design
Table 5.1-5: Follow-up Assessments (CA209650) for All Treatment Arms (Cohorts A, B, C, and D)	Added healthcare utilization	New endpoint added with change in study design.

Summary of key changes of Revised Protocol 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 5.8 Outcomes Research Assessments	Updated outcomes assessments collection for Cohort D	PRO instruments and analyses added to study to assess patient's symptoms, signs, or an aspect of functioning directly related to disease status.
Section 5.10 Health Economics OR Medical Resource Utilization and Health Economics	Added HCRU collection for Cohort D	HCRU collection updated with change in study design
Section 8.1 Sample Size Determination Section 8.1.1 Populations for Analyses Section 8.2 Endpoints Section 8.2.9 Outcomes Research Analyses	Statistical section updated	Statistical section updated with change in study design

Overall Rationale for the Revised Protocol 02, 28-Aug-2017

The purpose of this amendment is to discontinue randomization and enrollment into Cohort A. This discontinuation reflects the changing landscape of metastatic castration resistant prostate cancer (mCRPC) management whereby use of second generation hormonal therapies is preferred as the initial intervention in the pre-chemotherapy metastatic prostate cancer setting. This trial will now include 2 cohorts, Cohorts B and C.

Summary of key changes of Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	Updated the name and contact information of the Medical Monitor	Administrative change
Synopsis - Secondary Objectives; Synopsis - Study Design; Section 1.1.5 Rationale to Support Nivolumab plus Ipilimumab Dose and Schedule Selection; Section 1.3.2 Secondary Objectives; Section 1.5 Overall Risk/Benefit Assessment; Section 3.1 Study Design and Duration; [redacted]	Replaced "recurrence of disease" with "progression of disease" as a reason for treatment discontinuation.	To accurately reflect nivolumab program standards
Synopsis, Study Design; Section 1 Introduction; Section 3.1 Study Design and Duration; Section 8.1 Sample Size Determination	Notified that Cohort A enrollment is discontinued per Amendment 02.	Discontinuation of Cohort A enrollment due to slow accrual and changing treatment landscape for metastatic CRPC
Synopsis, Study Design and Statistical Considerations - Sample Size; Section 3.1 Study Design and Duration	Revised the number of subjects to be treated in Cohorts B and C from 30 to 45. Revised the numbers of participants required to have measurable (≥ 30 subjects) or non-measurable disease (≤ 15 subjects) based on a 2-cohort study design	To reflect discontinuation of Cohort A enrollment
Synopsis, Study Design; Section 3.1 Figure 3.1-1 Study Design Schematic	Updated study schematic to reflect discontinuation of Cohort A and revised the numbers of subjects allocated to Cohorts B and C	To reflect discontinuation of Cohort A enrollment
Synopsis, Study Population: Key Inclusion Criteria; Section 3.3.1 Inclusion Criteria, Criterion 2(g)	Deleted note (ii) regarding window for bone pain palliation by radiation therapy	To remove a redundancy with exclusion criterion 2(e)
Synopsis, Study Population: Key Inclusion Criteria; Section 3.3.1 Inclusion Criteria, Criterion 2(c)	Clarified that adenocarcinoma of the prostate confirmed by histology is mandatory for inclusion	To indicate the precise type of adenocarcinoma required for inclusion.
Synopsis, Statistical Analyses; Section 8.3.2 Efficacy Analyses; Section 8.3.6 Outcomes Research Analyses	Stated that efficacy and outcomes research analyses will be performed by cohort only, not combined	To reflect the change in statistical priorities
Section 1.1.9 Rationale for Evaluating Chemotherapy-Naive, Second Generation Hormone Therapy-Naive, Asymptomatic or Minimally Symptomatic Metastatic CPRC Subjects (Cohort A Subjects)	Added Addendum to describe changes in the treatment landscape for chemotherapy-naive and hormone therapy-naive mCRPC patients, resulting in the decision to discontinue Cohort A enrollment	To substantiate the decision to discontinue Cohort A enrollment
[redacted]		

