Official Title of Study:

A Phase 3, Randomized, Double-Blind Study of Nivolumab or Placebo in Combination With Docetaxel, in Men With Metastatic Castration-resistant Prostate Cancer

NCT Number: NCT04100018

Document Date (Date in which document was last revised): September 22, 2023

Protocol Number: CA2097DX
IND Number: 135,845
EUDRACT Number: 2019-002030-36
Date: 25-Jul-2019
Revised Date: 22-Sep-2023

CLINICAL PROTOCOL CA2097DX

A Phase 3 Randomized, Double-Blind Study of Nivolumab or Placebo in Combination with Docetaxel, in Men with Metastatic Castration-resistant Prostate Cancer (CheckMate 7DX: CHECKpoint pathway and nivoluMAB clinical Trial Evaluation 7DX)

Short Title:

A Study of Nivolumab or Placebo in Combination with Docetaxel in Men with Metastatic Castration-resistant Prostate Cancer

Protocol Amendment 04

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DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Protocol Amendment 04	22-Sep-2023	The purpose of this protocol amendment is to formally incorporate guidance provided in the "Dear Investigator" letters from 27-Jul-2023 and 10-Aug-2023, and further clarify participant management and study procedures as the study proceeds toward termination due to one of the primary efficacy endpoints not meeting the success criterion and the implausibility of success of the other primary endpoint. The decision to terminate the study was not based on any safety concerns or issues. On 26-Jul-2023 the study independent Data Monitoring Committee convened. Based on a clinical data cutoff of 01-Jun-2023, the addition of nivolumab to docetaxel plus prednisone did not result in a statistically significant improvement in radiographic progression-free survival (rPFS) (hazard ratio 0.96; 99% confidence interval [CI] 0.77, 1.19) at final analysis and overall survival (OS) at the first interim analysis (hazard ratio 1.09; 99.41% CI 0.84, 1.43) compared to placebo added to docetaxel plus prednisone. A Sponsor Executive Oversight Committee (EOC) requested to be unblinded to the study results. Further evaluation of OS results showed no plausible scenario of reaching OS statistical significance at subsequent, planned statistical analyses, including the second interim analysis and final analysis. Given the lack of clinical benefit from nivolumab added to docetaxel plus prednisone for the dual primary efficacy endpoints of rPFS and OS, the Sponsor EOC decided to terminate the study. Unblinding of study treatment assignment to full study teams and investigators occurred on 03-Aug-2023.
Dear Investigator Letter	10-Aug-2023	Study termination details and topline data.
Dear Investigator Letter	27-Jul-2023	Notification of study termination.
Protocol Amendment 03	13-Sep-2022	Major changes: • Changes to the statistical analysis section, in which the population for radiographic progression-free survival (rPFS) analysis has been changed from the first 544 participants randomized to all randomized and the number of events from 433 to 530 rPFS events. • Changes to clarify censoring rules for rPFS. • Increased overall survival (OS) events from 615 to 690. • Clarification of pharmacokinetic sampling at follow-up visits. • Clarification of SARS-CoV-2 serology at follow-up as optional.
Administrative Letter 05	20-Oct-2021	Study Personnel Updated
Administrative Letter 03	25-Mar-2021	Study Personnel updated
Protocol Amendment 02	17-Mar-2021	Major changes: [redacted] • Removed exclusion criterion for prior radium-223 exposure.

Document	Date of Issue	Summary of Change
		• Aligned dose modification criteria and immuno-oncology (IO) agent management algorithms with National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5. • Added serologic testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) status. • Incorporated additional updates in order to improve alignment between protocol sections and clarify remote monitoring, prior malignancy window, thyroid testing, and male contraception requirements.
Revised Protocol 01	06-May-2020	Major changes: [redacted] • Clarified the inclusion criteria for current evidence of metastatic disease and prior treatment with NAT. • Lesions that do not qualify as visceral disease clarified. • Frequency of tumor assessment revised to enhance precision of the radiographic progression-free survival (rPFS) endpoint, and the criteria for stable disease (SD) was revised based on frequency of tumor assessments. • The statistical section now specifies sample size for rPFS and corrects the number of events needed for analysis of rPFS. • Revisions [redacted] have been incorporated (France, Germany, Italy, Singapore, Czech Republic, US, N. Zealand). • Changes of Administrative Letters 02 and 01 now incorporated.
Administrative Letter 02	10-Dec-2019	Additional corrections were identified and corrected in administrative letter.
Administrative Letter 01	09-Nov-2019	Discrepancies in the protocol were corrected and clarifications to language were made to ensure proper alignment throughout all sections of the protocol.
Original Protocol	25-Jul-2019	Not applicable.

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 04:

The purpose of this protocol amendment is to formally incorporate guidance provided in the "Dear Investigator" letters from 27-Jul-2023 and 10-Aug-2023, and further clarify participant management and study procedures as the study proceeds toward termination due to one of the primary efficacy endpoints not meeting the success criterion and the implausibility of success of the other primary endpoint. The decision to terminate the study was not based on any safety concerns or issues. On 26-Jul-2023 the study independent Data Monitoring Committee convened. Based on a clinical data cutoff of 01-Jun-2023, the addition of nivolumab to docetaxel plus prednisone did not result in a statistically significant improvement in radiographic progression-free survival (rPFS) (hazard ratio 0.96; 99% confidence interval [CI] 0.77, 1.19) at final analysis and overall survival (OS) at the first interim analysis (hazard ratio 1.09; 99.41% CI 0.84, 1.43) compared to placebo added to docetaxel plus prednisone. A Sponsor Executive Oversight Committee (EOC) requested to be unblinded to the study results. Further evaluation of OS results showed no plausible scenario of reaching OS statistical significance at subsequent, planned statistical analyses, including the second interim analysis and final analysis. Given the lack of clinical benefit from nivolumab added to docetaxel plus prednisone for the dual primary efficacy endpoints of rPFS and OS, the Sponsor EOC decided to terminate the study. Unblinding of study treatment assignment to full study teams and investigators occurred on 03-Aug-2023.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 04

Section Number & Title	Description of Change	Brief Rationale
Title Page	Removed Clinical Scientist information.	Updated per Sponsor requirements.
Protocol Summary Section 3.1: Overall Rationale for Protocol Amendment 04 and Study Termination	Added the following text: "Per Protocol Amendment 04, the independent Data Monitoring Committee (DMC) convened on 26-Jul-2023 for a prespecified review of all available study data based on a clinical data cutoff of 01-Jun-2023. After reviewing the final analysis of the primary efficacy endpoint of radiographic progression-free survival (rPFS) per Blinded Independent Central Review (BICR) and the first interim analysis of the primary efficacy endpoint of overall survival (OS), the DMC agreed that the study did not meet the prespecified boundaries for declaring statistical significance for either endpoint. Although the number of events for OS at the second interim analysis and final analysis of OS had not been attained, based on the first interim analysis results for OS, the DMC determined that the prespecified boundaries for declaring significance were unlikely to be met. No new safety concerns were identified. A Sponsor Executive Oversight Committee (EOC) requested to be unblinded to the study results and decided to terminate the study. Full study teams and investigators were unblinded to study treatment assignment on 03-Aug-2023.	Provide an explanation for study termination.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
	Protocol Amendment 04 reflects changes in study conduct. For participants who are deemed appropriate to continue on nivolumab or docetaxel therapy through the CA2097DX study, re-consent will be required."	
Protocol Summary Section 5.1: Overall Design Figure 5.1-1: Study Design Schematic Section 5.1.2: Treatment Phase Section 7: Treatment Table 7-1: Study Treatments for CA2097DX Section 7.1: Treatments Administered Table 7.1-1: Selection and Timing of Dose Section 7.1.1: Nivolumab or Placebo Combined with Docetaxel Section 7.1.2: Nivolumab or Placebo Dosing Section 7.4: Dosage Modification Table 7.4-1: Adverse Event Criteria to Delay, Resume, or Discontinue Nivolumab/Placebo	Clarified that participants assigned to Arm B will no longer receive placebo.	Investigators and study teams have been unblinded to study treatment assignment as a result of study termination due to lack of efficacy benefit for nivolumab added to docetaxel plus prednisone compared to placebo added to docetaxel plus prednisone.
Protocol Summary Section 5.1.2: Treatment Phase	Clarified that decisions on docetaxel treatment will be based on the clinical judgment of the treating physician and on shared decision making with the participant. Participants who are not able to access local therapy may continue on study-provided docetaxel until local access is available. In the event that the investigator deems a participant is deriving clinical benefit from nivolumab therapy and, together with the counseled participant, wishes to continue treatment, this may be possible following discussion with the Medical Monitor to ensure a clinical rationale exists that justifies continuation of nivolumab treatment.	Ensure that participants currently receiving study-provided docetaxel do not undergo treatment interruptions.
Protocol Summary Section 5.2: Data Monitoring Committee and Other External Committees	Noted that the Data Monitoring Committee is no longer applicable.	No longer relevant due to study termination.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Protocol Summary Table 10.1-1: Sample Size Determination; footnote b Section 10.3.7.1: Interim Analysis for OS	Clarified that the second interim analysis for OS and final analysis for OS will not be performed, and the first interim analysis will be considered as the final analysis. At the time of study closeout, an updated descriptive OS analysis will be provided to report all death events.	Study termination.
Table 2-2: On-Study Treatment and Follow-up Procedural Outline for Arms A and B (CA2097DX) Section 5.1.2: Treatment Phase Section 5.1.3: Follow-up Phase Section 7.7.5: Re-assessment Following Initial Assessment of Progression Section 9: Study Assessments and Procedures Section 9.1.1: Imaging Assessment for the Study Section 9.1.1.2: Imaging and Clinical Assessment Section 9.1.2: BICR Confirmation of Progression Section 9.1.3: Patient-Reported Outcomes Section 9.1.4: The Brief Pain Inventory - Short Form Section 9.1.5: The Functional Assessment of Cancer Therapy - Prostate Cancer (FACT-P) Section 9.1.6: The 5-Level EQ-5D Section 9.2: Adverse Events Section 9.2.5: Pregnancy Section 9.2.6: Laboratory Test Result Abnormalities.	Provided clarification for on-treatment and follow-up assessments: • Safety Only applicable to: Participants continuing study-provided nivolumab. Participants up to 100 days after their last nivolumab infusion. All other participants will be discontinued from the study and switched to local standard of care for metastatic castration-resistant prostate cancer, outside of the study. • Adverse events (AEs) After completion of the 100-day safety follow-up requirement and resolution or stabilization of AEs, nivolumab-treated participants will be discontinued from the study. • Subsequent cancer therapy is no longer applicable. • PSA is no longer applicable. • Laboratory tests Will include local safety laboratory tests only and will exclude tests such as PSA, [redacted] and pharmacokinetics. In addition, the requirement for local safety laboratory tests will ONLY be applicable to: Participants continuing study-provided nivolumab. Participants up to 100 days from their last nivolumab infusion. All other participants will be discontinued from the study and switched to local standard of care for metastatic castration-resistant prostate cancer, outside of the study. • Efficacy is no longer applicable. • Radiographic tumor assessments per BICR and following Prostate Cancer Working Group 3 criteria are no longer applicable. All participants receiving study treatment will have radiographic tumor assessments based on the clinical judgment of the treating investigator and following local imaging tumor assessment	Study termination.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 9.2.7: Potential Drug Induced Liver Injury (DILI) Section 9.2.8: Other Safety Considerations Section 9.4: SafetySection 9.4.4: Clinical Safety Laboratory Assessments Section 9.5: PharmacokineticsSection [redacted] Section 9.8.2: Additional Research Collection Section 9.8.3: Immunogenicity Assessments [redacted] Section 9.9: Healthcare Resource Utilization and Health Economics Appendix 5: Prostate Cancer Working Group 3 (PCWG3) Guidelines (with Modified Response Evaluation Criteria in Solid Tumors (RECIST) Criteria for Soft Tissue Lesion Assessment)	guidelines for metastatic castration-resistant prostate cancer. . • Submission of tumor imaging assessments for central review will no longer apply. • Collection of survival data is no longer applicable. [redacted] • Health outcomes are no longer applicable. • The Brief Pain Inventory - Short Form (BPI-SF) is no longer applicable. • The Functional Assessment of Cancer Therapy - Prostate Cancer (FACT-P) is no longer applicable. • The 5-Level EQ-5D is no longer applicable. • Pregnancy is only applicable to female partners of male participants continuing study-provided nivolumab, and female partners of male participants up to 100 days after the last infusion of nivolumab. • Potential DILI assessments are only applicable to participants continuing study-provided nivolumab, and participants up to 100 days after the last infusion of nivolumab. [redacted] • Additional research collection is no longer applicable [redacted] • Healthcare resource utilization and health economics are no longer applicable. • Laboratory test result abnormalities are only applicable to participants continuing study-provided nivolumab, and participants up to 100 days after the last infusion of nivolumab. • Overdose is only applicable to participants continuing study-provided nivolumab, and participants up to 100 days after the last infusion of nivolumab.	

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-2: On-Study Treatment and Follow-up Procedural Outline for Arms A and B (CA2097DX) Section 5.1.3: Follow-up Phase	Clarified that the follow-up phase only applies to participants up to 100 days after the last infusion of nivolumab. After 100 days of follow-up have been completed, the nivolumab-treated participants will be permanently discontinued from the study.	Clarified participants applicable to the follow-up phase following study termination.
Section 5.1: Study Design	Added the following text: Per Protocol Amendment 04, full study teams and investigators were unblinded to study treatment assignment on 10-Aug-2023 and 11-Aug-2023, respectively, due to lack of rPFS and OS benefit from nivolumab added to docetaxel plus prednisone compared to placebo added to docetaxel plus prednisone.	Clarified unblinding of study teams and investigators due to study termination.
Section 5.4: End of Study Definition	Clarified that the first interim analysis will be considered the final analysis. and that the study will end when the last participant receiving study-provided nivolumab completes 100 days of safety follow-up after their last nivolumab infusion. Updated the total duration of the study from the date of first participant treated to the final analysis of both primary endpoints to approximately 31 months. Deleted the definition of the start of the study, and that the survival analysis may be conducted for up to 5 years after treatment initiation.	Clarified the end of study definition following study termination.
Section 7.2: Blinding	Noted that blinding is no longer applicable.	Investigators and full study teams have been unblinded to treatment assignment due to study termination.
Section 7.7.4: Treatment Beyond Progression	Noted as no longer applicable.	Study termination.
Section 7.8: Treatment After the End the of Study	Clarified that BMS recommends discontinuation of nivolumab in all participants receiving this study treatment. In the event that the investigator deems a participant is deriving clinical benefit from nivolumab therapy and, together with the counseled participant, wishes to continue nivolumab, this may be allowed following discussion with the Medical Monitor. Deleted the following text: 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 5.	Clarify the potential continued use of nivolumab following study termination.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 8.1.2: Post Study Treatment - Study Follow-up Section 8.2: Discontinuation from the Study	Clarified that only participants who received study-provided nivolumab and are up to 100 days after the last nivolumab infusion will have post-study treatment safety follow-up. After completion of the 100-day safety follow-up requirement and resolution or stabilization of AEs, nivolumab-treated participants will be discontinued from the study. All other participants currently on safety or survival follow-up with resolution or stabilization of AEs will be discontinued from the study.	Clarified the post-study follow-up and discontinuation from the study as a result of study termination.
Section 8.3: Lost to Follow-up	Noted that this section is no longer applicable.	Study termination.
Section 10.3: Statistical Analyses Section 10.3.1: Efficacy Analyses Section 10.3.3: Pharmacokinetic Analyses Section 10.3.4: Immunogenicity Analyses Section 10.3.5: Outcomes Research Analyses	Noted as not applicable.	Study termination.
All	Minor formatting and edits.	These changes are minor and, therefore, have not been summarized.

TABLE OF CONTENTS

1 SYNOPSIS

Protocol Title: A Phase 3 Randomized, Double-Blind Study of Nivolumab or Placebo in Combination with Docetaxel, in Men with Metastatic Castration-resistant Prostate Cancer (CheckMate 7DX: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 7DX)

Short Title:

A Study of Nivolumab or Placebo in Combination with Docetaxel in Men with Metastatic Castration-resistant Prostate Cancer (mCRPC)

Study Phase: 3

Rationale:

Prostate cancer tumor cells have been shown to have low tumor expression of programmed death ligand-1 (PD-L1), suggesting that treatments directed at the programmed death-1 (PD1)/PD-L1 interaction are unlikely to be successful as monotherapies.[1] This was confirmed by early clinical trials, where unselected men with mCRPC did not respond to PD-1 blockade as monotherapy.[2] However, several studies show that PD-L1 expression can be up-regulated in response to inflammatory cytokines, a phenomenon which has been termed "adaptive immune resistance.[3,4,5] This suggests that if prostate cancer treatments (ie, chemotherapy, androgen ablation) can increase PD-L1 expression on tumor cells by attracting infiltrating immune cells and triggering an adaptive immune response, there is a rationale for combining such therapies with immune check-point inhibitors.[6,7,8,9] The rationale for combining chemotherapy and immunotherapy is based on the findings that cytotoxic treatments such as chemotherapy may modulate tumor/immune-system interactions in favor of the immune system. Chemotherapy can result in tumor cell death as part of its intended therapeutic effect with a resultant increase in tumor antigen delivery to antigen-presenting cells.

These findings have led to the development of clinical trials evaluating the combination of docetaxel and PD1/PDL1 inhibitors which has shown promising activity in patients with mCRPC previously treated with second-generation hormonal therapies as described in Rationale for Population Section of the Protocol.

NCCN guidelines recommend to use docetaxel (category 1) as the preferred 1st line chemotherapy in men with symptomatic mCRPC and in patients with signs of rapid progression or visceral metastases despite lack of symptoms. In addition, docetaxel has a category 1 recommendation in second-line after prior enzalutamide/abiraterone.

The current study aims to demonstrate that treatment with docetaxel in combination with nivolumab will be efficacious in participants with mCRPC. Additional objectives of the study include characterization of safety and tolerability, as well as pharmacokinetics, [redacted] and changes in patient reported outcomes for quality of life assessments.

Per Protocol Amendment 04, the independent Data Monitoring Committee (DMC) convened on 26-Jul-2023 for a prespecified review of all available study data based on a clinical data

cutoff of 01-Jun-2023. After reviewing the final analysis of the primary efficacy endpoint of radiographic progression-free survival (rPFS) per Blinded Independent Central Review (BICR) and the first interim analysis of the primary efficacy endpoint of overall survival (OS), the DMC agreed that the study did not meet the prespecified boundaries for declaring statistical significance for either endpoint. Although the number of events for OS at the second interim analysis and final analysis of OS had not been attained, based on the first interim analysis results for OS, the DMC determined that the prespecified boundaries for declaring significance were unlikely to be met. No new safety concerns were identified. A Sponsor Executive Oversight Committee (EOC) requested to be unblinded to the study results and decided to terminate the study. Full study teams and investigators were unblinded to study treatment assignment on 03-Aug-2023.

Protocol Amendment 04 reflects changes in study conduct. For participants who are deemed appropriate to continue on nivolumab or docetaxel therapy through the CA2097DX study, re-consent will be required.

Study Population:

Male participants ages 18 or local age of majority.

Key Inclusion Criteria:

- Histologic confirmation of adenocarcinoma of the prostate. Diagnosis must be stated in a pathology report and confirmed by the investigator
- 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).
  - Participants whose disease spread is limited to regional pelvic lymph nodes (N1) measuring at least 2 cm in short axis will be considered eligible.
- Ongoing 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. Castrate levels of testosterone must be maintained by surgical or medical means (luteinizing hormone-releasing hormone [LHRH]/ GnRH analogues) throughout the conduct of the study. For participants who have not had an orchiectomy, this therapy must have been initiated at least 4 weeks prior to first dose of study treatment and treatment must be continued throughout the study
- Documented prostate cancer progression as per PCWG3 criteria within 6 months prior to screening with at least one of the following:
  - PSA progression defined by a minimum of 2 rising PSA levels with an interval of ≥ 1 week between each determination. The PSA value at the screening visit should be ≥ 2 µg/L (2 ng/mL).

    Note: Participants who received an anti-androgen must have PSA progression after withdrawal (≥ 4 weeks since last flutamide administration or ≥ 6 weeks since last bicalutamide or nilutamide administration)

  - Radiographic disease progression in soft tissue based on RECIST 1.1 criteria.
  - Radiographic disease progression in bone defined as appearance of 2 or more new bone lesions on bone scan

- Participants who are chemotherapy- naïve for mCRPC and have received at least 1 but no more than 2 second-generation hormonal manipulations (also known as novel antiandrogen therapies [NAT] eg, including but not limited to abiraterone acetate, enzalutamide, apalutamide, and darolutamide) in the recurrent non metastatic setting and/or the metastatic setting*(no more than 1 prior Novel Androgen Therapy (NAT) is allowed in the mCRPC setting), or have become intolerant of the drug. Patients must have progressed during or after NATs or have documented intolerance to the drug (ie, unacceptable toxicity in spite of comprehensive supportive therapy).

  * If the same NAT was given more than once in the context of a different disease setting or if intervening therapy was administered, then these NAT will be considered as separate NAT regimens.
- Participants already receiving agents for the management of skeletal-related events (SREs) are allowed to continue with anti-bone resorptive therapy (including, but not limited to, bisphosponate or receptor activator of nuclear factor kappa ligand inhibitor) if on stable dose for more than 28 days prior to start of study treatment.
- Prior prostate cancer vaccine therapy (eg, sipuleucel-T), radium-223, second-generation hormonal manipulations (eg, abiraterone acetate, enzalutamide, apalutamide, and darolutamide), antiandrogens (eg, flutamide), ketoconazole, and diethylstilbestrol (DES) or other estrogens, are allowed if treatment was completed at least 28 days prior to start of study treatment. Note: bicalutamide or nilutamide must be discontinued at least 6 weeks prior to the start of study treatment.
  - Participants with a history of response to an antiandrogen or adrenal androgen-production inhibitor and with subsequent progression while receiving that antiandrogen should be assessed for antiandrogen withdrawal response for 4 weeks, and must demonstrate progression as described in Inclusion Criterion 2e in the protocol and have stopped receiving the antiandrogen prior to start of study treatment.
  - For participants who have never responded to antiandrogens, observation for antiandrogen withdrawal response is not necessary.

[redacted]

[redacted]

Key Exclusion Criteria:

Medical Conditions:

- Participants with active brain metastases. Participants with brain metastases are eligible to enroll in this study if brain metastases have been treated and there is no magnetic resonance imaging (MRI except where contraindicated in which case 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. Such cases should be discussed with the BMS Medical Monitor or designee. Previously irradiated brain lesions are not considered measurable disease.
- Participants must have recovered from the effects of major surgery requiring general anesthesia or significant traumatic injury at least 14 days before start of study treatment.
- Prior radiation therapy within 2 weeks prior to start of study treatment. Patients should have recovered (ie, Grade ≤ 1 or at baseline) from radiation-related toxicities.
- All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue must have resolved to Grade 1 or baseline before administration of study treatment. Participants with toxicities attributed to prior anti-cancer therapy that are not expected to resolve and result in long-lasting sequelae, such as peripheral neuropathy after platinum based therapy, are permitted to enroll. Participants who have ≥ Grade 2 peripheral neuropathy are excluded.
- Participants with an active, known, or suspected autoimmune disease. Participants with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
- Participants who have received a live / attenuated vaccine within 30 days of first dose in the study.
- Dementia, altered mental status, or any psychiatric condition that would prohibit the understanding or rendering of informed consent or completing QoL questionnaire.
- Known history of a positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). NOTE: Testing for HIV must be performed at all sites in Germany and where mandated locally. (see Appendix 9).
- Participants with serious or uncontrolled medical disorders that, in the opinion of the investigator, would impair the ability of the participant to receive protocol therapy or obscure the interpretation of AEs, such as a condition associated with frequent diarrhea.
- 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. Additionally, in the case of prior severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, acute symptoms must have resolved and based on investigator assessment in consultation with the Medical Monitor, there are no sequelae that would place the participant at a higher risk of receiving investigational treatment (see Section 6.4.1).

- 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 tissue in association with absent or faint renal activity (absent kidney sign).
- Concurrent malignancy (present during screening) requiring treatment or history of prior malignancy active within the previous 2 years prior to randomization (ie participants with a history of prior malignancy are eligible if treatment was completed at least 2 years before randomization and the participant has no evidence of disease). Participants with history of prior early stage basal/squamous cell skin cancer or non-invasive or in situ cancers that have undergone definitive treatment at any time are also eligible.

Prior/Concomitant Therapy:

- Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of start of study treatment. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
- 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.
- Prior treatment with docetaxel or another chemotherapy agent for metastatic castration-resistant prostate cancer. Prior docetaxel for metastatic castration-resistant prostate cancer is allowed if ≥ 12 months elapsed from last dose of docetaxel.
- Treatment with complementary medications (eg, herbal supplements or traditional Chinese medicines) to treat the disease under study within 2 weeks prior to start of study treatment. Such medications are permitted if they are used as supportive care (refer to Section 7.7.1 for other prohibited therapies).
- Participants currently in other interventional trials, including those for coronavirus disease 2019 (COVID-19), may not participate in BMS clinical trials until the protocol-specific washout period is achieved. If a study participant has received an investigational COVID-19 vaccine or other investigational product designed to treat or prevent COVID-19 prior to screening, enrollment must be delayed until the biologic impact of the vaccine or investigational product is stabilized, as determined by discussion between the Investigator and the Medical Monitor.

Objectives and Endpoints:

Objective	Endpoint
Primary	
• To compare the rPFS (using PCWG3) of nivolumab in combination with docetaxel to placebo in combination with docetaxel, in men with metastatic castration-resistant prostate cancer (mCRPC).	• rPFS for randomized participants is the time between randomization and the first date of documented progression or death due to any cause, whichever occurs first. The radiographic progression will be assessed by Blinded Independent Central Review (BICR) per PCWG3. The rPFS will be censored at the last tumor assessment up to the start of subsequent systemic cancer therapy.

Objective	Endpoint
• To compare the OS of nivolumab in combination with docetaxel to placebo in combination with docetaxel in men with metastatic castration-resistant prostate cancer (mCRPC).	• OS for all randomized participants is the time between randomization and the date of death from any cause. For participants who are alive, their survival time will be censored at the last date that they were known to be alive. OS will be censored for participants at the date of randomization if they had no follow-up.
Secondary	
• To assess the antitumor activity of nivolumab in combination with docetaxel.	• Objective Response Rate per PCWG3 (ORR-PCWG3) is the proportion of participants who have a confirmed complete or partial best overall response (BOR) per PCWG3 among randomized participants who have measurable disease at baseline. The BOR is defined as the best response designation, as determined by the BICR, recorded between the date of randomization and the date of objectively documented progression per PCWG3 or the date of subsequent systemic cancer therapy, whichever occurs first. For participants without documented progression or subsequent systemic cancer therapy, all available response assessments will contribute to the BOR assessment. • Time to Response per PCWG3 (TTR-PCWG3) is the time from randomization to the date of the first documented CR or PR per PCWG3, as determined by BICR. • Duration of Response per PCWG3 (DOR-PCWG3) is the time between the date of first response (CR/PR per PCWG3) to the date of first documented radiographic progression per PCWG3, as determined by BICR, or death due to any cause. Participants who neither progress nor die will be censored at the last tumor assessment up to the start of subsequent systemic cancer therapy. • PSA Response Rate (PSA-RR) is the proportion of randomized 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. • Time to PSA Progression (TTP-PSA) is the time between randomization to the date of PSA progression per PCWG3 in randomized participants. 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 beyond Week 13. TTP-PSA will be censored at the date of last PSA evaluation prior to the start of subsequent systemic cancer therapy. The time will be censored at the date of

Objective	Endpoint
	randomization for participants with no post-baseline PSA evaluation.
• To characterize the safety and tolerability of nivolumab in combination with docetaxel.	• Overall safety and tolerability will be measured by the incidence of AEs, SAEs, AEs leading to discontinuation, immune-mediated AEs, select AEs, deaths, and laboratory abnormalities and changes from baseline.
• To evaluate the progression of pain during treatment.	• Median time to pain progression as assessed by Brief Pain Inventory-Short Form (BPI-SF).
Exploratory	
• To investigate the time to initiation of subsequent systemic therapy (TT-SST).	• TT-SST is the time from randomization to the start of subsequent systemic therapy, including hormonal therapy, chemotherapy, immunotherapy, or investigational therapy.
• To investigate the time to first symptomatic skeletal event (TT-SSE).	• TT-SSE is the time between randomization and the date of first symptomatic fracture, radiation or surgery to bone, or spinal cord compression.
• To evaluate the change in pain intensity and health-related cancer related symptoms and quality of life.	• Change in mean scores as assessed by BPI-SF • Median time to deterioration and change in mean scores as assessed by FACT-P total score and subscales.
• To assess the participant's quality of life and overall health status.	• Change in scores in both the EQ-5D-5L utility index and visual analog scale.
• To investigate the time to and duration of PSA response.	• Time to PSA response (TTR-PSA) is defined for PSA responders as the time from randomization to the date of the first PSA response. Duration of PSA response (DOR-PSA) is defined for PSA responders as the time between the date of first response and the date of PSA progression. Participants who neither progress by PSA nor die will be censored on the date of last PSA evaluation.
[redacted]	
• To evaluate the pharmacokinetics of nivolumab when administered in combination with docetaxel. To explore exposure response relationships between select exposure measures, and safety, and efficacy endpoints, as appropriate.	• Parameter estimates from Population PK analysis and exposure-response analysis, if data permit.
• To characterize the immunogenicity of nivolumab when administered in combination with docetaxel.	• Immunogenicity will be determined by measurement of anti-drug antibody (ADA) in serum and samples with positive ADA response may be analyzed for neutralizing ADA response to nivolumab.

Objective	Endpoint
[redacted]	
• To assess the impact of SARS-CoV-2 serologic status on participants with metastatic castration-resistant prostate cancer who are receiving nivolumab plus docetaxel, [redacted].	• Exploratory measurements of SARS-CoV-2 serology (anti-SARS-CoV-2 total or Immunoglobulin G [IgG]), from serum samples collected at baseline and during the study, and the potential association between these measurements and selected endpoints related to safety, efficacy, [redacted].

Overall Design:

CA2097DX is a Phase 3 randomized, double-blinded, multi-center clinical trial comparing nivolumab or placebo in combination with docetaxel, in men with metastatic castration-resistant prostate cancer.

Randomization will be stratified according to the following baseline factors:

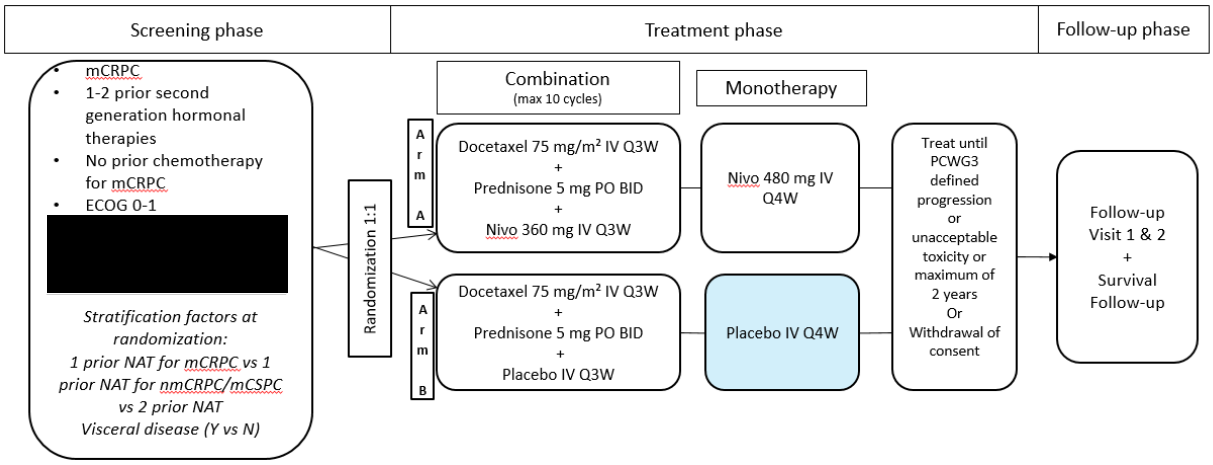
- 1 prior Novel Antiandrogen Therapy (NAT) for mCRPC vs 1 prior NAT for non-metastatic castration-resistant prostate cancer (nmCRPC) or metastatic castration-sensitive prostate cancer (mCSPC) vs 2 prior NAT
- Visceral disease (Y vs N)

Visceral disease status will be assessed by investigator based on the tumor assessment performed during screening. Visceral disease is defined as the presence of metastatic disease in the liver, lung, adrenal, peritoneum, brain or other internal organs. Bone, lymph node metastases and prostate lesion (or bladder/rectum if from direct invasion from prostate) are not considered visceral disease.

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

Figure 1-1: Study Design Schematic

Per Protocol Amendment 04, participants assigned to Arm B will no longer receive placebo.



Per Protocol Amendment 04, decisions on docetaxel treatment will be based on the clinical judgment of the treating physician and on shared decision making with the participant. Participants who are not able to access local therapy may continue on study-provided docetaxel until local access is available. In the event that the investigator deems a participant is deriving clinical benefit from nivolumab therapy and, together with the counseled participant, wishes to continue treatment, this may be possible following discussion with the Medical Monitor to ensure a clinical rationale exists that justifies continuation of nivolumab treatment.

Number of Participants:

Assuming a 25% screen failure rate, it is estimated that approximately 1312 participants with mCRPC will be enrolled in order to randomize approximately 984 participants.

The sample size determination of this study is based on a comparison of the rPFS and OS distribution between participants randomized to nivolumab in combination with docetaxel and participants randomized to placebo in combination with docetaxel.

