Official Title of Study:

Phase 2 Study of Nivolumab in Combination with Either Rucaparib, Docetaxel, or Enzalutamide in Men with Castration-resistant Metastatic Prostate Cancer (CheckMate 9KD: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 9KD)

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CLINICAL PROTOCOL CA2099KD

A Phase 2 Study of Nivolumab in Combination with Either Rucaparib, Docetaxel, or Enzalutamide in Men with Castration-resistant Metastatic Prostate Cancer (CheckMate 9KD: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 9KD)

Revised Protocol 04

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Replace all previous version(s) of the protocol with this revised protocol and please provide a copy of this revised protocol to all study personnel under your supervision, and archive the previous versions.

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 04	08-Aug-2019	This Global Revised Protocol 04 specifies an additional interim analysis (IA) in each arm, after enrollment has been completed and all treated patients have been followed for at least 16 weeks after first dose, in the event that the data from the first IA appear to be immature to support decision-making regarding arm expansion. Additionally, it specifies an IA in additional participants enrolled in any expanded arm or subgroup if needed to determine if the data may support a regulatory filing. Lastly, it makes minor changes to incorporate updated nivolumab clinical program protocol standards.
Revised Protocol 03	31-Jan-2019	This Global Revised Protocol 03 introduces an interim analysis in each arm when at least 50% of planned participants have been treated with at least 16 weeks of follow-up from first dose. The purpose of the interim analysis is to generate preliminary data that will inform internal decision-making related to external studies being planned or conducted by the Sponsor, as well as to determine if any of the arms should be expanded to generate additional data that may support regulatory filing. In addition, this revised protocol clarifies the timing of the final analysis for each arm, incorporates changes from administrative letters, incorporates updated nivolumab clinical program protocol standards, and makes minor clarifications for consistency throughout the protocol document. It also clarifies text regarding prednisone in Arm B and revised language regarding pain intensity and added relevant thresholds.
Administrative Letter 05	20-Nov-2018	To clarify how the participant allocation spots will be split across the different Arms within the study. Also, to clarify that super scan definition has been included, [redacted].
Revised Protocol 02	10-Sep-2018	Clarifies procedure requirement in the Schedule of Activities Clarifies requirements for inclusion and exclusion criteria Update study design to increase the patient population Adds language to allow plasma HRD testing and previous local results Provides further guidance for dexamethasone and corticosteroids use Clarifies language for rucaparib dosing Clarifies language for enzalutamide dosing Adds language to clarify disease progression by PSA Incorporates updated nivolumab clinical program protocol standards Minor clarifications for consistency throughout document
Revised Protocol 01	22-Mar-2018	Clarifies content in the Schedule of Activities Clarifies requirements for inclusion and exclusion criteria Provides further guidance for docetaxel discontinuation criteria Adds language to Prohibited and/or Restricted Treatments section Adds enzalutamide background information Provides additional guidance for PK sampling Incorporates updated nivolumab clinical program protocol standards

Document	Date of Issue	Summary of Change
		Updates Study Director information Minor clarifications for consistency throughout document
Original Protocol	21-Aug-2017	Not applicable

OVERALL RATIONALE FOR THE REVISED PROTOCOL 04

This Global Revised Protocol 04 specifies an additional interim analysis (IA) in each arm, after enrollment has been completed and all treated patients have been followed for at least 16 weeks after first dose, in the event that the data from the first IA appear to be immature to support decision-making regarding arm expansion. Additionally, it specifies an IA in additional participants enrolled in any expanded arm or subgroup if needed to determine if the data may support a regulatory filing. Lastly, it makes minor changes to incorporate updated nivolumab clinical program protocol standards.

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 04

Section Number & Title	Description of Change	Brief Rationale
Table 2-2 On-study Treatment and Follow-up Procedural Outline for Arms A or C (CA2099KD) Table 2-3 On-study Treatment and Follow-up Procedural Outline for Arm B (CA2099KD) 6.2 Exclusion Criteria 7.1.4 Treatment of Infusion-related Reactions (Nivolumab or Docetaxel) 10.3.2 Safety Analyses	Changed NCI CTCAE v 5.0 back to v 4.03	For consistency through-out the study
Table 2-2 On-study Treatment and Follow-up Procedural Outline for Arms A or C (CA2099KD) Table 2-3 On-study Treatment and Follow-up Procedural Outline for Arm B (CA2099KD)	For AE Assessment and Concomitant Medication Use, added columns for Safety Follow-up and Survival Follow-up and added "X" for Safety Follow-up	AE and concomitant medication use assessment occurs for a minimum of 100 days after last dose, not continuously, and are not assessed during Survival Follow-up
5.1 Overall Design	Clarified that enrollment in any study arm may be terminated early due to poor accrual	Permits early termination of enrollment in any arm due to poor accrual
5.4.9 Rationale for Interim Analysis 10.3.4 Interim Analysis	Added a potential second IA after completion of enrollment and at least 16 weeks follow-up after first dose in each arm if first IA is immature, as well as IA in additional participants treated in any expanded arm or subgroup with at least 16 weeks of follow-up after first dose if needed to support regulatory interactions	To include additional interim analyses that can support decisions regarding arm expansion and regulatory filing
6.1 Inclusion Criteria (3d)	Changed from 5 months to 7 months	Corrected time that male participants must be willing to refrain from sperm donation

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
7.3 Blinding	Clarified that the immediate study team members will remain blinded to Homologous recombination deficiency (HRD) status of individual study participants	To maintain blinding of immediate study team to maintain study integrity
Table 9.5.2-1 Pharmacokinetic [PK] [redacted] Sample Collections (CA2099KD)	Revised text in Safety row Revised text in footnote a to specify nivolumab treatment discontinuation	Clarification on nivolumab PK[redacted] collections was made to the PK Table 9.5.2-1 to indicate that if "nivolumab" is discontinued, the participant should move to follow-up PK[redacted] collections.
Table 10.1-1 Sample Size by Arm/Analysis Cohort	For ORR and RR-PSA/PFS in Arm A HRD subgroup, revised HRD status to "negative"	Updated to indicate accurate HRD status for the Arm A HRD-subgroup
Appendix 2 Study Governance Consideration	Slightly modified definition of "serious breach"; provided additional criteria for the CSR Signatory Investigator; added publication policy	Meets current standards
Appendix 3 AEs and SAEs Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Updated definitions and procedures for recording, evaluating, follow-up, and reporting AEs and SAEs	Meets current standards
Appendix 4 WOCBP Definitions and Methods of Contraception	Moved hormonal methods of contraception from User Independent to User Dependent. Added additional detail	Meets current standards
Appendix 6 Management Algorithms for Immuno-Oncology Agents 7.1.3 Management Algorithms for Immuno-Oncology Agents	Added algorithm on myocarditis and replaced all algorithms with version with "2019" date	Meets current standards
Appendix 8 Country Specific Requirements	Added relevant countries regarding exclusion of HIV positive participants where locally mandated	To update known countries to date

TABLE OF CONTENTS

1 SYNOPSIS

Protocol Title: A Phase 2 Study of Nivolumab in Combination with Either Rucaparib, Docetaxel, or Enzalutamide in Men with Castration-resistant Metastatic Prostate Cancer (CheckMate 9KD: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 9KD)

Study Phase: 2

Rationale:

Prostate cancer tumor cells have been shown to have low tumor expression of PD-L1, suggesting that treatments directed at the PD-1 / PD-L1 interaction are unlikely to be successful as monotherapies. This was confirmed by early clinical trials, where men with castration-resistant metastatic prostate cancer (mCRPC) did not respond to PD-1 blockade as monotherapy. 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". This suggests that, if prostate cancer treatments (ie, androgen ablation, chemotherapy, or PARP inhibitors) can increase PD-L1 expression on tumor cells by attracting infiltrating immune cells and triggering an adaptive immune response, then there is a rationale for combining such therapies with immune check-point inhibitors.

This study aims to demonstrate that treatment with nivolumab combined with rucaparib (Arm A), docetaxel (Arm B) or enzalutamide (Arm C) will have clinical activity in participants with mCRPC. Additional objectives of the study include further characterization of efficacy, safety and tolerability [redacted] as well as pharmacokinetics [redacted]. Response to study treatment and disease progression will be assessed using Prostate Cancer Clinical Trials Working Group 3 (PCWG3) criteria.

Study Population: The study population consists of participants 18 years of age or older with mCRPC (ie, histologically confirmed adenocarcinoma of the prostate with evidence of M1 metastatic disease, ongoing androgen deprivation therapy [ADT] or bilateral orchiectomy, and documented prostate cancer progression per PCWG3 criteria).

Key Inclusion Criteria:

Histologic confirmation of adenocarcinoma of the prostate. Diagnosis must be stated in a pathology report and confirmed by the investigator.

- Evidence of stage IV disease (as defined by the American Joint Committee on Cancer [AJCC] cancer staging criteria) on previous bone, CT, and/or MRI scan
- 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 subjects 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 with at least one of the following:
  - PSA progression* defined by a minimum of two rising PSA levels with an interval of ≥ 1 week between each determination The prostate-specific antigen (PSA) value at the screening visit should be ≥ 2 μg/L (2 ng/mL).

    * Participants who received an anti-androgen must have 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. Participants whose disease spread is limited to regional pelvic lymph nodes (N1) measuring at least 2 cm in short axis will be considered eligible.
  - Radiographic disease progression in bone defined as appearance of 2 or more new bone lesions on bone scan.

    NOTE: Radiographs must be collected and transmitted to the central imaging vendor at study entry
- ECOG Performance Status of 0-1
- mCRPC participants will be assigned to a study arm as follows:
  - **Arm A**: Participants must meet either of the following criteria:
    - **Arm A1**: Participants who have received at least 1 but no more than 2 prior taxane-based regimens for castration-resistant disease. If docetaxel chemotherapy is used more than once, this will be considered as one regimen. Up to 2 second generation hormonal manipulations for castration-resistant disease are allowed.
    - **Arm A2**: Participants who are chemotherapy-naive for mCRPC who have received prior treatment with abiraterone acetate and/or enzalutamide/apalutamide for castration-resistant disease up to 28 days prior to study arm assignment and are not candidates for or refuse immediate chemotherapy
  - **Arm B**: Participants who are chemotherapy-naive for mCRPC who are candidates to receive docetaxel chemotherapy. Up to 2 second-generation hormonal manipulations (eg, abiraterone acetate and/or enzalutamide/apalutamide) for castration-resistant disease are allowed up to 28 days prior to study arm assignment.
  - **Arm C**: Participants who are chemotherapy-naive for mCRPC who have received prior treatment with abiraterone acetate for castration-resistant disease up to 28 days prior to study arm assignment without prior enzalutamide/apalutamide, and are not candidates for or refuse immediate chemotherapy.
- For Arm A2 and Arm C, asymptomatic or minimally symptomatic according to BPI-SF performed during screening
- Sufficient plasma and, fresh or archival tumor tissue obtained within 5 years prior to enrollment from a metastatic tumor lesion or from a primary tumor lesion that has not been previously irradiated (formalin-fixed paraffin-embedded block or unstained tumor tissue sections). Tumor sample may be from core biopsy, punch biopsy, excisional biopsy, or surgical

specimen). Fine needle aspiration is unacceptable for submission. Central laboratory must confirm receipt of plasma and tumor samples prior to IRT treatment arm assignment.

Results of homologous recombination deficiency (HRD) testing by the central laboratory must be available to IRT prior to treatment arm assignment. If local HRD test results obtained prior to enrollment are provided to Sponsor, they should be confirmed to be acceptable for treatment assignment, and results will be transmitted to IRT prior treatment arm assignment.

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 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 must be discussed with the BMS Medical Monitor or designee. Previously irradiated brain lesions are not considered measurable disease.
- Less than 1 year since resolution of ≥ Grade 2 toxicity related to pelvic-targeted therapy (eg, radiation enteritis)
- All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue must have resolved to Grade 1 (NCI CTCAE version 5) 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.
- The following exclusion criteria apply to **Arm A** only:
  - Participants with myelodysplastic syndrome/acute myeloid leukemia.
  - Gastrointestinal disorders likely to interfere with absorption of the study medication
- The following exclusion criterion applies to **Arm B** only:
  - Participants who have ≥ Grade 2 peripheral neuropathy (NCI CTCAE version 5)
- The following exclusion criteria apply to **Arm C** only:
  - History of seizure or any condition that may have a predisposition to seizure. Also, history of loss of consciousness or transient ischemic attack within 12 months of enrollment (Day 1 visit)
  - History of prostate cancer progression on ketoconazole
  - Gastrointestinal disorders likely to interfere with absorption of the study medication
  - History of Mobitz II second degree or third degree heart block without a permanent pacemaker in place
  - Hypotension as indicated by systolic blood pressure < 86 mm Hg at the screening visit
  - Bradycardia as indicated by a heart rate of < 50 beats per minute on the screening ECG
  - Uncontrolled hypertension as indicated by systolic blood pressure > 170 mm Hg or diastolic blood pressure > 105 mm Hg at the screening visit

- Participants with superscan on Technecium-99m radionuclide bone scans are not eligible for the study

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.
- Radiotherapy to the pelvic region within 3 months prior to treatment arm assignment
- Radiotherapy to symptomatic bone lesions within 14 days prior to treatment arm assignment.
- The following exclusion criteria apply to **Arm A** only:
  - Prior PARP inhibitor treatment, mitoxantrone, cyclophosphamide, or platinum-based chemotherapy
  - Arm A2 only: Prior chemotherapy for mCRPC. Prior docetaxel for metastatic hormone-sensitive prostate cancer is allowed if ≥ 12 months elapsed from last dose of docetaxel
- The following exclusion criterion applies to **Arm B** only:
  - Prior treatment with docetaxel or another chemotherapy agent for metastatic castration-resistant prostate cancer. Prior docetaxel for metastatic hormone-sensitive prostate cancer is allowed if ≥ 12 months elapsed from last dose of docetaxel.
- The following exclusion criteria apply to **Arm C** only:
  - Prior chemotherapy for mCRPC. Prior docetaxel for metastatic hormone-sensitive prostate cancer is allowed if ≥ 12 months elapsed from last dose of docetaxel.
  - Prior treatment with enzalutamide, apalutamide , or other novel androgen receptor inhibitor.
  - Treatment with 5-α reductase inhibitors (eg, finasteride, dutasteride), estrogens, and/or cyproterone within 4 weeks prior to treatment arm assignment

Objectives and Endpoints:

Objective	Endpoint
Co-Primary	
• To evaluate the objective response rate per PCWG3 (ORR-PCWG3) in HRD+ participants and in all treated participants	• ORR-PCWG3 is the proportion of participants who have a confirmed complete or partial best overall response (BOR) per PCWG3 among treated participants who have measurable disease. The BOR will be assessed by the investigator per PCWG3 and is recorded between treatment initiation 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.