Summary of key changes of Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 3.3.1 Inclusion Criteria 2(g)i, 2(h)	Criteria 2(g)i and 2(h) not applicable per Amendment 02	To reflect discontinuation of Cohort A enrollment
Section 3.3.1 Inclusion Criteria, Criteria 2(g)ii	Bicalutamide discontinuation required within 6 weeks of study treatment.	To clarify prior treatment window permitted prior to first dose
Section 3.3.1, Inclusion Criteria, Criteria 4(e)	Removed requirement for female lab values	Not applicable for male only study
Section 3.4.1 Prohibited and/or Restricted Treatments	Prior systemic therapy to be discontinued within 4 weeks of Day 1 visit, and bicalutamide or nilutamide within 6 weeks of Day 1 visit. Added treatment window for concurrent neoplastic therapy administration.	To clarify prior treatment windows permitted prior to first dose
Section 3.5 Discontinuation of Subjects following any Treatment with Study Drug	For subjects with AE related to ipilimumab who discontinue ipilimumab treatment, inserted a paragraph after second paragraph describing requirement to delay nivolumab treatment until AE has resolved, and conditions for resuming nivolumab treatment.	To clarify conditions for continuation of nivolumab treatment after discontinuation of ipilimumab
Section 4.5.1 Dose Delay Criteria	Clarified that, during Part 1, nivolumab and ipilimumab should be discontinued if AE meeting criteria for dose delay is reported, regardless of causality	To correct a typographical error from “discontinued” to “delayed” in first paragraph
Section 4.5.3 Dose Discontinuation	Modified (increased) duration of dose delays due to Grade 3 AST or ALT elevations allowed prior to treatment discontinuation for Parts 1 and 2	To update conditions for discontinuation based on AST/ALT AEs.
Section 5.1 Flow Chart/Time and Events Schedule, Table 5.1-1 Screening Procedural Outline	For Laboratory Tests, required hematology/blood chemistry testing to be performed within 14 days prior to first dose	To provide a time limitation for obtaining hematology/blood chemistry test results prior to first dose
Section 5.1 Flow Chart/Time and Events Schedule, Table 5.1-1 Screening Procedural Outline	Added phosphate to screening labs	To be consistent with Section 5.4
Section 5.1 Flow Chart/Time and Events Schedule, Table 5.1-2 On Treatment Part I: Sequential Treatment with Nivolumab and Ipilimumab Procedural Outline	For Laboratory Tests, noted that repeated laboratory tests were not necessary if screening labs were performed within 14 days prior to first dose	To clarify the conditions for requiring repeat laboratory assessments prior to first dose
Section 5.1 Flow Chart/Time and Events Schedule, Table 5.1-2 On Treatment Part I: Sequential Treatment with Nivolumab and Ipilimumab Procedural Outline; Table 5.1-3 On Treatment Part 2:	For Efficacy Assessment CT/MRI and Tc99m based bone scans, specified that scans are to be performed until documented disease progression or treatment discontinuation, whichever occurs later	To clarify conditions for stopping efficacy assessments

Summary of key changes of Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Nivolumab Monotherapy Phase Procedural Outline; Table 5.1-4 Follow-up Assessments		
Section 5.1 Flow Chart/Time and Events Schedule, Table 5.1-3 On Treatment Part 2: Nivolumab Monotherapy Phase Procedural Outline; Table 5.1-4 Follow-up Assessments	Added SAE assessments	To be consistent with Part 1 and AE reporting requirements
[redacted]		
Section 5.4, Safety Assessments	Added reference to Schedule of Assessment table to determine time windows of screening procedures, and added albumin, amylase, and lipase to on study assessments.	To clarify time windows of screening procedures and provide consistency with Schedule of Assessments
Section 5.5.3 Disease Progression Criteria, Table 5.5.3-1 Definition of Radiographic Progression per protocol	In the case of unconfirmed progression for soft tissue lesion measurements, deleted the requirement for this to occur ≥ Week 14	To align with RECIST 1.1
Section 5.5.3 Disease Progression Criteria, Table 5.5.3-2 Definition of disease Progression by PSA (per PCWG2) and Clinical Progression; Section 8.2.1 Co-Primary Endpoints (under Radiographic Progression-Free Survival)	Specified that any one of the 3 definitions of Clinical Deterioration is applicable	To clarify that any one of the 3 definitions of Clinical Deterioration is applicable
[redacted]		

Summary of key changes of Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
	specifically circulating tumor DNA (ctDNA)	
[redacted]		
Section 8.2.1 Co-Primary Endpoint(s) - Radiographic Progression-Free Survival (rPFS)	Revised the definition of clinical progression in the context of rPFS such that only one of 3 criteria need to be met	To align with RECIST 1.1
Section 8.3.2 Efficacy Analyses	Stated that efficacy analyses for all treatment-assigned subjects (by cohort only) will be performed for Cohorts B and C only; these data will be listed for all treated subjects in Cohort A.	To reflect discontinuation of Cohort A enrollment
Section 8.3.3 Safety Analyses	Stated that safety analyses will be performed for all treated subjects in Cohorts B and C only and that these data will be listed for all treated subjects in Cohort A	To reflect change in statistical priorities and discontinuation of Cohort A enrollment
Section 11, List of Abbreviations	Added additional abbreviations included in the protocol and removed abbreviations that are not referenced	To reflect current language used in protocol
Appendix 3 Women of Child-Bearing Potential Definitions and Methods of Contraception	Updated appendix to provide more complete list of methods of contraception and to clarify definitions.	To align with nivolumab program standards