These endpoints will be evaluated for treatment effect using the following testing strategy:

- The analysis for rPFS will occur after enrollment for the study has completed and approximately 530 rPFS events are observed in all randomized global subjects. The number of events was estimated assuming an exponential distribution of rPFS for the Docetaxel arm (Arm B) and a piecewise exponential distribution with a 2-months delayed treatment effect for the Nivolumab + Docetaxel arm (Arm A). This number of events provides 90% power to detect an average HR of 0.67 (Arm A vs Arm B in all randomized global participants) with a 2-sided alpha of 0.01. The average HR of 0.67 resulted from an assumed targeted hazard ratio of 1 for the initial 2 months from randomization and a targeted hazard ratio of 0.58 for the time beyond 2 months from randomization.
- The analysis for OS has two planned interim analyses and a final analysis. The first interim analysis will occur at the time of rPFS analysis, the second interim analysis is planned at

approximately 80% of the total events, and the final analysis is planned at approximately 690 events among all randomized global participants. The number of events was estimated assuming an exponential distribution of OS for the Docetaxel arm (Arm B) and a piecewise exponential distribution with a 3-month delayed treatment effect for the Nivolumab + Docetaxel arm (Arm A). This number of events provides 92% power to detect an average HR of 0.76 (Arm A vs Arm B in all randomized participants) with a 2-sided alpha of 0.04. The average HR of 0.76 resulted from an assumed targeted hazard ratio of 1 for the initial 3 months from randomization and a targeted hazard ratio of 0.72 for the time beyond 3 months from randomization. **Per Protocol Amendment 04, given the decision to terminate the study early, the second interim analysis for OS and final analysis for OS will no longer be performed, and the first interim analysis will be considered as final. At the time of study closeout, an updated descriptive OS analysis will be provided to report all death events.**

- The stopping boundaries for OS at the interim and final analyses will be based on the actual number of events at the time of the analysis using Lan-DeMets alpha-spending function with O'Brien-Fleming boundaries, taking into account any alpha that was passed from the rPFS analysis (if applicable).
- These primary endpoints will be tested separately and if significant, the alpha allocated to each endpoint will be recycled to the other endpoint. For example, if rPFS is significant at the 0.01 level, then 0.01 will be transferred to the OS analysis for testing at 0.05 level.

Treatment Arms and Duration:

Per Protocol Amendment 04, full study teams and investigators were unblinded to study treatment assignment on 03-AUG-2023 due to lack of rPFS and OS benefit from nivolumab added to docetaxel plus prednisone compared to placebo added to docetaxel plus prednisone. Participants in the placebo arm will discontinue placebo and may be able to continue docetaxel for up to 10 cycles through the study if the participant is in the combination phase, and local access to docetaxel outside the study is not available. In addition, all participants should receive standard of care treatment for mCRPC per local guidelines.

Arm A:

- Combination Phase (maximum 10 cycles, 1 cycle is 3 weeks):
  - Docetaxel 75 mg/m^2 IV Q3W + Prednisone 5 mg PO BID + Nivo 360 mg IV Q3W
- Monotherapy Phase (1 cycle is 4 weeks):
  - Nivolumab 480 mg IV Q4W

Arm B:

Per Protocol Amendment 04, participants assigned to Arm B will no longer receive placebo.

- Combination Phase (maximum 10 cycles, 1 cycle is 3 weeks)
  - Docetaxel 75 mg/m^2 IV Q3W + Prednisone 5 mg PO BID + Placebo IV Q3W
- Monotherapy Phase (1 cycle is 4 weeks):
  - Placebo IV Q4W

Study Treatment:

Selection and Timing of Dose			
Study Treatment	**Unit dose strength(s)/ Dosage level(s)**	**Dosage formulation Frequency of Administration**	**Route of Administration**
Arm A			
Nivolumab[a]	360mg	Every 3 weeks	Intravenous
Prednisone	5mg	Twice daily (BID)	Oral
Docetaxel	75mg/m^2	Every 3 weeks through cycle 10	Intravenous
Arm B			
Prednisone	5mg	Twice daily (BID)	Oral
Docetaxel	75mg/m^2	Every 3 weeks through cycle 10	Intravenous
Not applicable per Protocol Amendment 04: Placebo	Not applicable	Every 3 weeks	Intravenous

[a] Nivolumab or placebo will be administered as combination therapy with docetaxel and prednisone for maximum 10 cycles, followed by nivolumab monotherapy (480 mg Q4W) or placebo until progression, unacceptable toxicity or withdrawal of Consent.

Data Monitoring Committee:

Not applicable per Protocol Amendment 04.

To provide independent oversight of safety, efficacy, and study conduct, an independent Data Monitoring Committee (DMC) will be established to provide oversight on safety and efficacy considerations. Details of the DMC responsibilities and procedures will be specified in the DMC charter.

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

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

References:

[1] Martin AM, Nirschl TR, Nirschl CJ, et al. Paucity of PD-L1 expression in prostate cancer: Innate and adaptive immune resistance. Prostate Cancer and Prostatic Diseases. 2015;18(4):325-332.

[2] Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med. 2012;366:2443-54.

[3] Dong H, Strome SE, Salomao DR, et al. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. Nat Med. 2002;8:793-800.

[4] Dong H, Zhu G, Tamada K, et al. B7-H1, a third member of the B7 family, co-stimulates T-cell proliferation and interleukin-10 secretion. Nat Med. 1999;5:1365-69.

[5] Pardoll D and Drake C. Immunotherapy earns its spot in the ranks of cancer therapy. J Exp Med. 2012;209:201-9.

[6] Gannon PO, Poisson AO, Delvoye N, et al. Characterization of the intra-prostatic immune cell infiltration in androgen-deprived prostate cancer patients. J Immunol Methods. 2009;348:9-17.

[7] Mercader M, Bodner BK, Moser MT, et al. T cell infiltration of the prostate induced by androgen withdrawal in patients with prostate cancer. Proc Natl Acad Sci USA. 2001;98:14565-70.

[8] Aragon-Ching JB, Williams KM, Gulley JL. Impact of androgen-deprivation therapy on the immune system: implications for combination therapy of prostate cancer. Front Biosci. 2007;12.

[9] Drake CG. Prostate cancer as a model for tumour immunotherapy. Nature Rev Immunol. 2010;10:580-93.

2 SCHEDULE OF ACTIVITIES

Table 2-1: Screening Procedural Outline (CA2097DX)

Procedure[a]	Screening Visit	Notes All windows are on calendar days.
Eligibility Assessments		
Informed Consent	X	Register in Interactive Response Technology (IRT) system to obtain participant number. Study permits re-enrollment of a participant who has discontinued the study as a pre-treatment failure (ie, participant has not been treated). If re-enrolled, the participant must be re-consented.
Inclusion/Exclusion Criteria	X	Must be confirmed prior to randomization in IRT.
Medical History	X	All medical history relevant to the disease under study. Includes clinical stage and Gleason score at initial diagnosis.
Prior Medications/Radiation for Cancer	X	Details and dates of prior therapy including all hormonal therapies.
Body Imaging	X	Technicium-99m bone scans, contrast enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease, within 28 days prior to randomization. Section 9.1.1 for further details. Please refer to Appendix 5 for PCWG3 guidelines for tumor assessments.
Brain Imaging	X	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 28 days prior to randomization. CT of the brain without and with contrast can be performed if MRI is contraindicated. See Section 9.1 for further details.
Safety Assessments		
Full Physical Examination	X	Height, Weight, ECOG Performance Status (Appendix 8) within 14 days prior to randomization. Vital signs (BP, heart rate, RR, temperature) to be measured at screening visit and within 72 hours prior to first dose.
Assessment of Signs and Symptoms	X	Within 14 days prior to randomization.
Prior/Concomitant Medication Use	X	Within 14 days prior to randomization.

Table 2-1: Screening Procedural Outline (CA2097DX)

Procedure[a]	Screening Visit	Notes All windows are on calendar days.
Serious Adverse Event (SAE) Assessment	X	SAEs collected from time of consent (see Section 9.2). All AEs (SAEs or nonserious AEs) associated with SARS-CoV-2 infection collected from time of consent. AEs are graded per NCI CTCAE v. 5.0
12 lead ECG	X	Within 14 days prior to randomization
Laboratory Tests		
Clinical Laboratory Tests CBC with differential, chemistry panel, thyroid testing	X	Must be performed within 14 days prior to randomization. Refer to Section 9.4 for list of laboratory tests to conduct The following must be performed up to 6 weeks prior to first dose: PSA (See Section 6.1, inclusion criteria) Testosterone (See Section 6.1, inclusion criteria).
[redacted]		
Review of Pathology Report		Histologic confirmation of adenocarcinoma of the prostate. Diagnosis must be stated in a pathology report and confirmed by the investigator. See Section 6.1 (Inclusion Criteria).
[redacted]		

Table 2-1: Screening Procedural Outline (CA2097DX)

Procedure[a]	Screening Visit	Notes All windows are on calendar days.
[redacted]		
SARS-CoV-2 Serology	X	Serum collected to be used for potential future measurements of anti-SARS-CoV-2 serology (anti-SARS-CoV-2 total or IgG [redacted], central lab).
IRT		
Randomization	X	Once a participant is deemed eligible for the study, the IRT system must be contacted to randomize the participant to a treatment group.

[a] Some of the assessments referred to in this section may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations. If a dose is delayed, the procedures scheduled for that same time point should also be delayed to coincide with when that time point's dosing actually occurs.

Table 2-2: On-Study Treatment and Follow-up Procedural Outline for Arms A and B (CA2097DX)

Procedure[a]	Combination Phase Max 10 Cycles (1 Cycle = 3 weeks) Day 1	Monotherapy Phase[b] (1 Cycle = 4 weeks) Day 1	Safety Follow-up[c] (30 days [FU1] and 100 days [FU2])	Survival Follow-up[d]	Notes
Study Treatment					
Dispense Study Treatment	X	X			First dose to be administered within 3 calendar days following randomization.[e]
Safety Assessments **Per Protocol Amendment 04, safety assessments will be applicable ONLY to:** • **Participants continuing study-provided nivolumab** • **Participants up to 100 days after their last nivolumab infusion** **All other participants will be discontinued from the study and switched to local standard of care for metastatic castration-resistant prostate cancer, outside of the study.**					
Targeted Physical Examination and Vital Signs	X	X	X		*Within 72 hours prior to dosing*: Weight, BP, HR, RR, and Temperature ECOG Performance Status.
Adverse Event and Serious Adverse Event Assessment	Continuously				Per NCI CTCAE version 5 Record at each visit. All AEs (SAEs or nonserious 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 dosing. * Beyond 100 days from the last dose of study therapy, participants will be followed for drug-related AEs/SAEs until resolution, return to

Table 2-2: On-Study Treatment and Follow-up Procedural Outline for Arms A and B (CA2097DX)

Procedure[a]	Combination Phase Max 10 Cycles (1 Cycle = 3 weeks) Day 1	Monotherapy Phase[b] (1 Cycle = 4 weeks) Day 1	Safety Follow-up[c] (30 days [FU1] and 100 days [FU2])	Survival Follow-up[d]	Notes
					baseline, deemed irreversible, or participant is lost to follow-up or withdraws study consent. See Section 9.2 (Adverse Events).
Concomitant Medication Use	X				Record at each visit.
Not applicable per Protocol Amendment 04: Subsequent Cancer Therapy					Include documentation of subsequent cancer therapy (ie, systemic therapy, tumor-directed surgery, or radiation therapy).
Laboratory Tests **Per Protocol Amendment 04, laboratory tests will include local safety laboratory tests only and will exclude tests such as PSA, [redacted] and pharmacokinetics. In addition, the requirement for local safety laboratory tests will ONLY be applicable to:** • **Participants continuing study-provided nivolumab** • **Participants up to 100 days after their last nivolumab infusion** **All other participants will be discontinued from the study and switched to local standard of care for metastatic castration-resistant prostate cancer, outside of the study.**					
Clinical Laboratory Tests CBC with differential, chemistry panel, thyroid testing	X (see notes)	X (see notes)	X (see notes)		For the first dose visit, labs need not be repeated if performed within 72 hours and results are available and have been reviewed for eligibility. Laboratory tests may be performed within 72 hours prior to dosing for each cycle. See Section 9.4 for list of laboratory tests.

Table 2-2: On-Study Treatment and Follow-up Procedural Outline for Arms A and B (CA2097DX)

Procedure[a]	Combination Phase Max 10 Cycles (1 Cycle = 3 weeks) Day 1	Monotherapy Phase[b] (1 Cycle = 4 weeks) Day 1	Safety Follow-up[c] (30 days [FU1] and 100 days [FU2])	Survival Follow-up[d]	Notes
					Specific labs required at Safety FU2 only if toxicity is present are noted in Section 9.4.
Not applicable per Protocol Amendment 04: (Local) PSA					Perform on D1 of every cycle. Participants who discontinue study treatment without PSA progression or radiographic progression will continue to have PSA performed at FU1, at FU2 and every 12 weeks thereafter. PSA collection will continue until PSA progression, radiographic progression or end of study treatment, whichever occurs last. Additional PSA collection outside of this schedule is encouraged to confirm PSA progression as needed, during prolonged dose delays or if clinically indicated.
[redacted]					
Continuous Assessment of Skeletal Events (SSE)	X (see notes)				Assessed from treatment initiation to first symptomatic fracture, radiation or surgery to bone, or spinal cord compression.

Table 2-2: On-Study Treatment and Follow-up Procedural Outline for Arms A and B (CA2097DX)

Procedure[a]	Combination Phase Max 10 Cycles (1 Cycle = 3 weeks) Day 1	Monotherapy Phase[b] (1 Cycle = 4 weeks) Day 1	Safety Follow-up[c] (30 days [FU1] and 100 days [FU2])	Survival Follow-up[d]	Notes
Efficacy Assessments **Not applicable per Protocol Amendment 04.. All participants receiving study treatment will have radiographic tumor assessments based on the clinical judgment of the treating investigator and following imaging tumor assessment local guidelines for mCRPC.**					
Body Imaging					Technicium-99m Bone Scans, Contrast enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease. Tumor assessments should occur every 9 weeks (± 7 days) from first dose, regardless of treatment schedule or dose delays for first 54 weeks. Thereafter switch to every 12 weeks (± 7 days). Imaging must continue until radiographic progression per PCWG3 is assessed by investigator and confirmed by BICR, or study treatment is discontinued, whichever occurs later. In case subsequent therapy has begun, imaging must continue until radiographic progression per PCWG3 is confirmed by BICR. See Section 9.1.1 and Section 9.1.2.
Brain Imaging					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. Imaging must continue until radiographic progression per PCWG3 is assessed by investigator and confirmed by BICR, or study treatment is discontinued, whichever occurs later. See Section 9.1.1 for further details.

Table 2-2: On-Study Treatment and Follow-up Procedural Outline for Arms A and B (CA2097DX)

Procedure[a]	Combination Phase Max 10 Cycles (1 Cycle = 3 weeks) Day 1	Monotherapy Phase[b] (1 Cycle = 4 weeks) Day 1	Safety Follow-up[c] (30 days [FU1] and 100 days [FU2])	Survival Follow-up[d]	Notes
Survival Status					During safety follow-up and every 3 months (clinic visit or by telephone) during survival phase. Include documentation of subsequent therapy.
Health Outcomes **Not applicable per Protocol Amendment 04.**					
BPI-SF					At Safety FU1 only.
FACT-P					Questionnaire should be completed after randomization but prior to dosing or prior to safety labs at safety follow-up visits.
FACT-P PCS					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.
EQ-5D-5L					Questionnaire should be completed after randomization but prior to dosing or prior to safety labs at safety follow-up visits. During survival follow-up visits, the questionnaire can be administered by phone if needed.
Healthcare Resource Utilization					Healthcare resource utilization data will be collected at each visit by study site staff using the case report form (CRF).

Table 2-2: On-Study Treatment and Follow-up Procedural Outline for Arms A and B (CA2097DX)

Procedure[a]	Combination Phase Max 10 Cycles (1 Cycle = 3 weeks) Day 1	Monotherapy Phase[b] (1 Cycle = 4 weeks) Day 1	Safety Follow-up[c] (30 days [FU1] and 100 days [FU2])	Survival Follow-up[d]	Notes
[redacted]					
[redacted]					
SARS-CoV-2 Serology					Serum collected approximately every 6 months during study treatment to be used for potential future measurements of anti-SARS-CoV-2 serology (anti-SARS-CoV-2 total or IgG). Serum should also be collected approximately 4 weeks after a documented or suspected SARS-CoV-2 infection [redacted]. If a documented or suspected SARS-CoV-2 infection occurs within 4 weeks of the 6-month sampling time point, a single serum sample will be collected to satisfy the requirements for both the every 6 month and approximately 4 weeks after infection time points.

Table 2-2: On-Study Treatment and Follow-up Procedural Outline for Arms A and B (CA2097DX)

Procedure[a]	Combination Phase Max 10 Cycles (1 Cycle = 3 weeks) Day 1	Monotherapy Phase[b] (1 Cycle = 4 weeks) Day 1	Safety Follow-up[c] (30 days [FU1] and 100 days [FU2])	Survival Follow-up[d]	Notes
Pharmacokinetic (PK) and Immunogenicity (IMG) Assessments **Not applicable per Protocol Amendment 04.**					
Collect blood samples for PK/IMG					

[a] Some of the assessments referred to in this section may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations. If a dose is delayed, the procedures scheduled for that same time point should also be delayed to coincide with when that time point's dosing actually occurs.

[b] Monotherapy Phase will start 3 weeks ± 3 days from last combination dose. If a dose is delayed, the procedures scheduled for that same time point (except tumor scans) should also be delayed to coincide with when that time point's dosing actually occurs. Nivolumab will be given up to a maximum duration of 24 months from date of first dose.

[c] Participants must be followed for at least 100 days after last dose of study treatment. Safety Follow-up Visit 1 (FU1) should occur 30 days from the last dose (±7 days) or can be performed on the date of discontinuation if that date is greater than 30 days from last dose. Specific labs required at Safety FU2 only if toxicity is present are noted in Section 9.4. Safety Follow-up Visit #2 (FU2) occurs approximately 100 days (+ 7 days) from last dose of study drug. Both Safety Follow-up visits should be conducted in person.

[d] **Per Protocol Amendment 04, the follow-up phase only applies to participants up to 100 days after the last infusion of nivolumab. After 100 days of follow-up has been completed, the nivolumab-treated participants will be permanently discontinued from the study.**

[e] No dose escalation or reductions of nivolumab are allowed. For Q3W and Q4W dosing cycles, all participants may be dosed within a ± 3-day window. For the Q3W dosing cycle, participants may be dosed no less than 18 days after the prior dose. Refer to Section 7.1.

3 INTRODUCTION

CA2097DX is a Phase 3, randomized, global study assessing the efficacy and safety of nivolumab or nivolumab placebo combined with standard of care docetaxel chemotherapy, in men with metastatic castration-resistant prostate cancer (mCRPC) who have progressed after second-generation hormonal manipulation, also known as Novel Antiandrogen Therapy (NAT), and have not received chemotherapy for mCRPC.

The study aims to demonstrate that treatment with nivolumab combined with docetaxel improves clinical efficacy in terms of overall survival (OS) or radiographic progression-free survival (rPFS), when compared to docetaxel alone.

A detailed description of the chemistry, pharmacology, efficacy, and safety of the study treatments is provided in the respective Investigator Brochures (IBs) and package inserts.

3.1 Overall Rationale for Protocol Amendment 04 and Study Termination

The independent Data Monitoring Committee (DMC) convened on 26-Jul-2023 for a prespecified review of all available study data based on a clinical data cutoff of 01-Jun-2023. After reviewing the final analysis of the primary efficacy endpoint of radiographic progression-free survival (rPFS) per Blinded Independent Central Review (BICR) and the first interim analysis of the primary efficacy endpoint of overall survival (OS), the DMC agreed that the study did not meet the prespecified boundaries for declaring statistical significance for either endpoint. Although the number of events for OS at the second interim analysis and final analysis of OS had not been attained, based on the first interim analysis results for OS, the DMC determined that the prespecified boundaries for declaring significance were unlikely to be met. No new safety concerns were identified. A Sponsor Executive Oversight Committee (EOC) requested to be unblinded to the study results and decided to terminate the study. Full study teams and investigators were unblinded to study treatment assignment on 03-AUG-2023.

Protocol Amendment 04 reflects changes in study conduct. For participants who are deemed appropriate to continue on nivolumab or docetaxel therapy through the CA2097DX study, re-consent will be required.

3.2 Study Rationale

Prostate cancer tumor cells have been shown to have low tumor expression of programmed death ligand-1 (PD-L1), suggesting that treatments directed at the programmed death (PD-1)/PD-L1 interaction are unlikely to be successful as monotherapies.[1] This was confirmed by early clinical trials, where unselected men with mCRPC did not respond to PD-1 blockade as monotherapy.[2] However, several studies show that PD-L1 expression can be up-regulated in response to inflammatory cytokines, a phenomenon which has been termed “adaptive immune resistance”[3,4,5] This suggests that if prostate cancer treatments (ie, chemotherapy, androgen ablation) can increase PD-L1 expression on tumor cells by attracting infiltrating immune cells and triggering an adaptive immune response, there is a rationale for combining such therapies with immune check-point inhibitors.[6,7,8,9] The rationale for combining chemotherapy and immunotherapy is based on the findings that cytotoxic treatments such as chemotherapy may modulate tumor/immune-system

interactions in favor of the immune system. Chemotherapy can result in tumor cell death as part of its intended therapeutic effect with a resultant increase in tumor antigen delivery to antigen-presenting cells.

Tumor cell death may also lead to a reduction in soluble and membrane-bound factors inhibiting tumor-infiltrating T-cells and disrupt immune system regulatory networks by decreasing numbers of T-regulatory cells. Docetaxel has been reported to increase the production of pro-inflammatory cytokines which may enhance the immune response. These findings have led to the development of several clinical trials evaluating the combination of docetaxel and PD1/PDL1 inhibitors (NCT03338790, NCT 03834506, NCT02861573).[10] Preliminary results from Keynote-365[10] have demonstrated promising activity with this combination in patients with mCRPC previously treated with NAT(s) as described in Section 5.5.1 (Rationale for Population).

The current study aims to demonstrate that treatment with docetaxel in combination with nivolumab will be efficacious in participants with mCRPC. Additional objectives of the study include characterization of safety and tolerability, as well as pharmacokinetics, [redacted] and changes in patient reported outcomes for quality of life assessments.

3.2.1 Research Hypothesis

1) The administration of nivolumab in combination with docetaxel will improve radiographic progression-free survival (PFS) assessed by BICR compared with docetaxel in participants with mCRPC
2) The administration of nivolumab in combination with docetaxel will improve overall survival (OS) compared with docetaxel in participants with mCRPC

3.3 Background

3.3.1 Background Indication and Treatment Landscape

Prostate cancer is a leading cause of cancer mortality in men worldwide,[11] with an estimated incidence of 1,276,106 new cases and 358,989 deaths globally[12] and 164,690 new cases and 29,430 deaths in US in 2018.[13] Prostate cancer is the most frequently diagnosed cancer and second most frequent cause of cancer deaths in US males. In the US, prostate cancer accounted for almost 1 in 5 new diagnoses of cancer in men in 2018. In Europe, prostate cancer was the most common primary sites in men in 2018 (21.8% of the total), with 450,000 new cases and 107,000 deaths from prostate cancer being reported in that year.[14]

In 1941, Huggins and Hodges first noted the beneficial effects of castration and injection of estrogens in participants with metastatic prostate cancer. Over time, androgen deprivation therapy (ADT), defined as medical castration when it is administered as neoadjuvant, concomitant or adjuvant therapy in combination with radiation, became the cornerstone of treatment for patients with metastatic disease, as well as for patients with localized or locally advanced prostate cancers. ADT results in disease remission in 90% of metastatic prostate cancer participants, evidenced by a decline in levels of prostate-specific antigen (PSA). Nevertheless, most participants become

resistant, with disease progression occurring within a median of 18 to 24 months of continuous hormonal manipulation.

In 1996, mitoxantrone plus prednisone was approved for the treatment of patients with mCRPC based on improvement in pain palliation. Docetaxel became the first chemotherapeutic agent to show an OS benefit in mCRPC in two randomized controlled clinical trials (TAX 327[15] and SWOG 99-16[16]), and was approved in combination with prednisone for this indication in the US in 2004. Since 2010, 6 new therapeutic agents with diverse mechanisms of action have been added to the therapeutic armamentarium, 5 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 (OS).

Cabazitaxel is another taxane-based chemotherapy that was approved by the FDA, in 2010, in patients with mCRPC previously treated with docetaxel.[17] In the FIRSTANA trial,[18] which studied cabazitaxel vs docetaxel as first-line therapy in chemotherapy-naïve mCRPC, different dosages of cabazitaxel did not show superiority over docetaxel.

Sipuleucel-T[19] was the first immunotherapy to receive FDA approval in men with asymptomatic mCRPC based on the Phase III IMPACT trial which showed a median survival of 25.8 months vs 21.7 months (placebo arm). Two androgen-directed therapies, abiraterone acetate and enzalutamide, were approved by the FDA for post chemotherapy[20,21] and chemotherapy-naïve[22,23] mCRPC patients. Furthermore, bone targeting alpha-emitting radionuclide radium-223 chloride (radium-223)[24] was approved in men with symptomatic bone metastases but no visceral disease, based on data from the ALSYMPCA trial which showed a median OS benefit (HR, 0.7; 14.9 vs 11.3 months; $P < 0.001$). However, cross-resistance has been observed between some of these agents (ie, enzalutamide and abiraterone; abiraterone and docetaxel) and a lack of consensus currently exists on optimal sequencing of these therapies in mCRPC.

The use of some of these agents has now expanded into earlier stages of the disease, with docetaxel[25] and abiraterone[26,27] demonstrating a significant OS improvement in metastatic cstration-sensitive prostate cancer (mCSPC) which led to their approval in this setting. Enzalutamide has also been tested in in men with mCSPC [28] and recently showed to significantly improve rPFS and other efficacy endpoints compared to ADT alone. Furthermore, both enzalutamide[29] and apalutamide[30], another second-generation antiandrogen that is an irreversible AR antagonist, showed improved metastasis-free survival in non-metastatic CRPC and were approved in 2018. More recently, darolutamide[31], an AR antagonist related to enzalutamide and apalutamide, but with a high affinity for AR and low affinity for GABA receptors, has demonstrated a significant improvement of metastasis-free survival (MFS) in M0 CRPC (HR 0.41; 40.4 months with darolutamide vs 18.4 months with placebo; $P < 0.0001$). It is unknown if using chemotherapy and AR-directed agent therapy for the upfront treatment of mCSPC and in non-metastatic CRPC will alter disease biology, clinical course, and sequencing of these agents in the mCRPC setting.

Significant progress has been made in the last few years in the treatment and understanding of the biology of CRPC and molecular classification is likely to guide future treatment strategies. Olaparib and rucaparib are two examples of PARP inhibitors that are being investigated in a molecularly defined mCRPC subgroup and received FDA breakthrough therapy designation in 2016 and in 2018, respectively. Olaparib as a treatment for BRCA1/2 or ATM-mutated mCRPC in patients who have received a prior taxane-based chemotherapy and at least one hormonal agent, either enzalutamide or abiraterone based on the initial results of Phase 2 TOPARP-A[32] trial, which found that 88% of participants with DNA-repair defects (DRD) (n=16) had a response (composite response endpoint including PSA response, objective response, and CTC conversion) to olaparib vs 6% of patient without DRD. Rucaparib as a treatment for BRCA1/2-positive mCRPC following at least 1 androgen receptor–directed therapy and taxane-based chemotherapy based on the ongoing TRITON-2[33] Phase II study, which showed that 44.0% (11/25) of patients with a BRCA1/2 alteration had a confirmed radiographic response. Recently, findings of TOPARP-B,[34] the second stage of the trial where 98 patients were pre-selected based on the detection of DNA repair defects, showed a response rate (combined primary endpoint) of 54% overall in the 400 mg olaparib cohort and 37% in the 300 mg cohort. Radiographic responses based on specific genomic alterations were 42.4% in patients with a BRCA1/2, PALB2 – 33.3%, ATM – 8.3%, and no responses in CDK12 or other genomic alterations.

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, none of these therapies result in durable clinical responses. Despite high initial response rates, remissions following second-generation hormone therapies are temporary due to the occurrence of resistance mechanisms, including androgen receptor (AR) reactivation. At this time, with judicious sequencing and use of available new therapies, participants with established mCRPC have a life expectancy in the range of 12 to 35 months. 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.

3.3.2 Nivolumab Mechanism of Action

Cancer immunotherapy rests on the premise that tumors can be recognized as foreign rather than as self and can be effectively attacked by an activated immune system. An effective immune response in this setting is thought to rely on immune surveillance of tumor antigens expressed on cancer cells that ultimately results in an adaptive immune response and cancer cell death. Meanwhile, tumor progression may depend upon acquisition of traits that allow cancer cells to evade immunosurveillance and escape effective innate and adaptive immune responses.[35,36,37] Current immunotherapy efforts attempt to break the apparent tolerance of the immune system to tumor cells and antigens by mechanisms such as introducing cancer antigens by therapeutic vaccination or by modulating regulatory checkpoints of the immune system. T-cell stimulation is a complex process involving the integration of numerous positive as well as negative co-stimulatory signals in addition to antigen recognition by the T-cell receptor (TCR).[38] Collectively, these signals govern the balance between T-cell activation and tolerance.

PD-1 is a member of the CD28 family of T-cell co-stimulatory receptors that also includes CD28, CTLA 4, ICOS, and BTLA.[39] PD-1 signaling has been shown to inhibit CD28-mediated upregulation of interleukin (IL)-2, IL-10, IL-13, interferon-gamma (IFN-γ) and Bcl-xL. PD-1 expression has also been noted to inhibit T-cell activation, and expansion of previously activated cells. Evidence for a negative regulatory role of PD-1 comes from studies of PD-1 deficient mice, which develop a variety of autoimmune phenotypes.[40] These results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self-antigens.

In vitro, nivolumab (BMS-936558) binds to PD-1 with high affinity (EC50 0.39 - 2.62 nM), and inhibits the binding of PD-1 to its ligands PD-L1 and PD-L2 (IC50 ± 1 nM). Nivolumab binds specifically to PD-1 and not to related members of the CD28 family such as CD28, ICOS, CTLA 4 and BTLA. Blockade of the PD-1 pathway by nivolumab results in a reproducible enhancement of both proliferation and IFN-γ release in the mixed lymphocyte reaction (MLR). Using a cytomegalovirus (CMV) re-stimulation assay with human peripheral blood mononuclear cells (PBMC), the effect of nivolumab on antigen specific recall response indicates that nivolumab augmented IFN-γ secretion from CMV specific memory T cells in a dose-dependent manner 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).[41]

3.3.3 Docetaxel Mechanism of Action

Docetaxel is an anti-neoplastic chemotherapeutic agent which acts by disrupting the microtubular network that is essential for mitotic and interphase cellular functions. See the current prescribing information for docetaxel (SmPC, USPI, or country-specific label) for more information.[42]

3.4 Benefit/Risk Assessment

Although multiple new agents have been approved for mCRPC over the last decade, benefits remain modest and the median survival of patients with mCRPC is unsatisfactory at approximately 12 to 35 months.[43,44,45,46,47] It is clear that there is an urgent need for new therapeutic options that offer further improvement in cancer control and overall survival.

Nivolumab has demonstrated significant clinical benefit in the treatment of advanced solid (eg, melanoma, renal cell carcinoma [RCC], and non-small cell lung cancer [NSCLC]) and hematologic (eg, classical Hodgkin Lymphoma [cHL]) malignancies as monotherapy or in combination with other agents such as ipilimumab, depending on the malignancy. Details of the clinical activity in these various malignancies are provided in the USPI[48] and SmPC[49].

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

A pattern of immune-mediated adverse events (IMAEs) associated with nivolumab has been defined, for which management algorithms have been developed; these are provided in Appendix 6. Most high-grade events were manageable with the use of corticosteroids or hormone replacement therapy (in the case of endocrinopathy) as instructed in these algorithms.

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

Notwithstanding that there have been several immunotherapy failures in prostate cancer, the approval of cancer vaccine sipuleucel-T in the US, together with the promising activity shown by the recent early phase trials of PD-1 inhibitors in combination with anti-CTLA-4 inhibitors or, with other non-immunotherapy agents (ie, docetaxel, enzalutamide and olaparib) have provided support for further exploring the use of immune therapies in prostate cancer.[50,51,52,53] As outlined in Section 5.5.2 the purpose of combination immune therapies is to enhance anti-tumor T-cell responses and several lines of evidence support combination of immune therapies with chemotherapy in men with mCRPC.

Docetaxel has a well-characterized AE profile as a cytotoxic chemotherapy, including the potential of pancytopenia, fluid retention, peripheral neuropathies, diarrhea, nausea and vomiting. Preliminary data from a NSCLC study suggest that nivolumab in combination with platinum doublet chemotherapy has additive anti-tumor activity in participants regardless of PD-L1 expression, but with a numerically higher ORR observed in non-squamous NSCLC.[54] The safety profile of nivolumab plus platinum-doublet chemotherapy reflected additive toxicities of the individual agents, which were manageable using established safety guidelines. In addition, the safety and tolerability of docetaxel in combination with pembrolizumab in patients with mCRPC appeared to be acceptable.[55] Grade 3-5 treatment-related AEs occurred in 27 (38%) pts, including 2 deaths from treatment-related AEs (pneumonitis). The most commonly reported grade ≥ 3 treatment-related AEs were febrile neutropenia (12%), decreased neutrophil count (6%), colitis (4%), and pneumonitis (4%). Most immune-mediated AEs were low grade with the most common being infusion-related reactions (11%) and colitis (10%).[55] Docetaxel is being tested in combination with nivolumab in Arm B of the ongoing Phase 2 CA209-9KD study (NCT03338790). Enrollment has been completed (n = 84) and preliminary results from the interim analysis have demonstrated promising anti-tumor activity with no new safety concerns and as described in Section 5.5.2 (Rationale for Immunotherapy in mCRPC).