Objective	Endpoint
• To evaluate PSA response rate (RR-PSA) in HRD+ participants and in all treated participants	• RR-PSA is the proportion of treated 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.
Secondary	
To evaluate radiographic progression-free survival (rPFS) in HRD+ participants and in all treated participants	• rPFS is the time between treatment initiation and the first date of documented progression or death due to any cause, whichever occurs first. The radiographic progression will be assessed by the investigator per PCWG3. The rPFS will be censored at the last tumor assessment up to the start of subsequent systemic cancer therapy.
• To evaluate time to response (TTR) and duration of response (DOR) per PCWG3 (TTR-PCWG3 and DOR-PCWG3) in HRD+ participants and in all treated participants	• TTR-PCWG3 is the time from treatment initiation to the date of the first documented CR or PR 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 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 cancer therapy.
• To estimate time to PSA progression (TTP-PSA) in HRD+ participants and in all treated participants	• TTP-PSA is the time between treatment initiation to the date of PSA progression per PCWG3 in treated participants. For participants with 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. TTP- PSA will be censored at the date of last PSA evaluation prior to start of subsequent systemic cancer therapy. The time will be censored at the date of treatment initiation for participants with no post- baseline PSA evaluation.
• To assess overall survival (OS) in HRD+ participants and in all treated participants	• OS is the time between treatment initiation 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 treatment initiation if they had no follow-up.
• To evaluate overall safety and tolerability	• Overall safety and tolerability will be measured by the incidence of AEs, SAEs, AEs leading to discontinuation, immune-mediated AEs, deaths, and laboratory abnormalities and changes from baseline

Overall Design:

This is an open-label Phase 2 study of nivolumab in combination with rucaparib (Arm A), docetaxel (Arm B), or enzalutamide (Arm C) in men with mCRPC. Arm A is split into 2 sub-groups according to whether participants have received prior chemotherapy (Arm A1) or are chemotherapy-naive for mCRPC (Arm A2) (**Figure 1-1:**). The study is not randomized, and treatment arm assignment will depend on prior systemic treatment history. Treatment arm assignment will also depend on 2 clinical variables: 1) the presence or absence of measurable disease on the baseline tumor assessment per investigator review; and 2) the presence or absence

of HRD based on testing of a submitted tumor tissue sample by the central laboratory. Within each treatment arm, 60% of the available spots will be designated for participants that have measurable disease and 40% of the available spots will be designated for those who do not have measurable disease. In the entire study, 50% of the available spots will be designated for participants who are HRD positive and 50% will be designated for participants who are HRD negative or HRD not evaluable. However, the number of HRD+ versus HRD- or HRD-not evaluable spots will vary in each arm as follows: 100 HRD+ and 80 HRD- or not evaluable in Arm A; 25 HRD+ and 60 HRD- or not evaluable in Arm B; 25 HRD+ and 40 HRD- or not evaluable in Arm C. The Interactive Response Technology (IRT) system will be used for treatment arm assignment. IRT will assign each participant to a treatment arm based on prior treatment history, measurable disease status, and HRD status.

The study will consist of 3 phases: screening, treatment, and follow-up. Study visits and endpoint measurements will occur as indicated in the procedural outlines (Schedule of Activities) in Section 2 of the protocol.

Number of Participants:

Approximately 330 participants are planned to be enrolled and treated in 1 of 3 parallel treatment arms as follows:

- **Arm A**: 180 participants to receive nivolumab plus rucaparib
  - Arm A1 = 80
  - Arm A2 = 100
- **Arm B**: 85 participants to receive nivolumab plus docetaxel plus prednisone plus dexamethasone
- **Arm C**: 65 participants to receive nivolumab plus enzalutamide

The sample size is calculated using the precision approach for the co-primary endpoints, ie, ORR as assessed by the investigator per PCWG3, among treated participants with measurable disease at baseline in an analysis cohort, and RR-PSA among treated participants in an analysis cohort. The precision for potential response rates is detailed in Section 10.1 of the protocol.

Treatment Arms and Duration:

Study Treatment:

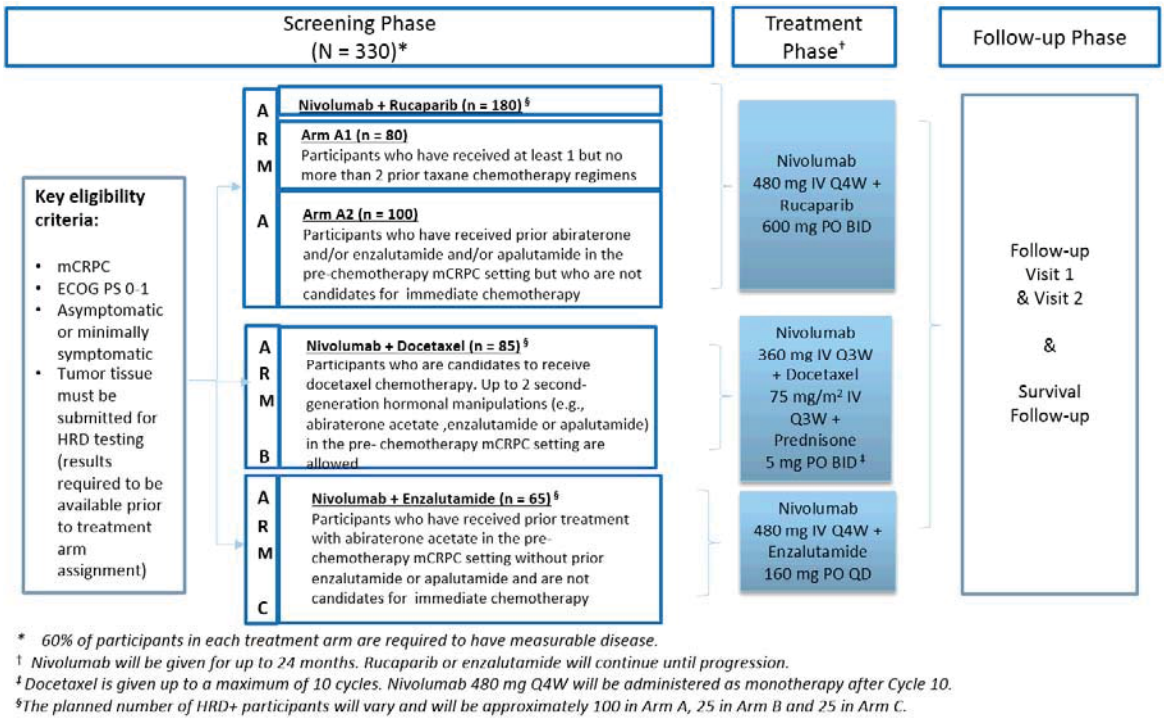
Study Drug for CA2099KD		
Medication	**Potency**	**IMP/Non-IMP**
BMS-936558-01 (Nivolumab) Solution for Injection	100 mg (10 mg/mL)	IMP
Rucaparib	200 mg/250 mg/300 mg	IMP

Study Drug for CA2099KD		
Medication	**Potency**	**IMP/Non-IMP**
Immediate Release Tablets		
Docetaxel	80 mg	IMP
Prednisone	5 mg	Non-IMP
Dexamethasone	4 mg	Non-IMP
Xtandi® (enzalutamide)	40 mg	IMP

Abbreviations: IMP = Investigational Medicinal Product

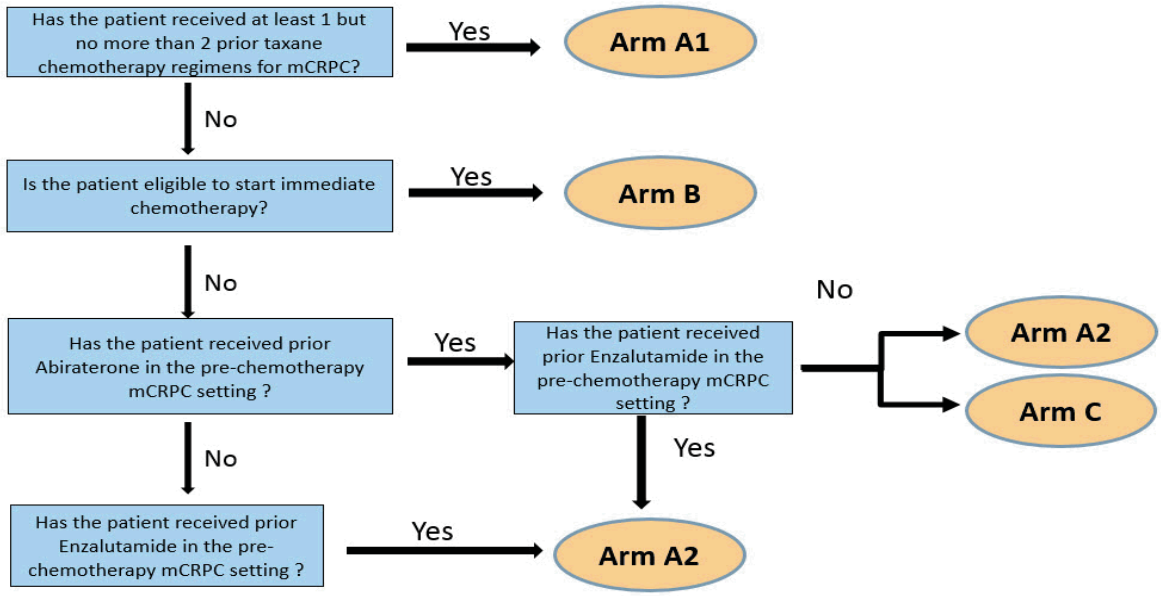
The study design schematic is presented in **Figure 1-1:**. The decision tree guiding treatment assignment is provided in **Figure 1-2:**.

Figure 1-1: Study Design Schematic



* 60% of participants in each treatment arm are required to have measurable disease.
† Nivolumab will be given for up to 24 months. Rucaparib or enzalutamide will continue until progression.
‡ Docetaxel is given up to a maximum of 10 cycles. Nivolumab 480 mg Q4W will be administered as monotherapy after Cycle 10.
§ The planned number of HRD+ participants will vary and will be approximately 100 in Arm A, 25 in Arm B and 25 in Arm C.

Figure 1-2: Decision Tree Guiding Treatment Arm Assignment



Treatment arm assignment will also depend on 2 clinical variables: 1) the presence or absence of measurable disease on the baseline tumor assessment per investigator review; and 2) the presence or absence of HRD based on testing of a blood plasma and/or tumor tissue sample by the central laboratory during screening or by local laboratory prior to enrollment.

A participant is considered HRD+ if they have a deleterious genomic alteration (protein truncating or splice site mutation, homozygous deletion, large protein truncating rearrangement, or deleterious missense mutation) in plasma and/or tumor sample in at least one of the following HR genes: BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK2, FANCA, NBN, PALB2, RAD51, RAD51B, RAD51C, RAD51D, or RAD54L. HRD status will be determined by central laboratory testing of a submitted blood plasma and/or tumor sample during screening or by local laboratory testing performed prior to enrollment. If local HRD testing has been performed prior to enrollment, the local HRD test results must be documented in the participant's medical records and local HRD laboratory report must be provided to the Sponsor. The local HRD laboratory report must clearly document the presence of a pathogenic or deleterious mutation in one of the HR genes noted above in order for it to be acceptable for assignment to an HRD+ spot. If the records do not clearly indicate the patient's HRD status, the local testing results must be submitted to the sponsor for further interpretation of the HRD status.

During the treatment phase, participants will receive:

- **In Arm A**: Nivolumab 480 mg IV Q4W for a maximum of 24 months from date of first dose and rucaparib 600 mg PO BID.
- **In Arm B**: Nivolumab 360 mg IV Q3W and docetaxel 75 mg/m^2 IV Q3W plus prednisone 5 mg PO BID and dexamethasone 8 mg PO as premedication at 12 hours, 3 hours, and 1 hour

before docetaxel infusion. Nivolumab will be administered for a maximum of 24 months from date of first dose, and docetaxel will be administered for a maximum of 10 cycles. After the completion of 10 cycles, nivolumab 480 mg IV Q4W will continue to be given alone as maintenance therapy. The total treatment duration for nivolumab (in combination with docetaxel or as monotherapy after completion of 10 cycles of docetaxel) is a maximum of 24 months from date of first dose.

- **In Arm C**: Nivolumab 480 mg IV Q4W for a maximum of 24 months from date of first dose and enzalutamide 160 mg PO QD.

Tumor Assessments:

Tumor assessments are scheduled to be performed every 8 weeks (± 7 days) for 24 weeks following treatment initiation and thereafter every 12 weeks (± 7 days) until radiographic progression or discontinuation of study treatment (whichever occurs later). Tumor assessments should be performed at these time points regardless of treatment schedule or dose delays.

Dose delays for all 4 investigational products are permitted for toxicity and other protocol-specified criteria. Dose reductions are permitted for rucaparib, docetaxel, and enzalutamide but not for nivolumab. The criteria for discontinuation due to toxicities are discussed in Section 8.1 of the protocol. The assessment for delay or discontinuation should be made separately for each study drug in the combination. Treatment may be prematurely discontinued due to withdrawal of consent, unacceptable toxicity, disease progression, completion of treatment cycles, or termination of the study, whichever occurs first.

A Data Monitoring Committee (DMC) will provide independent oversight of safety, study conduct and efficacy of nivolumab in combination with rucaparib, docetaxel or enzalutamide.

Duration:

The duration for accrual is approximately 15 months based on a monthly enrollment rate of 20 participants and the follow-up period will be 12 months. The final analysis of the co-primary endpoints of ORR and RR-PSA will occur approximately 2.5 years after the first participant is treated. This will allow sufficient follow up for a stable estimate of best overall response and duration and adequate safety assessment. Additional survival analyses may be conducted for up to 5 years after treatment initiation following the updated analysis of the co-primary endpoints.

2 SCHEDULE OF ACTIVITIES

Table 2-1: Screening Procedural Outline (CA2099KD)

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 treatment arm assignment in IRT
BPI-SF	X	To be completed for all participants and must be performed to establish eligibility in Arm A2 and Arm C. (See Section 6.1, inclusion criterion 2.i)
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
Blood plasma and Tumor Tissue Sample	X	Mandatory submission during screening. See Section 6.1 and Section 9.8.2 for specifications. Central HRD testing must be performed on submitted blood plasma and archival/fresh tumor sample unless local HRD test results obtained prior to enrollment are provided to Sponsor and confirmed to be acceptable for treatment arm assignment (see Section 5.1). Results from central or local HRD testing must be available to IRT prior to treatment arm assignment.
Baseline Tumor Assessments	X	Imaging should be done within 28 days prior to first dose. Bone lesions should be assessed with Technecium-99m radionuclide bone scans. CT/MRI scan of chest, abdomen, pelvis, and any suspected/known sites of soft tissue lesions. CT/MRI of the brain without and with contrast is required in participants with known or suspected brain metastases. Images will be collected and held centrally for potential future independent review. Please refer to Appendix 5 for PCWG3 guidelines for tumor assessments.

Table 2-1: Screening Procedural Outline (CA2099KD)

Procedure[a]	Screening Visit	Notes All windows are on calendar days.
Safety Assessments		
Full Physical Examination, Measurements and Vital Signs	X	Height, Weight, ECOG Performance Status (Appendix 7) within 14 days prior to treatment arm assignment 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 treatment arm assignment in IRT
Prior/Concomitant Medication Use	X	Within 14 days prior to treatment arm assignment in IRT Vaccine use must be collected within 30 days prior to treatment arm assignment.
Serious Adverse Event (SAE) Assessment	X	SAEs from time of consent. See Section 9.2.2.
12 lead ECG	X	Within 14 days prior to treatment arm assignment
Laboratory Tests		
CBC with differential, Chemistry, Endocrine, Viral, PSA	X	Must be performed within 14 days prior to treatment arm assignment. Refer to Section 9.4.1 for list of laboratory tests to conduct. The following must be performed up to 6 weeks prior to first dose: 1. PSA (See Section 6.1, inclusion criterion 2.d.1) 2. Testosterone (See Section 6.1, inclusion criterion 2.c)
IRT		
Treatment Arm Assignment	X	Treatment arm assignment via IRT will be based on prior treatment history, presence or absence of measurable disease, and HRD status per Section 7.2.

[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.

Table 2-2: On-study Treatment and Follow-up Procedural Outline for Arms A or C (CA2099KD)

Procedure[a]	C1[b] (Cycle Duration = 4 weeks) Days 1 and 15	C2 and Subsequent Cycles[c] (Cycle Duration = 4 weeks) Day 1	Safety Follow-up[d]	Survival Follow-up[e]	Notes
Study Treatment					
Dispense Study Treatment	X	X			First dose to be administered within 3 calendar days following treatment arm assignment.
Safety Assessments					
Targeted Physical Examination and Vital Signs	X	X	X		Weight, BP, heart rate, RR, Temperature and ECOG Performance Status; within 72 hours prior to dosing.
AEs Assessment (including SAEs)	Continuously		X		Per NCI CTCAE v. 4.03. Record at each visit
Concomitant Medication Use	Continuously		X		Record at each visit
Laboratory Tests					
CBC with differential, Chemistry panel, Thyroid testing	X*	X	X01-yes X02 - if toxicities are present		*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. See Section 9.4.1 for list of laboratory tests.
PSA (Local)	X	X	See notes	See notes	Perform on D1 of C1 to C4, then D1 of every even-numbered cycle (C6, C8, C10, etc.). Participants who discontinue study treatment without documented radiographic progression will continue to have PSA performed every 8 weeks (± 7 days) until radiographic progression or the start of subsequent systemic cancer therapy, whichever occurs later. PSA evaluation beyond radiographic

Table 2-2: On-study Treatment and Follow-up Procedural Outline for Arms A or C (CA2099KD)

Procedure[a]	C1[b] (Cycle Duration = 4 weeks) Days 1 and 15	C2 and Subsequent Cycles[c] (Cycle Duration = 4 weeks) Day 1	Safety Follow-up[d]	Survival Follow-up[e]	Notes
					progression or the start of subsequent systemic cancer therapy to confirm PSA response or PSA progression should be performed as needed. PSA should be performed by the same lab throughout the treatment period to avoid variations in results between cycles
[redacted]					
Efficacy Assessments					
CT/MRI of chest, abdomen, pelvis, and all known or suspected areas of disease		X	[X if progression is not documented prior to discontinuation of study treatment]	See notes	Every 8 weeks (± 7 days) from first dose, regardless of treatment schedule or dose delays for first 24 weeks. Following this, switch to every 12 weeks (± 7 days). CT/MRI must continue until disease progression is documented or treatment is discontinued (whichever occurs later). See Section 9.1.

Table 2-2: On-study Treatment and Follow-up Procedural Outline for Arms A or C (CA2099KD)

Procedure[a]	C1[b] (Cycle Duration = 4 weeks) Days 1 and 15	C2 and Subsequent Cycles[c] (Cycle Duration = 4 weeks) Day 1	Safety Follow-up[d]	Survival Follow-up[e]	Notes
Radionuclide Bone Scan		X	[X if progression is not documented prior to discontinuation of study treatment]	See notes	Every 8 weeks (± 7 days) from first dose, regardless of treatment schedule or dose delays for first 24 weeks. Following this, switch to every 12 weeks (± 7 days). Bone scans must continue until disease progression is confirmed or treatment is discontinued (whichever occurs later). See Section 9.1.
Survival Status			X	X	During safety follow-up and every 3 months (clinic visit or by telephone) during survival phase. Include documentation of subsequent therapy.
[redacted]					

Table 2-2: On-study Treatment and Follow-up Procedural Outline for Arms A or C (CA2099KD)

Procedure[a]	C1[b] (Cycle Duration = 4 weeks) Days 1 and 15	C2 and Subsequent Cycles[c] (Cycle Duration = 4 weeks) Day 1	Safety Follow-up[d]	Survival Follow-up[e]	Notes
[redacted]					
Pharmacokinetic (PK) [redacted]	**Assessments**				
Collect blood samples for PK[redacted]	Refer to Sampling Schedule Table 9.5.2-1				

[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] There is no nivolumab infusion at the Day 15 visit. Safety assessments are to be performed on Day 15.

[c] 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.

[d] Participants must be followed for a minimum of 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 42 days from last dose. 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.

[e] Survival Follow-up visits to occur every 3 months (± 14 days) from Safety Follow-up Visit 2. Survival Follow-up visits may be conducted in person or by telephone. BMS may request that survival data be collected on all treated participants outside of the 3 month specified window. 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.

Table 2-3: On-study Treatment and Follow-up Procedural Outline for Arm B (CA2099KD)

Procedure[a]	C1[b] (Cycle Duration = 3 weeks) Days 1 and 15	C2-C10 [c] (Cycle Duration = 3 weeks) Day 1	C11 and Subsequent Cycles [c,d] (Cycle Duration = 4 weeks) Day 1	Safety Follow-up[e]	Survival Follow-up[f]	Notes
Study Treatment						
Dispense Study treatment	X	X[g]	X			First dose to be administered within 3 calendar days following treatment arm assignment.
Safety Assessments						
Targeted Physical Examination and Vital Signs	X	X	X	X		Weight, BP, heart rate, RR, Temperature and ECOG Performance Status; within 72 hours prior to dosing.
Adverse Event (AE) Assessment	Continuously			X		Per NCI CTCAE v. 4.03. Record at each visit
Concomitant Medication Use	Continuously			X		Record at each visit
Laboratory Tests						
CBC with differential, Chemistry, Thyroid testing	X*	X	X	X01-yes X02 - if toxicities are present		*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. See Section 9.4.1 for list of laboratory tests.
PSA (Local)	X	X	X			Perform on D1 of C1 to C5, then D1 of every other cycle starting with C7. Participants who discontinue study treatment without documented radiographic progression will continue to have PSA performed every 8weeks (± 7 days) until radiographic progression or the start of subsequent

Table 2-3: On-study Treatment and Follow-up Procedural Outline for Arm B (CA2099KD)

Procedure[a]	C1[b] (Cycle Duration = 3 weeks) Days 1 and 15	C2-C10 [c] (Cycle Duration = 3 weeks) Day 1	C11 and Subsequent Cycles [c,d] (Cycle Duration = 4 weeks) Day 1	Safety Follow-up[e]	Survival Follow-up[f]	Notes
						systemic cancer therapy, whichever occurs later. PSA evaluation beyond radiographic progression or the start of subsequent systemic cancer therapy to confirm PSA response or PSA progression should be performed as needed
[redacted]						
Efficacy Assessments						
CT/MRI of chest, abdomen, pelvis, and all known or suspected areas of disease		X	X	[X if progression is not documented prior to discontinuation of study treatment]		Every 8 weeks (± 7 days) from first dose, regardless of treatment schedule or dose delays for first 24 weeks. Following this, switch to every 12 weeks (± 7 days). CT/MRI must continue until disease progression is documented or treatment is discontinued (whichever occurs later). See Section 9.1.

Table 2-3: On-study Treatment and Follow-up Procedural Outline for Arm B (CA2099KD)

Procedure[a]	**C1**[b] (Cycle Duration = 3 weeks) **Days 1 and 15**	**C2-C10** [c] (Cycle Duration = 3 weeks) **Day 1**	**C11 and Subsequent Cycles** [c,d] (Cycle Duration = 4 weeks) **Day 1**	**Safety Follow-up**[e]	**Survival Follow-up**[f]	**Notes**
Radionuclide Bone Scan		X	X	[X if progression is not confirmed prior to discontinuation of study treatment]		Every 8 weeks (± 7 days) from first dose, regardless of treatment schedule or dose delays for first 24 weeks. Following this, switch to every 12 weeks (± 7 days). Bone scans must continue until disease progression is confirmed or treatment is discontinued (whichever occurs later). See Section 9.1
Survival Status				X	X	During safety follow-up and every 3 months (clinic visit or by telephone) during survival phase. Include documentation of subsequent therapy.
[redacted]						

Table 2-3: On-study Treatment and Follow-up Procedural Outline for Arm B (CA2099KD)

Procedure[a]	C1[b] (Cycle Duration = 3 weeks) Days 1 and 15	C2-C10 [c] (Cycle Duration = 3 weeks) Day 1	C11 and Subsequent Cycles [c,d] (Cycle Duration = 4 weeks) Day 1	Safety Follow-up[e]	Survival Follow-up[f]	Notes
[redacted]						
Pharmacokinetic [redacted] Assessments						
Collect blood samples for PK[redacted]	Refer to Sampling Schedule Table 9.5.2-1					

[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] There is no nivolumab infusion at the Day 15 visit. Only safety assessments are to be performed on Day 15.

[c] 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.

[d] Three weeks after Cycle 10, nivolumab 480 mg Q4W monotherapy will be administered at Cycle 11 (± 3 days) and continue until completion of 24 months of treatment, disease progression, or unacceptable toxicity, whichever occurs first.

[e] Participants must be followed for a minimum of 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 42 days from last dose. 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.

[f] Survival Follow-up visits to occur every 3 months (±14 days) from Safety Follow-up Visit 2. Survival visit may be conducted in person or by telephone. BMS may request that survival data be collected on all treated participants outside of the 3 month specified window. 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.

[g] Docetaxel may be given for a maximum of 10 cycles. If docetaxel is discontinued prior to Cycle 10, nivolumab 360 mg Q3W should be continued alone until Cycle 10.

3 INTRODUCTION

CA2099KD is a Phase 2, open-label study of nivolumab in combination with either rucaparib, docetaxel or enzalutamide in men with metastatic castration-resistant prostate cancer (mCRPC). mCRPC is defined as castrate resistant prostate cancer and M1 metastatic disease on bone, CT and/or MRI scan, per the American Joint Committee on Cancer (AJCC) cancer staging manual[1]. Participants in this study will be evaluated in 3 parallel arms as follows:

- **Arm A** (nivolumab plus rucaparib):
  - **Arm A1**: Participants who have received at least one but no more than 2 prior taxane-based regimens for castration-resistant disease. If docetaxel chemotherapy is used more than once, this will be considered as one regimen. Up to 2 second generation hormonal manipulations for castration-resistant disease are allowed.
  - **Arm A2:** Participants who are chemotherapy-naive for mCRPC and have received prior treatment with abiraterone acetate and/or enzalutamide for castration-resistant disease up to 28 days prior to study arm assignment and are not candidates for or refuse immediate chemotherapy
- **Arm B** (nivolumab plus docetaxel): Participants who are chemotherapy-naive for mCRPC and are candidates to receive docetaxel chemotherapy. Up to 2 second-generation hormonal manipulations (eg, abiraterone acetate and/or enzalutamide) in the mCRPC setting are allowed up to 28 days prior to study arm assignment.
- **Arm C** (nivolumab plus enzalutamide): Participants who are chemotherapy-naive for mCRPC and have received prior treatment with abiraterone acetate in the mCRPC setting up to 28 days prior to study arm assignment without prior enzalutamide, and are not candidates for or refuse immediate chemotherapy.

Please refer to the Investigator Brochures (IBs) for nivolumab and rucaparib and the current prescribing information for enzalutamide for information not presented in this protocol. For docetaxel, the current prescribing information and local standards of practice should be considered.

3.1 Study Rationale

Prostate cancer tumor cells have been shown to have low tumor expression of PD-L1, suggesting that treatments directed at the PD-1 / PD-L1 interaction are unlikely to be successful as monotherapies.[2] This was confirmed by early clinical trials, where men with mCRPC did not respond to PD-1 blockade as monotherapy.[3] 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".[4,5,6] This suggests that, if prostate cancer treatments (ie, poly [ADP ribose] polymerase [PARP] inhibitors, chemotherapy, or androgen ablation) can increase PD-L1 expression on tumor cells by attracting infiltrating immune cells and triggering an adaptive immune response, then there is a rationale for combining such therapies with immune check-point inhibitors.[7,8,9,10]

This study aims to demonstrate that treatment with nivolumab combined with rucaparib, docetaxel or enzalutamide will have clinical activity in participants with mCRPC. Additional objectives of

the study include further characterization of efficacy, safety and tolerability [redacted] as well as pharmacokinetics [redacted]. Response to study treatment and disease progression will be assessed using Prostate Cancer Clinical Trials Working Group 3 (PCWG3) criteria (Appendix 5).

3.1.1 Research Hypothesis

Nivolumab in combination with rucaparib, docetaxel, or enzalutamide can be given safely and will demonstrate meaningful clinical activity in participants with mCRPC.