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:

- Institution of a Data Monitoring Committee (DMC) to provide independent oversight of safety, study conduct and efficacy of nivolumab in combination with docetaxel. In addition, a Study Steering Committee (consisting of selected participating investigators) will meet regularly to advise BMS regarding study-related issues, including safety concerns.
- 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 toxicity

management algorithms and toxicity management of docetaxel. A BMS Safety Management Team will review and evaluate all emerging data across the program for potential safety signal assessment in a timely manner.

- Risks will be further minimized by adherence to inclusion and exclusion selection criteria (see Section 6), avoidance of prohibited medication (see Section 7.7.1), close safety monitoring (see Section 9.2 Adverse Events and Section 9.4 Safety), and dose adjustment guidelines (see Section 7.4 Dose Modifications). These will also be clearly discussed and highlighted during site visits.

In conclusion, treatment of nivolumab in combination with docetaxel in men with mCRPC is expected to be tolerable, and toxicities of the treatment are expected to be manageable and reversible upon dose reduction, treatment interruption, or discontinuation. The overall risk-benefit of the combination is deemed acceptable.

Detailed information about the known and expected benefits and risks and reasonably anticipated AEs of nivolumab may be found in their respective IBs. Similar information is provided for docetaxel in the associated Patient Information Leaflet, USPI, country-specific label, Development Safety Update Report, or SmPC.

4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints

Objective	Endpoint
Primary	
• To compare the rPFS (using PCWG3) of nivolumab in combination with docetaxel to placebo in combination with docetaxel, in men with metastatic castration resistant prostate cancer (mCRPC).	• rPFS for randomized participants is the time between randomization and the first date of documented progression or death due to any cause, whichever occurs first. The radiographic progression will be assessed by Blinded Independent Central Review (BICR) per PCWG3. The rPFS will be censored at the last tumor assessment up to the start of subsequent systemic cancer therapy.
• To compare the OS of nivolumab in combination with docetaxel to placebo in combination with docetaxel, in men with metastatic castration resistant prostate cancer (mCRPC).	• OS for all randomized participants is the time between randomization and the date of death from any cause. For participants who are alive, their survival time will be censored at the last date that they were known to be alive. OS will be censored for participants at the date of randomization if they had no follow-up.
Secondary	
• To assess the antitumor activity of nivolumab in combination with docetaxel.	• Objective Response Rate per PCWG3 (ORR-PCWG3) is the proportion of participants who have a confirmed complete or partial best overall response (BOR) per PCWG3 among randomized participants who have measurable disease at baseline. The BOR is defined as the best response designation, as determined by the BICR, recorded between the date of randomization and the date of objectively documented progression per PCWG3 or the date of subsequent systemic cancer therapy, whichever occurs first. For participants without documented progression or subsequent

Table 4-1: Objectives and Endpoints

Objective	Endpoint
	systemic cancer therapy, all available response assessments will contribute to the BOR assessment. • Time to Response per PCWG3 (TTR-PCWG3) is the time from randomization to the date of the first documented CR or PR per PCWG3, as determined by BICR. • Duration of Response per PCWG3 (DOR-PCWG3) is the time between the date of first response (CR/PR per PCWG3) to the date of first documented radiographic progression per PCWG3, as determined by BICR, or death due to any cause. Participants who neither progress nor die will be censored at the last tumor assessment up to the start of subsequent systemic cancer therapy. • PSA Response Rate (PSA-RR) is the proportion of randomized 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. • Time to PSA Progression (TTP-PSA) is the time between randomization to the date of PSA progression per PCWG3 in randomized participants. 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 beyond Week 13. TTP-PSA will be censored at the date of last PSA evaluation prior to the start of subsequent systemic cancer therapy. The time will be censored at the date of randomization for participants with no post-baseline PSA evaluation.
• To characterize the safety and tolerability of nivolumab in combination with docetaxel.	• Overall safety and tolerability will be measured by the incidence of AEs, SAEs, AEs leading to discontinuation, immune-mediated AEs, select AEs, deaths, and laboratory abnormalities and changes from baseline.
• To evaluate the progression of pain during treatment.	• Median time to pain progression as assessed by Brief Pain Inventory-Short Form (BPI-SF).
Exploratory	
• To investigate the time to initiation of subsequent systemic therapy (TT-SST).	• TT-SST is the time from randomization to the start of subsequent systemic therapy, including hormonal therapy, chemotherapy, immunotherapy, or investigational therapy.
• To investigate the time to first symptomatic skeletal event (TT-SSE).	• TT-SSE is the time between randomization and the date of first symptomatic fracture, radiation or surgery to bone, or spinal cord compression.
• To evaluate the change in pain intensity and health-related cancer	• Change in mean scores as assessed by BPI-SF.

Table 4-1: Objectives and Endpoints

Objective	Endpoint
related symptoms and quality of life.	• Median time to deterioration and change in mean scores as assessed by FACT-P total score and subscales.
• To assess the participant's quality of life and overall health status.	• Change in scores in both the EQ-5D-5L utility index and visual analog scale.
• To investigate the time to and duration of PSA response.	• Time to PSA response (TTR-PSA) is defined for PSA responders as the time from randomization to the date of the first PSA response. Duration of PSA response (DOR-PSA) is defined for PSA responders as the time between the date of first response and the date of PSA progression. Participants who neither progress by PSA nor die will be censored on the date of last PSA evaluation.
[redacted]	
• To evaluate the pharmacokinetics of nivolumab when administered in combination with docetaxel. To explore exposure response relationships between select exposure measures, and safety, and efficacy endpoints, as appropriate.	• Parameter estimates from Population PK analysis and exposure-response analysis, if data permit.
• To characterize the immunogenicity of nivolumab when administered in combination with docetaxel.	• Immunogenicity will be determined by measurement of anti-drug antibody (ADA) in serum and samples with positive ADA response may be analyzed for neutralizing ADA response to nivolumab.
[redacted]	
• To assess the impact of SARS-CoV-2 serologic status on participants with metastatic castration-resistant prostate cancer who are receiving study treatment [redacted]	• Exploratory measurements of SARS-CoV-2 serology (anti-SARS-CoV-2 total or IgG), from serum samples collected at baseline and during the study, and the potential association between these measurements and selected endpoints related to safety, efficacy, [redacted]

5 STUDY DESIGN

5.1 Overall Design

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

CA2097DX is a Phase 3 randomized, double-blinded, multi-center clinical trial comparing nivolumab or placebo in combination with docetaxel, in men with metastatic castration-resistant prostate cancer.

The study will randomize up to approximately 984 participants 1:1 into 1 of the 2 treatment arms (nivolumab combined with docetaxel or docetaxel combined with placebo). The primary endpoints of the study are rPFS and OS, as described in Section 4.

Per Protocol Amendment 04, full study teams and investigators were unblinded to study treatment assignment on 03-AUG-2023 due to the lack of rPFS and OS benefit from nivolumab added to docetaxel plus prednisone compared to placebo added to docetaxel plus prednisone.

Arm A:

- Combination Phase (maximum 10 cycles, 1 cycle is 3 weeks):
  - Docetaxel 75 mg/m² IV Q3W + Prednisone 5 mg PO BID + Nivo 360 mg IV Q3W
- Monotherapy Phase (1 cycle is 4 weeks):
  - Nivolumab 480 mg IV Q4W

Arm B:

Per Protocol Amendment 04, participants assigned to Arm B will no longer receive placebo.

- Combination Phase (maximum 10 cycles, 1 cycle is 3 weeks)
  - Docetaxel 75 mg/m² IV Q3W + Prednisone 5 mg PO BID + Placebo IV Q3W
- Monotherapy Phase (1 cycle is 4 weeks):
  - Placebo IV Q4W

Randomization will be stratified according to the following baseline factors:

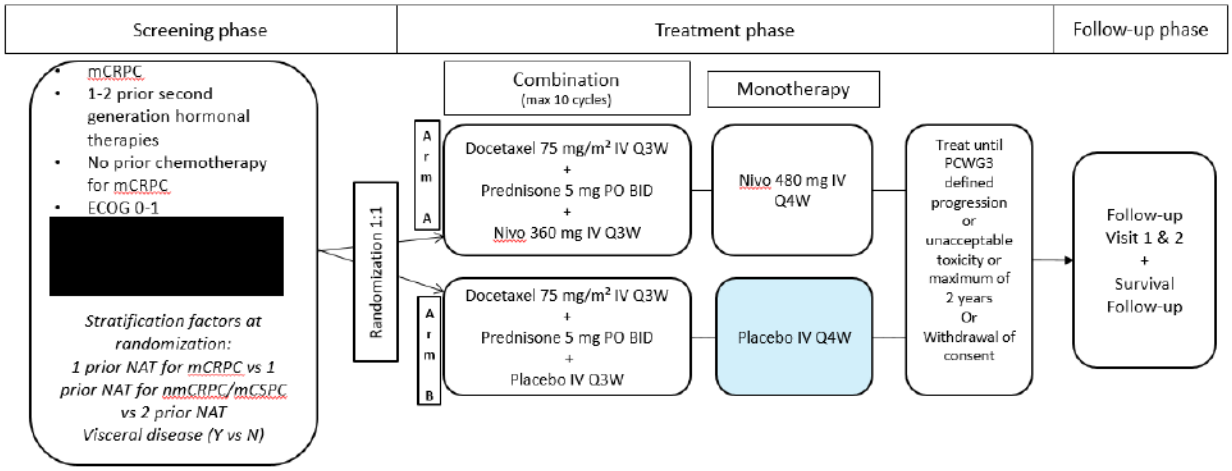
- 1 prior Novel Antiandrogen Therapy (NAT) for mCRPC vs 1 prior NAT for non-metastatic castration-resistant prostate cancer (nmCRPC) or metastatic castration-sensitive prostate cancer (mCSPC) vs 2 prior NAT
- Visceral disease (Y vs N)

Visceral disease status will be assessed by investigator based on the tumor assessment performed during screening. Visceral disease is defined as the presence of metastatic disease in the liver, lung, adrenal, peritoneum, brain or other internal organs. Bone, lymph node metastases and prostate

lesions (or bladder/rectum if from direct invasion from prostate) are not considered visceral disease.

Figure 5.1-1: Study Design Schematic

Per Protocol Amendment 04, participants assigned to Arm B will no longer receive placebo.



This study will consist of three phases: Screening, Treatment, and Follow-up. For a complete list of study required procedures, please refer to Section 2.

5.1.1 Screening Phase

Participants will provide written informed consent to participate in the study before completing any protocol-specified procedures or evaluations not considered to be part of the participants' standard of care (refer to Section 2 Schedule of Activities for details). After signing the informed consent form (ICF), participants will be evaluated for entry criteria during the screening period before administration of study drug(s). Re-enrollment after screen failure will be allowed and labs/procedures may be retested (see Section 6.4.1 (Retesting During Screening or Lead-In Period).

[redacted]

Tumor imaging is required within 28 days of randomization.

5.1.2 Treatment Phase

Per Protocol Amendment 04 and the decision to terminate the study due to a lack of efficacy, the full study teams and investigators have been unblinded to treatment assignments. Participants in the placebo arm will discontinue placebo and may be able to continue docetaxel for up to 10 cycles through the study if they are in the combination phase, and local access to docetaxel outside the study is not available. In addition, all participants should receive standard of care treatment for mCRPC per local guidelines.

Following confirmation of eligibility, participants will be randomized to receive nivolumab or placebo in combination with docetaxel.

The treatment period will consist of a combination phase (nivolumab or placebo in combination with docetaxel for up to 10 cycles) and a monotherapy phase (nivolumab or placebo) as described above in Section 5.1. Treatment with nivolumab will be given for a maximum of 24 months from date of first dose in the absence of disease progression, unacceptable toxicity or other reasons specified in the protocol. See Section 7.1 (Treatments administered) for details of treatments.

Not applicable per Protocol Amendment 04: PK samples and immunogenicity samples will be collected according to schedules in Table 9.5-1

Not applicable per Protocol Amendment 04: Tumor assessments should occur every 9 weeks (± 7 days) from first dose, regardless of treatment schedule or dose delays, for first 54 weeks. Thereafter switch to every 12 weeks (± 7 days). Imaging must continue until radiographic progression per PCWG3 is assessed by investigator, and confirmed by BICR, or treatment is discontinued, whichever occurs later. See Section 9.1.1 (Imaging Assessment for the Study) and Section 9.1.2 (BICR Confirmation of Progression). **Per Protocol Amendment 04, all participants receiving study treatment will have radiographic tumor assessments based on the clinical judgment of the treating investigator and following imaging tumor assessment local guidelines for mCRPC.**

Per Protocol Amendment 04, decisions on docetaxel treatment will be based on the clinical judgment of the treating physician and on shared decision making with the participant. Participants who are not able to access local therapy may continue on study-provided docetaxel until local access is available. In the event that the investigator deems a participant is deriving clinical benefit from nivolumab therapy and, together with the counseled participant, wishes to continue treatment, this may be possible following discussion with the Medical Monitor to ensure a clinical rationale exists that justifies continuation of nivolumab treatment.

Not applicable per Protocol Amendment 04: In certain circumstances, participants with progressive disease (PD) per PCWG3, but with otherwise stable or improved performance and clinical status, may continue to be treated in the event of a perceived benefit per investigator; see Section 7.7.4 for treatment beyond progression criteria.

This phase ends when the participant is discontinued from study therapy.

5.1.3 Follow-up Phase

Per Protocol Amendment 04, the follow-up phase only applies to participants up to 100 days after their last infusion of nivolumab. After 100 days of follow-up have been completed, the nivolumab-treated participants will be permanently discontinued from the study.

Begins when the decision to discontinue a participant from study therapy is made (no further treatment with study therapy). **Not applicable per Protocol Amendment 04:** Every effort should be made to continue tumor assessments for participants who discontinue treatment for reasons other than disease progression or consent withdrawal, according to the schedule in Table 2-2 until

progression. **Not applicable per Protocol Amendment 04:** After completion of the first two safety follow-up visits, participants will be followed every 3 months for survival, and include documentation of subsequent therapy.

Not applicable per Protocol Amendment 04: BMS may request that survival data be collected on all treated participants outside of the protocol defined window as detailed in the Schedule of Activities in Section 2. At the time of this request, each participant will be contacted to determine their survival status unless the participant has withdrawn consent for all contact.

5.2 Data Monitoring Committee and Other External Committees

Not applicable per Protocol Amendment 04 due to study termination.

To provide independent oversight of safety, efficacy, and study conduct, an independent Data Monitoring Committee (DMC) will be established to provide oversight on safety and efficacy considerations. Details of the DMC responsibilities and procedures will be specified in the DMC charter.

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

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

5.3 Number of Participants

Assuming a 25% screen failure rate, it is estimated that approximately 1,312 participants with mCRPC, will be enrolled in order to randomize approximately 984 participants. See Section 10.1 for a description of the sample size calculation. Recruitment was completed globally as of 13-Jun-2022. China region will continue enrolling until required number of participants to satisfy regulatory requirements is achieved (approximately 15% of the global participants).

5.4 End of Study Definition

Per Protocol Amendment 04, the study will be terminated, and the first interim analysis will be considered the final analysis. The end of the trial is defined as when the last participant receiving study-provided nivolumab completes 100 days of safety follow-up after their last nivolumab infusion. Study completion is defined as the final date on which data for the primary endpoint was or is expected to be collected, if this is not the same.

The total duration of the study from the date of first participant treated to the final analysis of both primary endpoints is expected to be approximately 31 months.

5.5 Scientific Rationale for Study Design

5.5.1 Rationale for Population

Men with metastatic CRPC who have progressed after 1 or 2 NATs and have not received chemotherapy for mCRPC will be included in this study. Although most patients without symptoms are not treated with chemotherapy, the survival benefit reported with docetaxel applies to those with or without symptoms. NCCN guidelines recommends to use docetaxel (category 1)

as the preferred 1st line chemotherapy in men with symptomatic mCRPC and in patients with signs of rapid progression or visceral metastases despite lack of symptoms. Docetaxel also has a category 1 recommendation in second-line after prior enzalutamide/abiraterone. Clinical data from a number of small retrospective cohort studies suggests that once participants with mCRPC 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.[56]

Given that abiraterone and enzalutamide are the preferred 1st line option for men with asymptomatic, chemotherapy-naïve mCRPC and the recent approvals of next generation hormonal therapies in mCSPC and M0 CRPC settings, it is expected that most patients will have received one of these agents when they develop mCRPC. Therefore, the current study will include chemo-naïve mCRPC patients who are post-1 or 2 prior lines of second-generation hormonal therapies. No more than 1 prior NAT is allowed in the mCRPC setting. The study will stratify by prior NAT (1 prior NAT for mCRPC vs 1 prior NAT for nmCRPC/mCSPC vs 2 prior NAT) in order to account for potential differences in survival outcomes.

Significant progress made over the last few years in understanding the biology and molecular classification of CRPC, with Olaparib and rucaparib being two examples of PARP inhibitors that are being investigated in a molecularly defined mCRPC subgroup, namely patients with mutations in specific HRD genes, such as BRCA1/2 and ATM. Data from the Phase 2 Check-Mate 650 study (NIVO1+IPI3) presented at ASCO-GU in Feb-2019[57] demonstrated clinical activity in mCRPC, with ORR of 10% and 25% in chemotherapy-pretreated and chemotherapy-naïve patients, respectively, and preliminary evidence of tumor mutational burden (TMB) as a biomarker for immuno-oncology (IO) activity in a subgroup of patients with tumor samples evaluable for whole exome sequencing. However, little published data are available on the efficacy of chemotherapy by biomarker status in advanced prostate cancer as several older trials did not include next-generation sequencing of tumor samples. [redacted]

5.5.2 Rationale for Immunotherapy in mCRPC

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.[58] 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.[59] The induction of regulatory or suppressor T cells[60] 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.[61,62]

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.[63] 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. 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.

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, although some patients achieved sustained complete responses and treatment with ipilimumab was associated with longer median PFS and higher PSA response rate.[64,65] More recently, the approval of cancer vaccine sipuleucel-T in the US, together with the promising activity shown by the recent early phase trials of immune checkpoint inhibitors[66,10,52,53,57] have provided support for further exploring the use of immune therapies in prostate cancer.

The IMPACT study evaluated sipuleucel-T (Provenge®, Dendreon Corp., Seattle, WA), an autologous therapeutic vaccine, vs placebo in chemotherapy-naïve CRPC participants and reported a 4.1-month survival improvement in asymptomatic or minimally symptomatic CRPC participants.[67] While these data show little overall impact on delaying progression of disease, the reported benefits in OS may be considered "proof of concept" that immunotherapeutic agents can play an important role in treating advanced prostate cancer.[68]

Prostate cancer has been shown to have low tumor expression of PD-L1[2] and single-agents anti-programmed death-1 (PD-1)/programmed death ligand 1 (PD-L1) immunotherapies have shown limited clinical success in prostate cancer patients, particularly when compared to other cancer types such as melanoma and non-small cell lung cancers. In a cohort of 17 subjects with mCRPC, nivolumab 10 mg/kg showed no objective responses.[69] 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. Atezolizumab monotherapy was evaluated in a Phase 1a study, including 15 heavily pretreated subjects with mCRPC.[70] There were no objective responses per RECIST 1.1, although 1 subject had a PR per immune-related response criteria (irRC). Pembrolizumab was recently evaluated in a Phase 2 study of mCRPC patients previously treated with docetaxel.[71] Among those with measurable disease, ORR was 3% and 5% in PD-L1 negative (n = 66) and positive (n = 133) 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.

However, immunotherapy-based combinations could potentially result in increasing immune-mediated anti-tumor activity in subjects with prostate cancer. Nivolumab plus ipilimumab demonstrated antitumor activity in patients with mCRPC and further evaluation of the clinical activity of this combination, as well as the potential association between biomarkers is currently ongoing in study CA209650.[57] In addition to this study, an open-label Phase 2 trial of nivolumab combined with rucaparib, docetaxel, or enzalutamide in patients with mCRPC (NCT03338790) is ongoing.

Other clinical trials are underway evaluating the role of PD-1/PDL1 inhibitors in combination with other agents that work via varied mechanisms of action and are potentially synergistic (NCT02861573, NCT03834506, NCT03834519, NCT03834493, NCT03016312, NCT02814669). The addition of pembrolizumab upon enzalutamide failure was evaluated in a single-arm, Phase 2 study.[66] The study demonstrated meaningful clinical activity to PD-1 blockade in men with mCRPC and no unexpected AEs. Furthermore, recent results from other early phase studies combining permbrolizumab with olaparib, docetaxel or enzalutamide have shown acceptable safety profile and promising anti-tumor activity, supporting further evaluation of these combinations in the ongoing Phase 3 studies (NCT03834506, NCT03834519, NCT03834493).[10,52,53]

ADT, which has been shown to alter the immune environment in prostate cancer, plays a central role in the treatment of high-risk early PCa and recurrent or metastatic disease. Therefore, it is crucial that immune-based therapies are compatible and, preferably, show synergistic activity.[8] For example, neoadjuvant ADT of prostate cancer patients results in increased numbers of infiltrating CD4 T-cells, CD8 T-cells, natural killer (NK) cells, and macrophages in prostate tissues.[6,7] Similarly, there is growing evidence that chemotherapy can induce immuno-modulatory effects that could facilitate the induction of antitumor immunity.

Nivolumab in combination with Docetaxel

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 and SWOG 99-16), and was approved in combination with prednisone for this indication in the US in 2004.[15,16] In the landmark TAX 327 Phase 3 trial, 1006 participants with mCRPC were randomized to receive daily prednisone and either mitoxantrone 12 mg/m2 Q3W, docetaxel 75 mg/m^2 Q3W, or docetaxel 30 mg/m^2 QW for 5 of every 6 weeks.[15] Participants who received docetaxel Q3W had a median survival of 19.2 months, compared to 16.3 months in the mitoxantrone Q3W and 17.8 months in the docetaxel QW arms. The hazard ratio for the docetaxel Q3W arm was 0.76 (95% confidence interval [CI], 0.62 to 0.94; P = 0.009). It is hypothesized that chemotherapy may modify the immune response to tumors by influencing multiple mechanisms, including inducing immunogenic cell death, stimulating release of tumor antigens and/or depleting immuno-suppressive Tregs. Chemotherapies (docetaxel, cabazitaxel) can have profound effects on the immune system, including acute reductions in NK, T, and B cells. Paradoxically, while treatment with docetaxel may induce lymphocytopenia in patients,[72] upon regeneration of immune cell populations, an enhanced anti-tumor immune response can occur through a reduction of immunosuppressive cell types, including myeloid-derived suppressor cell (MDSC) suppression[73] and the selective depletion of Treg cells.[74] In mouse models, the administration of docetaxel after vaccine-based immunotherapy increased the response compared to either treatment alone,[75] potentially as a result of increased T cell response and neoantigen presentation.[76] Docetaxel has been reported to increase the production of proinflammatory cytokines which may enhance the immune response.[77] In patient studies, evaluating immune response to taxanes in breast cancer,

increased T-Cell and natural killer (NK) activation is also correlated with the use of docetaxel.[78] These findings indicate that use of immunotherapy may augment the enhanced immune response seen following the use of standard-of-care chemotherapy and have led to the development of clinical trials evaluating the combination of docetaxel and various immune therapy approaches.

Nivolumab has been combined with docetaxel and other taxane agents, such as paclitaxel, and also with other cytotoxic agents. The combination of nivolumab with platinum-based doublet chemotherapy has shown promising activity and limited added toxicity in a Phase 1 study in NSCLC.[79] In this study, 14 participants were treated with nivolumab 5 mg/kg (equivalent to a 360 mg flat dose), 200 mg/m^2 paclitaxel, and carboplatin Q3W for 4 cycles, followed by nivolumab alone until disease progression or unacceptable toxicity. The most common toxicities reported with the combination were those expected for chemotherapy alone and included fatigue, nausea, and decreased appetite. Treatment-related select AEs (those AEs with an immunological etiology) were slightly higher than seen with nivolumab monotherapy. Select AEs of skin rash occurred in 5 participants (36%, with 1 Grade 3-4 AE), diarrhea in 3 participants (21%, Grade 1-2), acute renal failure in 2 participants (14%, Grade 3-4), and pneumonitis in 2 participants (with 1 Grade 3-4). All select AEs were effectively managed with corticosteroids, and none resulted in death. Compared to historical controls, the activity of the combination, even in such a small cohort, was encouraging. The ORR was 43%, with 6 participants achieving a partial response (PR). The median DOR was 19.6 months, the median PFS was 7.1 months, and the 6-month PFS rate was 51%. Median OS had not been reached at the time of the database lock, but 1-year and 2-year OS rates were 86% and 62%, respectively.

In a Phase 1, open-label, uncontrolled study of nivolumab in combination with chemotherapy in participants with Stage IIIB/IV or recurrent NSCLC (ONO-4538-04, see the current IB for nivolumab for more information), nivolumab 10 mg/kg was administered in combination with docetaxel in 6 Japanese participants. The most common drug-related AEs reported in at least 2 participants were neutrophil count decreased, white blood cell count decreased, lymphocyte count decreased and alopecia. AEs leading to nivolumab discontinuation were observed in 3 participants (hypothyroidism, lung infection, and infusion-related reaction); hypothyroidism and infusion-related reaction were considered possibly related to nivolumab.

In mCRPC, docetaxel is being tested in combination with nivolumab in Arm B of the ongoing Phase 2 CA209-9KD study (NCT03338790) in patients who had received up to two prior second-generation hormonal manipulation in the pre-chemotherapy setting. Enrollment has been completed (n = 84) and an interim analysis was conducted in 41 patients with at least 16 weeks of follow-up (Database lock date 09-May-2019). The safety of the combination was consistent with the profiles of individual agents, with 49% of patients experiencing Grade 3-4 treatment-related adverse events. Preliminary antitumor activity appeared promising, with ORR being 37%, PSA-RR 47% and rPFS 8.2 months.

In addition, the combination of pembrolizumab and docetaxel was tested in 72 pts with mCRPC who progressed after either abiraterone or enzalutamide.[10] The preliminary results showed that the combination was generally well tolerated with promising anti-tumor activity (ORR 14%; PSA-RR

31%; time to PSA progression 5.5 and 7 months for patients with measurable and non-measurable disease, respectively; rPFS 8 months; OS NR [12.9 to NR]), and potential benefit vs docetaxel alone.

Given the well characterized AE profile of docetaxel (ie, pancytopenia, fluid retention, peripheral neuropathies, diarrhea, nausea, and vomiting) and the evidence from combination studies showing that the safety profile of nivolumab plus chemotherapy can be managed using established safety guidelines, the proposed combination of nivolumab and docetaxel is expected to bring clinical benefits with manageable safety to men with mCRPC.

5.5.3 Rationale for Choice of Endpoints

OS is easily measured, unambiguous, objective, and unaffected by the timing of assessment. It is considered the gold standard among efficacy endpoints (clinically and regulatory accepted), and an appropriate measure of treatment benefit for immune checkpoint inhibitors. However, given the availability of effective systemic therapies to treat mCRPC patients in the post-docetaxel setting (eg, abiraterone, enzalutamide, cabazitaxel, radium-223), rPFS has been chosen as a second primary endpoint as it will not be confounded by subsequent treatments.

5.5.4 Rationale for Sample Size Determination

The sample size of the study accounts for the two primary endpoints: rPFS and OS. The assumptions of rPFS and OS were derived from the following studies:

- two Phase 3 studies that led to docetaxel approval (TAX327[15]: OS 19.9 mo; SWOG9916[16]: rPFS 6.3 mo; OS 17.5 mo).
- two retrospective docetaxel studies conducted in the post-abiraterone setting (Azad 2014[80]: rPFS 4 mo, OS 11.6 mo; Mezynski 2012[81]: OS 12.5 mo).

Since the pivotal Phase 3 studies were conducted approximately 15 years ago prior to novel antiandrogen therapies approval and survival outcomes have improved since then, a more recent study evaluating 1st line docetaxel vs cabazitaxel (Firstana: rPFS 12. 1 mo derived from composite PFS endpoint) was also used for rPFS assumptions.[82]

Therefore, the expected rPFS and OS with docetaxel monotherapy in the chosen population are 6 months and 15 months, respectively.

Delayed separation of KM curves is included in the alternative hypotheses for rPFS and OS because a delayed immunotherapy effect was observed in various tumors.[83 84 85 86]

See Section 10.1 (Sample Size Determination) for a description of the sample size determination.

5.5.5 Rationale for Duration of Study Treatment

5.5.5.1 Nivolumab

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 to 4

months,[87,88,89,90,91] and emerging data suggest 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 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 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% to18% 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 to 1.20]). Of note, the PFS curves in both groups plateau approximately 1 year after randomization (ie, 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 2 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.

5.5.5.2 Docetaxel

The duration of treatment for docetaxel, should be based on the assessment of benefit and toxicities. In a pivotal trial establishing the survival advantage of docetaxel chemotherapy, participants received up to 10 cycles of treatment.[15] Administering more than 10 cycles of docetaxel has not demonstrated any further improvement in survival and is associated with more adverse effects.[99,100] Therefore, in the present study, docetaxel will be administered for a maximum of 10 cycles, or until disease progression, unacceptable toxicity, withdrawal of participant consent, or the end of the study, whichever occurs sooner.

Please consult the current prescribing information for docetaxel for further details concerning administration.

5.5.6 Rationale for Nivolumab 30-Minute Infusion

Long infusion times place a burden on participants and treatment centers. Nivolumab was originally approved in the US with a 60-minute infusion using 3 mg/kg Q2W body weight-based dosing and is now approved in the US using a 30 minute infusion for the 240 mg Q2W and 480 mg Q4W flat doses. Previous clinical studies show that nivolumab has been administered safely over 60 minutes at doses ranging up to 10 mg/kg over long treatment durations. In Study CA209010 (a Phase 2, randomized, double-blind, dose-ranging study of nivolumab in participants with advanced/metastatic clear cell RCC), a dose association was observed for infusion site reactions and hypersensitivity reactions (1.7% at 0.3 mg/kg, 3.7% at 2 mg/kg, and 18.5% at 10 mg/kg). All the events were Grade 1-2 and were manageable. An infusion duration of 30 minutes for 360 mg or 480 mg doses of nivolumab is not expected to present safety concerns compared to the prior experience at 10-mg/kg nivolumab dose infused over a 60-minute duration. Nivolumab 480 mg Q4W and nivolumab 360 mg Q3W infused over 30 minutes are also being investigated in several ongoing clinical studies. Overall, preliminary safety analysis suggests that the safety profile of nivolumab administered IV over 30 minutes at 480 mg Q4W or 360 mg Q3W is consistent with nivolumab 240 mg Q2W or 3 mg/kg Q2W administered IV over 30 or 60 minutes across multiple tumor types with respect to Grade 3-4 AEs, serious adverse events (SAEs), AEs leading to

discontinuation, and immune-mediated AEs (IMAEs) including hypersensitivity/infusion reaction IMAEs. There were no new safety concerns identified. For study CA2099KD (a Phase 2 study of nivolumab in combination with either rucaparib, docetaxel or enzalutamide in men with mCRPC), the protocol specifies monitoring and management of safety events including nivolumab-related infusion reactions. In summary, nivolumab 360 mg Q3W or nivolumab 480 mg Q4W infused over 30 minutes is expected to provide a comparable safety profile to that seen with a 60-minute infusion, and is not expected to present additional safety concerns.

[redacted]

5.6 Justification for Dose

5.6.1 Justification for Nivolumab Dose

Nivolumab will be administered as a flat dose of 360 mg once every 3 weeks (Q3W) in combination with docetaxel for a maximum of 10 cycles, in order to maintain synchronized dosing of both agents on the same day and then switch to a nivolumab dose of 480 mg given every 4 weeks (Q4W) for dosing convenience.

Nivolumab PK has been extensively studied in multiple tumor types, including melanoma, NSCLC, RCC, cHL, SCCHN, CRC and urothelial carcinoma and has been safely administered at doses up to 10 mg/kg Q2W. Nivolumab monotherapy was originally approved as a body-weight based dose of 3 mg/kg Q2W, and was recently updated to 240 mg Q2W or 480 mg Q4W in multiple indications.[101,102] Nivolumab 360 mg Q3W is also under evaluation in monotherapy and in combination therapy studies. Less frequent 360 mg Q3W and 480 mg Q4W dosing regimens can reduce the burden to patients of frequent, lengthy IV treatments and allow combination of nivolumab with other agents using alternative dosing regimens.

The benefit-risk profiles of nivolumab 240 mg Q2W, 360 mg Q3W and 480 mg Q4W are predicted to be comparable to 3 mg/kg Q2W. This assessment is based on a comprehensive characterization of nivolumab PK, safety, efficacy, and exposure-response relationships across indications. Population PK (PPK) analyses have shown that the PK of nivolumab is linear with proportional exposures over a dose range of 0.1 to 10 mg/kg; no clinically meaningful differences in PK across ethnicities and tumor types were observed. Using the PPK model, the exposures following administration of several dosing regimens of nivolumab administered as a flat dose were simulated, including 240 mg Q2W, 360 mg Q3W and 480 mg Q4W. The simulated average serum concentration at steady state [Cavgss] following administration of nivolumab 360 mg Q3W and

480 mg Q4W are predicted to be similar to those following administration of nivolumab 240 mg Q2W and nivolumab 3 mg/kg Q2W administered to participants over a wide body weight range (34 to 180 kg) across tumor types.