3.2 Background

The attainment of meaningful, durable clinical response to treatment of mCRPC presents a daunting challenge, given the disease's ability to acquire resistance to standard of care (SOC) options. Study treatment combinations with nivolumab that are investigated in the present study could represent viable additions to the current therapeutic armamentarium in this area of unmet medical need.

Detailed descriptions of the chemistry, pharmacology, efficacy, and safety of nivolumab and rucaparib are provided in the respective current Investigator Brochures (IBs). Similar details for docetaxel and enzalutamide can be found in the current prescribing information (ie, United States Prescribing Information [USPI], Summary of Product Characteristics [SmPC], and/or country-specific product labels).

3.2.1 Indication Background

Prostate cancer is a leading cause of cancer mortality in men worldwide.[11] With an estimated incidence of 161,360 new cases and 26,730 deaths in 2017, prostate cancer is the most frequently diagnosed cancer and third most frequent cause of cancer deaths in US males.[12] In the US, 1 in every 7 men is diagnosed with prostate cancer.[13] In Europe, prostate cancer was the third most common cancer in 2012, with 417,000 new cases and 92,000 deaths from prostate cancer being reported in that year.

In 1941, Huggins and Hodges first noted the beneficial effects of castration and injection of estrogens in participants with metastatic prostate cancer.[14] 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).[15] Nevertheless, most participants become resistant, with disease progression occurring within a median of 18 to 24 months of continuous hormonal manipulation.[16]

In 1996, mitoxantrone plus prednisone was approved for the treatment of patients with mCRPC based on improvement in pain palliation.[17] In 2004, two Phase 3 studies (TAX327 and SWOG S9916) demonstrated that docetaxel-based regimens can improve overall survival of

patients with mCRPC.[18,19] However, docetaxel-based treatment is associated with clinically significant toxicities that greatly limit its use in the management of lower risk, asymptomatic or minimally symptomatic mCRPC participants without visceral metastases. 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). 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[20] due to the occurrence of resistance mechanisms, including androgen receptor (AR) reactivation.[21] 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.[22] 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.

3.2.2 Nivolumab Mechanism of Action

Cancer immunotherapy rests on the premise that tumors can be recognized as foreign rather than as self and can be effectively attacked by an activated immune system. An effective immune response in this setting is thought to rely on immune surveillance of tumor antigens expressed on cancer cells that ultimately results in an adaptive immune response and cancer cell death. Meanwhile, tumor progression may depend upon acquisition of traits that allow cancer cells to evade immunosurveillance and escape effective innate and adaptive immune responses.[23,24,25] Current immunotherapy efforts attempt to break the apparent tolerance of the immune system to tumor cells and antigens by either introducing cancer antigens by therapeutic vaccination or by modulating regulatory checkpoints of the immune system. T-cell stimulation is a complex process involving the integration of numerous positive as well as negative co-stimulatory signals in addition to antigen recognition by the T-cell receptor (TCR).[26] 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.[27] PD-1 signaling has been shown to inhibit CD-28-mediated upregulation of IL-2, IL-10, IL-13, interferon-γ (IFN-γ), and Bcl-xL. PD-1 expression also been noted to inhibit T-cell activation and expansion of previously activated cells. Evidence for a negative regulatory role of PD-1 comes from studies of PD-1-deficient mice, which develop a variety of autoimmune phenotypes.[28] These results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self-antigens.

In vitro, nivolumab (BMS-936558) binds to PD-1 with high affinity (EC50 0.39-2.62 nM), and inhibits the binding of PD-1 to its ligands PD-L1 and PD-L2 (IC50 ± 1 nM). Nivolumab binds

specifically to PD-1 and not to related members of the CD28 family such as CD28, ICOS, CTLA-4, and BTLA. Blockade of the PD-1 pathway by nivolumab results in a reproducible enhancement of both proliferation and IFN-γ release in the mixed lymphocyte reaction (MLR). Using a CMV re-stimulation assay with human PBMC, the effect of nivolumab on antigen-specific recall response indicates that nivolumab augmented IFN-γ secretion from CMV-specific memory T-cells in a dose-dependent manner versus isotype-matched control. In vivo blockade of PD-1 by a murine analog of nivolumab enhances the anti-tumor immune response and result in tumor rejection in several immunocompetent mouse tumor models (MC38, SA1/N, and PAN02).[29] See the nivolumab IB for more information on the clinical pharmacology of this agent.

3.2.3 Mechanism of Action of Co-administered Therapeutic Agents

3.2.3.1 Rucaparib

Rucaparib is an inhibitor of PARP enzymes, including PARP-1, PARP-2, and PARP-3, which play a role in DNA repair. In vitro studies have shown that rucaparib-induced cytotoxicity may involve inhibition of PARP enzymatic activity and increased formation of PARP-DNA complexes resulting in DNA damage, apoptosis, and cell death. Increased rucaparib-induced cytotoxicity was observed in tumor cell lines with deficiencies in BRCA1/2 and other DNA repair genes. Rucaparib has been shown to decrease tumor growth in mouse xenograft models of human cancer with or without deficiencies in BRCA. See the rucaparib IB for more information.

3.2.3.2 Docetaxel

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.

3.2.3.3 Enzalutamide

Enzalutamide is an AR inhibitor that acts on different steps in the AR signaling pathway. See the current prescribing information for enzalutamide (SmPC, USPI, or country-specific label) for more information.

3.3 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.[22,30,31,32,33,34] 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.

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-related 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 [35,36], have provided support for further exploring the use of immune therapies in prostate cancer. Currently, clinical trials are underway evaluating the role of PD-1 inhibitor pembrolizumab, either alone or in combination with other immune therapies such as vaccines or cryosurgery, in hormone sensitive metastatic prostate cancer (HSPC) and mCRPC (NCT02312557, NCT02499835, NCT02489357, NCT02787005). Nivolumab is currently being evaluated in mCRPC in combination with ipilimumab in study CA209650. [37]

As outlined in Section 5.4.1, several lines of evidence support combination of immune therapies with chemotherapy, hormonal therapy and targeted therapy in men with mCRPC. The purpose of combination immune therapies is to enhance anti-tumor T-cell responses. There are robust clinical data suggesting the potential improvement in clinical outcomes in mCRPC with the combinations chosen in this study.

- Recently published early phase studies evaluating the combination of immune checkpoint blockade and PARP inhibitors demonstrated preliminary evidence of durable activity and a good safety profile in an unselected population with mCRPC[38], as well as in advanced solid tumors.[39,40] The majority of AEs, primarily hematologic toxicities, were manageable with supportive care, and no new AEs were noted.[39] To date, PARP inhibitors administered as monotherapy have been most extensively studied in the ovarian cancer population. Those PARP inhibitors furthest along in clinical development have demonstrated clinical activity and a manageable safety profile.'[41,42,43,44,45,46] Arm A of this study will evaluate nivolumab in combination with the PARP inhibitor rucaparib. Homologous recombination deficiency (HRD) status will be assessed in all participants. Given the hypothesis that increased DNA damage by PARP inhibition will increase the number of tumor neoantigens, thereby creating a more antigenic environment in which to stimulate the immune microenvironment, and the promising anti-tumor activity of similar combinations in patients without germline or somatic mutations in BRCA or other homologous recombination (HR) genes[39], both HRD-positive (HRD+) and HRD-negative (HRD-) participants will be enrolled (2:1 ratio).
- 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.[47] 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, ongoing internal and external studies of PD-L1 inhibitors in combination with chemotherapy suggest that this type of combination is tolerable and manageable, with no new safety signals being detected.

- In light of its immunomodulatory capacity, enzalutamide is an attractive combination agent with other immune treatments. Meaningful clinical activity and no unexpected AEs were seen when the combination of PD-1 inhibitor pembrolizumab and enzalutamide was evaluated in men with mCRPC.[48]

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 rucaparib, docetaxel or enzalutamide
- 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 the coadministered agents. In addition, a Study Steering Committee (consisting of selected participating investigators) will meet regularly to advise BMS regarding study-related issues, including safety concerns.
- Open-label drug administration of study treatments to allow for prompt and accurate assessment of the unique toxicities associated with study treatments

In conclusion, the overall risk-benefit of nivolumab in combination with rucaparib, docetaxel or enzalutamide in men with mCRPC is deemed acceptable.

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

4 OBJECTIVES AND ENDPOINTS

The following are the objectives and associated endpoints in this study of nivolumab combined with either rucaparib, docetaxel, or enzalutamide in participants with mCRPC and measureable disease at baseline:

Table 4-1: Objectives and Endpoints

Objectives	Endpoint
Co-Primary	
To evaluate the objective response rate per PCWG3 (ORR-PCWG3) in HRD+ participants and in all treated participants	ORR-PCWG3 is the proportion of participants who have a confirmed complete or partial best overall response (BOR) per PCWG3 among treated participants who have measurable disease. The BOR will be assessed by the investigator per PCWG3 and is recorded between treatment initiation 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.
To evaluate PSA response rate (RR-PSA) in HRD+ participants and in all treated participants	RR-PSA is the proportion of treated 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.
Secondary	
To evaluate radiographic progression-free survival (rPFS) in HRD+ participants and in all treated participants	rPFS is the time between treatment initiation and the first date of documented progression or death due to any cause, whichever occurs first. The radiographic progression will be assessed by the investigator per PCWG3. The rPFS will be censored at the last tumor assessment up to the start of subsequent systemic cancer therapy for those without progression/death.
To evaluate time to response (TTR) and duration of response (DOR) per PCWG3 (TTR-PCWG3 and DOR-PCWG3) in HRD+ participants and in all treated participants	TTR-PCWG3 is the time from treatment initiation to the date of the first documented CR or PR 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 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.
To estimate time to PSA progression (TTP-PSA) in HRD+ participants and in all treated participants	TTP-PSA is the time between treatment initiation to the date of PSA progression per PCWG3 in treated 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 at or 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 treatment initiation for participants with no post-baseline PSA evaluation.

Table 4-1: Objectives and Endpoints

Objectives	Endpoint
To assess overall survival (OS) in HRD+ participants and in all treated participants	OS is the time between treatment initiation 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 treatment initiation if they had no follow-up.
To evaluate overall safety and tolerability	Overall safety and tolerability will be measured by the incidence of AEs, SAEs, AEs leading to discontinuation, immune-mediated AEs, deaths, and laboratory abnormalities and changes from baseline
[redacted]	

Table 4-1: Objectives and Endpoints

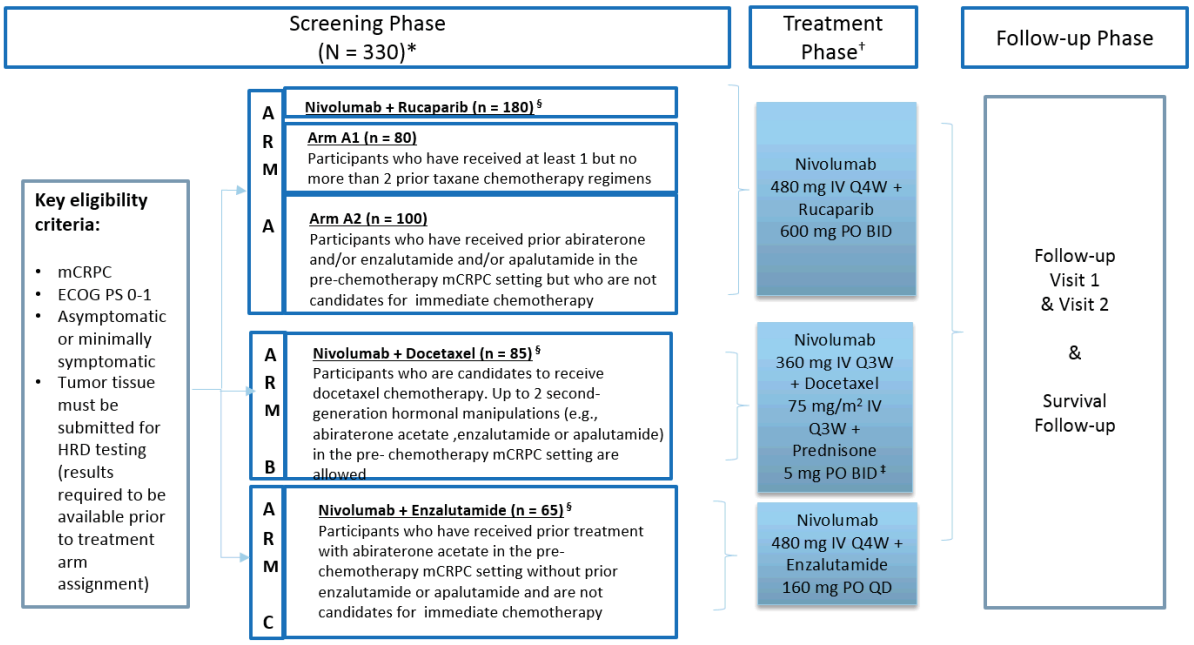
Objectives	Endpoint
[redacted]	

5 STUDY DESIGN

5.1 Overall Design

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

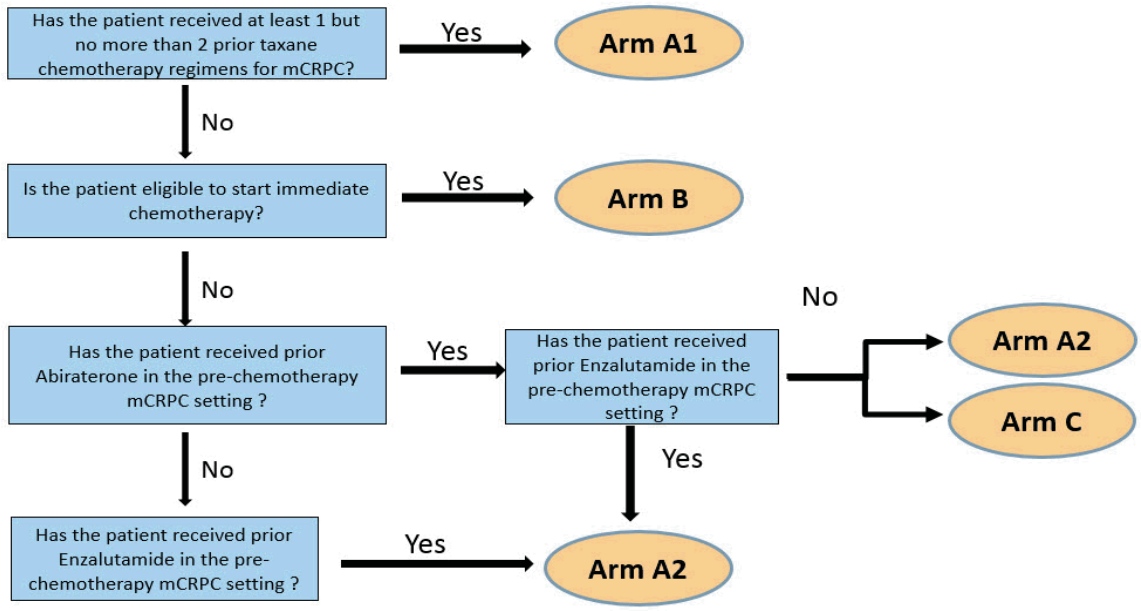
Figure 5.1-1: Study Design Schematic



* *60% of participants in each treatment arm are required to have measurable disease.*
† *Nivolumab will be given for up to 24 months. Rucaparib or enzalutamide will continue until progression.*
‡ *Docetaxel is given up to a maximum of 10 cycles. Nivolumab 480 mg Q4W will be administered as monotherapy after Cycle 10.*
§ *The planned number of HRD+ participants will vary and will be approximately 100 in Arm A, 25 in Arm B and 25 in Arm C.*

This is an open-label Phase 2 study of nivolumab in combination with rucaparib (Arm A), docetaxel (Arm B), or enzalutamide (Arm C) in men with mCRPC. Arm A is split into 2 sub-groups according to whether participants have received prior chemotherapy (Arm A1) or are chemotherapy naive (Arm A2). The study is not randomized, and treatment arm assignment will depend on prior systemic treatment history, as specified in protocol Section 6.1 and as illustrated in the decision tree provided in Figure 5.1-2.