Extensive exposure-response (E-R) analyses of multiple PK measures (maximum serum concentration at Day 1 [Cmax1], average serum concentration at Day 28 [Cavg28], and trough serum concentration at Day 28 [Cmin28]) and efficacy and safety endpoints indicated that the efficacy of the flat-dose 480 mg IV regimen are similar to that of 3 mg/kg Q2W IV regimen. In E-R efficacy analyses for OS and ORR conducted in melanoma, RCC, and NSCLC using Cavg28 as the exposure measure, probabilities of achieving a response and survival probabilities at 1 year and 2 years for IV 480 mg Q4W were similar to that of IV 3 mg/kg Q2W. In E-R safety analyses, it was demonstrated that the exposure margins for safety are maintained following nivolumab 480 mg Q4W, and the predicted risks of discontinuations due to AEs or death, AE Grade 3+, and immune-mediated AEs (IMAEs) Grade 2+ are similar following nivolumab 480 mg Q4W relative to nivolumab 3 mg/kg Q2W across tumor types. In addition, nivolumab exposures with 240 mg Q2W, 360 mg Q3W, and 480 mg Q4W flat-dose IV regimens across tumor types are maintained well below the corresponding exposures observed with the well-tolerated 10 mg/kg IV nivolumab Q2W dose regimen.

Additional details on nivolumab posologies and risk-benefit can be found in the investigator brochure.

6 STUDY POPULATION

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

6.1 Inclusion Criteria

1) Signed Written Informed Consent

a) Participants or their legally acceptable representative (see Appendix 2), must have signed and dated an IRB/IEC approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol-related procedures that are not part of normal patient care.

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

2) Type of Participant and Target Disease Characteristics

a) Histologic confirmation of adenocarcinoma of the prostate without small cell features. Diagnosis must be stated in a pathology report and confirmed by the investigator

b) 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).

i) Participants whose disease spread is limited to regional pelvic lymph nodes (N1) measuring at least 2 cm in short axis will be considered eligible.

c) ECOG performance status 0-1

d) 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. Castrate levels of testosterone must be maintained by surgical or medical means (luteinizing hormone-releasing hormone [LHRH]/ GnRH analogues) throughout the conduct of the study. For participants who have not had an orchiectomy, this therapy must have been initiated at least 4 weeks prior to first dose of study treatment and treatment must be continued throughout the study

e) Documented prostate cancer progression as per PCWG3 criteria within 6 months prior to screening with at least one of the following:

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

   Note: *Participants who received an anti-androgen must have PSA progression after withdrawal (≥ 4 weeks since last flutamide administration or ≥ 6 weeks since last bicalutamide or nilutamide administration)

   ii) Radiographic disease progression in soft tissue based on RECIST 1.1 criteria.

   iii) Radiographic disease progression in bone defined as appearance of 2 or more new bone lesions on bone scan

f) Participants who are chemotherapy- naïve for mCRPC and have received at least 1 but no more than 2 second-generation hormonal manipulations (also known as novel antiandrogen therapies [NAT] eg, including but not limited to abiraterone acetate, enzalutamide, apalutamide, and darolutamide) in the recurrent non-metastatic setting and/or the metastatic setting (no more than 1 prior Novel Androgen Therapy (NAT) is allowed in the mCRPC setting*), or have become intolerant of the drug. Patients must have progressed during or after NATs or have documented intolerance to the drug (ie, unacceptable toxicity in spite of comprehensive supportive therapy).

   * If the same NAT was given more than once in the context of a different disease setting or if intervening therapy was administered, then these NAT will be considered as separate NAT regimens.

g) Participants already receiving agents for the management of skeletal-related events (SREs) are allowed to continue with anti-bone resorptive therapy (including, but not limited to bisphosponate or receptor activator of nuclear factor kappa ligand inhibitor) if on stable dose for more than 28 days prior to start of study treatment.

[redacted]

i) Prior prostate cancer vaccine therapy (eg, sipuleucel-T), radium-223, second-generation hormonal manipulations (eg, abiraterone acetate, enzalutamide, apalutamide, and darolutamide), antiandrogens (eg, flutamide), ketoconazole, and diethylstilbestrol (DES)

or other estrogens, are allowed if treatment was completed at least 28 days prior to start of study treatment. Note: bicalutamide or nilutamide must be discontinued at least 6 weeks prior to the start of study treatment.

i) Participants with a history of response to an anti-androgen or adrenal androgen-production inhibitor and with subsequent progression while receiving that antiandrogen should be assessed for antiandrogen withdrawal response for 4 weeks, and must demonstrate progression as described in Inclusion Criterion 2e and have stopped receiving the antiandrogen prior to start of study treatment.

ii) For participants who have never responded to antiandrogens, observation for antiandrogen withdrawal response is not necessary.

[redacted]

3) Age and Reproductive Status

a) Males, ages 18 or local age of majority

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

Investigators shall counsel male participants who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise male participants who are sexually active with WOCBP on the use of highly effective methods of contraception (Appendix 4). Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly.

6.2 Exclusion Criteria

1) Medical Conditions

a) Not applicable per Protocol Amendment 02 (see new criterion m) below): *Prior malignancy active within the previous 3 years (ie participants with a history of prior malignancy are eligible if treatment was completed at least 3 years before enrollment) 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.*

b) Participants with active brain metastases. Participants with brain metastases are eligible to enroll in this study if brain metastases have been treated and there is no magnetic resonance imaging (MRI except where contraindicated in which case 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. Such cases should be discussed with the BMS Medical Monitor or designee. Previously irradiated brain lesions are not considered measurable disease. Participants must have recovered from the effects of major surgery requiring general anesthesia or significant traumatic injury at least 14 days before start of study disease.

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

d) Prior radiation therapy within 2 weeks prior to start of study treatment. Patients should have recovered (ie, Grade ≤ 1 or at baseline) from radiation-related toxicities.

e) All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue must have resolved to Grade 1 or baseline before administration of study treatment. Participants with toxicities attributed to prior anti-cancer therapy that are not expected to resolve and result in long-lasting sequelae, such as peripheral neuropathy after platinum based therapy, are permitted to enroll. Participants who have ≥ Grade 2 peripheral neuropathy are excluded.

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

g) Participants who have received a live/attenuated vaccine within 30 days of first dose in the study.

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

i) Known history of a positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). NOTE: Testing for HIV must be performed at all sites in Germany and where mandated locally (see Appendix 9).

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

k) 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. Additionally, in the case of prior severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, acute symptoms must have resolved and based on investigator assessment in consultation with the Medical Monitor, there are no sequelae that would place the participant at a higher risk of receiving investigational treatment (see Section 6.4.1).

l) 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 tissue in association with absent or faint renal activity (absent kidney sign).

m) Concurrent malignancy (present during screening) requiring treatment or history of prior malignancy active within the previous 2 years prior to randomization (ie, participants with a history of prior malignancy are eligible if treatment was completed at least 2 years before randomization and the patient has no evidence of disease). Participants with history of prior early stage basal/squamous cell skin cancer or non-invasive or in situ cancers that have undergone definitive treatment at any time are also eligible.

2) Prior/Concomitant Therapy

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

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

c) Prior treatment with docetaxel or another chemotherapy agent for metastatic castration-resistant prostate cancer. Prior docetaxel for metastatic castration-sensitive prostate cancer is allowed if ≥ 12 months elapsed from last dose of docetaxel.

d) Not applicable per Protocol Amendment 02: *Prior treatment with radium-223 or other therapeutic radiopharmaceuticals for prostate cancer*.

e) Treatment with complementary medications (eg, herbal supplements or traditional Chinese medicines) to treat the disease under study within 2 weeks prior to start of study treatment. Such medications are permitted if they are used as supportive care. Refer to Section 7.7.1 for other prohibited therapies.

f) Participants currently in other interventional trials, including those for coronavirus disease 2019 (COVID-19), may not participate in BMS clinical trials until the protocol-specific washout period is achieved. If a study participant has received an investigational COVID-19 vaccine or other investigational product designed to treat or prevent COVID-19 prior to screening, enrollment must be delayed until the biologic impact of the vaccine or

investigational product is stabilized, as determined by discussion between the investigator and the Medical Monitor.

3) Physical and Laboratory Test Findings

a) WBC < 2000/μL

b) Neutrophils < 1500/μL

c) Platelets < $100*10^3$/μL

d) Hemoglobin < 9.0 g/dL

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

f) AST/ALT > 3.0 x ULN

g) Total bilirubin > 1.0 x ULN (except participants with Gilbert Syndrome who must have a total bilirubin level of < 3.0 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)

i) AST and/or ALT > 1.5 x ULN concomitant with alkaline phosphatase > 2.5 x ULN.

Note: Testing for asymptomatic SARS-CoV-2 infection, eg, by reverse transcription polymerase chain reaction (RT-PCR) or viral antigen is not required. However, some participants may develop suspected or confirmed symptomatic SARS-CoV-2 infection, or be discovered to have asymptomatic SARS-CoV-2 infection during the screening period. In such cases, participants may be considered eligible for the study after meeting all inclusion/exclusion criteria related to active infection, and after meeting the following criteria:

- At least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared or positive RT-PCR or viral antigen test result, and
- At least 24 hours have passed since last fever without the use of fever-reducing medications, and
- Acute symptoms (eg, cough, shortness of breath) have resolved, and
- In the opinion of the investigator, there are no COVID-19-related sequelae that may place the participant at a higher risk of receiving investigational treatment, and
- Negative follow-up SARS-CoV-2 RT-PCR or viral antigen test based on institutional, local, or regional guidelines.

4) Allergies and Adverse Drug Reaction

a) History of allergy or hypersensitivity to study drug components

b) History of hypersensitivity to docetaxel or polysorbate 80

5) Other Exclusion Criteria

a) Prisoners or participants who are involuntarily incarcerated. (Note: under certain specific circumstances and only in countries where local regulations permit, a person who has

been imprisoned may be included or permitted to continue as a participant. Strict conditions apply and Bristol-Myers Squibb approval is required.

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

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

6.3 Lifestyle Restrictions

Participants receiving docetaxel should be advised to use appropriate sun protection due to the potential risk of photosensitivity which may cause sunburn with minimal sun exposure.

6.4 Screen Failures

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

6.4.1 Retesting During Screening

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

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

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

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

7 TREATMENT

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

An investigational product, also known as investigational medicinal product in some regions, is defined a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or

assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

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

Per Protocol Amendment 04, due to lack of rPFS benefit at the final analysis and OS benefit at the first interim analysis for nivolumab added to docetaxel plus prednisone compared to placebo added to docetaxel plus prednisone, on 26-Jul-2023, a BMS EOC decided to terminate the study. The decision to terminate the study was not based on any safety concerns or issues. Full study teams and investigators were unblinded to study treatment assignment on 03-Aug-2023; therefore, no participant receiving study treatment will receive placebo.

In this protocol, the following are considered Investigational [Medicinal] Product (IP/IMP):

- Nivolumab (BMS-936558)
- Docetaxel
- **Not applicable per Protocol Amendment 04:** Nivolumab-Placebo (0.9% Sodium Chloride Injection, USP, or 5% Dextrose Injection)

Solutions used as placebo (ie, 0.9% Sodium Chloride Injection or 5% Dextrose Injection) or as diluent should be sourced by investigative sites.

In this protocol, the following is considered as a Non-investigational [Medicinal] Product (Non-IP/Non-IMP):

- Prednisone

Table 7-1: Study Treatments for CA2097DX

Product Description/Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per label)
BMS-936558-01 (Nivolumab) Solution for Injection[a]	100mg (10mg/mL)	IMP	Open Label[b]	Vial (multiple vials per carton)	Store at 2° – 8°C. Protect from light and freezing.
0.9% Sodium Chloride for Injection	N/A	IMP	Open-Label[b]	Various (local commercial product)	As per package insert
5% Dextrose for Injection	N/A	IMP	Open-Label[b]	Various (local commercial product)	As per package insert
Docetaxel	80mg	IMP	Open Label	Vial in various packaging configurations	Refer to storage conditions on container label.
Prednisone	5mg	Non-IMP	Open Label	Tablets in various packaging configurations.	Refer to storage conditions on container label.

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

[b] The term "open label" refers to the medication as it is upon receipt at the pharmacy. **Not applicable per Protocol Amendment 04:** Unblinded pharmacy staff at the sites will prepare blinded Nivolumab-placebo.

7.1 Treatments Administered

Per Protocol Amendment 04, due to lack of rPFS benefit at the final analysis and OS benefit at the first interim analysis for nivolumab added to docetaxel plus prednisone compared to placebo added to docetaxel plus prednisone, on 26-Jul-2023, a BMS EOC decided to terminate the study. The decision to terminate the study was not based on any safety concerns or issues. Study teams and investigators were unblinded to study treatment assignment on 03-Aug-2023 and, therefore, no participant receiving study treatment will receive placebo.

The selection and timing of dose for each participant, based on allocation to an arm, is presented in Table 7.1-1. Duration of treatment per arm is discussed in the sections below the table.

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

Table 7.1-1: Selection and Timing of Dose

Per Protocol Amendment 04, investigators and study teams were unblinded to study treatment assignment; therefore, no participant receiving study treatment will receive placebo.

Study Treatment	Unit dose strength(s)/Dosage level(s)	Dosage formulation Frequency of Administration	Route of Administration
Arm A			
Nivolumab[a]	360 mg	Every 3 weeks	Intravenous
Prednisone	5 mg	Twice daily (BID)	Oral
Docetaxel	75 mg/m^2	Every 3 weeks through cycle 10	Intravenous
Arm B			
Prednisone	5 mg	Twice daily (BID)	Oral
Docetaxel	75 mg/m^2	Every 3 weeks through cycle 10	Intravenous
Not applicable per Protocol Amendment 04: Placebo	Not applicable	Every 3 weeks	Intravenous

[a] Nivolumab or placebo will be administered as combination therapy with docetaxel and prednisone for maximum 10 cycles, followed by nivolumab monotherapy (480 mg Q4W) or placebo until progression, unacceptable toxicity or withdrawal of Consent.

Nivolumab:

There will be no dose escalations or reductions of nivolumab allowed. For Q3W and Q4W dosing cycles, all participants may be dosed within a ± 3 day window. For the Q3W dosing cycle, participants may be dosed no less than 18 days after the prior dose. Premedications are not recommended for the first dose of nivolumab.

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

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

Nivolumab infusions are compatible with polyvinyl chloride (PVC) or polyolefin containers and infusion sets, and glass bottles.

7.1.1 Nivolumab or Placebo Combined with Docetaxel

Per Protocol Amendment 04, due to lack of rPFS benefit at the final analysis and OS benefit at the first interim analysis for nivolumab added to docetaxel plus prednisone compared to placebo added to docetaxel plus prednisone, on 26-Jul-2023, a BMS EOC decided to terminate the study. The decision to terminate the study was not based on any safety concerns or issues. Full study teams and investigators and study teams were unblinded to study treatment assignment on 03-Aug-2023; therefore, no participant receiving study treatment will receive placebo.

Participants will receive nivolumab or placebo IV at a flat dose of 360 mg as a 30-minute infusion in combination with docetaxel IV at 75 mg/m^2 as a 1-hour infusion Q3W and prednisone (or prednisolone) 5 mg orally twice daily continuously. Oral dexamethasone 8 mg (or equivalent dose of another corticosteroid) to be administered at 12 hours, 3 hours, and 1 hour before the docetaxel infusion. Other schedules and routes of administration are also acceptable according to local standards

After the nivolumab or placebo infusion, there is a 30-minute delay before the start of the docetaxel infusion to monitor the participant for signs of possible infusion reactions and differentiate any such reaction from one related to the subsequent docetaxel infusion. Dosing of docetaxel and prednisone (or prednisolone) 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.

Dosing calculations of docetaxel 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.

Participants should begin study treatment within 3 calendar days of start of randomization.

7.1.2 Nivolumab or Placebo Dosing

Per Protocol Amendment 04, due to lack of rPFS benefit at the final analysis and OS benefit at the first interim analysis for nivolumab added to docetaxel plus prednisone compared to placebo added to docetaxel plus prednisone, on 26-Jul-2023, a BMS EOC decided to terminate the study. The decision to terminate the study was not based on any safety concerns or issues. Full study teams and investigators were unblinded to study treatment assignment on 03-Aug-2023; therefore, no participant receiving study treatment will receive placebo.

After the completion of maximum 10 cycles of combination treatment, nivolumab dosing will change to 480 mg. Nivolumab 480 mg or placebo IV will continue to be given alone as a 30-minute infusion as maintenance therapy Q4W (± 3 days). The treatment with nivolumab or placebo will be given until progression, unacceptable toxicity, completion of 24 months of treatment, withdrawal of consent, or the study ends, whichever occurs first.

There will be no dose escalations or reductions of nivolumab or placebo allowed. For Q4W dosing cycles, all participants may be dosed within a ± 3 day window.

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

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

Nivolumab infusions are compatible with polyvinyl chloride (PVC) or polyolefin containers and infusion sets, and glass bottles.

Premedication:

Premedications are not recommended for the first dose of nivolumab or placebo.

For docetaxel, given the concurrent use of prednisone, the recommended premedication regimen is oral dexamethasone 8 mg (or equivalent dose of another corticosteroid) to be administered at 12 hours, 3 hours, and 1 hour before the docetaxel infusion, however other corticosteroids and/or schedules and routes of administration are also acceptable according to local standards. Antiemetic premedication will be administered according to local standards.

If one of the study drugs is discontinued, the other study drug may be continued for the remainder of the cycles.

Participants should be carefully monitored for infusion reactions during nivolumab and docetaxel administration. If an acute infusion reaction is noted, participants should be managed according to Section 7.4.6 and Section 7.4.7.

7.2 Blinding

Not applicable per Protocol Amendment 04.Due to lack of rPFS and OS benefit from nivolumab added to docetaxel plus prednisone compared to placebo added to docetaxel plus prednisone, on 26-Jul-2023 a BMS EOC decided to terminate the study. The decision to terminate the study was not based on any safety concerns or issues. Full study teams and investigators were unblinded to study treatment assignment on 03-Aug-2023.

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

Before breaking the blind of an individual participant's treatment, the investigator should determine that the unblinded information is necessary, ie, that it will alter the participant's immediate management. In many cases, particularly when the emergency is clearly not related to the investigational product, the problem may be properly managed by assuming that the participant is receiving active product. It is highly desirable that the decision to unblind treatment assignment be discussed with the Medical Monitor, but the investigator always has ultimate authority for the decision to unblind. The actual TASK of unblinding can be delegated by the investigator to a designee assigned the task on the Delegation of Authority. The Principal Investigator or appointed designee should only call in for emergency unblinding AFTER the decision to unblind the participant has been documented.

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

In cases of accidental unblinding, contact the Medical Monitor and ensure every attempt is made to preserve the blind. Any request to unblind a participant for non-emergency purposes should be discussed with the Medical Monitor. Scientist in the Bioanalytical Science department of BMS (and/or a designee in the external bioanalytical laboratory) will be unblinded to the randomized treatment assignments in order to minimize unnecessary bioanalytical analysis of samples. Any results shared by the Bioanalytical Science group with the sponsor's study team will be blinded to ensure integrity of the study. The independent central review is blinded to the study therapy administrated as well.

7.3 Method of Treatment Assignment

All participants will be centrally randomized using an Interactive Response Technology (IRT). Before the study is initiated, each user will receive log in information and directions on how to access the IRT.

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

Within each panel, participants will be randomized in a 1:1 ratio to receive either Docetaxel + Nivolumab arm (Arm A) or Docetaxel + Placebo arm (Arm B) according to a computer-generated randomization scheme prepared by a Randomization Coordinator within the Drug Supply Management Department of BMS Research and Development. Randomization will be stratified by the following factors:

- 1 prior Novel Antiandrogen Therapy (NAT) for mCRPC vs 1 prior NAT for nmCRPC/mCSPC vs 2 prior NAT
- Visceral disease (Y vs N)

Visceral disease status will be assessed by investigator based on the tumor assessment performed during screening. Visceral disease is defined as the presence of metastatic disease in the liver, lung, adrenal, peritoneum, brain or other internal organs. Bone, lymph node metastases and prostate lesions (or bladder/rectum if from direct invasion from prostate) are not considered visceral disease.

Enrolled participants, including those not dosed, will be assigned sequential participant numbers starting with [redacted]. Sequential numbering may restart at [redacted] for each participating site as the distinct patient identification number (PID) will ultimately be comprised of the site number and participant number [redacted]. Those enrolled participants meeting inclusion and exclusion criteria will be eligible to be randomized. Randomization numbers will be assigned prior to dosing.

7.4 Dosage Modification

Per Protocol Amendment 04, full study teams and investigators were unblinded to study treatment assignment on 03-Aug-2023; therefore, no participant receiving study treatment will receive placebo.

Table 7.4-1 shows AE criteria to delay, resume, or discontinue nivolumab/placebo. Table 7.4-2 shows AE criteria to delay, reduce, resume, or discontinue docetaxel.

Table 7.4-1: Adverse Event Criteria to Delay, Resume, or Discontinue Nivolumab/Placebo

Per Protocol Amendment 04, full study teams and investigators were unblinded to study treatment assignment; therefore, no participant receiving study treatment will receive placebo.

Drug-Related Adverse Event (AE) per NCI CTCAE v.5.0	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Gastrointestinal			
Colitis or diarrhea	Grade 2	Delay dose	Dosing may resume when AE resolves to baseline.
	Grade 3	Delay dose	Dosing may resume when AE resolves to baseline. If Grade 3 diarrhea or colitis recurs while on nivolumab, permanently discontinue.
	Grade 4	Permanently discontinue	N/A
Renal			
Serum creatinine increased	Grade 2 or 3	Delay dose	Dosing may resume when AE resolves to Grade ≤ 1 or baseline value.
	Grade 4	Permanently discontinue	N/A
Pulmonary			
Pneumonitis	Grade 2	Delay dose	Dosing may resume after pneumonitis has resolved to ≤ Grade 1
	Grade 3 or 4	Permanently discontinue	N/A
Hepatic			
Aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin (T.bili) increased	AST or ALT > 3x and ≤ 5 x upper limit of normal (ULN) or T.bili > 1.5 x and ≤ 3 x ULN, regardless of baseline value	Delay dose	Dosing may resume when laboratory values return to baseline.
	AST or ALT > 5 x ULN or T.bili > 3 x ULN, regardless of baseline value	Permanently discontinue	In most cases of AST or ALT > 5 x ULN, study treatment will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, a discussion between the investigator and the Medical Monitor/designee

Table 7.4-1: Adverse Event Criteria to Delay, Resume, or Discontinue Nivolumab/Placebo

Per Protocol Amendment 04, full study teams and investigators were unblinded to study treatment assignment; therefore, no participant receiving study treatment will receive placebo.

Drug-Related Adverse Event (AE) per NCI CTCAE v.5.0	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
			must occur and approval must be obtained from the Medical Monitor prior to resuming therapy.
	Concurrent AST or ALT > 3 x ULN and T.bili > 2 x ULN, regardless of baseline value	Permanently discontinue	N/A
Endocrinopathy			
Adrenal insufficiency	Grade 2 adrenal insufficiency	Delay dose	Dosing may resume after adequately controlled with hormone replacement.
	Grade 3 or 4 adrenal insufficiency or adrenal crisis	Delay dose or permanently discontinue	Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If adrenal insufficiency resolves or is adequately controlled with physiologic hormone replacement, participant may not require discontinuation of study drug.
Hyperglycemia	Hyperglycemia requiring initiation or change in daily management (Grade 2 or 3)	Delay dose	Dosing may resume if hyperglycemia resolves to Grade ≤ 1 or baseline value, or is adequately controlled with glucose-controlling agents.
	Grade 4	Delay dose or permanently discontinue	Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If hyperglycemia resolves, or is adequately controlled with glucose-controlling agents, participant may not require discontinuation of study drug.
Hypophysitis or hypopituitarism	Symptomatic Grade 1-3 that is also associated with corresponding abnormal lab and/or pituitary scan	Delay dose	Dosing may resume if endocrinopathy resolves to be asymptomatic, or is adequately controlled with only physiologic hormone replacement.
	Grade 4	Delay dose or permanently discontinue	Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If

Table 7.4-1: Adverse Event Criteria to Delay, Resume, or Discontinue Nivolumab/Placebo

Per Protocol Amendment 04, full study teams and investigators were unblinded to study treatment assignment; therefore, no participant receiving study treatment will receive placebo.

Drug-Related Adverse Event (AE) per NCI CTCAE v.5.0	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
			endocrinopathy resolves or is adequately controlled with physiologic hormone replacement, participant may not require discontinuation of study drug.
Hyperthyroidism or hypothyroidism	Grade 2 or 3	Delay dose	Dosing may resume if endocrinopathy resolves to be asymptomatic, or is adequately controlled with only physiologic hormone replacement or other medical management.
	Grade 4	Delay dose or permanently discontinue	Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If endocrinopathy resolves or is adequately controlled with physiologic hormone replacement or other medical management, participant may not require discontinuation of study drug.
Skin			
Rash	Grade 2 rash covering >30% body surface area or Grade 3 rash	Delay dose	Dosing may resume when rash reduces to ≤ 10% body surface area.
	Suspected Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), or drug reaction with eosinophilia and systemic symptoms (DRESS)	Delay dose	Dosing may resume if SJS, TEN, or DRESS is ruled out and rash reduces to is ≤10% body surface area.
	Grade 4 rash or confirmed SJS, TEN, or DRESS	Permanently discontinue	N/A
Neurological			
Guillain-Barré Syndrome (GBS)	Any Grade	Permanently discontinue	N/A

Table 7.4-1: Adverse Event Criteria to Delay, Resume, or Discontinue Nivolumab/Placebo

Per Protocol Amendment 04, full study teams and investigators were unblinded to study treatment assignment; therefore, no participant receiving study treatment will receive placebo.

Drug-Related Adverse Event (AE) per NCI CTCAE v.5.0	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Myasthenia gravis (MG)	Any Grade	Permanently discontinue	N/A
Encephalitis	Any Grade encephalitis	Delay dose	After workup for differential diagnosis (ie, infection, tumor-related), if encephalitis is not drug related, then dosing may resume when AE resolves.
	Any Grade drug-related encephalitis	Permanently discontinue	N/A
Myelitis	Any Grade myelitis	Delay dose	After workup for differential diagnosis (ie, infection, tumor-related), if myelitis is not drug related, then dosing may resume when AE resolves.
	Any Grade drug-related myelitis	Permanently discontinue	N/A
Neurological (other than GBS, MG, encephalitis, or myelitis)	Grade 2	Delay dose	Dosing may resume when AE resolves to baseline.
	Grade 3 or 4	Permanently discontinue	N/A
Myocarditis			
Myocarditis	Symptoms induced from mild to moderate activity or exertion	Delay dose	Dosing may resume after myocarditis has resolved.
	Severe or life-threatening, with symptoms at rest or with minimal activity or exertion, and/or where intervention indicated.	Permanently discontinue	N/A
Other Clinical AE			
Pancreatitis:	Grade 3 with symptoms	Delay dose	Note: Grade 3 increased amylase or lipase without signs or symptoms of pancreatitis does not require dose delay. Dosing may resume when patient becomes asymptomatic.

Table 7.4-1: Adverse Event Criteria to Delay, Resume, or Discontinue Nivolumab/Placebo

Per Protocol Amendment 04, full study teams and investigators were unblinded to study treatment assignment; therefore, no participant receiving study treatment will receive placebo.

Drug-Related Adverse Event (AE) per NCI CTCAE v.5.0	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Amylase or lipase increased	Grade 4	Permanently discontinue	N/A
Uveitis	Grade 2 uveitis	Delay dose	Dosing may resume if uveitis responds to topical therapy (eye drops) and after uveitis resolves to Grade ≤ 1 or baseline. If patient requires oral steroids for uveitis, then permanently discontinue study drug.
	Grade 3 or 4 uveitis	Permanently discontinue	N/A
Other drug-related AE **(not listed above)**	Grade 2 non-skin AE, except fatigue	Delay dose	Dosing may resume when AE resolves to Grade ≤ 1 or baseline value.
	Grade 3 AE - First occurrence lasting ≤ 7 days	Delay dose	Dosing may resume when AE resolves to Grade ≤ 1 or baseline value.
	Grade 3 AE- First occurrence lasting > 7 days	Permanently discontinue	N/A
	Recurrence of Grade 3 AE of any duration	Permanently discontinue	N/A
	Grade 4 or Life-threatening adverse reaction	Permanently discontinue	N/A
Other Laboratory Abnormalities			
Other drug-related laboratory abnormality **(not listed above)**	Grade 3	Delay dose	Exceptions: No delay required for: Grade 3 lymphopenia. Permanent discontinuation for: Grade 3 thrombocytopenia > 7 days or associated with bleeding.
	Grade 4	Permanently discontinue	Exceptions: The following events do not require discontinuation of study drug: • Grade 4 neutropenia ≤ 7 days

Table 7.4-1: Adverse Event Criteria to Delay, Resume, or Discontinue Nivolumab/Placebo

Per Protocol Amendment 04, full study teams and investigators were unblinded to study treatment assignment; therefore, no participant receiving study treatment will receive placebo.

Drug-Related Adverse Event (AE) per NCI CTCAE v.5.0	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
			• Grade 4 lymphopenia or leukopenia Grade 4 isolated electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are responding to supplementation/appropriate management within 72 hours of their onset.
Infusion Reactions (manifested by fever, chills, rigors, headache, rash, pruritus, arthralgia, hypotension, hypertension, bronchospasm, or other allergic-like reactions.)			
Hypersensitivity reaction or infusion reaction	Grade 3 or 4	Permanently discontinue	Refer to Section 7.4.6 on Treatment of Related Infusion Reactions.

Table 7.4-2: Adverse Event Criteria to Delay, Resume, Reduce or Discontinue Docetaxel			
Drug-Related Adverse Event (AE) per NCI CTCAE v.5.0	**Severity**	**Action Taken**	**Clarifications, Exceptions, and Resume Criteria**
Hematological			
Neutropenia	Grade 2	Delay dose/reduce dose[a]	If not recovered on the day of administration, delay next infusion until neutrophil counts ≥ 1.5 x 109/ L. • 1st episode: no dose reduction is required. • 2nd episode: consider dose reduction by 1 dose level[a]. Granulocyte colony-stimulating factor (G-CSF) may be administered at the discretion of the investigator and following local guidelines.
	Grade 3 or Grade 4	Delay dose/reduce dose[a] or permanently discontinue	Delay next infusion until neutrophil counts ≥ 1.5 x 10^9/ L. No dose reduction if isolated and duration £ 7 days. If duration > than 7 days or not recovered on D21: • 1st episode: consider prophylactic G-CSF in subsequent cycles. • 2nd episode or 1st episode despite prophylactic G-CSF: Reduce dose by 1 dose level[a]. • 3rd episode or 2nd episode despite prophylactic G-CSF: permanently discontinue.
Febrile neutropenia or neutropenic infection	Grade 3 or Grade 4	Delay dose/reduce dose[a] or permanently discontinue	Delay next infusion until neutrophil counts ≥ 1.5 x 10^9/ L. • 1st episode: reduce the dose[a] and consider prophylactic G-CSF in subsequent cycles. • 2nd episode: permanently discontinue.
Thrombocytopenia	Grade 2	Delay dose	Dosing may resume when AE resolves to Grade ≤ 1 or baseline.

Table 7.4-2: Adverse Event Criteria to Delay, Resume, Reduce or Discontinue Docetaxel			
Drug-Related Adverse Event (AE) per NCI CTCAE v.5.0	**Severity**	**Action Taken**	**Clarifications, Exceptions, and Resume Criteria**
			No dose reduction required.
	Grade 3 or Grade 4	Delay dose/reduce dose[a] or permanently discontinue	Dosing may resume when AE resolves to Grade ≤ 1 or baseline. 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[a]. • 2nd episode: permanently discontinue. Permanent discontinuation for: Grade 3 thrombocytopenia > 7 days or associated with bleeding.
Gastrointestinal			
Diarrhea	Grade 2	Delay dose	Dosing may resume when AE resolves to baseline.
	Grade 3	Delay dose/reduce dose[a] or permanently discontinue	1st episode: reduce dose by 1 dose level[a]. 2nd episode: permanently discontinue.
	Grade 4	Permanently discontinue	N/A
Colitis or enterocolitis	Grade 2	Delay dose	Dosing may resume when AE resolves to baseline.
	Grade 3	Permanently discontinue	Rare cases of gastrointestinal events, gastrointestinal perforation, ischaemic colitis, colitis, neutropenic enterocolitis, ileus, and intestinal obstruction have been reported with docetaxel. Participants with obvious signs of enterocolitis or peritoneal irritation should be referred urgently to the appropriate specialist (ie, gastroenterologist) for assessment, and full details of the participant's exposure to docetaxel should be provided.
	Grade 4	Permanently discontinue	
Oral mucositis	Grade 2	Delay dose	Dosing may resume when AE resolves to baseline.

Table 7.4-2: Adverse Event Criteria to Delay, Resume, Reduce or Discontinue Docetaxel			
Drug-Related Adverse Event (AE) per NCI CTCAE v.5.0	**Severity**	**Action Taken**	**Clarifications, Exceptions, and Resume Criteria**
	Grade 3 or Grade 4	Delay dose/reduce dose[a] or permanently discontinue	Dosing may resume when AE resolves to Grade ≤ 1 or baseline. • 1st episode: reduce dose by 1 dose level[a]. • 2nd episode: permanently discontinue.
Skin			
Rash	Grade 2 rash covering <30% body surface area	Delay dose	Dosing may resume when AE resolves to Grade ≤ 1 or baseline. Dosing may resume when rash reduces to ≤ 10% body surface area
	Grade 2 rash covering >30% body surface area or Grade 3 rash	Delay dose/reduce dose[a] or permanently discontinue	Dosing may resume when AE resolves to Grade ≤ 1 or baseline. • 1st episode: reduce dose by 1 dose level[a]. • 2nd episode: permanently discontinue.
	Grade 4	Permanently discontinue	N/A
Renal			
Creatinine increase	Grade 2 or Grade 3	Delay dose/reduce dose[a]	Dosing may resume when AE resolves to Grade ≤ 1 or baseline. Dose reduction may be considered for Grade 3 events at the discretion of the investigator and following local guidelines.
	Grade 4	Permanently discontinue	N/A
Neurological			
Neurological toxicity	Grade 2	Reduce dose[a]	Reduce dose by 1 dose level[a].
	Grade 3 or Grade 4	Permanently discontinue	N/A

Table 7.4-2: Adverse Event Criteria to Delay, Resume, Reduce or Discontinue Docetaxel			
Drug-Related Adverse Event (AE) per NCI CTCAE v.5.0	**Severity**	**Action Taken**	**Clarifications, Exceptions, and Resume Criteria**
Hepatic			
Aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin (T.bili) increased with or without alkaline phosphatase increase	AST or ALT > 3 x and ≤5 x upper limit of normal (ULN) or T.bili > 1.5 x and ≤3 x ULN, regardless of baseline value or T.bili > ULN and/or AST/ALT > 1.5 x ULN associated with alkaline phosphatase > 2.5 x ULN	Delay dose/reduce dose[a]	Dose reduction may be considered at the discretion of the investigator and following local guidelines[a]. Dosing may resume when laboratory values return to baseline.
	AST or ALT > 5 x ULN or T.bili > 3 x ULN, regardless of baseline value or T.bili > ULN and/or ALT and AST > 3.5 x ULN associated with alkaline phosphatase > 6 x ULN	Permanently discontinue	N/A
	Concurrent AST or ALT > 3 x ULN and T.bili > 2 x ULN, regardless of baseline value	Permanently discontinue	N/A
Infusion Reactions (manifested by fever, chills, rigors, headache, rash, pruritus, arthralgia, hypotension, hypertension, bronchospasm, or other allergic-like reactions.)			
Hypersensitivity reaction or infusion reaction	Grade 3 or 4	Permanently discontinue	Refer to Section 7.4.7: Docetaxel-related Hypersensitivity Reactions.
Other Clinical AE			
Cystoid macular oedema (CMO) diagnosed by ophthalmologic examination	Any Grade	Permanently discontinue docetaxel	CMO has been reported in participants treated with docetaxel. Participants with impaired vision should undergo a prompt and complete ophthalmologic examination. In case CMO is diagnosed, docetaxel

Table 7.4-2: Adverse Event Criteria to Delay, Resume, Reduce or Discontinue Docetaxel			
Drug-Related Adverse Event (AE) per NCI CTCAE v.5.0	**Severity**	**Action Taken**	**Clarifications, Exceptions, and Resume Criteria**
			treatment should be discontinued and appropriate treatment initiated.
Other drug-related AE **(not listed above)**	Grade 2 non-skin AE, except fatigue	Delay dose	Dosing may resume when AE resolves to Grade ≤ 1 or baseline value.
	Grade 3 AE	Delay dose/reduce dose[a] or permanently discontinue	Dosing may resume when AE resolves to Grade ≤ 1 or baseline value. • 1st episode: dose reduction may be considered at the discretion of the investigator[a]. • 2nd episode: permanently discontinue.
	Grade 4 or life-threatening adverse reaction	Permanently discontinue	N/A
Other Laboratory Abnormalities			
Other drug-related laboratory abnormality **(not listed above)**	Grade 3	Delay dose or reduce dose[a]	Dose reduction may be considered at the discretion of the investigator and following local guidelines[a]. Exceptions: No delay required for: Grade 3 lymphopenia.
	Grade 4	Permanently discontinue	Exceptions: The following events do not require discontinuation of study drug: • Grade 4 lymphopenia or leukopenia. • Grade 4 isolated electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are responding to supplementation/appropriate management within 72 hours of their onset.
Participants receiving docetaxel may receive growth factors (including G-CSF and erythropoietin) at the discretion of the investigator and following local guidelines.			

[a] Please refer to section 7.4.2 for instructions on docetaxel dose reduction.

7.4.1 Nivolumab or Placebo

There will be no dose modifications permitted for nivolumab or placebo

7.4.2 Docetaxel Dose Reduction

Dose reductions of docetaxel may be required and will be performed according to Table 7.4.2-1.

Table 7.4.2-1: Dose Reductions for Docetaxel

Dose Level	Docetaxel
Starting dose	75 mg/m²
First dose reduction	60 mg/m²
Second dose reduction	Discontinue docetaxel

Docetaxel dose can be reduced when necessary as described in Table 7.4.2-1. The dose which has been reduced for toxicity must not be re-escalated. Up to a maximum of 1 dose reduction will be allowed per participant. If a second dose reduction is required per the modifications above, the patient should discontinue study treatment.

Prednisone (or prednisolone)

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 participant will continue docetaxel treatment in the absence of major toxicity, disease progression or any other discontinuation criteria as defined in Section 8.

7.4.3 Dose Delay Criteria

Dose delay criteria apply for all drug-related AEs regardless of whether the event is attributed to nivolumab/placebo or docetaxel or both. Delay administration of both nivolumab/placebo and docetaxel if any of the delay criteria in Table 7.4-1 and Table 7.4-2 are met. Delay nivolumab/placebo and docetaxel dosing for any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication. Delay administration of all drugs if SARS-CoV-2 infection either confirmed or suspected.

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

If treatment is delayed > 8 weeks (Q3W cycle) or > 10 weeks (Q4W cycle), nivolumab/placebo treatment must be permanently discontinued, except as specified in Section 8. Prior to re-initiating treatment in a participant with a dosing delay lasting > 8 weeks (Q3W cycle) or > 10 weeks (Q4W cycle), the Medical Monitor (or designee) must be consulted.

7.4.4 Criteria to Resume Study Treatment

Participants may resume dosing when resuming criteria for BOTH nivolumab and docetaxel are met if they have completed AE management (ie, corticosteroid taper) or are on ≤ 10 mg prednisone or equivalent, and meet the requirements per Table 7.4-1 and Table 7.4-2. That is, nivolumab or placebo and docetaxel must be administered together until completion of Cycle 10 or until one or both agents are discontinued. The only exception is immune-related toxicities that require prolonged nivolumab delay (ie, toxicities treated with a prolonged corticosteroid taper). In such cases, dosing with docetaxel may resume prior to nivolumab, when the criteria to resume dosing for docetaxel have been met. Nivolumab or placebo dosing may be resumed later, after completion of the corticosteroid taper and when criteria to resume nivolumab or placebo dosing have been met. It is allowed to administer either nivolumab/placebo or docetaxel if the other is discontinued because of toxicity if, in the opinion of the treating investigator, it is in the best interest of the participant.

Prior to re-initiating treatment in a participant with a dosing delay lasting > 8 weeks (Q3W cycle) or > 10 weeks (Q4W cycle), the Medical Monitor (or designee) must be consulted. Continue tumor assessments per protocol even if dosing is delayed. Continue periodic study visits to assess safety and laboratory studies as clinically indicated during such dosing delays.

Participants with SARS-CoV-2 infection (either confirmed or suspected) may resume treatment after all of the following criteria are met: 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 have 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; and 4) consultation with 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.

7.4.5 Management Algorithms for Nivolumab

Immuno-oncology (IO) agents are associated with AEs that can differ in severity and duration from AEs caused by other therapeutic classes. Nivolumab is considered an IO agent, and the management algorithms in Appendix 6 provide guidance on assessing and managing the following groups of AEs:

- Gastrointestinal
- Renal
- Pulmonary
- Hepatic
- Endocrinopathy
- Skin
- Neurological
- Myocarditis

7.4.6 Treatment of Related Infusion Reactions

Since nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. Report all Grade 3 or 4 infusion reactions as SAEs (if they meet the criteria) within 24 hours of onset.

Treatment recommendations are provided below based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5. Grading definitions and may be modified based on local treatment standards and guidelines, as appropriate:

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

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

For Grade 2 symptoms: (Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, nonsteroidal anti-inflammatory drugs [NSAIDS], narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hrs**)**:

- Stop the study drug infusion, begin an IV infusion of normal saline, and treat the participant with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor participant until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor participant closely. If symptoms recur, then no further study medication 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 administered at least 30 minutes before nivolumab infusions. If necessary, corticosteroids (up to 25 mg of hydrocortisone or equivalent) may be used.

For Grade 3 or 4 symptoms: (severe reaction, Grade 3: Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. Grade 4: Life-threatening consequences; urgent intervention indicated):

- Immediately discontinue infusion of study drug. Begin an IV infusion of normal saline and treat the participant as follows: Recommend bronchodilators: epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration; and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Monitor participant until the

investigator judges that the symptoms will not recur. Study drug will be permanently discontinued. Follow institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor participant until symptoms resolve.

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

7.4.7 Docetaxel-related Hypersensitivity Reactions

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 docetaxel, thus facilities for the treatment of hypotension and bronchospasm should be available. If hypersensitivity reactions occur, minor symptoms such as flushing or localized cutaneous reactions do not require interruption of therapy. However, severe reactions (≥ Grade 3), such as severe hypotension, bronchospasm or generalized rash/erythema require immediate discontinuation of docetaxel and appropriate therapy. Patients who have developed severe hypersensitivity reactions should not be re-challenged with docetaxel. Patients who have previously experienced a hypersensitivity reaction to paclitaxel may be at risk to develop hypersensitivity reaction to docetaxel, including more severe hypersensitivity reaction. These patients should be closely monitored during initiation of docetaxel therapy.

7.5 Preparation/Handling/Storage/Accountability

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

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

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

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

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

For docetaxel and prednisone, refer to the current prescribing information for the complete storage, handling, dispensing and administration information.

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

7.5.1 Retained Samples for Bioavailability/Bioequivalence/Biocomparability

Not applicable

7.6 Treatment Compliance

Treatment compliance will be monitored by drug accountability as well as the participant's medical record and eCRF.

7.7 Concomitant Therapy

Drug-drug interactions (DDI) between nivolumab and co-administered medications are unlikely. See the recent nivolumab IB for information concerning DDI studies conducted with nivolumab.

7.7.1 Prohibited and/or Restricted Treatments

7.7.1.1 All Participants

For both treatment arms, the following medications are prohibited during the study (unless utilized to treat a drug-related AE):

- Immunosuppressive agents and immunosuppressive doses of systemic corticosteroids (except as stated in Section 7.7.2) are prohibited during the treatment with nivolumab
- 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 non-palliative radiation therapy (unless specified per protocol). Limited radiation therapy administered with palliative intent (ie, for pain, bleeding, spinal cord compression, brain metastasis, new or impending pathologic fracture, superior vena-cava syndrome, or obstruction) is permitted
- Any complementary medications (eg, herbal supplements or traditional Chinese medicines) intended to treat the disease under study. Such medications are permitted if they are used as supportive care.
- 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.
- Initiation or dose adjustment of approved bone targeting agents is prohibited within 28 days prior to start of study treatment. Initiation of these agents is allowed during study treatment, if clinically indicated, and should not result in study treatment discontinuation.

7.7.1.2 Nivolumab Combined with Docetaxel

Strong CYP3A4 inhibitors and inducers should be avoided during the treatment with docetaxel. Please refer to Appendix 7 for a list of common strong CYP3A4 inhibitors and inducers.

7.7.1.3 Imaging Restriction and Precautions

It is the local imaging facility's responsibility to determine, based on participant attributes (eg, allergy history, diabetic history, and renal status), the appropriate imaging modality and

contrast regimen per imaging study. Imaging contraindications and contrast risks are to be considered in this assessment. Participants with renal insufficiency are to be assessed as to whether or not they should receive contrast and if so, which contrast agent and dose is appropriate. Specific to MRI, participants with severe renal insufficiency (ie, estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m2) are at increased risk of nephrogenic systemic fibrosis, therefore MRI contrast is contraindicated. In addition, participants may be excluded from MRI if they have tattoos, metallic implants, pacemakers, etc. This will be outlined in the image acquisition manual.

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

7.7.2 Permitted Therapy

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

7.7.3 Palliative Local Therapy

Palliative local therapy, including palliative radiotherapy and palliative surgical resection, to symptomatic tumor lesions is permitted. 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 PCWG3 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 7.7.4) in order to resume study treatment after the completion of palliative local therapy.

In cases where palliative radiotherapy is required, nivolumab 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.

For docetaxel local standard of care guidelines should be followed.

7.7.4 Treatment Beyond Progression

Not applicable per Protocol Amendment 04.

Participants will be permitted to continue treatment beyond initial PCWG3-defined PD, as assessed by the investigator, up to a maximum of 24 months from date of first dose, as long as the following criteria are considered:

- Investigator-assessed clinical benefit
- Tolerance of study drug
- Stable performance status

- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases)
- Participant provides written informed consent prior to receiving additional treatment with the study drug regimen. All other elements of the main consent including description of reasonably foreseeable risks or discomforts, or other alternative treatment options will still apply.

7.7.5 Re-assessment Following Initial Assessment of Progression

Not applicable per Protocol Amendment 04. Radiographic tumor assessments by BICR following PCWG3 criteria will no longer apply. All participants receiving study treatment will have radiographic tumor assessments based on the clinical judgment of the treating investigator and following local imaging tumor assessment guidelines for mCRPC. Submission of tumor imaging assessments for central review will no longer apply.

Radiographic assessment/scan(s) should continue in accordance with Section 2 (Schedule of Activities) for the duration of the treatment beyond progression and should be submitted to the central imaging vendor. This assessment will allow determination of whether there has been a decrease in the tumor size or continued PD. The assessment of clinical benefit should be balanced by clinical judgment as to whether the participant is clinically deteriorating and unlikely to receive any benefit from continued treatment with nivolumab.

For the participants 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 measurable 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-measurable at the time of initial progression may become measurable 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 PCWG3-defined progression of bone disease.

Study treatment should be discontinued permanently upon documentation of any further progression as described above. Confirmed PSA progression alone is not necessarily an indication to stop treatment.

7.8 Treatment After the End of the Study

Per Protocol Amendment 04, due to lack of rPFS benefit at the final analysis and OS benefit at the first interim analysis for nivolumab added to docetaxel plus prednisone compared to placebo added to docetaxel plus prednisone, on 26-Jul-2023, a BMS EOC decided to terminate the study. The decision to terminate the study was not based on any safety concerns or issues. Based on these results, BMS recommends discontinuation of nivolumab in all participants receiving this study treatment. In the event that the investigator deems a participant is deriving clinical benefit from nivolumab therapy and, together with the counseled participant, wishes to continue nivolumab, this may be allowed following discussion with the Medical Monitor to ensure a clinical rationale exists that justifies continuation of nivolumab treatment.

Study treatment will be provided via an extension of the study, a rollover study requiring approval by responsible health authority and ethics committee or through another mechanism at the discretion of BMS.

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

8 DISCONTINUATION CRITERIA

8.1 Discontinuation from Study Treatment

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

- Participant's request to stop study treatment. Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant
- Termination of the study by Bristol-Myers Squibb (BMS) for reasons including but not limited to the following: safety concerns, termination of drug development, lack of efficacy, and lack of meeting study objectives/endpoints.
- 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.)

- Participant meets criteria for radiographic progression per PCWG3 criteria (as defined in Appendix 5) unless criteria for treatment beyond progression have been met (see Section 7.7.4). PSA progression alone is not an indication to discontinue study treatment (see Section 9.1.2).

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

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

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

8.1.1 Discontinuation of Specific Study Treatments

The assessment for discontinuation of nivolumab and docetaxel should be made separately for each study drug. Although there is overlap among the discontinuation criteria, if discontinuation criteria are met for one study treatment but not the other, it may be acceptable to continue treatment with the study treatment that is not felt to be related to the toxicity. If the investigator considers the toxicity to be related to both study treatments or is unable to determine which study treatment is the cause of toxicity, then both study treatments should be discontinued, and the recommendations for management of toxicity related to both study treatments should be promptly initiated.

Nivolumab and/or docetaxel treatment must be permanently discontinued per criteria in Table 7.4-1 and Table 7.4-2.

Discontinue nivolumab and/or docetaxel for any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the participant with continued nivolumab and/or docetaxel dosing.

Any event that leads to delay in dosing lasting > 8 weeks (Q3W cycle) or > 10 weeks (Q4W cycle), from the previous dose requires discontinuation of study drug, with the following exceptions:

- Dosing delays to allow for prolonged steroid tapers to manage drug-related adverse events are allowed.
- Dosing delays lasting > 8 weeks (Q3W cycle) or > 10 weeks (Q4W cycle) from the previous dose that occur for non-drug-related reasons may be allowed if approved by the Medical Monitor (or designee).

8.1.2 Post Study Treatment - Study Follow-up

Not applicable per Protocol Amendment 04. Only participants who received study provided nivolumab and are up to 100 days after their last nivolumab infusion will have post-study treatment safety follow-up. After completion of the 100-day safety follow-up requirement and resolution or stabilization of AEs, nivolumab-treated participants will be discontinued from the study. All other participants currently on safety or survival follow-up with resolution or stabilization of AEs will be discontinued from the study.

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

BMS may request that survival data be collected for all treated participants outside the protocol-defined window (as detailed in the Schedule of Activities in Section 2). At the time of this request, each participant will be contacted to determine his or her survival status, unless the participant has withdrawn consent for all contact or is lost to follow-up.

8.2 Discontinuation from the Study

Not applicable per Protocol Amendment 04. Only participants continuing study-provided nivolumab and are up to 100 days after their last nivolumab infusion will have post-study treatment safety follow-up. After completion of the 100-day safety follow-up requirement and resolution or stabilization of AEs, nivolumab-treated participants will be discontinued from the study. All other participants currently on safety or survival follow-up with resolution or stabilization of AEs will be discontinued from the study.

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

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

8.3 Lost to Follow-Up

Not applicable per Protocol Amendment 04.

- All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with persons authorized by the participant.
- Lost to follow-up is defined by the inability to reach the participant after a minimum of three documented phone calls, faxes, or emails as well as lack of response by participant to one registered mail letter. All attempts should be documented in the participant's medical records.
- If it is determined that the participant has died, the site will use permissible local methods to obtain date and cause of death.
- If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the participant's informed consent, then the investigator may use a sponsor retained third-party representative to assist site staff with obtaining participant's contact information or other public vital status data necessary to complete the follow-up portion of the study.
- The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information.
- If after all attempts, the participant remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the participant's medical records.

9 STUDY ASSESSMENTS AND PROCEDURES

- **Per Protocol Amendment 04:**
  - **Participants continuing study-provided nivolumab and deriving treatment benefit per investigator assessment, as well as participants up to 100 days after the last infusion of nivolumab, will continue study participation. All other participants will be discontinued from the study.**
  - **Safety clinical and laboratory assessments will apply only to participants continuing study-provided nivolumab, and participants up to 100 days after their last nivolumab infusion.**
  - **Radiographic tumor assessments will be performed based on the clinical judgment of the treating investigator and following local imaging tumor assessment guidelines for mCRPC. The same applies for PSA collection.**
- Study procedures and timing are summarized in Section 2 (Schedule of Activities).
- Protocol waivers or exemptions are not allowed.
- All immediate safety concerns must be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue treatment.
- Adherence to the study design requirements, including those specified in Section 2 (Schedule of Activities), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before randomization. The investigator will maintain a

screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Schedule of Activities.
- Perform additional measures, including non-study required laboratory tests, as clinically indicated or to comply with local regulations. Laboratory toxicities (eg, suspected drug-induced liver enzyme evaluations) will be monitored during the follow-up phase via on-site/local labs until all study drug-related toxicities resolve, return to baseline, or are deemed irreversible.
- Evaluate participant immediately to rule out cardiac or pulmonary toxicity if participant shows cardiac or pulmonary-related signs (hypoxia, abnormal heart rate, or changes from baseline) or symptoms (eg, dyspnea, cough, chest pain, fatigue, palpitations).
- Some of the assessments referred to in this section may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

9.1 Efficacy Assessments

9.1.1 Imaging Assessment for the Study

Not applicable per Protocol Amendment 04: Radiographic tumor assessments by BICR following PCWG3 criteria will no longer apply. Moving forward from Protocol Amendment 04, all participants receiving study treatment will have radiographic tumor assessments based on the clinical judgment of the treating investigator and following local imaging tumor assessment guidelines for mCRPC. Submission of tumor imaging assessments for central review will no longer apply.

Images will be submitted to a central imaging vendor for BICR 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 CA2097DX Imaging Manual provided by the central imaging.

Screening and on study images should be acquired as outlined in Section 2 (Schedule of Activities).

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 bone scans, CT/MRI should be submitted to central imaging vendor. X-rays that clearly demonstrate interval progression of disease, for example most commonly as unequivocal lesions that are unmistakably new since the prior CT/MRI, should be submitted to central imaging vendor. Otherwise, they do not need to be submitted centrally.

9.1.1.1 Methods of Measurement

Bone lesions, including those with soft tissue component, will be assessed using technetium-99m (Tc-99m) based radionuclide bone scans.

Contrast-enhanced CT of the, chest, abdomen, pelvis, and all other known and/or suspected sites of disease should be performed for tumor assessments. Bone lesions, including those with or without a soft tissue component, will be assessed by radionuclide bone scans and not by CT or MRI. Images should be acquired with slice thickness of 5 mm or less with no intervening gap (contiguous). Every attempt should be made to image each participant using an identical acquisition protocol on the same scanner for all imaging timepoints. Tumor measurements should be made by the same investigator or radiologist for each assessment, whenever possible. Change in tumor measurements and tumor response to guide ongoing study treatment decisions will be assessed by the investigator using the PCWG3 criteria.

If a participant has a contraindication for CT intravenous contrast, then a non-contrast CT of the chest and a contrast-enhanced MRI of the abdomen, pelvis, and other known/suspected sites of disease should be obtained.

If a participant has a contraindication for both MR and CT intravenous contrasts, then a noncontrast CT of the chest and a non-contrast MRI of the abdomen, pelvis, and other known/suspected sites of disease should be obtained.

If a participant has a contraindication for MRI (eg, incompatible pacemaker) in addition to contraindication to CT intravenous contrast, then a non-contrast CT of the chest, abdomen, pelvis, and other known/suspected sites of disease is acceptable.

MRI of brain (without and with contrast) should be acquired as outlined in Section 2 (Schedule of Activities). CT of the Brain (without and with contrast) can be performed if MRI is contraindicated.

9.1.1.2 Imaging and Clinical Assessment

Not applicable per Protocol Amendment 04: Radiographic tumor assessments will no longer apply. Moving forward from protocol Amendment 04, all participants receiving study treatment will have radiographic tumor assessments based on the clinical judgment of the treating investigator and following local imaging tumor assessment guidelines for mCRPC. Submission of tumor imaging assessments for central review will no longer apply.

Tumor assessments should continue even if dosing is delayed or discontinued. Changes in tumor measurements and tumor responses will be assessed by the same investigator or designee using PCWG3 criteria. Assessments of PR and CR must be confirmed at least 4 weeks (28 days) after initial response. A Best Overall Response (BOR) of SD requires a minimum of 56 days on study from date of first dose to the date of the first imaging assessment.

9.1.2 BICR Confirmation of Progression

Not applicable per Protocol Amendment 04. Moving forward from Protocol Amendment 04, all participants receiving study treatment will have radiographic tumor assessments by

BICR following PCWG3 criteria based on the clinical judgment of the treating investigator and following local imaging tumor assessment guidelines for mCRPC. Submission of tumor imaging assessments for central review will no longer apply.

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 PCWG3 criteria 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 Imaging Manual.

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 participants discontinue treatment without radiographic progression, tumor assessments will continue according to the protocol-specified schedule, as noted in Section 2 (Schedule of Activities) until progression has been confirmed by BICR. In case subsequent therapy has begun, imaging must continue until radiographic progression per PCWG3 is confirmed by BICR.

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

Disease Progression Criteria

Radiographic Progression in soft tissue lesions (Target lesions, Non-target [non-bone] lesions) and bone lesions is described in Table 9.1.2-1. See Appendix 6 for more information.

Table 9.1.2-1: Definition of Radiographic Progression

Parameter	Progression	Date of Progression
Soft tissue lesions (target, non-target lesions with CT or MRI)	Progression of soft tissue lesions (target, non-target, new lesions with CT or MRI)	Date of first unequivocal progression of soft tissue lesion (target, non-target, or new lesions) as per PCWG3[a]
Bone lesions on radionuclide bone scan per PCWG3	At least 2 new lesions on the first post-treatment bone scan, with at least 2 additional lesions on the next scan (performed at least 6 weeks later) as compared to the first post-treatment bone scan.	Date of first post-treatment scan
	For scans after the first post-treatment scan, at least 2 new lesions relative to the first post treatment scan AND confirmed on a subsequent scan (performed at least 6 weeks later)	Date of progression is the date of the scan that first documents at least 2 new lesions relative to the first post-treatment scan

[a] RECIST v1.1 criteria are modified for assessing soft tissue lesions per PCWG3. See Appendix 5.

Disease progression by PSA (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, participants must discontinue study treatment upon radiographic progression criteria per PCWG3 for measurable disease and/or bone disease (Table 9.1.2-1 above). Participants who discontinue treatment without PSA progression or radiographic progression will continue to have PSA at FU1, FU2, and every 12 weeks thereafter (or sooner if needed to confirm PSA progression or if clinically indicated. PSA collection will continue until PSA progression, radiographic progression or end of study treatment, whichever occurs last.

9.1.3 Patient-Reported Outcomes

Not applicable per Protocol Amendment 04.

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.

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 5-level version of the EuroQol Group's EQ-5D (EQ-5D-5L) in the participant's preferred language when available. The assessments will be given before any clinical activities are performed during on-

treatment dosing visits and at safety follow-up visits. Additionally, the EQ-5D-5L and the Prostate Cancer Subscale (PCS) from the FACT-P will be administered at survival follow-up visits by telephone. A standardized guide can be used the EQ-5D-5L by telephone. A similar guide does not exist for the PCS. Participants will be provided with a hard copy of the PCS to take home and use as a visual aid during telephone interviews. See Section 2 (Schedule of Activities) for more information on timing of assessments. If exceptional circumstances preclude the continued administration of measures using planned modalities, alternate administration methods may be required.

9.1.4 The Brief Pain Inventory - Short Form

Not applicable per Protocol Amendment 04.

The BPI-SF[103] measures both pain severity and functional interference caused by pain through the use of a numerical rating scale. Participants 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 participants 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 patients with the following four tumor types: breast, prostate, colorectal, and gynecological.[104] The BPI-SF has been validated in cancer patients in several countries with psychometrically validated translations in over 25 countries.

9.1.5 The Functional Assessment of Cancer Therapy - Prostate Cancer (FACT-P)

Not applicable per Protocol Amendment 04.

The FACT-P is a multidimensional, self-report instrument specifically designed for use with prostate cancer patients.[105] The FACT-P includes the 27-item FACT-General (FACT-G), a generic cancer-related core, to assess physical well-being (PWB; seven items), social/family well-being (SWB; seven items), emotional well-being (EWB; six items), and functional well-being (FWB; seven items). In addition, the FACT-P includes a 12-item disease-specific Prostate Cancer Subscale that assesses prostate-related symptoms. Each of the 39 items is rated on a 0 (Not at all) to 4 (Very much) Likert-type scale, then combined to produce subscale scores for each domain, a Trial Outcome Index (TOI) 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. The FACT-P uses a recall period of the past 7 days.

9.1.6 The 5-Level EQ-5D

Not applicable per Protocol Amendment 04.

The EQ-5D-5L is a standardized instrument used to measure self-reports of general health status.[106] The instrument has two components, a descriptive system, and a visual analogue scale (VAS). The descriptive system consists of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has five levels, reflecting no problems, slight problems, moderate problems, severe problems, and extreme problems. A dimension for which there are no problems is said to be at level 1, while a dimension for which there are extreme problems is said to be at level 5. Thus, the vectors 11111 and 55555 represent the best health state and the worst health state, respectively. Altogether, the instrument describes 3,125 different health states. Empirically-derived weights can be applied to an individual's responses to the EQ-5D-5L descriptive system to generate a utility index measuring the value to society of his or her current health.[107]

The EQ-5D-5L VAS allows participants to rate their own current health on a 0 to 100 point scale ranging from "the worst health you can imagine" to the "best health you can imagine," respectively.

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

9.2 Adverse Events

Per Protocol Amendment 04, AE assessments will only be applicable to participants continuing study-provided nivolumab, and participants up to 100 days after their last infusion of nivolumab. After completion of the 100-day safety follow-up requirement and resolution or stabilization of AEs, nivolumab-treated participants will be discontinued from the study. All other participants will be discontinued from the study.

The definitions of an AE or serious adverse event (SAE) are classified according to NCI CTCAE version 5 and can be found in Appendix 3.

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

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

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

Contacts for SAE reporting specified in Appendix 3

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

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.

All SAEs must be collected from the time of signing the consent, including those thought to be associated with protocol-specified procedures and within 100 days of discontinuation of dosing. For participants assigned to treatment and never treated with study drug, SAEs should be collected for 30 days from the date of treatment assignment.

The investigator must report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure, (eg, a follow-up skin biopsy), Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the appropriate section of the CRF module.

- All SAEs will be recorded and reported to sponsor or designee within 24 hours, as indicated in Appendix 3.
- The investigator will submit any updated SAE data to the sponsor or designee within 24 hours of updated information being available.

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

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

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

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

9.2.2 Method of Detecting AEs and SAEs

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

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 participant's case report form.

9.2.3 Follow-up of AEs and SAEs

- Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Appendix 3).
- Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study treatment and for those present at the end of study treatment as appropriate.

- All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic). Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, nonserious AEs of special interest (as defined in Section 9.1.3 Adverse Events), and AEs (SAEs and nonserious AEs) associated with confirmed or suspected SARS-CoV-2 infection will be followed until resolution; until the condition stabilizes; until the event is otherwise explained; the event is deemed irreversible; until the participant is lost to follow-up (as defined in Section 8.3); or, for suspected cases, until SARS-CoV-2 infection is ruled out.

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

9.2.4 Regulatory Reporting Requirements for SAEs

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

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

9.2.5 Pregnancy

Per Protocol Amendment 04, only applicable to female partners of male participants continuing study-provided nivolumab, and female partners of male participants up to 100 days after their last infusion of nivolumab.

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

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

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

9.2.6 Laboratory Test Result Abnormalities

Per Protocol Amendment 04, only applicable to participants continuing study-provided nivolumab, and participants up to 100 days after their last infusion of nivolumab, as required in Table 2-2.

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

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

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

9.2.7 Potential Drug Induced Liver Injury (DILI)

Per Protocol Amendment 04, only applicable to participants continuing study-provided nivolumab, and participants up to 100 days after their last infusion of nivolumab.

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 9.2.1 and Appendix 3 for reporting details).

Potential drug induced liver injury is defined as:

1) AT (ALT or AST) elevation > 3 X upper limit of normal (ULN)

AND

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

AND

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

9.2.8 Other Safety Considerations

Per Protocol Amendment 04, only applicable to participants continuing study-provided nivolumab, and participants up to 100 days after their last infusion of nivolumab.

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

9.3 Overdose

Per Protocol Amendment 04, only applicable to participants continuing study-provided nivolumab, and participants up to 100 days after their last infusion of nivolumab.

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. Overdoses that meet the regulatory definition of SAE will be reported as an SAE (refer to Appendix 3).

All instances of accidental overdose and/or dosing errors should be reported on the Dosage Administration Record eCRF.

There are a few reports of docetaxel overdose. There is no known antidote for docetaxel overdose.

In case of overdose, the participant should be kept in a specialized unit and vital functions closely monitored. In cases of overdose, exacerbation of AEs may be expected. The primary anticipated complications of overdose would consist of bone marrow suppression, peripheral neurotoxicity and mucositis. Participants should receive therapeutic G-CSF as soon as possible after discovery of overdose. Other appropriate symptomatic measures should be taken, as needed.

9.4 Safety

Per Protocol Amendment 04, only applicable to participants continuing study-provided nivolumab, and participants up to 100 days after their last infusion of nivolumab.

Planned time points for all safety assessments are listed in Section 2 (Schedule of Activities).

9.4.1 Physical Examinations

Refer to Schedule of Activities (Section 2).

9.4.2 Vital signs

Refer to Schedule of Activities (Section 2).

9.4.3 Electrocardiograms

Refer to Schedule of Activities (Section 2).

9.4.4 Clinical Safety Laboratory Assessments

Per Protocol Amendment 04, laboratory tests will include local safety laboratory tests only and will exclude tests such as PSA, [redacted] and pharmacokinetics. In addition, the requirement for local safety laboratory tests will ONLY be applicable to participants continuing study-provided nivolumab and participants up to 100 days after their last nivolumab infusion. All other participants will be discontinued from the study and switched to local standard of care for metastatic castration-resistant prostate cancer outside of the study.

Investigators must document their review of each laboratory safety report.

Hematology	
Hemoglobin	
Hematocrit	
Total leukocyte count, including differential	
Platelet count	
Chemistry	
Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Total bilirubin Alkaline phosphatase Lactate dehydrogenase (LDH)** Creatinine** Blood Urea Nitrogen (BUN) or Serum Urea Fasting glucose** TSH, Free T3 (fT3), Free T4 (fT4)** (screening) TSH with reflexive fT3*** and fT4 if TSH is abnormal on treatment	Albumin* Sodium Potassium Chloride Calcium Phosphorus** Magnesium** Creatinine clearance (CLcr)- screening only (Cockcroft-Gault method)
Serology	
Serum for hepatitis C antibody, hepatitis B surface antigen, HIV-1 and -2 antibody (screening only) Note: Testing for HIV must be performed at sites where mandated locally (see Appendix 9).	
Other Analyses	
Prostate Specific Antigen (PSA) (PSA should be performed by the same lab throughout the treatment period to avoid variations in results between cycles) Testosterone (at screening only)	

*Screening only.