Figure 5.1-2: Decision Tree Guiding Treatment Arm Assignment



Treatment arm assignment will also depend on 2 clinical variables: 1) the presence or absence of measurable disease on the baseline tumor assessment per investigator review; and 2) the presence or absence of HRD based on testing of a blood plasma and/or tumor tissue sample by the central laboratory during screening or by local laboratory prior to enrollment.

A participant is considered HRD+ if they have a deleterious genomic alteration (protein truncating or splice site mutation, homozygous deletion, large protein truncating rearrangement, or deleterious missense mutation) in plasma and/or tumor sample in at least one of the following HR genes: BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK2, FANCA, NBN, PALB2, RAD51, RAD51B, RAD51C, RAD51D, or RAD54L. HRD status will be determined by central laboratory testing of a submitted blood plasma and/or tumor sample during screening or by local laboratory testing performed prior to enrollment. If local HRD testing has been performed prior to enrollment, the local HRD test results must be documented in the participant's medical records and local HRD laboratory report must be provided to the Sponsor. The local HRD laboratory report must clearly document the presence of a pathogenic or deleterious mutation in one of the HR genes noted above in order for it to be acceptable for assignment to an HRD+ spot. If the records do not clearly indicate the patient's HRD status, the local testing results must be submitted to the sponsor for further interpretation of the HRD status.

Within each treatment arm, 60% of the available spots will be designated for participants who have measurable disease and 40% of the available spots will be designated for those who do not have measurable disease. In the entire study, approximately 45% of the available spots will be designated for participants who are HRD positive and approximately 55% will be designated for participants who are HRD negative or HRD not evaluable. However, the number of HRD+ versus

HRD- or HRD-not evaluable spots will vary in each arm as follows: 100 HRD+ and 80 HRD- or not evaluable in Arm A; 25 HRD+ and 60 HRD- or not evaluable in Arm B; 25 HRD+ and 40 HRD- or not evaluable in Arm C. Since the estimated prevalence of HRD+ status in this patient population is approximately 20%, it is anticipated that the HRD- or not evaluable spots will be filled before HRD+ spots, and the rate of accrual of HRD+ participants will largely determine the duration of the enrollment period. Enrollment in any of the study arms may be terminated early due to poor accrual.

The Interactive Response Technology (IRT) system will be used for treatment arm assignment. IRT will assign each participant to a treatment arm based on prior treatment history, measurable disease status, and HRD status. Additional details are specified in Section 7.2.The study will consist of 3 phases: screening, treatment, and follow-up.

Screening Phase:

- Begins by participant signing of the informed consent form (ICF) and establishing the participant's initial eligibility
- Participant is enrolled using the Interactive Response Technology (IRT).
- Obtain mandatory pre-treatment blood plasma and archival or fresh tumor tissue specimen. Central lab must provide IRT with the results of HRD testing on a submitted blood plasma and/or tumor sample prior to treatment assignment unless local lab HRD results obtained prior to enrollment are provided to the Sponsor and confirmed to be acceptable for treatment assignment.(Additional details can be found in Section 9.8.2.)

Tumor assessments must be performed within 28 days of treatment arm assignment.

Treatment Phase:

- Begins with the treatment arm assignment using the IRT
- Within 3 calendar days from treatment arm assignment the participant must receive the first dose of study medication (Day 1 of Cycle 1). See Section 7.1 for details on treatment administration.
  - Arm A dosing: nivolumab 480 mg IV Q4W plus rucaparib 600 mg PO BID
  - Arm B dosing: nivolumab 360 mg IV Q3W plus docetaxel 75 mg/m^2 IV Q3W plus prednisone 5 mg PO BID co-administered with docetaxel plus dexamethasone 8 mg PO administered in 3 doses prior to docetaxel infusion
  - Arm C dosing: nivolumab 480 mg IV Q4W plus enzalutamide 160 mg PO QD
- During the first cycle, a Day 15 study visit will occur. No study treatment will be administered.
- On-study laboratory assessments should be drawn within 72 hours prior to dosing.
- AE assessments should be documented at each clinic visit.
- PK samples [redacted] samples will be collected according to schedules in Section 9.5.
- Study drug dosing may be delayed for toxicity as described in Section 7.1.1.

- Each cycle during the treatment phase is expected to last 4 weeks for Treatment Arms A and C, through to PD or unacceptable toxicity, unless there are delays. For Arm B only, each cycle will last 3 weeks up to and through Cycle 10, at which point, cycle duration will change to 4 weeks and nivolumab 480 mg will be administered as monotherapy.
- Tumor assessments are scheduled to be performed every 8 weeks (± 7 days) for 24 weeks following treatment initiation and thereafter every 12 weeks (± 7 days) until radiographic progression or discontinuation of study treatment (whichever occurs later). Tumor assessments should be performed at these time points regardless of treatment schedule or dose delays.

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

Follow-Up Phase:

- Begins when the decision to discontinue a participant from study therapy is made (no further treatment with study therapy)
- If biopsy or surgical resection is performed at progression, a tumor sample (block or slides) should be submitted to the central laboratory
- Two safety follow-up visits will be conducted which include collection of PK [redacted] samples.
- 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 and Table 2-3 until progression.
- Participants will be followed for drug-related toxicities until these toxicities resolve, return to baseline or are deemed irreversible. All AEs will be documented for a minimum of 100 days after last dose.
- 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

The procedures specified in each phase can be found in Section 2.

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

5.1.1 Data Monitoring Committee and Other External Committees

To provide independent oversight of safety, efficacy, and study conduct, a DMC will be instituted. The DMC will meet regularly to ensure that participant safety is carefully monitored. The DMC will convene additional ad hoc meetings if necessary. Following each meeting, the DMC will recommend continuation, modification, or discontinuation of the study based on observed toxicities and efficacy. A separate DMC charter will describe the activities of this committee in more detail.

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.

Regarding external committees, no prospective Blinded Independent Central Review (BICR) is planned. The study will collect and hold images for future BICR assessments, as needed, per the Sponsor.

5.2 Number of Participants

Approximately 330 participants are planned to be enrolled and assigned treatment in 1 of 3 parallel treatment arms as follows:

- Arm A: 180 participants to receive nivolumab plus rucaparib
  - Arm A1 = 80
  - Arm A2 = 100
- Arm B: 85 participants to receive nivolumab plus docetaxel plus prednisone and dexamethasone
- Arm C: 65 participants to receive nivolumab plus enzalutamide

See Section 10.1 for a description of the sample size calculation.

5.3 End of Study Definition

The start of the trial is defined as the first visit for the first participant treated. End of trial is defined as the last visit or scheduled procedure shown in the Schedule of Activities for the last participant. Study completion is defined as the final date on which data for the co-primary endpoints are expected to be collected.

The total duration of the study from the date of first participant treated to final analysis of co-primary endpoints is expected to be approximately 2.5 years. In addition, survival analysis may be conducted for up to 5 years after treatment initiation following the analysis of the co-primary endpoints.

5.4 Scientific Rationale for Study Design

5.4.1 Rationale for Immunotherapy in mCRPC

Immunotherapy agents represent a promising approach for the management of asymptomatic and minimally symptomatic CRPC participants.

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.[49] 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.[50] The induction of regulatory or suppressor T cells[51] 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.[52,53]

An analysis of the prognostic significance of PD-1 and/or PD-L1 expression in a cohort of 535 prostate cancer tumors showed that a high density of PD-1+ lymphocytes independently predicted shorter clinical failure-free survival.[54] This may indicate that tumor immune escape, and thus tumor immune elimination, are important mechanisms in prostate cancer and the association of pathway molecules with poor prognosis makes them attractive targets for inhibition. 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.

- The inherent characteristics of prostate cancer make it an ideal target for immunotherapy. Prostate cancer is generally considered a slow growing tumor, which may allow adequate time for an immunotherapy agent to activate the immune system. Prostate cancer has many well-described tumor-associated antigens (TAAs), which may be ideal targets for immunotherapy, such as vaccines because they are specific to the cancer. Examples of TAAs for prostate cancer include PSA, prostatic acid phosphatase (PAP), and prostate-specific membrane antigen (PSMA). Targeting TAAs has led to the evaluation of therapeutic cancer vaccines designed to break immune tolerance[55] and are currently being explored in participants with early CRPC, ie, before chemotherapy, with vaccines of autologous origin[56], poxvirus[57], and PSA TRICOM.[58]

  Prostvac® (developed by the National Cancer Institute and licensed to BN Immunotherapeutics, Mountain View, CA), is a therapeutic prostate cancer vaccine, consisting of a recombinant vaccinia vector, as a primary vaccination engineered to express PSA and a triad of human T-cell costimulatory molecules (designated TRICOM). A multicenter randomized Phase 2 study that randomized minimally symptomatic mCRPC participants to Prostvac vs placebo showed preliminary evidence of improved overall survival.[59] 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.[22] While these preliminary 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.[60]

  While antigen-specific therapies such as vaccines have shown evidence of potential for benefit in the clinic, this approach has many limitations[10,61,62,63], underscoring the need to explore immunotherapy that does not rely mainly on the expression of a specific antigen.

- Prostate cancer has been shown to have low tumor expression of PD-L1.[3] In a Phase 1 study targeting PD-1, treatment with nivolumab was ineffective in unselected participants with CRPC (0/17 responses). However, immunotherapy agents in conjunction with SOC therapy could potentially result in increasing immune-mediated anti-tumor activity in subjects with prostate cancer as outlined in Section 5.4.2. Androgen-deprivation therapy (ADT), a mainstay of treatment for both high-risk early prostate cancer and recurrent and/or metastatic disease,

has been shown to alter the immune environment in prostate cancer.[9] For example, neoadjuvant ADT of prostate cancer patients results in increased numbers of infiltrating CD4 T-cells, CD8 T-cells, natural killer cells, and macrophages in prostate tissues.[7,8] Similarly, there is growing evidence that chemotherapy and PARP inhibitors can induce immuno-modulatory effects that could facilitate the induction of antitumor immunity.

Taken together, these lines of evidence strongly support the continued investigation of immunotherapy agents to improve outcomes in mCRPC by employing different agents that work via varied mechanisms of action and are potentially synergistic.

5.4.2 Rationale for Co-administration of Nivolumab with Selected Therapeutic Agents in mCRPC

5.4.2.1 Nivolumab plus Rucaparib

PARP inhibitors, a cancer therapy targeting poly (ADP-ribose) polymerase, are the first clinically approved drugs designed to exploit synthetic lethality. DNA replication and error-repair are a critical component of cancer cell survival. Suppression of PARP leads to stalling of replication forks due to the accumulation of unrepaired single-strand breaks (SSBs). Stalled replication forks degrade into highly cytotoxic double-strand breaks (DSBs) if not corrected by appropriate repair mechanisms, which are essentially absent in HR-mutated cells.[64] Since HR-mutated cells are incapable of homologous repair (considered the most precise DSB repair mechanism), PARP inhibition results in genomic instability and cell death.[65] Thus, tumors that harbor a defect in HR (and likewise a defect in DSB repair) seem to be highly vulnerable to the effects of PARP inhibition. Notably, these tumors include somatic and germline BRCA-1 and BRCA-2 mutations. In prostate cancer, there is a large subset of tumors with somatic mutations in genes involved in HR that have been reported to confer sensitivity to PARP inhibitors, including ATM, FANCA, CDK12, RAD51B, RAD51C, PALB2, CHEK2, and ETS gene fusions (TMPRSS2:ERG).[66,67,68,69] It would be premature to draw conclusions about which PARP inhibitors are most effective in particular patient populations; at present, the different clinical trial designs and distinct patient populations used to assess different PARP inhibitors preclude such direct comparisons.

Olaparib was approved in the US and EU in 2014 for the treatment of BRCA-mutation-related ovarian cancer in the treatment (US) or maintenance (EU) setting. Rucaparib was approved in the US in December 2016 for the treatment of patients with deleterious BRCA-mutation (germline and/or somatic)-associated, advanced ovarian cancer who have been treated with 2 or more chemotherapies. In March 2017, niraparib was approved in the US for the maintenance treatment of adult patients with recurrent ovarian, fallopian tube, or primary peritoneal cancer who have a complete or partial response to platinum-based chemotherapy.

Olaparib received a Food and Drug Administration (FDA) breakthrough therapy designation in 2016 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 acetate. The designation is based on data from the Phase 2 TOPARP-A trial which enrolled 50 participants. Ninety-six percent (96%) of the participants included in the study had received

prior enzalutamide, while 28% had received prior abiraterone. In addition, 100% of the participants had received prior docetaxel, and 58% had received prior cabazitaxel. In this study, the response rate to olaparib monotherapy (a composite endpoint defined as any of the following: response per RECIST v1.1; PSA response; or conversion of circulating tumor cell count) was 33% in the 49 evaluable participants. In the 16 participants with DNA-repair defects (DRD), 88% of participants had a response to olaparib vs 6% without DRD.[69] rPFS and OS for participants who had DRD or "biomarker positivity" were 9.8 months and 13.8 months, respectively, versus 2.7 months and 7.5 months, respectively, in those participants who were biomarker negative ($p < 0.001$ and $p = 0.05$ for respective analyses). Anemia (in 20% of participants) and fatigue (in 12% of participants) were the most common Grades 3 and 4 AEs, in keeping with other studies of olaparib. Ongoing clinical trials are testing the use of olaparib alone or in combination in participants with prostate cancer who have never received chemotherapy (NCT03047135, NCT03012321, and NCT02324998).