**Assess as indicated in Table 2-1 and Table 2-2. Assess at Safety FU2 only if toxicities are present.

***Total T3 may be obtained when free T3 is not available.

9.4.5 Imaging Safety Assessment

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

9.5 Pharmacokinetics

[redacted]

[redacted] All on treatment PK time points are intended to align with days on which study treatment is administered. If it is known that a dose is going to be delayed, then the predose sample should be collected just prior to the delayed dose. However, if a predose sample is collected but the dose is subsequently delayed, an additional predose sample should not be collected.

Serum concentration analyses for nivolumab will be performed by validated bioanalytical method. Further details of sample collection, processing, and shipment will be provided in the laboratory procedures manual. Bioanalytical samples designated for assessments (eg, immunogenicity, PK, [redacted]) from the same collection time point may be used interchangeably for analyses, if required (eg, insufficient volume for complete assessment, to follow-up on suspected immunogenicity related AE, etc.).

Additionally, residual bioanalytical samples will be archived and may be used for potential exploratory bioanalysis (including but not limited to: analysis of drug-ADA immune complexes, metabolite analyses, etc.) and or for additional method purposes (including, but not limited to, cross-validation, ADA/PK selectivity, cut point, etc.).

Table 9.5-1: Pharmacokinetic Sampling Schedule for all Arms

Study Day of Sample Collection[a] **Combination Phase (max 10 cycles):** **1 Cycle = 3 weeks** **Monotherapy Phase: (1 Cycle = 4 weeks)**	**Event**	**Time Relative to Nivolumab/Placebo Dose** **Hour: Min**	**Nivolumab PK Serum Sample**	**Nivolumab IMG Serum Sample**
Cycle 1 Day 1	Predose[b]	00:00	X	X
	EOI[c]	00:30	X	
Cycle 2 Day 1	Predose[b]	00:00	X	X
Cycle 4 Day 1	Predose[b]	00:00	X	X
Cycle 6 Day 1	Predose[b]	00:00	X	X
Cycle 10 Day 1[d]	Predose[b]	00:00	X	X
	EOI[c]	00:30	X	
Every 4 Cycles (D1) starting at first cycle of Monotherapy Phase Day 1 until 2 years (e.g. C11, C15, C19, C23)	Predose[b]	00:00	X	X
Follow Up Period				
Follow Up 30 Days Note: from the last dose of nivolumab during treatment period			X	X
Follow Up 100 Days Note: from the last dose of nivolumab during treatment period			X	X

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

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

[c] Since the end of infusion pharmacokinetic (EOI-PK) sample is drawn with the intent of accurately estimating the maximum concentration (Cmax) of the drug, draw the EOI-PK sample when all of the study drug has been infused. If the site infuses drug without a flush, then collect the EOI-PK sample within approximately 5 minutes after end of infusion. If a flush is administered to clear the IV lines of the drug and to ensure delivery of the entire drug dose, then draw the EOI-PK sample within approximately 5 minutes after end of the flush. Do not draw EOI-PK samples from the same IV access through which that the drug was administered.

[d] If combination therapy ends before 10 cycles, switch directly to the monotherapy phase sampling schedule starting at Cycle 11.

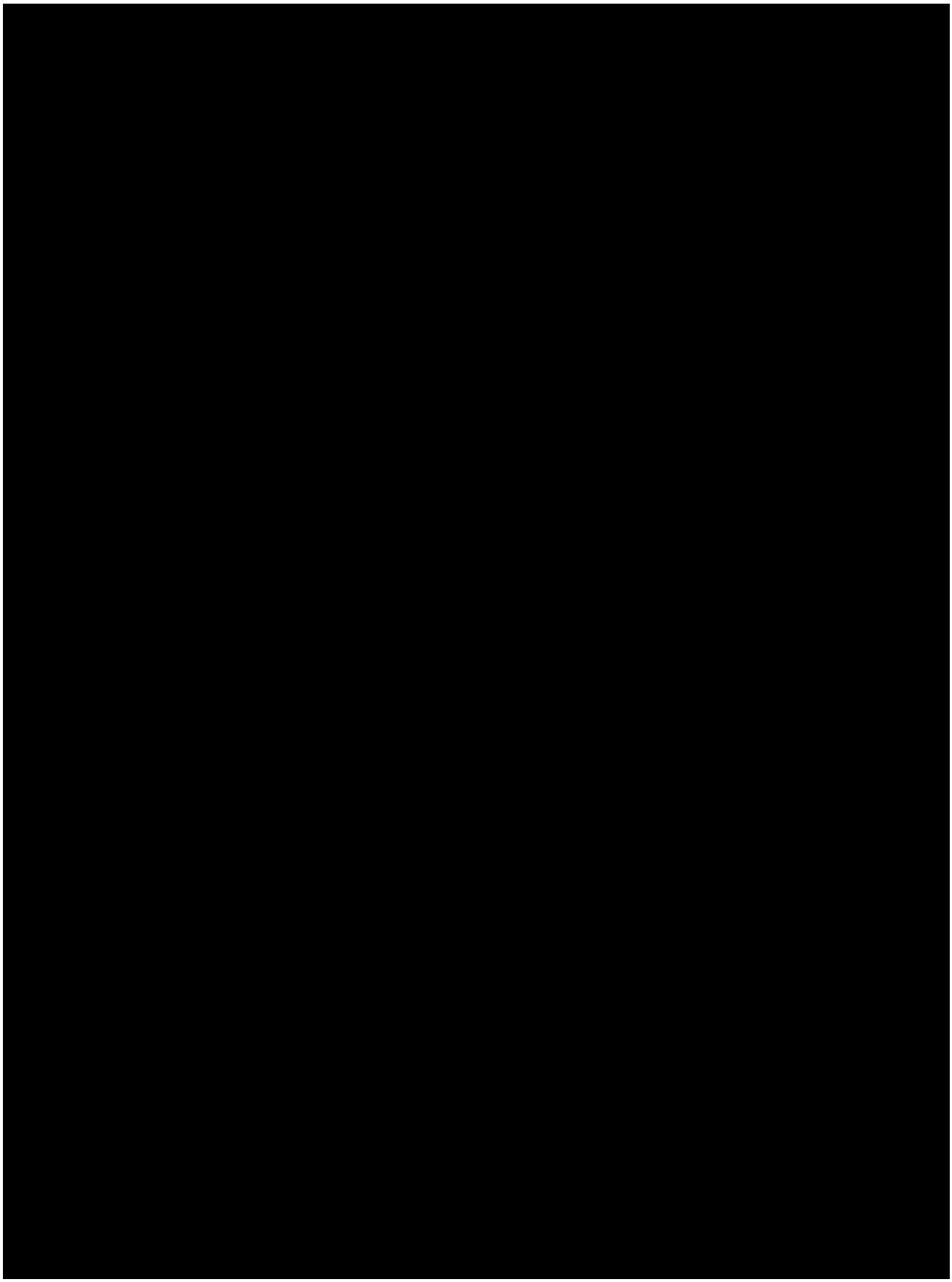
9.6 Pharmacodynamics

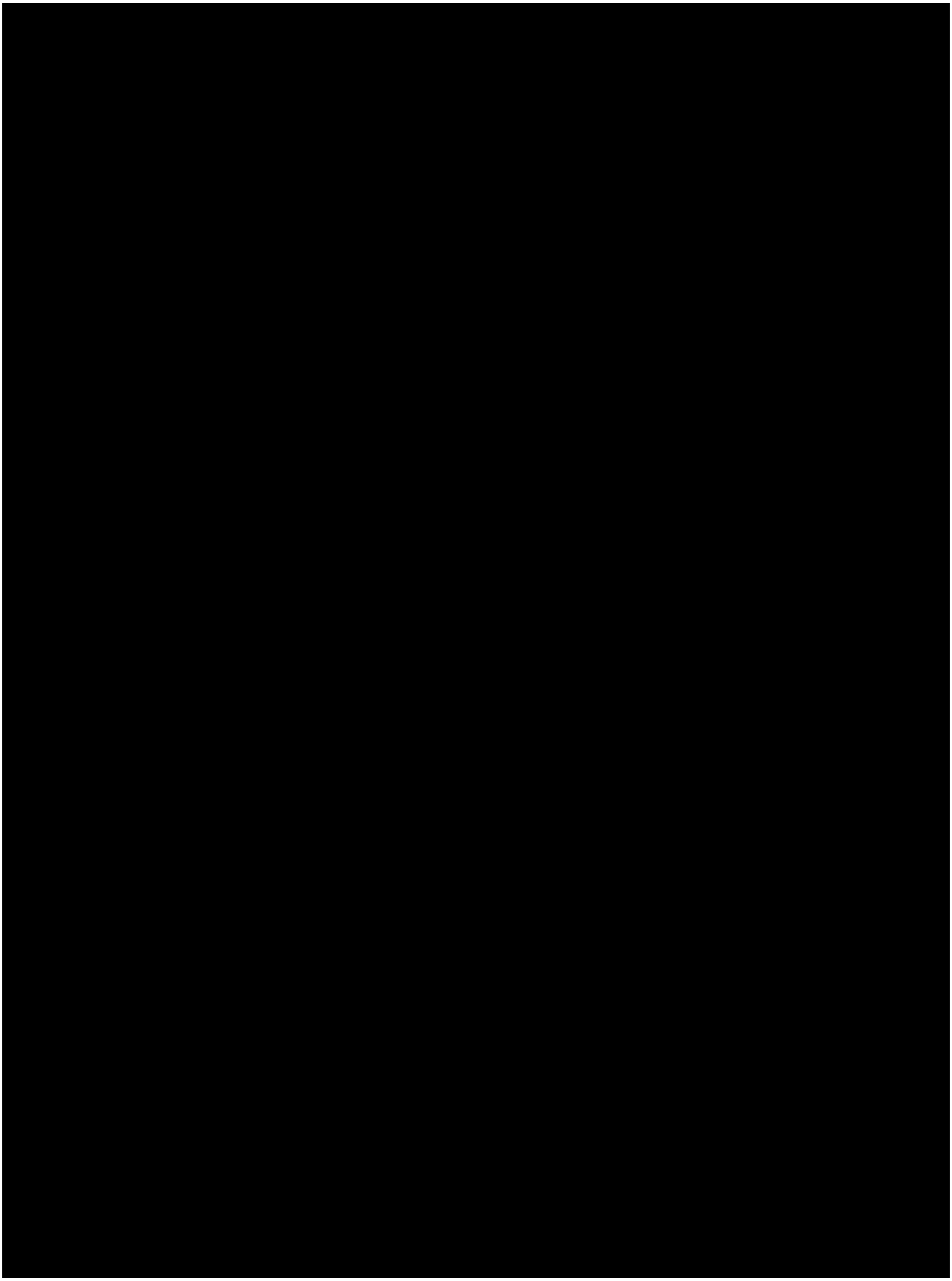
[redacted]

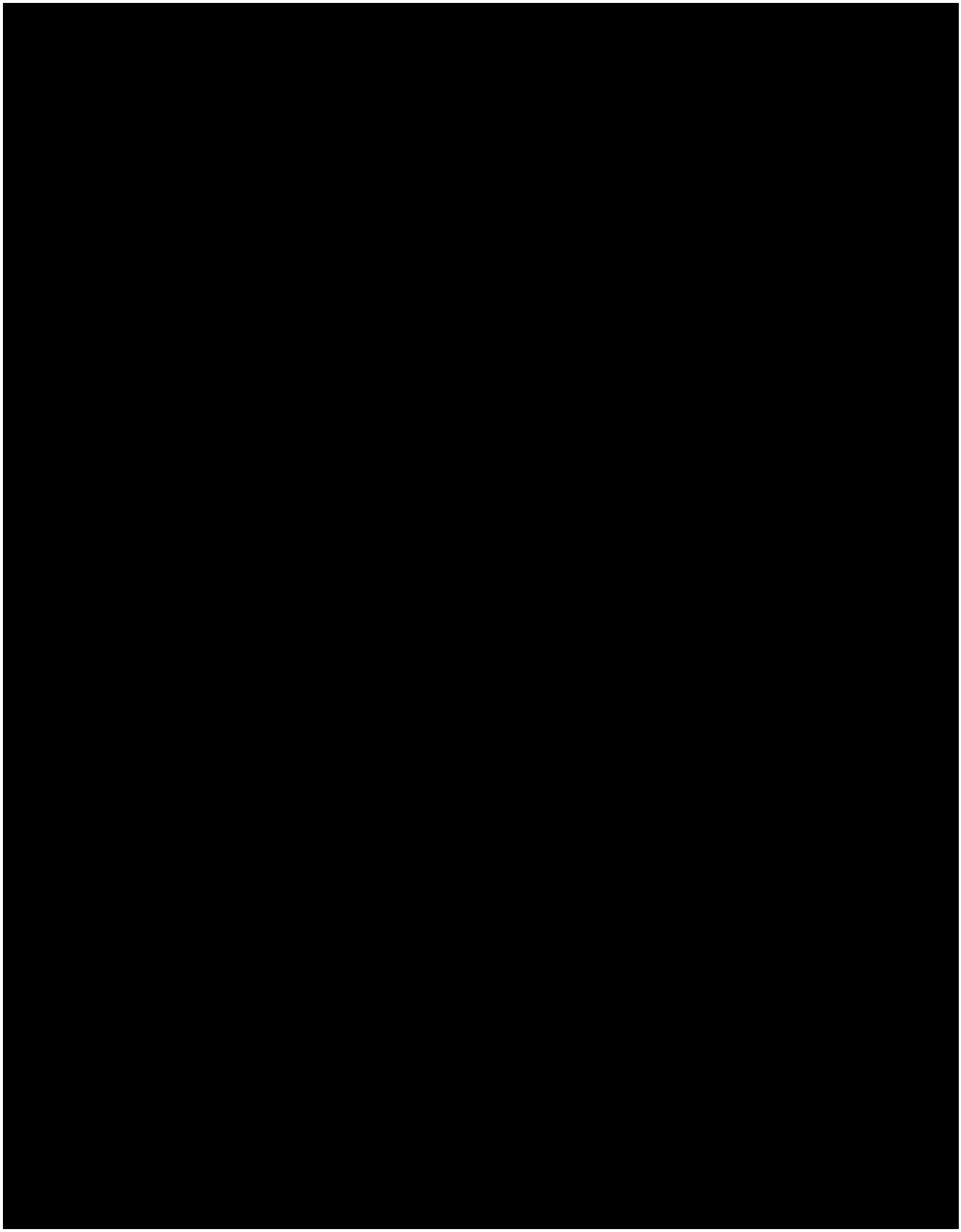
9.7 Pharmacogenomics

Not applicable

[redacted]







[redacted]

9.8.2 Additional Research Collection

[redacted]

This protocol will include residual sample storage for additional research.

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

For All US sites:

Additional research participation is required for all investigational sites in the US.

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

For non-US Sites:

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

This additional research is intended to expand the translational R&D capability at Bristol-Myers Squibb, and will support as yet undefined research aims that will advance our understanding of disease and options for treatment. It may also be used to support health authority requests for

analysis, and advancement of pharmacodiagnostic development to better target drugs to the right patients. This may also include [redacted] aimed at exploring disease [redacted] progression and response to treatment etc.

Sample Collection and Storage:

All requests for access to samples or data for additional research will be vetted through a diverse committee of the sponsor's senior leaders in R&D to ensure the research supports appropriate and well-defined scientific research activities.

[redacted]

[redacted]

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

The manager of these samples will ensure they are properly used throughout their usable life and will destroy the samples at the end of the scheduled storage period, no longer than fifteen (15) years after the end of the study or the maximum allowed by applicable law.

Transfers of samples by research sponsor to third parties will be subject to the recipient's agreement to establish similar storage procedures.

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

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

9.8.3 Immunogenicity Assessments

[redacted]

Blood samples for immunogenicity analysis will be collected according to the schedule given in Section 9.5 (Pharmacokinetics and Immunogenicity). Samples collected will be evaluated for development of Anti-Drug Antibody (ADA) by a validated electrochemiluminescent (ECL) immunoassay. Samples may also be analyzed for neutralizing antibodies and PK samples may be used for ADA analysis in the event of insufficient volume, to complete immunogenicity assessment, or to follow up on suspected immunogenicity-related AEs.

[redacted]

9.9 Healthcare Resource Utilization and Health Economics

Not applicable per Protocol Amendment 04.

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

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

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

10 STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

The primary objectives of this study are to compare rPFS and OS between treatment groups in all randomized participants. The primary endpoints, rPFS and OS comprise the primary endpoint family and will be compared at the 0.01 level and 0.04 level respectively, ensuring family-wise control of the Type I error rate. These endpoints will be tested separately and if significant, the alpha allocated to each endpoint will be recycled to the other endpoint. For example, if rPFS is

significant at the 0.01 level, then 0.01 will be transferred to the OS analysis for testing at 0.05 level. Sample size estimation is conducted using EAST 6.4 and further verified in Solara.

Approximately 984 participants will be randomized in a 1:1 ratio to Arm A and Arm B. Sample size is calculated assuming exponential distribution for time-to-event endpoints. See Table 10.1-1 for a summary of the sample size assumptions.

Sample size justification for rPFS endpoint

The number of events was estimated assuming an exponential distribution of rPFS for the Docetaxel arm (Arm B) and a piecewise exponential distribution with a 2 months delayed treatment effect for the Nivolumab + Docetaxel arm (Arm A). Approximately 530 rPFS events, observed among the 984 randomized participants, provides 90% power to detect an average hazard ratio (HR) of 0.67 with a type 1 error of 0.01 (two-sided). The average HR of 0.67 resulted from an assumed targeted hazard ratio of 1 for the initial 2 months from randomization and a targeted hazard ratio of 0.58 for the time beyond 2-months from randomization.

Sample size justification for OS endpoint

The number of events was estimated assuming an exponential distribution of OS for the Docetaxel arm (Arm B) and a piecewise exponential distribution with a 3-months delayed treatment effect for the Nivolumab + Docetaxel arm (Arm A). Approximately 690 OS events, observed among the 984 randomized participants, provides 92% power to detect an average hazard ratio of 0.76 with a type 1 error of 0.04 (two-sided). The average hazard ratio of 0.76 resulted from an assumed targeted hazard ratio of 1 for the initial 3 months from randomization and a targeted hazard ratio of 0.72 for the time beyond 3-months from randomization.

For all randomized participants, two interim OS analyses are planned. The two interim OS analyses are planned at approximately 47% and 80% of the total events observed at final analysis, respectively. The first interim analysis will occur at the time of rPFS analysis. The stopping boundaries at the interim and final analyses will be based on the actual number of OS events at the time of the analysis using Lan-DeMets alpha-spending function with O'Brien-Fleming boundaries, taking into account any alpha that was passed from the rPFS analysis (if applicable). Details of the interim analysis will be included in Section 10.3.6 (Interim Analysis).

Assuming an average enrollment rate of 2, 20, 45, and 70 participants randomized per month during months 1 to 7, 8 to 15, 16 to 21, and 22 to 29, respectively, with a 29-month accrual period, it will take approximately 51 months from the date of randomization of the first participant to observe the required number of events for OS analyses in all randomized population. The number of events needed for the analyses will be monitored by the unblinded independent statistician supporting the IDMC.

Table 10.1-1: Sample Size Determination

Endpoint	rPFS
Hypothesized median survival time (month)	Arm A= 9: Arm B = 6

Table 10.1-1: Sample Size Determination

Endpoint	**rPFS**
Target Hazard Ratio	HR=1 for t < 2m; Hazard Ratio =0.58 for t ≥2 months Average Hazard Ratio =0.67
Critical Hazard Ratio	0.80
2-Sided Alpha	0.01
Sample Size	984
Accrual Duration	29 months
Power	90%
Expected Number of Events	530 events[a]
Expected Timing of rPFS Final Analysis (from randomization of first participant)	31 months
Endpoint	**OS**
Hypothesized median survival time (month)	Arm A= 19.7 : Arm B = 15
Target Hazard Ratio	HR=1 for t < 3m; HR=0.72 for t≥3 months Average Hazard Ratio =0.76
Critical Hazard Ratio	
The 1st IA	0.70
The 2nd IA[b]	0.82
Final Analysis	0.85
2-Sided Alpha	0.040 (full allocation)
The 1st IA	0.0014
The 2nd IA[b]	0.018
Final Analysis[b]	0.034 (nominal)
Sample Size	984
Accrual Duration	29 months
Power	92%
Expected Number of Events for	
The 1st IA	326 events
The 2nd IA[b]	552 events
Final Analysis[b]	690 events
Expected Timing of OS Analysis (from randomization of first participant)	
The 1st IA	31 months

Table 10.1-1: Sample Size Determination

Endpoint	rPFS
The 2nd IA[b]	42 months
Final Analysis[b]	51 months

Abbreviations: HR = hazard ratio; IA = Interim Analysis; OS = overall survival.

[a] rPFS analysis is performed after enrollment completes and observing 530 events in all randomized subjects.

[b] **Per Protocol Amendment 04, the second IA for OS and final analysis for OS will not be performed, and the first IA will be considered as the final analysis. At the time of study closeout, an updated descriptive OS analysis will be provided to report all death events.**

10.2 Populations for Analyses

Table 10.2-1: Populations for Analyses

Population	Description
Enrolled	All participants who signed an informed consent and were registered into the IRT.
Randomized	All participants who were randomized to either treatment arm in the study. Primary efficacy analysis, demography, protocol deviations, and baseline characteristics will be performed on this population.
All Treated	All treated participants who receive any dose of study drug. Participants are grouped within the all treated population according to the treatment they actually receive. This is the analysis set for all safety analyses and study drug administration.
All Response Evaluable Population	All randomized participants who have measurable disease at baseline as assessed by investigator per PCWG3.
PK	All treated participants with available serum concentration data for nivolumab.
Immunogenicity	All treated participants with baseline and at least 1 pre-infusion immunogenicity assessment.
[redacted]	

10.3 Statistical Analyses

Not applicable per Protocol Amendment 04.

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

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

10.3.1 Efficacy Analyses

Not applicable per Protocol Amendment 04.

Statistical analyses for efficacy are shown in Table 10.3.1-1.

Table 10.3.1-1: Efficacy Statistical Analyses

Endpoint	Statistical Analysis Methods
Primary	
rPFS is defined as the time from randomization initiation to the first date of documented radiographic progressions per PCWG3 or death due to any cause, whichever occurs first. The rPFS will be censored at the last tumor assessment up to the start of subsequent systemic cancer therapy. It will also be censored at the date of last tumor assessment prior to the missed tumor assessments for participants who had progressive disease (PD) or death immediately after more than one consecutive missed tumor assessments. The following radiographic progressive diseases will be collected and documented as assessed by BICR. • Soft tissue disease progression per PCWG3. Date of first unequivocal progression of soft tissue lesion will be recorded per BICR assessment. • Bone disease progression per PCWG3. Date of bone progression will be recorded per BICR assessments.	rPFS in all randomized participants will be compared using a stratified 2-sided log rank test with alpha=0.01. The log-rank test p-value will be reported. The hazard ratio and the corresponding 2-sided 99% CI will be estimated in a stratified Cox proportional hazard model using the randomized arm as a single covariate. The rPFS function for each treatment arm will be estimated using the KM product limit method and will be displayed graphically. A 2-sided 95% CI for median rPFS in each arm will be estimated via the log-log transformation method (primary comparison where 0.01 alpha will be spent). In addition, descriptive estimates for 6 months and 12-months rPFS rates will be presented along with their associated 95% CIs.
OS is the time from randomization initiation to the date of death from any cause.	The OS for all randomized participants will be compared using a stratified 2-sided log rank test with adjusted alpha at each interim analysis and final analysis (alpha will be recycled from rPFS to OS if rPFS test is significant). The log-rank test p-value will be reported. The hazard ratio and the corresponding 2-sided (1-adjusted alpha)*100% CI will be estimated in a stratified Cox proportional hazard model using the randomized arm as a single covariate. The OS function for each treatment arm will be estimated using the KM product limit method and will be displayed graphically. A 2-sided 95% CI for median OS in each arm will be estimated via the log-log transformation method (primary comparison where up to 0.04 alpha will be spent). In addition, descriptive estimates for 12-months and 24-months OS rate will be presented along with their associated 95% CIs.

Table 10.3.1-1: Efficacy Statistical Analyses

Endpoint	Statistical Analysis Methods
Secondary	
Objective response rate (ORR) per PCWG3 assessed by BICR	ORRs per PCWG3 and corresponding 2-sided exact 95% CIs will be calculated using the Clopper-Pearson method for all Response Evaluable participants by treatment arm.
PSA response rate (PSA-RR)	PSA-RRs per PCWG3 and corresponding 2-sided exact 95% CIs will be calculated using the Clopper-Pearson method for all randomized participants with PSA values at baseline and at least one post baseline assessment by treatment arm.
Time to response (TTR) and duration of response (DOR) per PCWG3 assessed by BICR	Summary statistics of time to objective response (TTR) will be provided for all randomized participants with a BOR of CR or PR by each treatment arm. Duration of response (DOR) will be summarized for participants with a BOR of PR or CR per BICR using the Kaplan-Meier methodology. Median values, along with 2-sided 95% CIs will also be calculated.
Time to PSA progression	Kaplan-Meier plots of time to PSA progression will be presented for all randomized participants by treatment arm. The estimates of the median and corresponding log-log transformed 2-sided 95% CIs will be calculated. The rates at months 6 and 12 and corresponding 95% CIs will be estimated via the Kaplan-Meier methodology.

10.3.2 Safety Analyses

Statistical analyses for efficacy are shown in Table 10.3.2-1

Table 10.3.2-1: Safety Statistical Analyses

Secondary	Statistical Analysis Methods
Incidence of AE, SAE, AE leading to discontinuation, immune-related AEs, deaths, and laboratory abnormalities	Descriptive statistics of safety will be presented using NCI CTCAE v5.0 by treatment arm. All on-study AEs, treatment-related AEs, SAEs, and treatment-related SAEs will be tabulated using worst grade per NCI CTCAE v5.0 criteria by system organ class and preferred term. On-study laboratory parameters including hematology, chemistry, liver function, and renal function will be summarized using worst grade NCI CTCAE v5.0 criteria.

10.3.3 Pharmacokinetic Analyses

Not applicable per Protocol Amendment 04.

The nivolumab concentration data obtained in this study may be combined with data from other studies in the clinical development program to develop population PK models.

These models may be used to evaluate the effects of intrinsic and extrinsic covariates on the PK of nivolumab and to determine measures of individual exposure (such as steady state peak, trough and time averaged concentration). Model determined exposures may be used for exposure-response analyses of selected efficacy and safety endpoints. If the analyses are conducted, the results of population PK and exposure response analyses will be reported separately.

10.3.4 Immunogenicity Analyses

Not applicable per Protocol Amendment 04.

Methodology for analysis of immunogenicity will be described in the statistical analysis plan.

10.3.5 Outcomes Research Analyses

Not applicable per Protocol Amendment 04.

Analyses of BPI-SF, FACT-P, and EQ-5D-5L data will be performed by treatment arm in all treated participants who have an assessment at baseline (Day 1, assessment prior to administration of drug on day of first dose) Change from baseline analyses also require at least 1 other assessment post-baseline. 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. Further details will be provided in the Statistical Analysis Plan.

Thresholds for change scores judged to be important to patients are summarized in Table 10.3.5-1

Table 10.3.5-1: Thresholds Values for Change Scores Judged to be Important to Patients

Instruments and Domains	Thresholds reported in the literature	Main analyses thresholds
BPI-SF[110]	2	2
FACT-P		
Total Score[111]	6-10	8
Total Outcome Index (TOI)[112]	5-9	7
Prostate Cancer Scale (PCS)[112]	2-3	3
Emotional Well Being Score[113]	2-3	3
Functional Well Being Score[114]	2-3	3
Physical Well Being Score[114]	2-3	3
Social Well Being Score[114]	2-3	3
EQ-5D-5L VAS[110]	7	7

10.3.5.1 BPI-SF

Time to Pain Progression

The participant's assessment of pain with BPI-SF Item #3 (pain symptoms at their worst over the last 24 hours) will form the basis for the analysis of median time to pain progression.[112] Pain progression will be considered to have occurred,[114] if an increase in the worst pain intensity of ≥ 2 points is observed from baseline and maintained over 2 consecutive time periods. Participants who die without a reported pain progression will be considered to have progressed on the date of their death. Those who neither progress nor die will be censored at the time of their last BPI-SF assessment prior to subsequent therapy, while those who neither die nor have any BPI-SF assessments after randomization will be censored on the date of randomization. Time to pain progression for all randomized participants will be summarized and plotted using the Kaplan-Meier methodology. Median values, along with two-sided 95% CIs will also be calculated. The rate of pain progression at select timepoints and corresponding 95% CIs will also be estimated.

Change in Pain Intensity

The mean value of least pain (Item #4), average pain (Item #5), and current pain (Item #6), along with Item #3, will also be analyzed as a composite assessment of change in pain intensity.[110] Summary statistics at each assessment point will be provided for each treatment group. The mean change from baseline will also be reported at each post-baseline assessment point.

10.3.5.2 FACT-P

Time to Deterioration in Cancer-Related Symptoms and Quality of Life

The analysis of FACT-P will be performed for the total score and all subscales. Participants who die without a reported deterioration will be considered to have deteriorated on the date of their death. Those who neither deteriorate nor die will be censored at the time of their last FACT-P assessment, while those who neither die nor have any FACT-P assessments after randomization will be censored on the date of randomization.

Change in Cancer-Related Symptoms and Quality of Life

For FACT-P total scores and all subscales, summary statistics at each assessment point will be provided for each treatment group. The mean change from baseline will also be reported at each post-baseline assessment point.

10.3.5.3 EQ-5D-5L

Summary statistics for health status and health utility using EQ-5D-5L data at each assessment point will be provided for each treatment group. The mean change from baseline will also be reported at each post-baseline assessment point.

10.3.6 Other Analyses

Methodology for analysis of other exploratory objectives [redacted] will be described in the statistical analysis plan.

10.3.7 Interim Analyses

The Statistical Analysis Plan will further describe the planned interim analyses.

10.3.7.1 Interim Analysis for OS

For the randomized population, two interim OS analyses and one final analysis is planned using an alpha of 0.04 if rPFS is not significant and 0.05 if rPFS is significant (0.01 alpha passed). The two interim OS analyses are planned at approximately 47% and 80% of the total events observed at final analysis, respectively. The stopping boundaries at the interim and final analyses will be based on the actual number of OS events at the time of the analysis using Lan-DeMets alpha-spending function with O'Brien-Fleming boundaries, taking into account any alpha that was passed from the rPFS analysis (if applicable). If the interim analyses are performed exactly at 326 and 552 events, respectively, and the rPFS was not significant, the study could be stopped for OS superiority if the p-values are ≤ 0.0014 and 0.018, respectively. The nominal significance level for the final look of OS in all randomized participants after 690 events would then be 0.034.

An independent statistician external to BMS will perform interim analysis.

Per Protocol Amendment 04 and the decision to terminate the study early, the second interim analysis for OS and final analysis for OS will no longer be performed, and the first interim analysis will be considered as final. At the time of study closeout, an updated descriptive OS analysis will be provided to report all death events.

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12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
ADA	anti-drug antibody
ADT	androgen deprivation therapy
AE	adverse event
[redacted]	
AJCC	American Joint Committee on Cancer
ALT	alanine aminotransferase
[redacted]	
AST	aspartate aminotransferase
AT	aminotransaminases
AUC	area under the concentration-time curve
[redacted]	
BID, bid	bis in die, twice daily
BICR	Blinded Independent Central Review
[redacted]	
BMS	Bristol-Myers Squibb
BP	blood pressure
BPI-SF	brief pain inventory short form
BUN	blood urea nitrogen
C	Celsius
[redacted]	
CBC	complete blood count
[redacted]	
CFR	Code of Federal Regulations

Term	Definition
CI	confidence interval
[redacted]	
CLcr	creatinine clearance
cm	centimeter
Cmax, CMAX	maximum observed concentration
[redacted]	
CMO	cystoid macular oedema
CNS	central nervous system
COVID-19	coronavirus disease 2019
CRC	Clinical Research Center
CRF	Case Report Form, paper or electronic
CTAg	Clinical Trial Agreement
CTC	circulating tumor cells
[redacted]	
CYP	cytochrome p-450
[redacted]	
dL	deciliter
DMC	Data monitoring committee
DRESS	drug reaction with eosinophilia and systemic symptoms
[redacted]	
ECG	electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
[redacted]	
eg	exempli gratia (for example)
EOC	Executive Oversight Committee
EOI-PK	end of infusion pharmacokinetic
[redacted]	

Term	Definition
FACT-P	Functional Assessment of Cancer Therapy-Prostate
FACT-P-PCS	Functional Assessment of Cancer Therapy-Prostate Prostate Cancer Subscale
[redacted]	
FDA	Food and Drug Administration
[redacted]	
FSH	follicle stimulating hormone
g	gram
GBS	Guillain-Barré syndrome
[redacted]	
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
[redacted]	
h	hour
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
[redacted]	
HIV	Human Immunodeficiency Virus
HR	heart rate
[redacted]	
IA	Interim Analysis
[redacted]	
ICH	International Conference on Harmonisation
ie	id est (that is)
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IHC	immunohistochemistry
[redacted]	

Term	Definition
IMP	investigational medicinal products
IND	Investigational New Drug Exemption
IO	immuno-oncology
IRB	Institutional Review Board
IRT	Interactive Response Technology
[redacted]	
IV	intravenous
[redacted]	
kg	kilogram
L	liter
[redacted]	
LDH	lactate dehydrogenase
[redacted]	
MDSC	myeloid-derived suppressor cell
mg	milligram
[redacted]	
MG	myasthenia gravis
min	minute
mCRPC	metastatic castration-resistant prostate cancer
mCSPC	metastatic castration-sensitive prostate cancer
mL	milliliter
[redacted]	
MR	medical research
[redacted]	
MTD	maximum tolerated dose
nmCRPC	non-metastatic castration-resistant prostate cancer
µg	microgram

Term	Definition
N	number of subjects or observations
NAT	Novel antiandrogen therapy
[redacted]	
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ng	nanogram
[redacted]	
NK	natural killer
[redacted]	
OS	overall survival
PCWG3	Prostate Cancer Working Group
PD	pharmacodynamics
PD-1	programmed death-1
PD-L1	programmed death ligand 1
PK	pharmacokinetics
PO	per os (by mouth route of administration)
PSA	Prostate-specific antigen
[redacted]	
rPFS	radiographic progressive free survival
[redacted]	
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation
SJS	Stevens-Johnson syndrome
[redacted]	

Term	Definition
t	temperature
T	time
[redacted]	
T.bili	total bilirubin
TEN	toxic epidermal necrolysis
[redacted]	
ULN	upper limit of normal
[redacted]	
WBC	white blood cell
[redacted]	
WOCBP	women of childbearing potential
WNOCBP	women **not** of childbearing potential
x g	times gravity

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

The term 'Participant' is used in the protocol to refer to a person who has consented to participate in the clinical research study. The term 'Subject' used in the CRF is intended to refer to a person (Participant) who has consented to participate in the clinical research study.

REGULATORY AND ETHICAL CONSIDERATIONS

GOOD CLINICAL PRACTICE

This study will be conducted in accordance with:

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

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

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

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

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

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

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

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

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

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

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

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

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

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

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

FINANCIAL DISCLOSURE

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

INFORMED CONSENT PROCESS

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

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

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

Investigators must:

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

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

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

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

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

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

SOURCE DOCUMENTS

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

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

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

STUDY TREATMENT RECORDS

Records for study treatments (whether supplied by BMS, its vendors, or the site) must substantiate study treatment integrity and traceability from receipt, preparation, administration, and through destruction or return. Records must be made available for review at the request of BMS/designee or a Health Authority.

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

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

CASE REPORT FORMS

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

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

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

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

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

MONITORING

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

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

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

In addition, the study may be evaluated by Sponsor or designee internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to Sponsor or designee.

RECORDS RETENTION

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

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

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

RETURN OF STUDY TREATMENT

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

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

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

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

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

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

CLINICAL STUDY REPORT

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

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

- External Principal Investigator designated at protocol development
- Study Steering Committee chair or their designee
- Participant recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design
- Regional representation (eg, among top quartile of enrollers from a specified region or country)

SCIENTIFIC PUBLICATIONS

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

Sponsor or designee at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTAg.

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

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

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

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

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

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

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

ADVERSE EVENTS

Adverse Event Definition:

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

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

Events Meeting the AE Definition

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

Events NOT Meeting the AE Definition

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

DEFINITION OF SAE

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

SERIOUS ADVERSE EVENTS

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
Requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below) NOTE: The following hospitalizations are not considered SAEs in BMS clinical studies: • a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event) • elective surgery, planned prior to signing consent • admissions as per protocol for a planned medical/surgical procedure • routine health assessment requiring admission for baseline/trending of health status (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 (applies to oncology protocols)
Results in persistent or significant disability/incapacity
Is a congenital anomaly/birth defect
Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the participant or may require intervention [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 9.3.7 for the definition of potential DILI.)

Pregnancy and potential drug induced liver injury (DILI) must follow the same transmission timing and processes to BMS as used for SAEs (see Section 9.3.5 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).

EVALUATING AES AND SAES

Assessment of Causality

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

Follow-up of AEs and SAEs

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

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

All SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

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

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

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

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

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

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

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

CONTRACEPTION GUIDANCE FOR MALE PARTICIPANTS WITH PARTNER(S) OF CHILDBEARING POTENTIAL DURING TREATMENT WITH DOCETAXEL

Male participants with female partners of childbearing potential are eligible to participate if they agree to the following during treatment with docetaxel 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 6 months after the end of study treatment with docetaxel.
- 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 6 months after the end of treatment with docetaxel 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 6 months after the end of study treatment with docetaxel.

- Refrain from donating sperm for the duration of the study treatment and until 6 months after the end of study treatment with docetaxel.

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 9.3.5 and the Appendix for Adverse Events and Serious Adverse Events Definitions and procedures for Evaluating, Follow-up and Reporting.

APPENDIX 5 PROSTATE CANCER WORKING GROUP 3 (PCWG3) GUIDELINES (WITH MODIFIED RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) CRITERIA FOR SOFT TISSUE LESION ASSESSMENT)

Not applicable per Protocol Amendment 04.

1 EVALUATION OF LESIONS

Bone lesions should be evaluated with Technecium-99m based radionuclide bone scan as per PCWG3[1].

At baseline, soft tissue lesions/lymph nodes will be categorized as measurable or non-measurable as follows.

1.1 Measurable

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

10 mm by CT/MRI scan (scan slice thickness no greater than 5 mm), or ≥ 2x slice thickness if greater than 5 mm.

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

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

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

1.2 Non-Measurable

All other soft tissue lesions are considered non-measurable, including small lesions (longest diameter < 10mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal

disease, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

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

1.3 Special considerations regarding bone lesions

Bone lesions will be assessed (as non-target lesions) with Technecium-99m based radionuclide bone scans as per PCWG3.

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

When more than one measurable lesion is present at baseline all lesions up to a maximum of 20 lesions total (and a maximum of 5 lesions per organ system) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.

Note: A maximum of 5 lesions can be selected per organ system. For example, a maximum of 5 lung lesions can be selected. A maximum of 5 lymph nodes can be selected at baseline, as the lymphatic system is considered one organ.

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

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

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Pelvic lymph nodes and extrapelvic lymph nodes (retroperitoneal, mediastinal, thoracic and other) may be reported separately, per PCWG3. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

2 RESPONSE CRITERIA

2.1 Evaluation of Target Lesions

- **Complete Response (CR):** Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- **Partial Response (PR):** At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

- **Progressive Disease (PD):** At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
- **Not Evaluable (NE):** If one or more target lesions cannot be measured or adequately assessed as either fully resolved or too small to measure (due to missing or poor quality images), and the sum of diameters of the remaining measured target lesions (if any) has not increased sufficiently to meet Progressive Disease as defined above.

2.1.1 Special Notes on the Assessment of Target Lesions

2.1.1.1 Lymph nodes

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

2.1.1.2 Target lesions that become 'too small to measure'

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

2.1.1.3 Lesions that split or coalesce on treatment

When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

2.2 Evaluation of Non-Target Lesions

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

- **Complete Response (CR):** Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (< 10mm short axis).
- **Non-CR/Non-PD:** Persistence of one or more non-target lesion(s)
- **Progressive Disease (PD):** Unequivocal progression (see below) of existing non-target lesions.

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

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

2.2.1.1 When the patient also has measurable disease

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

2.2.1.2 When the patient has only non-measurable disease

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

increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include, an increase in lymphangitic disease from localized to widespread, or may be described as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore the increase must be substantial.

2.2.2 New Lesions

New bone lesions

New bone lesions should be evaluated as per PCWG3 criteria. Bone lesions will be assessed by radionuclide bone scan only. Radiographic progression on bone scan is defined by the following criteria:

- At least 2 new lesions on the first post-treatment bone scan, with at least two additional lesions on the next scan (performed at least 6 weeks later)as compared to the first post-treatment bone scan. Date of progression is then the date of first post-treatment scan.
- For scans after the first post-treatment scan, at least 2 new lesions relative to the first post-treatment scan AND confirmed on a subsequent scan (performed at least 6 weeks later). Date of progression is the date of the scan that first documents at least 2 new lesions relative to the first post-treatment scan.

New soft tissue lesions

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

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

If a new lesion is equivocal, for example because of its small size, continued follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

2.3 Response Assessment

2.3.1 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until disease progression per PCWG3 criteria, or the last response recorded, taking into account any requirement for confirmation and censoring rules regarding subsequent therapy. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement.

2.3.2 Time Point Response

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

Table 2.3.2-1: Time Point Response

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

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

Table 2.3.2-2: Time Point Response

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

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

2.3.3 Best Overall Response

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

For example, if the first scheduled follow-up imaging visit is Week 6 (± 7 days) for a particular protocol, a Best Response of SD can only be made after the subject is on-study for a minimum of 6 weeks (42 days) minus 7 days, for an absolute minimum time on-study of 35 days from the reference start date (reference date is considered Day 1 on study). If the subject is not on-study for at least this amount of time, any tumor assessment indicating stable disease before this time period will have a Best Response of NE unless PD is identified.

Special note on response assessment: When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (CRF).

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

Overall Response First Time Point	Overall Response Subsequent Time Point	BEST Overall Response
CR	CR	CR
CR	PR	SD, PD OR PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

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

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

2.3.4 Confirmation Scans

Verification of Response: To be assigned a status of CR or PR, changes in tumor measurements must be confirmed by consecutive or subsequent repeat assessments that should be performed no less than 28 days after the criteria for response are first met. Subsequent documentation of a CR may provide confirmation of a previously identified CR even with an intervening NE or PR (eg, CR NE CR or CR PR CR). Subsequent documentation of a PR may provide confirmation of a previously identified PR even with an intervening NE or SD (eg, PR NE PR or PR SD PR). However, only one (1) intervening time point will be allowed between PR/CRs for confirmation.

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

REFERENCES

[1] Scher HI, Morris MJ, Stadler WM et al. Trial design and objectives for castration-resistant prostate cancer: Updated recommendations from the Prostate Cancer Clinical Trials Working Group 3. J Clin Oncol 2016, 34(12):1402-18.

APPENDIX 6 MANAGEMENT ALGORITHMS FOR STUDIES UNDER NCI CTCAE VERSION 5

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.

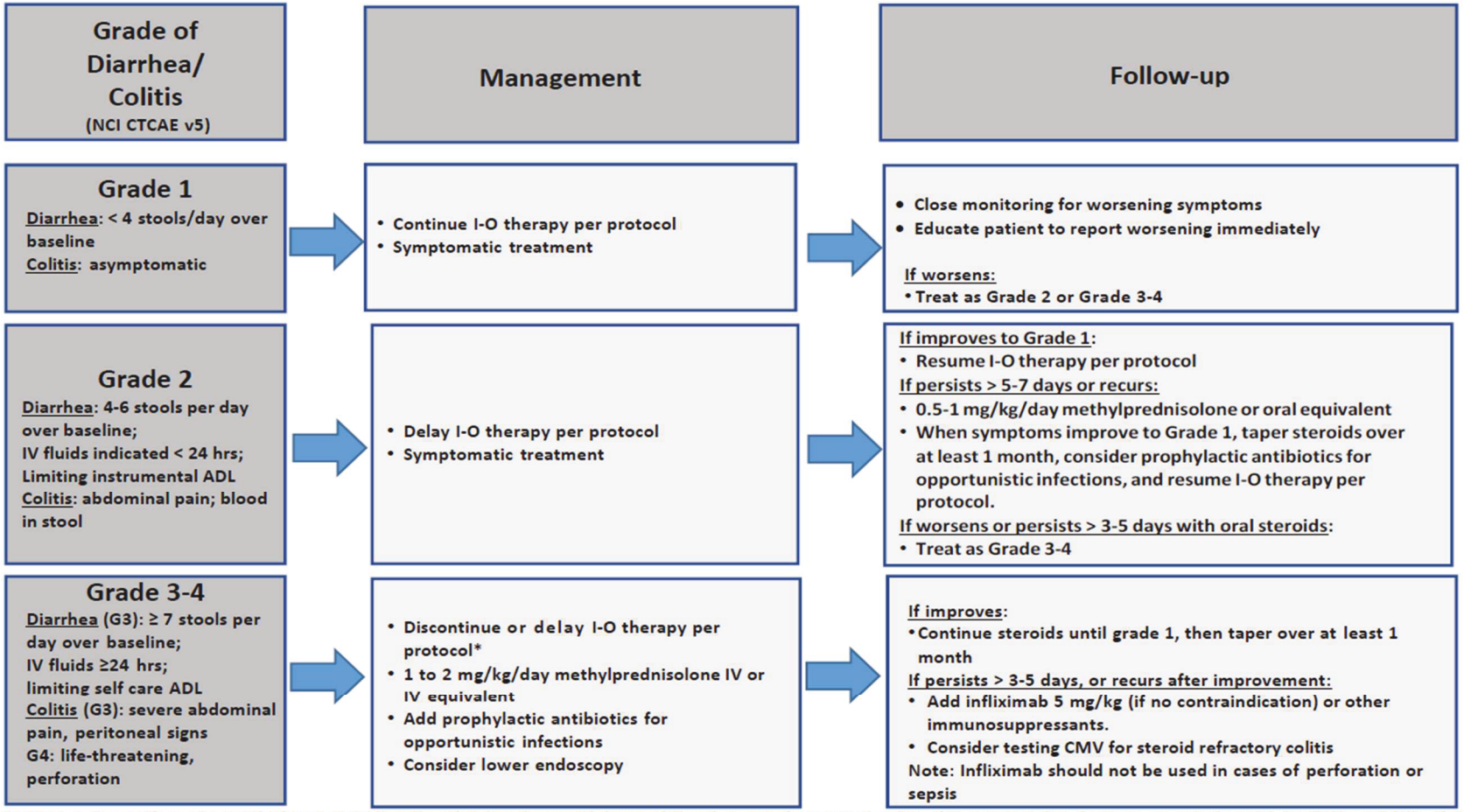
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the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

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

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

GI Adverse Event Management Algorithm

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



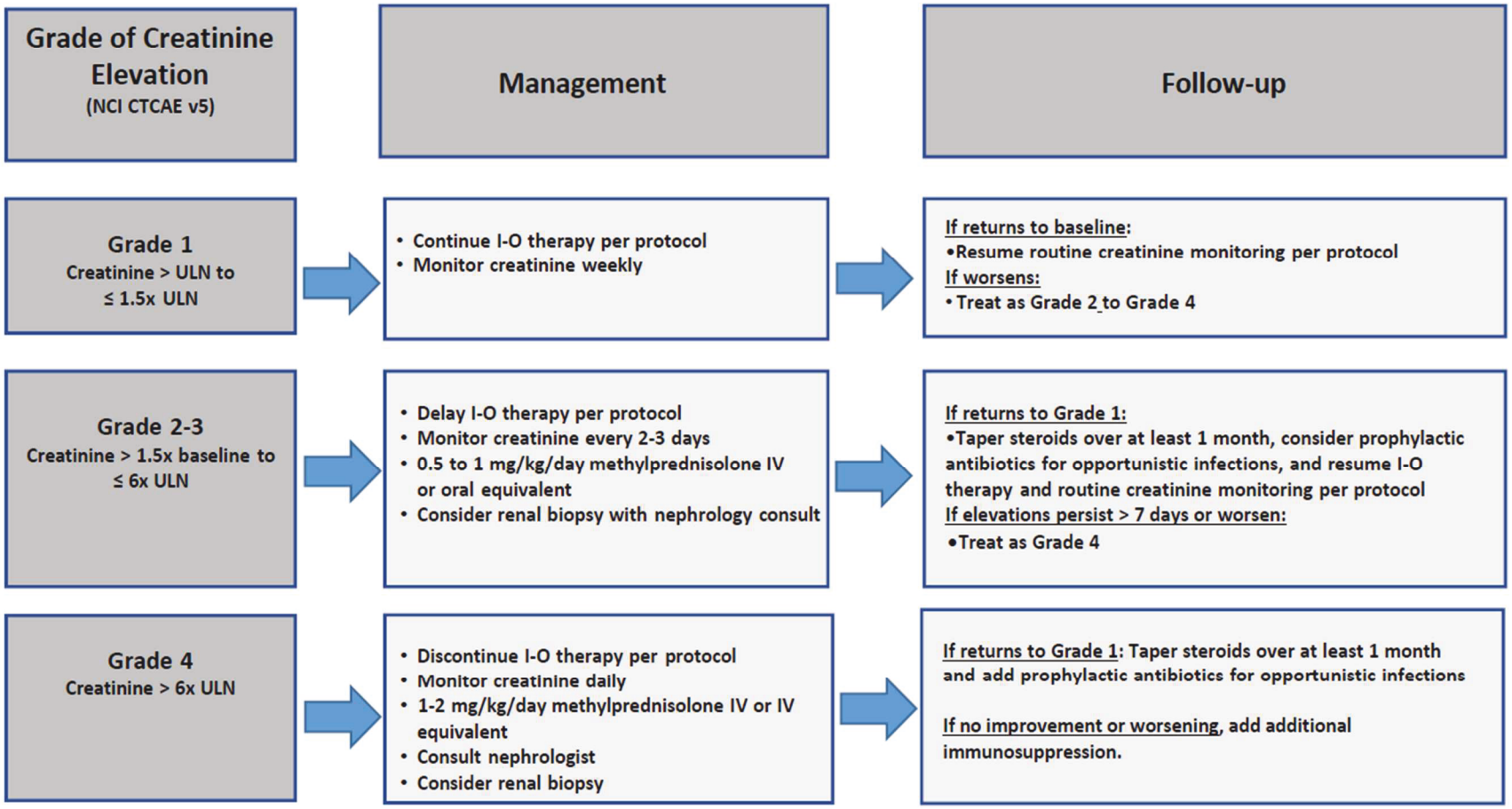
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

28-Sep-2020

Renal Adverse Event Management Algorithm

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

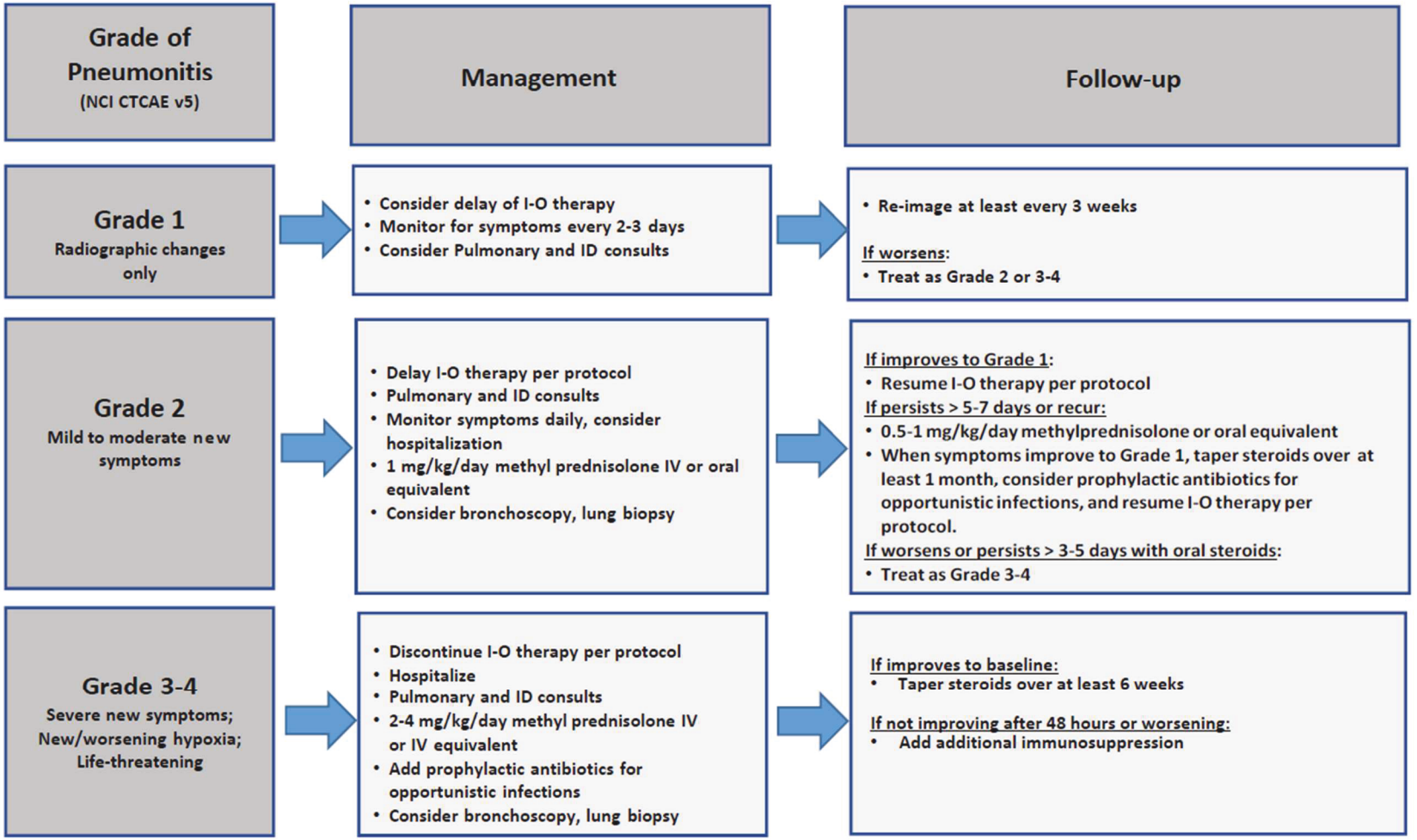


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

28-Sep-2020

Pulmonary Adverse Event Management Algorithm

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

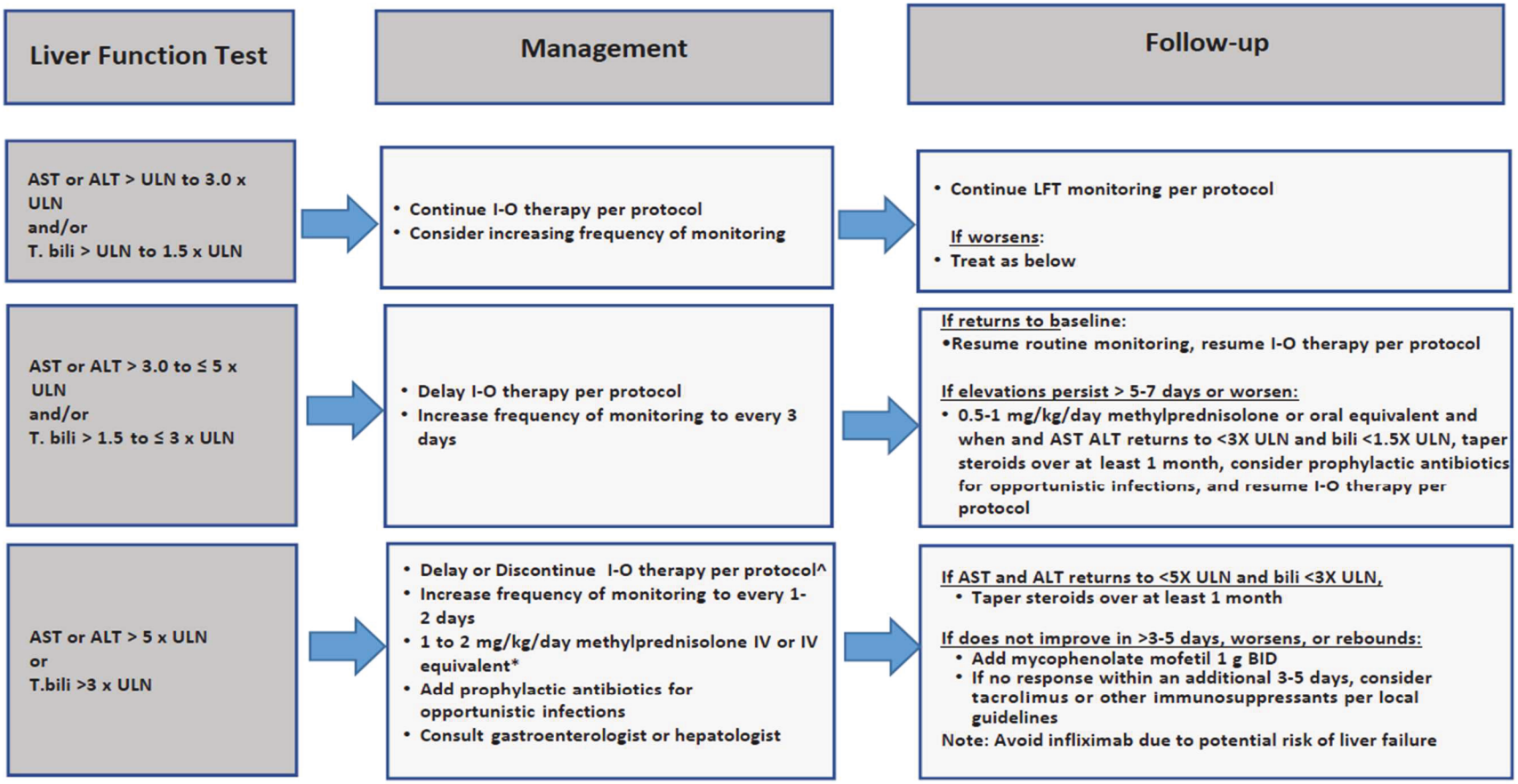


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

28-Sep-2020

Hepatic Adverse Event Management Algorithm

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

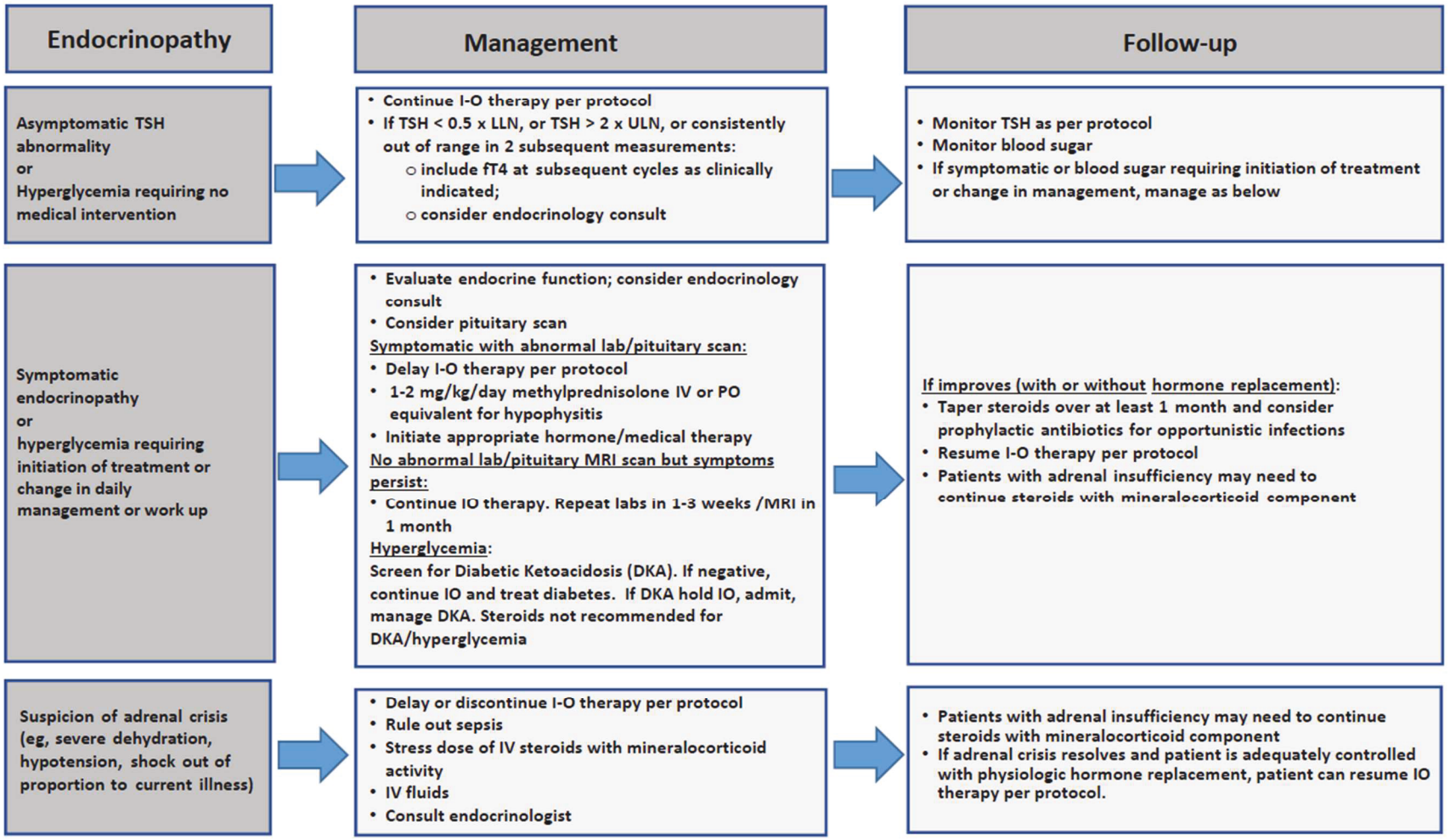


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

28-Sep-2020

Endocrinopathy Adverse Event Management Algorithm

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

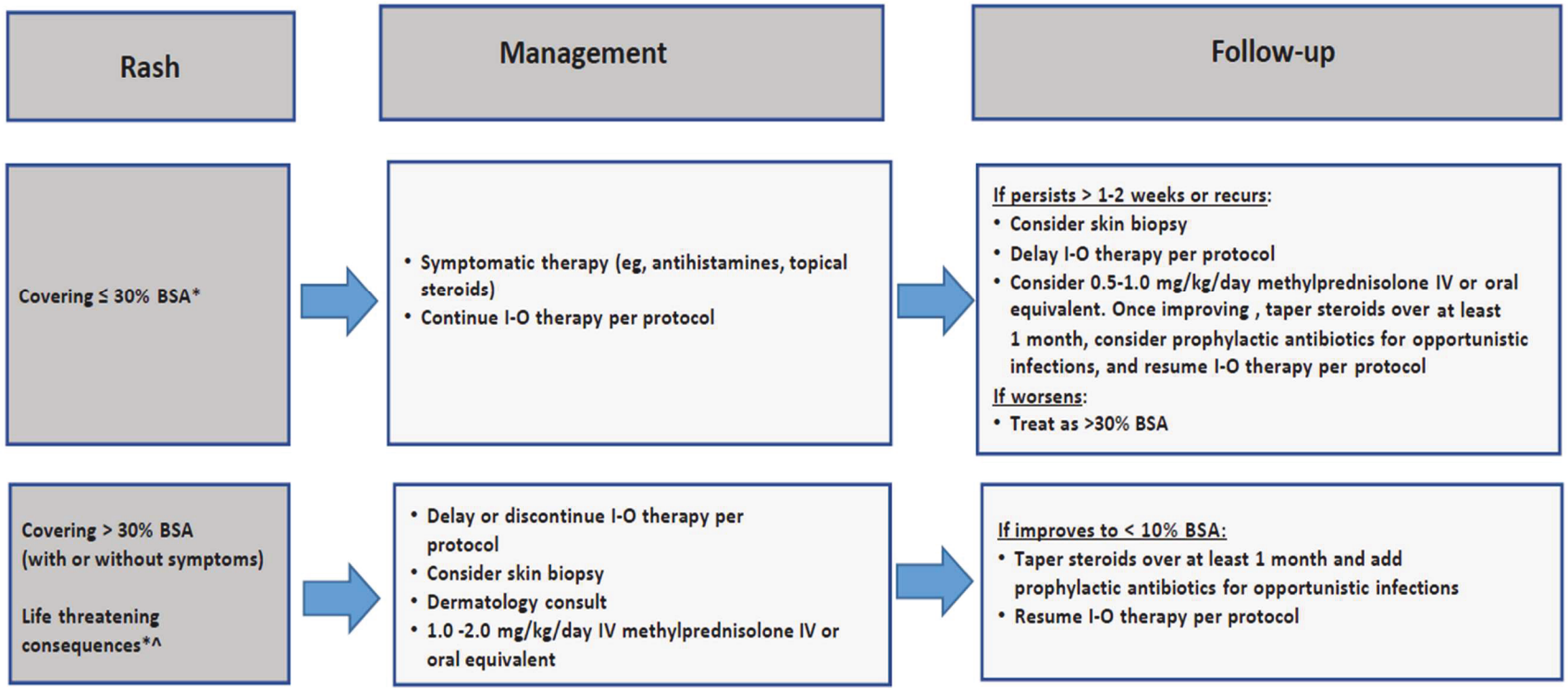


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

28-Sep-2020

Skin Adverse Event Management Algorithm

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



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

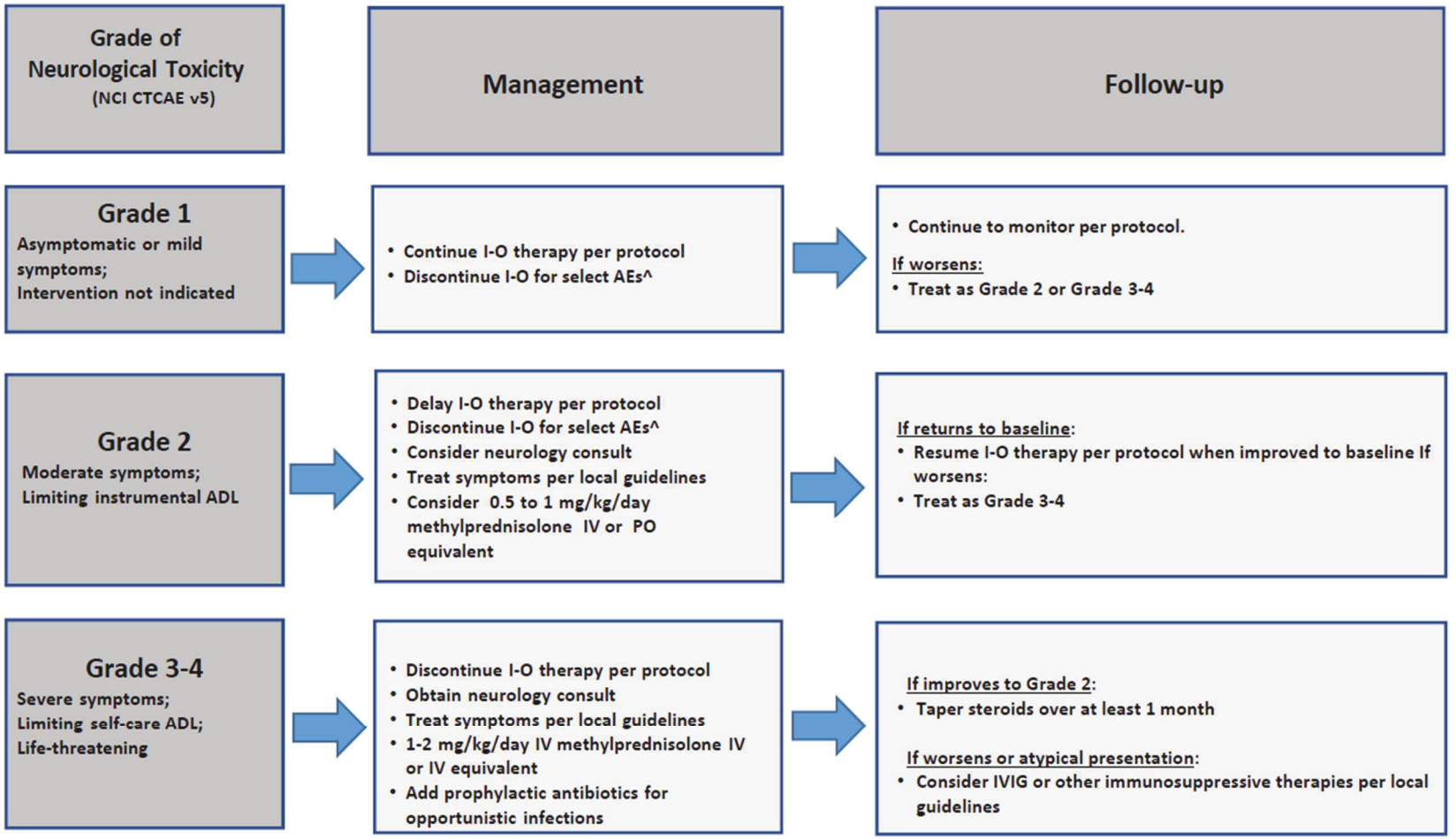
*Refer to NCI CTCAE v5 for term-specific grading criteria.