Currently, rucaparib is being evaluated in men with mCRPC in a Phase 2 study (NCT02952534) and a Phase 3 study (NCT02975934). Overall, the safety profile of rucaparib is manageable and generally consistent across completed and ongoing clinical trials. The recently published results from the ARIEL2 (Part 1) study show that treatment-related AEs in ≥ 15% of participants were generally low grade and included (in decreasing order of frequency) nausea, fatigue, dysgeusia, transient transaminitis, decreased appetite, vomiting, constipation, anemia, and diarrhea.[43] Additional details on the safety profile of rucaparib, including results from other clinical studies, are also available in the rucaparib IB.

The rationale for combining rucaparib with nivolumab in mCRPC derives from emerging data which demonstrate an important association between genomic loss of heterozygosity (LOH), high neoantigen load, and high expression of PD-1/PD-L1 in HRD tumors when compared with HR proficient ovarian cancers.[70,71,72] BRCA1 and BRCA2 mutations have been reported to increase the number of tumor-infiltrating lymphocytes (TILs) and are associated with improved overall survival.[73] A high mutational burden increases the likelihood of the development of tumor-specific neoepitopes that would confer clinical benefit from CTLA-4 and PD-1 blockade. Thus, it is hypothesized that increased DNA damage by PARP inhibition will increase the number of tumor neoantigens, creating a more antigenic environment in which to stimulate the immune microenvironment.

The combination of immune checkpoint inhibitors and PARP inhibitors has been recently evaluated in 3 early phase studies.[38,39,40] In a Phase 1 dose-escalation study of PD-L1 inhibitor durvalumab in combination with PARP inhibitor olaparib in 12 heavily pretreated participants (10 with ovarian cancer and 2 with triple-negative breast cancer), there were 4 participants with partial response (duration of response ≥ 15 months and ≥ 11 months) and 8 participants with stable disease ≥ 4 months (median, 8 months [4 to 14.5 months]), yielding an 83% disease control rate.[39] The most common treatment-emergent AE (TEAE) with durvalumab plus olaparib was hematologic toxicity, with no dose-limiting toxicity reported at the highest dose combination tested (olaparib 300 mg twice daily and durvalumab 1500 mg Q4W). The same combination is being

evaluated in an ongoing Phase 2 study in participants with mCRPC and appears to have clinical activity and to be well tolerated in an unselected patient population. Based on preliminary results in 19 participants (10 of whom are chemotherapy-naive), Grade 3/4 AEs included anemia (3/14, 21%), thrombocytopenia, lymphopenia, leukopenia, neutropenia, nausea, vomiting, hypertension, syncope, fatigue, UTI, and lung infection (1/14 each). Seven (7) out of 16 participants (44%) on-study for more than 2 months had PSA declines > 50%. Four (4) out of 17 response evaluable participants (23.5%) achieved a partial response per RECIST v1.1, with 3 responders demonstrating BRCA2 mutations. Six (6)-month and 9-month PFS were 86.7% and 57.8%, respectively. Median PFS had not yet been reached.[38] In a Phase 1/1b study, the combination of anti-PD-1 BGB-A317 and PARP inhibitor BGB-290 was generally well tolerated in 43 participants with advanced solid tumors.[40] Liver-related AEs were observed in 12 participants; all events were reversible with or without corticosteroid treatment. Complete or partial response was observed in 11 participants, 4 of whom had confirmed PR or CR; responses were durable and observed in participants with wild‑type and mutant germline BRCA (gBRCA) status. Taken together, these studies have not identified any new safety signals with the combination of a PARP inhibitor and a PD-L1 inhibitor.

PARP inhibitors have demonstrated activity in patients with HRD, which often occurs through genomic alterations (eg, BRCA1 and BRCA2 mutations) or epigenetic (eg, methylation) modifications.[43,69,74,75] They have also demonstrated activity in platinum-sensitive, recurrent ovarian cancer patients, regardless of the presence or absence of a gBRCA or a sBRCA mutation or other evidence of HRD.[43] In patients treated with rucaparib who had platinum-sensitive ovarian carcinomas associated with a BRCA mutation or whose tumors were BRCA wild-type and LOH high, PFS was longer than in patients with tumors which were BRCA wild-type and LOH low. This has also been confirmed by topline data from the Phase 3 ARIEL3 trial, where the rucaparib arm improved PFS over placebo in both BRCA wild type/HRD+ and BRCA wild type/HRD- subgroups, extending the potential usefulness of PARP inhibitors in the treatment setting beyond BRCA mutant tumors.

In addition, the combination of rucaparib and nivolumab has the potential for immuno-modulatory effects that may expand the activity of these agents beyond tumors with HRD. In the combination study of olaparib and durvalumab[39], none of the women receiving durvalumab plus olaparib for more than 9 months had a germline or somatic mutation in BRCA or other HR genes. In order to explore both of these populations, Arm A will evaluate the combination of rucaparib and nivolumab in both HRD+ and HRD-/not evaluable participants.

Both post-chemotherapy (Arm A1) and chemotherapy-naïve participants (Arm A2) will be included in Arm A. Although the TOPARP-A clinical trial included only post-chemotherapy patients, a reduction in the intratumoral PARP1 protein expression has been observed after administration of chemotherapy, suggesting that treating chemotherapy-naïve patients with PARP inhibitors might increase the responsiveness to PARP1 inhibition.[76] In the ongoing Phase 2 study evaluating the combination of olaparib and durvalumab in mCRPC, approximately 47% of participants enrolled thus far have not received prior chemotherapy. Furthermore, as previously

mentioned, several clinical trials are currently evaluating rucaparib (NCT02975934) and olaparib (NCT03012321; NCT03012321) in chemotherapy-naive, mCRPC participants. Therefore, based on the available evidence and on the potential benefit of adding nivolumab, this combination of nivolumab and rucaparib is also anticipated to be effective in the pre-chemotherapy setting.

5.4.2.2 Nivolumab plus Docetaxel

Docetaxel became the first chemotherapeutic agent to show an OS benefit in mCRPC, and was approved in combination with prednisone for this indication in the US in 2004. In the landmark TAX 327 Phase 3 trial[18], 1006 participants with mCRPC were randomized to receive daily prednisone and either mitoxantrone 12 mg/m^2 Q3W, docetaxel 75 mg/m^2 Q3W, or docetaxel 30 mg/m^2 QW for 5 of every 6 weeks. 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], 0.62-0.94; p = 0.009).

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. [77 , 78] Docetaxel has been reported to increase the production of proinflammatory cytokines which may enhance the immune response.[79] These findings have led to the development of clinical trials evaluating the combination of docetaxel and various immune therapy approaches. [80,81]

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 non-small cell lung cancer (NSCLC).[47] 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.

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 who are considered candidates to receive standard chemotherapy. Prednisone 5 mg PO BID will be administered to participants assigned to the docetaxel arm, per prescribing information.

In light of these data, Arm B will evaluate the combination of nivolumab and docetaxel in mCRPC participants eligible for chemotherapy.

5.4.2.3 Nivolumab plus Enzalutamide

Enzalutamide was approved in the US for post-chemotherapy and chemotherapy-naïve mCRPC patients in 2012 and 2014, respectively. A double-blind, placebo-controlled Phase 3 study, AFFIRM, showed that enzalutamide improved median OS compared to the placebo group in men with mCRPC who had previously received docetaxel (18.4 vs. 13.6 months, respectively; $p < 0.001$)[82]. A similar trend was seen in the double-blind, randomized, placebo-controlled, Phase 3 PREVAIL study, where enzalutamide was evaluated in men with chemotherapy-naïve mCRPC that had progressed despite the use of ADT[83]. The study met its coprimary endpoints, with significant improvements for enzalutamide versus placebo in both rPFS and OS. At 12 months of follow-up, the rate of rPFS was 65% for enzalutamide-treated participants versus 14% for participants receiving placebo (81% risk reduction; hazard ratio, 0.19; 95% CI 0.15, 0.23; $p < 0.001$). In an updated analysis of efficacy endpoints, median investigator-assessed rPFS was 20.0 months (95% CI 18.9–22.1) in the enzalutamide arm and 5.4 months (95% CI 4.1–5.6) in the placebo arm. Median OS was 35.3 months (95% CI 32.2–not yet reached) in the enzalutamide arm and 31.3 months (95% CI 28.8– 34.2) in the placebo arm[84].

While second-generation hormonal therapies such as enzalutamide and abiraterone represent significant advances in the treatment of mCRPC, approximately 20% to 40% of patients have primary resistance to these agents and exhibit no response with respect to PSA levels or other measures of clinical benefit [85, 86, 87, 88]. Furthermore, among patients who initially have a serological or clinical response to enzalutamide or abiraterone, virtually all eventually acquire secondary resistance over time.

The immunogenic modulation potential of ADT was first described using the murine TRAMP (transgenic adenocarcinoma of the mouse prostate) model of prostate carcinoma[89]. Exposure of TRAMP-C2 prostate tumor cells to enzalutamide significantly enhanced cell-surface expression of the death receptor Fas and MHC Class I resulting in improved sensitivity to immune-mediated lysis *in vitro*. Mice receiving the combination of enzalutamide and a therapeutic vaccine targeting Twist had significantly increased overall survival as compared to either no treatment or monotherapy alone. Notably, the effectiveness of the combination therapy increased with disease stage, with the greatest survival benefit seen in mice with advanced-stage prostate tumors.

A follow-up study has demonstrated that prostate tumor cells harboring AR amplification, a major mechanism of ADT resistance, were rendered more sensitive to immune-mediated lysis in response to enzalutamide treatment, highlighting the potential efficacy of ADT-induced immunogenic modulation even in ADT-resistant patients.[90] Various AR-dependent as well as AR-independent mechanisms likely play a role in the development of resistance to these novel antiandrogens, including upregulation of AR and CYP17, induction of AR splice variants, AR point mutations, activation of alternative oncogenic signaling pathways, and immune evasion via PD-L1 upregulation. While both enzalutamide and abiraterone significantly prolonged OS for chemotherapy-naïve men with mCRPC, the efficacy of enzalutamide after abiraterone has only been evaluated in small retrospective studies which have indicated potential cross-resistance between treatment with abiraterone and enzalutamide.[91,92] No robust criteria exist clinically to select one drug rather than the other.[91,93] The presence of AR splice variants without the ligand-binding domain has been associated with resistance to abiraterone and enzalutamide and could be one explanation for this significant cross-resistance.[94]

Furthermore, recent studies have shown that treatment of certain prostate cancer cell lines with anti-androgens (including enzalutamide) can induce tumoral PD-L1 expression and that enzalutamide-resistant prostate cancer cell lines demonstrate striking expression of PD-L1.[95]These results are aligned with preclinical findings indicating increased amounts of circulating PD-L1/2-positive dendritic cells and increased levels of tumor-intrinsic PD-L1 in mice with enzalutamide-resistant tumors.[95,96] As such, immune evasion of prostate cancer via upregulation of PD-L1 may possibly play a role in the development of resistance to novel antiandrogen therapy such as enzalutamide or abiraterone. Based on these observations, the addition of pembrolizumab upon enzalutamide failure was evaluated in a single-arm, Phase 2 study. The study demonstrated meaningful clinical activity to PD-1 blockade in men with mCRPC and no unexpected AEs.[48]

Findings from these studies provide a rationale for combination strategies that include ADT, particularly with enzalutamide, and immunotherapy as a promising treatment option for prostate cancer. In light of enzalutamide's immunomodulatory capacity and the existing clinical data on the combination of pembrolizumab and enzalutamide, Arm C will explore the combination of enzalutamide and nivolumab in men with mCRPC who have demonstrated either primary or secondary resistance to abiraterone.

5.4.3 Rationale for Sample Size Determination

Estimates of reference ORR-PCWG3 and RR-PSA in analysis cohorts from the 3 arms are provided in Table 5.4.3-1 for power assessments. See Section 10.1 for a description of the sample size calculation for each analysis cohort.

Table 5.4.3-1: Estimates of Reference ORR and PSA Response (≥ 50%) Rate in Target Populations

Monotherapy in Target Population	ORR	PSA Response Rate
Rucaparib for target population in Arm A1	10%	20%
Rucaparib for target population in Arm A2	21%	47%
Docetaxel for target population in Arm B	21%	47%
Enzalutamide for target population in Arm C	10%	25%

For the power assessment with expected benefit in each analysis cohort in Arm A, the estimates of ORR and RR-PSA are based on the current SOC:

- Arm A1 will include participants in the post-chemotherapy setting who would be treated with either second-line cabazitaxel or with supportive care only if they had already received 2 prior taxane-based regimens. The estimates of ORR and RR-PSA for second-line cabazitaxel are 14% and 30%, respectively. According to studies conducted in the post-chemotherapy setting that compared second-generation hormone therapies with placebo, participants who received placebo had a 3% to 4% ORR and a 2% to 6% RR-PSA.[82,88] Therefore, the estimates of 10% ORR and 20% RR-PSA for SOC in the chosen population are considered appropriate.
- Arm A2 will include participants who are chemotherapy-naive for mCRPC who have received prior treatment with abiraterone acetate and/or enzalutamide. The current SOC after progression with second-generation hormone therapies is docetaxel chemotherapy. Estimates of ORR and RR-PSA for docetaxel monotherapy were extrapolated from the FIRSTANA Phase 3 study which evaluated docetaxel vs cabazitaxel as the first-line treatment of mCRPC.[97] In the docetaxel arm (n = 391), ORR was 30.9% (RECIST v1.1) and 68% of participants had a PSA decline > 50%. Considering that a) the administration of docetaxel after one or both of newer AR pathway inhibitors may have less activity than in the pivotal trials [98], b) in the FIRSTANA study, only approximately 3% of participants had received prior abiraterone or enzalutamide, and c) the target population in Arm B will include a much higher percentage of participants who have received prior abiraterone or enzalutamide, the estimates based on the FIRSTANA study would be considered too optimistic. The estimate of RR-PSA was therefore modified taking into account the data from the COU-AA-302 post-hoc analysis where docetaxel post-abiraterone treatment led to a PSA response rate of 27%. [99] A null RR-PSA of 47%, which is between those obtained in the FIRSTANA study and COU-AA-302 post hoc analysis, has been chosen. A similar RR-PSA was achieved in the docetaxel arm of TAX327 study where 45% of participants had at least a 50% decrease in the serum PSA level.[18] As the COU-AA-302 post-hoc analysis did not report the rate of radiological responses, the estimate of 21% ORR for docetaxel monotherapy was obtained by taking into account the ORR from

the FIRSTANA study and the ORR from a retrospective evaluation of the activity of docetaxel in patients previously treated with abiraterone (ORR of 11%).[100]

For the power assessment with expected benefit in Arm B, the estimates of 21% for ORR and 47% for RR-PSA are based on docetaxel monotherapy and follow the same rationale described in Arm A2.