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

28-Sep-2020

Neurological Adverse Event Management Algorithm

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



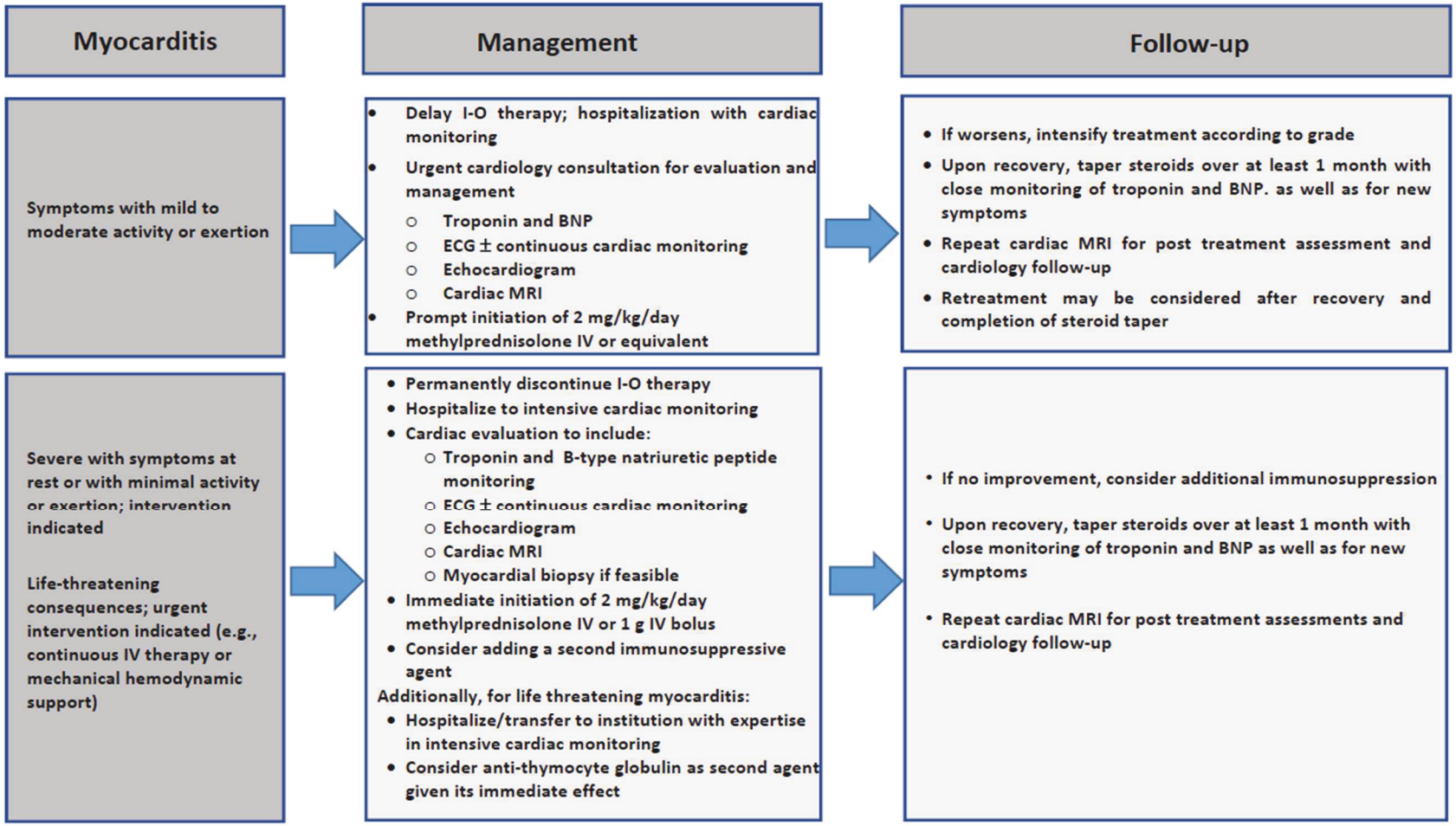
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

28-Sep-2020

Myocarditis Adverse Event Management Algorithm

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



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

28-Sep-2020

APPENDIX 7 CYP3A4 STRONG INHIBITOR AND INDUCER GUIDANCE

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

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

Table 7-1: Representative examples of Drugs that are strong CYP3A4 Inhibitors or Inducers

CYP Enzyme	Strong Inhibitors[a] ≥ 5 fold Increase in AUC Or > 80% Decrease in CL	Strong Inducers ≥ 80% Decrease in AUC
CYP3A	Boceprevir, clarithromycin, conivaptan, grapefruit juice[b], indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil[c], nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole	Avasimibe[d], carbamazepine, phenytoin, rifampin, St. Johns Wort[e]

Abbreviations: AUC = area under the concentration time curve; ; CL = clearance; CYP = cytochrome P450

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

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

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

[d] Not a marketed Drug.

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

APPENDIX 8 ECOG PERFORMANCE STATUS

ECOG PERFORMANCE STATUS[a]	
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all 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

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

APPENDIX 9 COUNTRY SPECIFIC AMENDMENTS: HIV TESTING

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

Table 2-1 Screening Procedural Outline (CA2097DX)	Add "HIV testing" to list of laboratory tests.
Section 6.2 Exclusion Criteria, 1) Medical Conditions i)	Replace "Known history of a positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). Note: Testing for HIV must be performed at all sites in Germany and where mandated by locally" with "Positive test for HIV"
Section 9.6.1 Clinical Safety Laboratory Assessments	Replace "Testing for HIV must be performed at sites where mandated locally" with "Testing for HIV must be performed."

APPENDIX 10 PROTOCOL AMENDMENT SUMMARY OF CHANGE HISTORY

Overall Rationale for the Protocol Amendment 03, 13-Sep-2022

Protocol Amendment 03 includes changes to expand the radiographic progression-free survival (rPFS) analysis population and clarify censoring rules for rPFS [redacted], and clarification of pharmacokinetic (PK) sampling at follow-up visits, and clarification of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) serology at follow-up as optional.

Main changes have been included in the statistical analysis section, in which the population for the number of rPFS analysis has been changed from the first 544 randomized participants to all randomized [redacted] for expansion to Intention-to-treat (ITT). By incorporating the delayed treatment effect, the number of rPFS events has been increased from 433 to 530, the number of and the number of overall survival (OS) events has been increased from 615 to 690 for final analysis. Additional revisions in the statistical analysis section have been added to align and clarify the populations for analysis.

Additional revisions, including to sections of the Synopsis, have been made to align the protocol with respect to these changes. This protocol amendment applies to all participants.

Summary of key changes for Protocol Amendment 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	Changed one of the [redacted] Medical Monitor from [redacted] to [redacted]. Changed [redacted] from [redacted] to [redacted].	To reflect updated personnel
Section 4 Objectives and Endpoints. Table 4-1	Added clarification of the censoring rules for rPFS	[redacted]
Section 5.3 Number of Participants	Added wording regarding global recruitment completion and China continuation of enrollment	To clarify recruitment status at the moment of the global amendment
Section 9.6 Pharmacokinetics. Table 9.6-1: Pharmacokinetic Sampling Schedule for All Arms	Notes added to collection follow-up to clarify this is 30 or 100 days from the discontinuation of nivolumab	To clarify PK collection when nivolumab is discontinued during the treatment period but not docetaxel, making clear that PK collection is always related to nivolumab infusion
[redacted]		
Section 10.1 Sample Size Determination, and Table 10.1-1	Expanded rPFS analysis population from first 544 to all global randomized, and changed the number of target rPFS events from 433 to 530. OS events increased from 615 to 690. Updated enrollment rate.	[redacted] rPFS analysis was expanded to the entire Intention-to-treat (ITT) population. Another rationale for this change that is based on the curent observed event rate, it is not feasible to observe 433 events in the first 544 randomized participants. Based on previous observed delayed effect of nivolumab

Summary of key changes for Protocol Amendment 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
		and ipilimumab across tumors, implementation of delayed treatment effect was applied for both rPFS and OS resulting in modification to the number of target events. Enrollment rate was updated because current enrollment rate significantly deviates from that of the previous protocol.
Table 10.3.1-1 Efficacy Statistical Analyses	Updated statistical analysis method to increase population for rPFS analysis from first 544 to all randomized Updated rPFS censoring rule to include censoring at the date of last tumor assessment prior to the missed tumor assessments for participants who had progressive disease (PD) or death immediately after more than one consecutive missed tumor assessments.	Updated to stay consistent with changes made in Table 10.1-1
Section 10.3.7.1 Interim Analysis for OS	Reduced % OS events estimated for the first interim analysis from 59% to 47%	Updated to stay consistent with changes made in Table 10.1-1
All	Minor formatting and typographical corrections	To correct minor errors

Overall Rationale for the Protocol Amendment 02, 17-Mar-2021

Protocol Amendment 02 includes changes [redacted] to allow inclusion of patients who have received prior radium-223.

Dose modification criteria and immuno-oncology (IO) agent management algorithms have been aligned with National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5. Serologic testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) status has been added. Additional updates have been incorporated in order to improve alignment between protocol sections and clarify remote monitoring, prior malignancy window, thyroid testing, and male contraception requirements.

Additional revisions, including to sections of the Synopsis, have been made to align the protocol with respect to these changes. This protocol amendment applies to all participants.

Summary of key changes for Protocol Amendment 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	Updated contact information.	To reflect changes in study personnel and align with changes in the BMS protocol model document.
Synopsis	Updated synopsis to align with changes to protocol.	To align with changes to protocol.

Summary of key changes for Protocol Amendment 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 2: Schedule of Activities	Table 2-1 and Table 2-2: Updated notes for AE/SAE assessment to include SARS-CoV-2. Tables 2-1 and Table 2-2: Added SARS CoV-2 serology procedure.	Serum and AE/SAE collection in the context of SARS-CoV-2 was added in the event that coronavirus disease 2019 (COVID-19) sequelae may increase toxicity or impact interpretation of study events/results.
	[redacted]	
	Table 2-2: Included Subsequent Cancer Therapy row.	To clarify requirements for reporting subsequent systemic therapies.
	Table 2-2: Updated notes for Brain Imaging.	To clarify timing of brain MRI.
	Table 2-2: Updated health outcome questionnaire requirements.	To clarify timing of questionnaire completion.
Section 2: Schedule of Activities	Added minor clarifications and references to the notes across Tables 2-1 and Table 2-2.	To improve understanding of the procedures.
Section 3.3: Benefit/Risk Assessment	Updated source information for nivolumab clinical activity in various malignancies.	To clarify source information of clinical activity for nivolumab.
Section 4: Objectives and Endpoints Table 4-1: Objectives and Endpoints	Table 4-1: Added SARS-CoV-2 exploratory objective and endpoint.	[redacted] related to SARS-CoV-2.
Section 5.1.1: Screening Phase	[redacted]	[redacted]
Section 6.1: Inclusion Criteria	Updated criterion 2i to specify allowed prior cancer vaccine therapy (eg, sipuleucel-T), and radium-223 therapy, and clarify the time required between the	To provide examples of prior prostate cancer vaccine therapy allowed in the study.

Summary of key changes for Protocol Amendment 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
2) Type of Participant and Target Disease Characteristics	prior therapy and the beginning of the study treatment.	
	[redacted]	[redacted]
Section 6.1: Inclusion Criteria 3) Age and Reproductive Status	Updated criterion 3b to reflect contraception requirements for males treated with docetaxel (ie, 6 months after the last dose of docetaxel).	To update contraceptive requirements based on current safety information.
Section 6.2: Exclusion Criteria 1) Medical Conditions	Removed criterion 1a, as not applicable per Protocol Amendment 02, and replaced with criterion 1m, which clarifies study eligibility based on prior and/or concurrent malignancies.	To update requirements for inclusion of patients with concurrent or prior malignancies and prior SARS-CoV-2 infection.
	Updated criterion 1k to include eligibility condition for participants with prior SARS-CoV-2 infection.	To clarify of eligibility condition for participants with prior SARS-CoV-2 infection.
Section 6.2: Exclusion Criteria 2) Prior/Concomitant Therapy	Removed criterion 2d, as not applicable per Protocol Amendment 02.	To allow inclusion of patients who have received prior radium-223 or other radiopharmaceuticals, as data suggest that prior treatment with these agents does not affect safety of subsequent docetaxel treatment.
	Updated criterion 2e to clarify use of complementary medications.	To clarify use of complementary medications.
	Added criterion 2f, which clarifies eligibility of participants who received products designed to treat or prevent COVID-19.	To clarify eligibility of participants currently in other interventional trials, including those for COVID-19.
Section 6.2: Exclusion Criteria 3) Physical and Laboratory Test Findings	Added clarification for eligibility of participants with symptomatic or asymptomatic SARS-CoV-2 infection.	Included language to clarify expectations for eligibility and retesting for participants with suspected or confirmed symptomatic COVID-19.
Section 7.4: Dosage Modification Tables 7.4-1 and Table 7.4-2	Added Table 7.4-1: Adverse Event Criteria to Delay, Resume, or Discontinue Nivolumab/Placebo and Table 7.4-2: Adverse Event Criteria to Delay, Reduce, Resume, or Discontinue Docetaxel.	To align with NCI CTCAE version 5.

Summary of key changes for Protocol Amendment 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
	Updated entire section to align with new tables and remove redundant content.	
Section 7.4.2: Docetaxel Dose Reduction Section 7.4.3: Dose Delay Criteria Section 7.4.4: Criteria to Resume Study Treatment Section 7.4.5: Management Algorithms for Nivolumab Section 7.4.6: Treatment of Related Infusion Reactions	Removed redundant content, updated section title, aligned content with CTCAE version 5, added SARS-CoV-2 language, and renumbered sections as needed. Updated Section 7.4.2 to include one allowed dose reduction. Updated Section 7.4.3 to align with Table 7.4-1 and Table 7.4-2. Updated Section 7.4.4 to align with Table 7.4-1 and to provide criteria for resuming treatment after SARS-CoV-2 infection. Updated Section 7.4.6 title to align with Table 7.4-1	To align with NCI CTCAE version 5 and include SARS-CoV-2 language.
Section 7.6.2: Other Restrictions and Precautions Section 7.7: Concomitant Therapy	Removed redundant content.	Revised to align with NCI CTCAE version 5.
Section 7.7.1: Prohibited and/or Restricted Treatments	Updated to clarify use of complementary medications.	To clarify use of complementary medications.
Section 7.7.4: Treatment Beyond Progression	Updated to specify permitted treatment up to a maximum of 24 months from date of first dose.	To clarify treatment beyond progression.
Section 8.1.1: Discontinuation of Specific Study Treatments	Updated to align with Table 7.4-1 and Table 7.4-2.	To align with Table 7.4-1 and Table 7.4-2.
Section 8.1.2: Post Study Treatment - Study Follow-up	Updated to clarify collection of survival data.	To align with Section 5.1.3.
Section 9: Study Assessments and Procedures	Added clarification for additional measures and procedures.	Included language for AE/SAE follow-up in the context of SARS-CoV-2 in the event that COVID-19 sequelae may increase toxicity or impact interpretation of study events/results.
Section 9.1.3: Patient-Reported Outcomes	Added clarification for alternative administration methods.	To clarify alternative administration methods.
Section 9.2.1: The 5-Level EQ-5D	Made necessary clarifications and corrections.	To clarify content.
Section 9.3: Adverse Events	Made necessary clarifications and corrections.	To clarify content.

Summary of key changes for Protocol Amendment 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 9.3.1: Time Period and Frequency for Collecting AE and SAE Information Section 9.3.3: Follow-up of AEs and SAEs	Updated to include details related to follow-up of SAEs and nonserious AEs associated with confirmed or suspected SARS-CoV-2 infection.	Included language for AE/SAE follow-up in the context of SARS-CoV-2 in the event that COVID-19 sequelae may increase toxicity or impact interpretation of study events/results.
Table 9.6-1 Pharmacokinetic Sampling Schedule for all Arms	Updated footnote c to provide detailed instructions for PK blood sampling at the end of nivolumab infusion.	To align with EPE version 6.
Section 9.6.1: Clinical Safety Laboratory Assessments	Updated table and footnotes to clarify T3 sampling requirements.	To allow total T3 when free T3 is not available.
[redacted]		
Section 11: References	Updated references to reflect changes in the content.	To align with updated protocol content.
Appendix 1: Abbreviations and Trademarks	Updated abbreviations to reflect changes in the content.	To align with updated protocol content.
Appendix 2: Study Governance Considerations	Made necessary clarifications and corrections.	To clarify content.
Appendix 4: Childbearing Potential Definitions and Methods of Contraception	Updated contraception guidance for male participants with partners of childbearing potential to reflect requirements for participants treated with docetaxel. Changed definition of relevant systemic	To align methods of contraception with updates made to male contraceptive requirements in Section 6.1.

Summary of key changes for Protocol Amendment 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
	exposure to 6 months after end of docetaxel treatment.	
Appendix 6: Management Algorithms for Studies Under NCI CTCAE version 5	Updated title to include NCI. Replaced IO agent management algorithms with those aligned with NCI CTCAE version 5.	Updated management algorithms for immune-mediated AEs to align with NCI CTCAE version 5 and nivolumab Investigator Brochure.
All	Minor formatting, typographical and style corrections.	These changes are minor and therefore have not been summarized.

Overall Rationale for the Revised Protocol 01, 06-May-2020

Revised Protocol 01 includes changes [redacted] to clarify the inclusion criteria for current evidence of metastatic disease and prior treatment with NAT, and to clarify lesions that do not qualify as visceral disease. Frequency of tumor assessment was revised to enhance precision of the radiographic progression-free survival (rPFS) endpoint and the criteria for stable disease (SD) was revised based on frequency of tumor assessments. The statistical section now specifies sample size for rPFS.

In addition Revised Protocol 01 includes revisions made [redacted]. These include providing guidance on treatment of infusion reactions for nivolumab and docetaxel, clarifying the purpose of 30-minute observation period between nivolumab and docetaxel, mandating discontinuation of docetaxel for cystoid macular oedema (CMO) and for Grade ≥ 3 hypersensitivity reaction, and modifying the rules for dose reduction of docetaxel to align with docetaxel labeling. In addition to changes made for clarity and alignment with nivolumab program-wide standards, changes were also made to explicitly state the time period for collection for all non-serious adverse events and to exclude participants with HIV, as described below.

Summary of Key Changes for Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title page	BMS Research and Development address changed.	Administrative correction.
• Synopsis Key Inclusion Criteria • Section 2: Schedule of Activities: Table 2-1, Screening Procedural Outline (CA2097DX); Eligibility Assessments: [redacted]	Update of text that specifies required evidence of metastatic disease Added specification that if the same NAT is given more than once in the context of a different disease setting, these NAT will	Clarified patient eligibility [redacted]

Summary of Key Changes for Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted] • Section 6.1 Inclusion Criteria 2) Type of Participant and Target Disease Characteristics b), f), h) and j).	be considered as separate NAT regimens [redacted]	[redacted]
• Synopsis Key Inclusion Criteria • Section 6.1 Inclusion Criteria 2) Type of Participant and Target Disease Characteristics b) and e)	The criterion presented below is now moved (synopsis) and numbered separately (Section 6.1) as 2) b i and deleted from criterion 2 e) ii Participants whose disease spread is limited to regional pelvic lymph nodes (N1) measuring at least 2 cm in short axis will be considered eligible	Revised for clarity.
• Synopsis Key Inclusion Criteria • Section 6.1 Inclusion Criteria 2) Type of Participant and Target Disease Characteristics i)	Added to criterion: second-generation hormonal manipulations (eg, abiraterone acetate, enzalutamide, apalutamide, and darolutamide). Radiation therapy, previously included in this criterion is moved to and clarified in Section 6.2: Exclusion Criteria Medical Conditions 1) d)	Clarification.
• Synopsis Key Exclusion Criteria • Section 6.2: Exclusion Criteria Medical Conditions 1) a)	Added the following clarification to prior malignancy active within the previous 3 years: (i.e. participants with a history of prior malignancy are eligible if treatment was	Clarification

Summary of Key Changes for Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
	completed at least 3 years before enrollment)	
• Synopsis Key Exclusion Criteria • Section 6.2: Exclusion Criteria Medical Conditions 1) d)	Revised to: Prior radiation therapy must be completed prior to 2 weeks before start of study treatment and patients should have recovered (Grade ≤ 1) from radiation-related toxicities	Clarification of exclusion for prior radiation therapy and recovery from radiation-related toxicities.
• Synopsis Key Exclusion Criteria • Section 6.2: Exclusion Criteria, 1) Medical Conditions i) • Section 9.4.4 Clinical Safety Laboratory Assessments	Reference to Appendix 9 added	Appendix 9 specifies modifications in specific protocol sections regarding exclusion of HIV-positive subjects in countries where exclusion of HIV-positive participants is locally mandated.
• Synopsis: Prior/Concomitant Therapy • Section 6.2: Exclusion Criteria, 2) Prior/Concomitant Therapy	Botanical preparations intended for general health have been removed from exclusion criterion.	Adjustment in program standard.
• Synopsis: Overall Design • Section 5.1 Overall Design • Section 7.3 Method of Treatment Assignment	In addition to bone and lymph node metastases, prostate lesion (or bladder/rectum if from direct invasion from prostate) are specified as not to be considered as visceral disease.	To clarify lesions that do not qualify as visceral disease.
• Synopsis: Number of Participants • Section 10.1 Sample Size Determination • Table 10.1-1: Sample Size Determination	Text/table data added to state that rPFS analysis will be based on the first 544 randomized participants only. In addition, the number of rPFS events for the rPFS analysis was changed from 372 to 433.	To clarify the number of subjects for the rPFS analysis and correct the number of events needed for rPFS analysis.
• Synopsis: Objectives and Endpoints	Minor changes in endpoint text for rPFS.	Aligned with specification that rPFS analysis will be

Summary of Key Changes for Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
• Section 4. Objectives and Endpoints Table 4-1 Objectives and Endpoints		based on the first 544 randomized participants.
Section 2: Schedule of Activities Table 2-1, Screening Procedural Outline (CA2097DX): Eligibility Assessments: Brain Imaging and Body Imaging	MRI brain imaging for eligibility is required as part of screening, unless the participant has completed an imaging study of the brain now within 28 days of randomization, rather than from the beginning of study drug administration	To clarify timing of screening MRI brain.
[redacted]		
• IRT	Note specifies that once a participant is eligible for the study, IRT must be contacted to randomize the participant.	Clarification.
• Section 2: Schedule of Activities Table 2-1, Screening Procedural Outline (CA2097DX): Laboratory Tests • Section 2: Schedule of Activities Table 2-2: On-Study Treatment and Follow-up Procedural Outline for Arms A and B (CA2097DX); Laboratory Tests • Section 9.4.4 Clinical Safety Laboratory Assessments	Removed urinalysis from laboratory tests to be conducted at screening or on treatment.	Alignment with specified program-wide laboratory tests.
Section 2: Schedule of Activities	Footnote added to specify that no dose escalation or reductions	Clarification.

Summary of Key Changes for Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-2: On-Study Treatment and Follow-up Procedural Outline for Arms A and B (CA2097DX) • Study Treatment: Dispense Study Treatment	for nivolumab are allowed. Additional details for Q3W and Q4W dosing are also included.	
• Safety: Assessment: AEs Assessment • Safety: Assessments: SAE Assessment	The row was updated and text was added to the note for AE assessment to state that all non-serious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 100 days following discontinuation of study treatment. In addition to the existing row for AE assessment, a separate row was added for SAE assessment during treatment and follow-up periods	To explicitly state the time period for collection for non-serious AEs and SAEs.
Section 2: Schedule of Activities Table 2-2: On-Study Treatment and Follow-up Procedural Outline for Arms A and B (CA2097DX)	Assessment of concomitant medication use has been removed as an assessment during survival follow-up.	Aligned to program standard.
• Section 2: Schedule of Activities: Table 2-2: On-Study Treatment and Follow-up Procedural Outline for Arms A and B (CA2097DX) Laboratory Tests: Clinical Laboratory Tests	Note added to allow for labs to be conducted 72 hours prior to dosing for each cycle.	Clarifies window to perform labs prior to each cycle.

Summary of Key Changes for Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Efficacy Assessments: Body Imaging • Section 5.1.2 Treatment Phase • Section 9.1.2, BICR Confirmation of Progression (clarification on imaging and subsequent therapy only)	Tumor assessments should occur every 9 weeks (± 7 days) from first dose, regardless of treatment schedule or dose delays for first 54 weeks, rather than for the first 28 weeks. In addition, clarified that imaging must continue until radiographic progression per PCWG3 is confirmed by BICR, even in cases where subsequent therapy has begun.	[redacted] frequency of tumor assessment was revised to enhance precision of the rPFS endpoint. Clarification.
Section 2: Schedule of Activities Table 2-2: On-Study Treatment and Follow-up Procedural Outline for Arms A and B (CA2097DX) • Footnote c [follow-up] • Notes for Clinical Laboratory Tests • Section 9.4.4. Clinical Safety Laboratory Assessments	In Footnote c, Safety Follow-up Visit 1 (FU1) can be performed on the date of discontinuation if that date is greater than 30 days rather than 42 days from last dose. In addition, text or footnote added to indicate specific tests to be performed at FU2 only if toxicities are present.	Revised in conjunction with nivolumab standards. Clarification for study sites.
[redacted]		
Section 2: Schedule of Activities Table 2-2: On-Study Treatment and Follow-up Procedural Outline for Arms	Text added to indicate assessments to be performed only at safety FU1	Clarification for study sites.

Summary of Key Changes for Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
A and B (CA2097DX): Notes for the following assessments BPI-SF. FACT-P, FACT-P PCS		
[redacted]		
Section 6.2 Exclusion Criteria 3) Physical and Laboratory Test Findings i)	Added as new exclusion criterion: AST and/ or ALT > 1.5 x ULN concomitant with alkaline phosphatase > 2.5 x ULN	Aligned with criteria in docetaxel labeling.
Section 7 Treatment Table 7-1, Study Treatments for CA2097DX	Study medications have each been defined in-text as investigational product or non-investigational product	To more clearly define study treatments.
	Placebos (0.9% sodium chloride and 5% dextrose for injection) added to Table 7-1	To more clearly define study treatments.
Section 7.1.1 Nivolumab or Placebo Combined with Docetaxel	Text describing nivolumab monotherapy or placebo dosing removed Text describing monitoring for docetaxel infusion reactions added.	To better organize the information in Section 7.1.1 to focus on Q3W nivolumab or placebo dosing in combination with docetaxel and to add additional information on the purpose of 30-minute observation period between the end of nivolumab or placebo infusion and the start of docetaxel infusion.
• Section 7.1.1 Nivolumab or Placebo Combined with Docetaxel.	Specification of 8 mg dose and clarification of dexamethasone administration schedule.	To align with dexamethasone

Summary of Key Changes for Revised Protocol 01		
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• Section 7.1.2 Nivolumab or Placebo Dosing		premedication specified in docetaxel product label.
Section 7.1.2 Nivolumab or Placebo Dosing	Text describing nivolumab monotherapy or placebo dosing from Section 7.1.1 added Text describing Q3W dosing removed.	To better organize the information in Section 7.1.2 to focus on Q4W nivolumab monotherapy or placebo dosing.
• Section 7.4.2 Docetaxel Dose Reduction • Table 7.4.2-1: Dose Reductions for Docetaxel	Second dose reduction of docetaxel removed from text and from Table 7.4.2-1. If a second dose reduction is required, the protocol now indicates that the participant should discontinue docetaxel treatment. Reference to Section 8.1.1.2 Docetaxel Discontinuation added	To align with docetaxel product label. For clarity.
Section 7.4.3.2 Docetaxel Dose Delay	Bulleted list reformatted	Clarification.
• Section 7.4.3.2 Docetaxel Dose Delay • Section 8.1.1.2 Docetaxel Discontinuation	Addition of information on impaired vision and cystoid macular oedema (CMO) to the list of events for which docetaxel dose delay or permanently discontinued should be considered.	Added to align with docetaxel label.
Section 7.4.6 Treatment of Nivolumab-related Infusion Reactions	Addition of information for treatment of infusion reactions related to nivolumab	Alignment with standards for studies with nivolumab.
Section 7.4.7 Docetaxel-related Infusion Reactions	New section added	Updated to align with the EU SmPC for docetaxel.
Section 7.7.1 Prohibited and/or Restricted Treatments: 7.7.1.1 All Participants	Specification added for restriction/allowance of non-palliative and palliative radiation. Restriction of botanical preparations to provide supportive care has been removed from this section.	Adjustment in program standard.

Summary of Key Changes for Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 8.1 Discontinuation from Study Treatment	The following text added: Termination of the study by Bristol-Myers Squibb (BMS) <u>for reasons including but not limited to the following: safety concerns, termination of drug development, lack of efficacy, and lack of meeting study objectives/endpoints.</u>	To clarify reasons for sponsor-mandated discontinuation.
	Clinical progression has been deleted from criteria for discontinuation from study treatment.	For consistency with the protocol: discontinuation is only mandated for radiographic progression
• Section 8.1 Discontinuation from Study Treatment • Section 9.1.2, BICR Confirmation of Progression	Text added to clarify that PSA progression alone is not an indication to stop treatment. Discontinuation from study treatment is only mandated for radiographic progression per PCWGS criteria for measurable disease and/or bone disease.	Clarification.
Section 8.1.1.2 Docetaxel Discontinuation	Permanent discontinuation for any Grade ≥3 drug-related hypersensitivity reaction added.	Updated to align with the EU SmPC for docetaxel.
Section 9.1.1.2 Imaging and Clinical Assessment	A Best Overall Response (BOR) of SD requires a minimum of 56 days rather than 49 days on study from date of first dose to the date of the first imaging assessment	Clarification of minimum criteria for SD based on frequency of tumor assessments.
Section 9.2 Adverse Events	Paragraph added: 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	Alignment with nivolumab standards.

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Section Number & Title	**Description of Change**	**Brief Rationale**
	were exacerbated by the induction of autoimmunity. Information supporting the assessment will be collected on the participant's case report form.	
Section 9.2.1 Time Period and Frequency for Collecting AE and SAE Information	Text added. For participants assigned to treatment and never treated with study drug, SAEs should be collected for 30 days from the date of treatment assignment. Text was added to state that all non-serious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 100 days following discontinuation of study treatment.	Alignment with nivolumab standards. To explicitly state the time period for collection for non-serious adverse events.
Section 9.2.2, Method of Detecting AEs and SAEs	Paragraph added. 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 participant's case report form.	Alignment with nivolumab program standard.
Section 9.4.4 Clinical Safety Laboratory Assessments	BUN or Serum Urea Uric acid, creatine kinase, total protein, and direct bilirubin removed from lab assessments.	Revised to align with the most recent language for BMS studies and to align with specified program-wide laboratory assessments.
[redacted]		

Summary of Key Changes for Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 11. References	References added.	New references added in support of changes [redacted]
Appendix 1 Abbreviations and Trademarks	Addition of terms to align with protocol content	Updated for clarity.
Appendix 5 APPENDIX 5: Prostate Cancer Working Group 3 (PCWG3) Guidelines (With Modified Response Evaluation Criteria In Solid Tumors (RECIST) Criteria For Soft Tissue Lesion Assessment) Section 1.3 Special considerations regarding bone lesions	Added text to specify that bone lesions will be assessed as non-target lesions.	Clarification.
Appendix 9 Country Specific Amendments: HIV Testing	New Appendix added that describes procedures for HIV testing to be performed in Germany and any other site where exclusion of HIV-positive participants is mandated	Appendix 9 specifies modifications in specified protocol sections regarding exclusion of HIV-positive subjects in countries where exclusion of HIV-positive participants is locally mandated.