For the power assessment with expected benefit in Arm C, the estimates of ORR and RR-PSA were extrapolated from a Phase 4, multicenter, open-label, single-arm study of enzalutamide in participants with mCRPC who had progressive disease (PD) following prior treatment with abiraterone plus prednisone.[101] The overall ORR in participants with measurable disease at study entry was 12% and PSA response rate was 26.5%. Although this prospective series included only participants likely to respond to enzalutamide (ie, those who previously responded for at least 6 months to abiraterone) as opposed to the target population in Arm C which will include participants regardless of prior response to abiraterone, a similar RR-PSA (23.5%) was also reported in a small retrospective study in mCRPC participants treated with enzalutamide after abiraterone.[102] Therefore, the estimates of 10% ORR and 25% RR-PSA for enzalutamide monotherapy post-abiraterone are considered appropriate in the chosen population.

Rationale for increasing the number of HRD negative/not evaluable participants in ARM A (amendment 02) [103],[104]

Results of recent studies suggest a benefit of PARPi combinations regardless of homologous recombination repair (HRR) mutation status. In a recently published phase II trial[103], 142 patients with mCPRC were randomly assigned to receive olaparib and abiraterone (n=71) or placebo and abiraterone (n=71). Olaparib in combination with abiraterone provided clinical efficacy benefit for patients with mCRPC compared with abiraterone alone regardless of HRR mutation status (rPFS in HRR mutation-positive subgroup: 17·8 months in the olaparib group vs 6·5 months in the placebo group; rPFS in wild-type HRR subgroup: 15·0 months in the olaparib group vs 9·7 months in the placebo group). Furthermore, the combination with nivolumab has the potential for immuno-modulatory effects that may expand the activity of the combination beyond tumors with HRD. An update on the results of the combination of immune checkpoint inhibitor durvalumab and PARP inhibitor olaparib[104] showed that rPFS of the biomarker-negative group was greater than the rPFS reported with monotherapy olaparib (4.8 months vs 2.7 months, respectively). In this study, 2 out of the 9 patients with PSA responses were HRD-/not evaluable.

Thus, the sample size of HRD negative/not evaluable patients in ARM A will be increased by a total of 30 subjects: 15 additional subjects in ARM A1 and 15 additional subjects in ARM A2. This will extend the potential clinical benefit of the combination to additional HRD negative/not evaluable mCRPC patients and will increase the precision approach for the co-primary endpoints in treated subjects with measurable disease at baseline and HRD- status (please refer to Table 10.1-1 for further statistical details).

5.4.4 Rationale for Evaluating Asymptomatic or Minimally Symptomatic Metastatic CPRC Participants (ARM A2 and ARM C subjects)

Treatment for metastatic prostate cancer is not curative and treatment-related side effects can adversely affect QoL. Therefore, a question remains for asymptomatic patients as to whether to start therapy as soon as metastatic disease is diagnosed or whether to delay treatment until significant symptoms are present. In 2004, in the IMPACT trial, docetaxel became the first approved therapy to prolong survival for men with mCRPC. [18,19] Subsequently, since 2010, 6 novel therapies have been shown to prolong survival in men with mCRPC.[105] The trials have demonstrated prolongation of OS as well as trends toward preserved QoL, albeit less rigorously assessed and documented.[106] Of note, all of these new therapies in mCRPC have distinct mechanisms of action and include unique classes of agents: novel AR pathway inhibitors (abiraterone acetate [abiraterone] and enzalutamide) as well as a bone-targeting, alpha-emitting radionuclide, radium-223 chloride (radium-223) taxanes (docetaxel and cabazitaxel), and an immunotherapeutic agent (sipuleucel-T).

Of the 6 new therapies that have been approved since 2010 for mCRPC, sipuleucel-T prolonged OS among asymptomatic men with mCRPC, with a relative reduction of 22% in the risk of death as compared to the placebo group, and an improvement of 4.1 months in median survival. It is believed that improved survival in the absence of significant PSA or tumor growth effects perhaps is a result of the effects on tumor progression kinetics, with slowed growth over time rather than immediate tumoral kill as evidenced with the use of cytotoxic chemotherapy.[107] Therefore, patients who exhibit aggressive disease would not be appropriate candidates for initial vaccine therapy, as the potential benefits from vaccine treatment tend to be delayed. Although the IMPACT trial shows that the separation of the curves was first apparent after about 6 months post-therapy across all participants, about half of the men subsequently commenced chemotherapy at a median of 12–13 months, suggesting that anticipation of a need for chemotherapy perhaps in the next 6 months to 1 year should prompt the question regarding the appropriateness of institution of sipuleucel-T. Similar observations were also reported in other vaccine trials. For instance, in the National Cancer Institute PSA-TRICOM studies, participants were divided into those who have aggressive and indolent disease. Not surprisingly, those with a predicted Halabi nomogram survival of less than 18 months showed no marked improvement in survival while those who had a predicted Halabi nomogram survival of more than 18 months had a median survival that was not reached at the time of reporting.[108] More recently, 2 second-generation hormone therapies, abiraterone acetate[85] and enzalutamide[84] targeting inhibition of the AR signaling pathway have been investigated and shown to prolong OS in large Phase 3 trials in minimally symptomatic participants in the pre-docetaxel setting. Enzalutamide extended time to radiographic progression and death as well as improved OS in men with asymptomatic or minimally symptomatic mCRPC prior to receiving chemotherapy.[84] Enzalutamide also delayed PSA progression, decline in performance status and time until the first skeletal-related event, and delayed median time to chemotherapy by 17 months, with a favorable tolerability profile. Similar to enzalutamide,

abiraterone was shown to delay radiographic progression and time to chemotherapy in men with mCRPC.[85]

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

For example, the timing of chemotherapy had always been a matter of debate, and with the advent of novel androgen therapies, the initiation of chemotherapy has become more protracted.[109] One of the greatest concerns with the use of chemotherapy is myelosuppression, especially in light of potential comorbidities. Therefore, chemotherapy is often reserved for the more symptomatic patients (eg, those with pain or with rapid progression) such as those with fast PSA doubling times. However, patients who have symptomatic disease tend to have less benefit from docetaxel treatment and the presence of pain confers a worse OS .[110,111]

The first St Gallen Advanced Prostate Cancer Consensus Conference (APCCC) Expert Panel reviewed the available evidence for the 10 most important areas of controversy in advanced prostate cancer (APC) management to provide management recommendations based on expert opinion in these situations.[106] Of note, for participants with mCRPC in the absence of symptoms and imminent complications, two-thirds of the APCCC panel recommended that agents with potential for survival prolongation should be initiated within 4 to 8 weeks.

Taken together, these data suggest that asymptomatic or minimally symptomatic mCRPC participants may in fact be optimal candidates for the evaluation of immunotherapy in combination with other therapeutic agents in ARM A2 and ARM C, with the possibility of achieving long term remission from disease.

5.4.5 Rationale for Treatment Beyond PSA Elevation

For consistency of trial reporting, the PCWG3 defines PSA progression as the date that an increase of 25% or more and an absolute increase of 2 ng/mL or more from the nadir are documented. For participants who had an initial PSA decline during treatment, this must be confirmed by a second consecutive value 3 or more weeks later. However, PSA progression alone is not necessarily an indication to stop treatment, because in some cases, PSA levels may rise slowly after an initial rise or stabilize after an initial rise with no other sign of clinical progression. Because there are cases in which additional years of disease control would not have been realized had therapy been stopped on the basis of PSA change alone, therapy will not be stopped for participants with apparent PSA progression alone. However, participants meeting criteria for discontinuation of therapy (Section 8) and PSA elevation will discontinue study treatment.

5.4.6 Rationale for Duration of Treatment

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 2-4 months, and emerging data suggests that benefit can be maintained in the absence of continued treatment. A recent analysis in a melanoma study suggests the majority of patients who discontinue nivolumab for toxicity maintain disease control in the absence of further treatment.[112] 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.

Accumulating data suggest that 2 years of PD-1 checkpoint inhibitor treatment may be sufficient for long term benefit. CA209003, a dose-escalation cohort expansion trial evaluating the safety and clinical activity of nivolumab in patients with previously treated advanced solid tumors (including 129 subjects with NSCLC), specified a maximum treatment duration of 2 years. Among 16 subjects with non-small cell lung cancer (NSCLC) who discontinued nivolumab after completing 2 years of treatment, 12 subjects were alive >5 years and remained progression-free without any subsequent therapy. In the CA209003 NSCLC cohort, the overall survival (OS) curve begins to plateau after 2 years, with an OS rate of 25% at 2 years and 18% at 3 years.[113] These survival outcomes are similar to phase 3 studies in previously treated NSCLC, in which nivolumab treatment was continued until progression or unacceptable toxicity (2 year OS rates of 23% and 29%, and 3 year OS rates of 16%-18% for squamous and non-squamous NSCLC respectively).[114]

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.[115]

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.[116]

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

In contrast, a shorter duration of nivolumab of only 1 year was associated with increased risk of progression in previously treated patients with NSCLC, suggesting that treatment beyond 1 year is likely needed. In CA209153, patients with previously treated advanced NSCLC who completed

1 year of nivolumab therapy were randomized to either continue or stop treatment, with the option of retreatment upon progression. Among 163 patients still on treatment at 1 year and without progression, those who were randomized to continue nivolumab had significant improvement in progression-free survival (PFS) compared to those who were randomized to stop treatment, with median PFS (post-randomization) not reached vs 10.3 months, respectively; HR=0.42 (95% CI, 0.25 to 0.71). With a median follow-up of 14.9 months post-randomization, there also was a trend for patients on continued treatment to live longer (OS HR = 0.63 [95% CI: 0.33, 1.20]). Of note, the PFS curves in both groups plateau approximately 1 year after randomization (i.e., 2 years after treatment initiation), suggesting that there may be minimal benefit in extending treatment beyond a total of 2 years. [117]

Collectively, these data suggest that there is minimal if any benefit derived from continuing I-O treatment beyond two years in advanced tumors. However, even though immunotherapy is well tolerated, patients will be at risk for additional toxicity with longer term treatment. For these reasons, in study CA2099KD, treatment with nivolumab will be given for a maximum of 2 years from the start of study treatment, in the absence of disease progression, unacceptable toxicity, withdrawal of participant consent, or the end of the study, whichever occurs sooner.

Co-administered Medications

The duration of treatment for rucaparib, docetaxel, and enzalutamide 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.[18] Administering more than 10 cycles of docetaxel has not demonstrated any further improvement in survival and is associated with more adverse effects.[118,119] 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. Rucaparib and ezalutamide will also be administered until disease progression, unacceptable toxicity, withdrawal of participant consent, or the end of the study, whichever occurs sooner.

Please consult the rucaparib IB and current prescribing information for docetaxel and enzalutamide for further details concerning administration.

5.4.7 Rationale for Nivolumab 30-Minute Infusion

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

5.4.9 Rationale for Interim Analysis

An interim analysis will be performed in each arm when at least 50% of planned subjects have been treated, with at least 16 weeks of follow-up after first dose. The purpose of the interim analysis is to generate preliminary data that will inform decisions related to external studies, as well as determine if any of the study arms should be expanded to generate additional data that may support a regulatory filing. If the data from the initial interim analysis appear to be immature to support decision-making on the expansion of a specific study arm, a second interim analysis of that arm may be performed after enrollment has been completed and all treated patients have been followed for at least 16 weeks after first dose.

Expansion guidance for each arm, based on a comparison between interim ORR in that arm and the standard of care for the patient population in that arm, are described in Section 10.3.4. Given that arm expansion is intended to support a potential regulatory filing, the assumptions for standard of care references noted below may be different than those noted above in Table 5.4.3-1 in order to meet regulatory standards.

In Arms A1 and A2, given the differential activity of PARP inhibitors in patients with HRD mutations, HRD+ and HRD-/NE subgroups may be analysed separately with independent expansion rules for each subgroup. The estimate of reference ORR for HRD+ subgroups in these arms is based on preliminary data from TRITON-2, where rucaparib monotherapy showed an ORR of 28% (13/46) in men with HRD+ mCRPC.[120]

For the HRD-/NE subgroup in Arm A1, the estimate of reference ORR is based on the standard of care cabazitaxel in the docetaxel-pretreated mCRPC population (ORR 14%). For the HRD-/NE subgroup in Arm A2, the reference ORR is based on the standard of care docetaxel (ORR 21%) in chemo-naive mCRPC patients. Please refer to Section 10.1 for details on how the estimate of 21% ORR for docetaxel monotherapy was obtained.

In Arms B and C, the expansion rules will apply to the all-comer population, as the impact of HRD status on sensitivity or resistance to docetaxel or novel hormonal therapies remains unclear at this time. A reference ORR of 21% for docetaxel monotherapy in mCRPC will be used in both arms.

Estimates for the reference ORR in each arm or subgroup may be adjusted as new data for treatments in these settings become available.

In any arm or subgroup that is expanded, interim analyses in the additional participants treated in the expansion with at least 16 weeks of follow-up after first dose may be performed if needed to determine if the data may be sufficient to support a regulatory filing.

5.5 Justification for Dose

5.5.1 Dose Justification for Nivolumab

Nivolumab monotherapy has been extensively studied in multiple tumor types, including melanoma, NSCLC, RCC, cHL, small cell carcinoma of the head and neck (SCCHN) and urothelial carcinoma (UC), using body weight normalized dosing (mg/kg), and has been safely administered at doses up to 10 mg/kg Q2W. Nivolumab is currently approved for the treatment of the above-mentioned tumors using a regimen of either nivolumab 240 mg Q2W or nivolumab 3 mg/kg Q2W. Additionally, nivolumab is currently approved for advanced melanoma in combination with ipilimumab using a regimen of nivolumab 1 mg/kg with ipilimumab 3 mg/kg administered every 3 weeks for 4 doses, and then nivolumab 3 mg/kg or 240 mg every 2 weeks in the maintenance phase.

5.5.1.1 Dose Justification for Nivolumab 480 mg IV Q4W

A nivolumab dose of 480 mg given every 4 weeks (Q4W) was selected for this study based on available PK, safety, and efficacy data.

Nivolumab PK has been extensively studied in multiple tumor types, including melanoma, 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 indications1,2. 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 (34-180 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.

5.5.1.2 Dose Justification for Nivolumab 360 mg IV Q3W

Additionally, nivolumab will be administered as a flat dose of 360 mg once every 3 weeks (Q3W) in combination with docetaxel, in order to maintain synchronized dosing of both agents. The safety and efficacy of 360 mg Q3W flat dose of nivolumab is expected to be similar to the approved dose of 3 mg/kg Q2W. The nivolumab dose of 360 mg Q3W was selected based on clinical data and modeling and simulation approaches using PPK and exposure-response analyses of data from studies in multiple tumor types (melanoma, NSCLC, and RCC) where body-weight normalized dosing (mg/kg) has been used. Using the PPK model, the overall distributions of nivolumab average steady-state exposures (Cavgss) are comparable after treatment with either nivolumab 3 mg/kg Q2W or 360 mg Q3W. The flat dose regimen of 360 mg Q3W is predicted to result in approximately 23% higher maximum steady state concentrations (Cmaxss) and approximately 6% lower steady state trough concentrations (Cminss) compared to the reference regimen of 3 mg/kg Q2W. Across the various tumor types in the clinical program, nivolumab has been shown to be safe and well tolerated up to a dose level of 10 mg/kg, and the relationship between nivolumab exposure and efficacy and safety has been found to be relatively flat. Although nivolumab Cmaxss is predicted to be higher following 360 mg Q3W, these exposures are predicted to be below the exposure ranges observed at doses up to 10 mg/kg Q2W used in the nivolumab clinical program,

and are not considered to put participants at increased risk. Similar to nivolumab 480 mg Q4W regimen as described above, the exposures predicted following administration of nivolumab 360 mg Q3W are on the flat part of the exposure-response curves for previously investigated tumors, melanoma, NSCLC, and RCC, and are not predicted to affect efficacy. Based on these data, nivolumab 360 mg Q3W is expected to have similar efficacy and safety profiles to nivolumab 3 mg/kg Q2W. The nivolumab Q3W regimen with docetaxel is being investigated to allow the participant to receive both study medications on the visits to the clinic.

5.5.2 Dose Justification for Nivolumab 480 mg IV Q4W and Rucaparib 600 mg PO BID

As discussed in Section 5.4.2.1, a Phase 1 dose-escalation study of durvalumab in combination with olaparib in pretreated ovarian and triple-negative breast cancer patients is being conducted.[39] The dose levels for this combination are also being evaluated in an ongoing Phase 2 study in participants with mCRPC and appears to be well tolerated, with the most common Grade 3/4 AEs also being hematologic toxicity.[38] These studies have not identified any new safety signals when giving PARP inhibitor and an anti-PD-L1 antibody in combination. The starting dose for the combination of nivolumab plus rucaparib in this study will be the standard monotherapy doses for each agent, the mechanisms of action of the 2 agents are different and their toxicities are not predicted to be cumulative. Dosing of rucaparib in combination with nivolumab is based upon doses recommended in the current prescribing information for these agents. Please see this prescribing information and the respective IBs for nivolumab and rucaparib for further information on dosing. Dose Justification for Docetaxel 75 mg/m^2 Q3W and Enzalutamide 160 mg PO QD.

Dosing of docetaxel and enzalutamide in combination with nivolumab is based upon doses recommended in the current prescribing information for these agents. Please see this prescribing information for more information.

6 STUDY POPULATION

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

6.1 Inclusion Criteria

1) **Signed Written Informed Consent**
   a) Willing and able to provide informed consent
2) **Type of Participant and Target Disease Characteristics**
   a) Histologic confirmation of adenocarcinoma of the prostate. Diagnosis must be stated in a pathology report and confirmed by the investigator.
   b) Evidence of stage IV disease (as defined by AJCC criteria[1]) on previous bone, CT, and/or MRI scan
   c) 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 subjects 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.

d) Documented prostate cancer progression as per PCWG3 criteria[121] 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).

      * Participants who received an anti-androgen must have 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. Participants whose disease spread is limited to regional pelvic lymph nodes (N1) measuring at least 2 cm in short axis will be considered eligible.
   iii) Radiographic disease progression in bone defined as appearance of 2 or more new bone lesions on bone scan.

   NOTE: Radiographs must be collected and transmitted to the central imaging vendor at study entry
e) ECOG performance status 0-1 (Appendix 7)
f) mCRPC participants will be assigned to a study arm as follows:
   i) **Arm A**: Participants must meet either of the following criteria:
      (1) **Arm A1:** Participants who have received at least 1 but no more than 2 prior taxane-based regimens for castration-resistant disease. If docetaxel chemotherapy is used more than once, this will be considered as one regimen. Up to 2 second generation hormonal manipulations for castration-resistant disease are allowed.
      (2) **Arm A2**: Participants who are chemotherapy-naive for mCRPC who have received prior treatment with at least 1 but no more than 2 second-generation hormonal manipulations (eg, abiraterone acetate,enzalutamide, apalutamide) for castration-resistant disease up to 28 days prior to study arm assignment and are not candidates for or refuse immediate chemotherapy
   ii) **Arm B**: Participants who are chemotherapy-naive for mCRPC who are candidates to receive docetaxel chemotherapy. Up to 2 second-generation hormonal manipulations (eg, abiraterone acetate, enzalutamide, apalutamide) for castration-resistant disease are allowed up to 28 days prior to study arm assignment.
   iii) **Arm C**: Participants who are chemotherapy-naive for mCRPC who have received prior treatment with abiraterone acetate for castration-resistant disease up to 28 days prior to study arm assignment without prior enzalutamide or apalutamide, and are not candidates for or refuse immediate chemotherapy.
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 treatment arm assignment.

h) Prior prostate cancer vaccine therapy, radiation therapy, radium-223, antiandrogens (eg, flutamide), ketoconazole, and diethylstilbestrol (DES) or other estrogens, are allowed up to 28 days prior to study arm assignment. Note: bicalutamide or nilutamide must be discontinued within 6 weeks of study arm assignment.
   i) Participants with a history of response to an anti-androgen or adrenal androgen-production inhibitor and with subsequent progression while receiving that anti-androgen should be assessed for anti-androgen withdrawal response for 4 weeks, and must demonstrate progression as described in Inclusion Criterion 2d, and have stopped receiving the anti-androgen prior to treatment arm assignment.
   ii) For participants who have never responded to anti-androgens, observation for anti-androgen withdrawal response is not necessary.

i) For Arm A2 and Arm C, asymptomatic or minimally symptomatic mCRPC according to Brief Pain Inventory - Short Form (BPI-SF) performed during screening:
   i) Asymptomatic is defined as BPI-SF item #3 score of 0 to 1
   ii) Minimally symptomatic is defined as BPI-SF item #3 score of 2 to 4

   Note: Any cancer-related pain must not require any opiate analgesics (including codeine and dextropropoxyphene) within 5 days prior to treatment initiation.

j) Sufficient plasma and, fresh or archival tumor tissue obtained within 5 years prior to enrollment from a metastatic tumor lesion or from a primary tumor lesion that has not been previously irradiated (formalin-fixed paraffin-embedded [FFPE] block or unstained tumor tissue sections). Tumor sample may be from core biopsy, punch biopsy, excisional biopsy, or surgical specimen). Fine needle aspiration is unacceptable for submission. See Section 9.8.2 for additional details. Central laboratory must confirm receipt of plasma and tumor samples prior to IRT treatment arm assignment.

k) Results of central HRD testing of the submitted plasma or tumor samples must be available in IRT prior to treatment arm assignment. If local HRD test results obtained prior to enrollment are provided to Sponsor, they should be confirmed to be acceptable for treatment assignment, and results will be transmitted to IRT prior treatment arm assignment

3) Age and Reproductive Status

a) Males, ages 18 or local age of majority and older, inclusive.

b) Males who are sexually active with women of child-bearing potential (WOCBP) must agree to follow instructions for method(s) of contraception for the duration of study treatment and 7 months after the last dose of study treatment (ie, 90 days [duration of sperm turnover] plus the time required for the investigational drug to undergo approximately five half-lives).

c) Azoospermic males are exempt from contraceptive requirements.

d) Male participants must be willing to refrain from sperm donation during the entire study and for 7 months after the last dose of study treatment plus 90 days (5 half-lives plus the duration of sperm turnover) after dosing has been completed.

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) Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the breast.

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 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 must be discussed with the BMS Medical Monitor or designee. Previously irradiated brain lesions are not considered measurable disease.

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

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

e) All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue must have resolved to Grade 1 (NCI CTCAE version 4.03) 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.

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

h) 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.

i) 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.

j) 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.

k) The following exclusion criteria apply to **Arm A** only:

   i) Participants with myelodysplastic syndrome/acute myeloid leukemia.

   ii) Gastrointestinal disorders likely to interfere with absorption of the study medication

l) The following exclusion criterion applies to **Arm B** only:
   i) Participants who have ≥ Grade 2 peripheral neuropathy (NCI CTCAE version 4.03)

m) The following exclusion criteria apply to **Arm C** only:
   i) History of seizure or any condition that may have a predisposition to seizure. Also, history of loss of consciousness or transient ischemic attack within 12 months of enrollment (Day 1 visit)
   ii) History of prostate cancer progression on ketoconazole
   iii) Gastrointestinal disorders likely to interfere with absorption of the study medication
   iv) History of Mobitz II second-degree or third-degree heart block without a permanent pacemaker in place
   v) Hypotension as indicated by systolic blood pressure < 86 mm Hg at the screening visit
   vi) Bradycardia as indicated by a heart rate of < 50 beats per minute on the screening ECG
   vii) Uncontrolled hypertension as indicated by systolic blood pressure > 170 mm Hg or diastolic blood pressure > 105 mm Hg at the screening visit

n) 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 of faint renal activity (absent kidney sign).

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) Radiotherapy to the pelvic region within 3 months prior to treatment arm assignment

d) Radiotherapy to symptomatic bone lesions within 14 days prior to treatment arm assignment.

e) The following exclusion criteria apply to **Arm A** only:
   i) Prior PARP inhibitor treatment[122], mitoxantrone, cyclophosphamide, or platinum-based chemotherapy
   ii) Arm A2 only: Prior chemotherapy for mCRPC. Prior docetaxel for metastatic hormone-sensitive prostate cancer is allowed if ≥ 12 months elapsed from last dose of docetaxel

f) The following exclusion criterion applies to **Arm B** only:
   i) Prior treatment with docetaxel or another chemotherapy agent for metastatic castration-resistant prostate cancer. Prior docetaxel for metastatic hormone-sensitive prostate cancer is allowed if ≥ 12 months elapsed from last dose of docetaxel.

g) The following exclusion criteria apply to **Arm C** only:
   i) Prior chemotherapy for mCRPC. Prior docetaxel for metastatic hormone-sensitive prostate cancer is allowed if ≥ 12 months elapsed from last dose of docetaxel.
   ii) Prior treatment with enzalutamide, apalutamide, or other novel androgen receptor inhibitor.
   iii) Treatment with 5-α reductase inhibitors (eg, finasteride, dutasteride), estrogens, and/or cyproterone within 4 weeks prior to treatment arm assignment

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

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

3) Physical and Laboratory Test Findings

a) WBC < 2000/μL

b) Neutrophils < 1500/μL

c) Platelets $<100\times10^3$/μL

d) Hemoglobin < 9.0 g/dL or ≤ 5.6 mmol/L

Note: Hemoglobin and platelet requirements cannot be met by use of recent transfusion or growth factor support (GSCF or erythropoietin) within 2 weeks prior to treatment allocation.

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

f) AST/ALT: > 3.0× ULN

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

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

4) Allergies and Adverse Drug Reaction

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

5) Other Exclusion Criteria

a) Prisoners or participants who are involuntarily incarcerated. (Note: under specific circumstances, and only in countries where local regulations permit, a person who has been imprisoned may be included as a participant. Strict conditions apply and 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 assigned to Arm A should be advised to use appropriate sun protection due to the increased susceptibility to sunburn while taking rucaparib.

6.4 Screen Failures

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

6.4.1 Retesting During Screening or Lead-In Period

Participant re-enrollment: This study permits the re-enrollment of a participant 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 treatment arm assignment 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 (IP), also known as investigational medicinal product (IMP) 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 SOC for a given diagnosis, may be considered as non-investigational products (non-IMP).

Table 7-1: Study treatments for CA2099KD

Product Description / Class and Dosage Form	Potency	IMP/ Non-IMP	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per label)
BMS-936558-01 (Nivolumab) Solution for Injection[a]	100 mg (10 mg/mL)	IMP	Open Label	Vial (multiple vials per carton)	Store at 2° - 8 °C. Protect from light and freezing.
Rucaparib Immediate Release Tablets	200 mg/250mg/300 mg	IMP	Open Label	Tablets are provided in HDPE bottles	Store in the provided containers between 15° and 30°C.
Docetaxel[b]	80 mg	IMP	Open Label	Vials in various packaging configurations.	Refer to storage conditions on container label.
Prednisone[b]	5 mg	Non-IMP	Open Label	Tablets in various packaging configurations.	Refer to storage conditions on container label.
Dexamethasone[b]	4 mg	Non-IMP	Open Label	Tablets in various packaging configurations	Refer to storage conditions on container label.
Xtandi® (enzalutamide)	40 mg	IMP	Open Label	Capsules in various packaging configurations.	Refer to storage conditions on container label.

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

[b] Dexamethasone which is required for premedication, docetaxel and andprednisone are provided by BMS. Other corticosteroids as an alternative to dexamethasone can be used according to local standards. In countries where local sourcing is allowed, sites may use their local institutional equivalent of dexamethasone and prednisone.

7.1 Treatments Administered

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.

Table 7.1-1: Selection and Timing of Dose

Study Treatment	Unit dose strength(s)/ Dosage level(s)	Dosage formulation Frequency of Administration	Route of Administration
Arm A			
Nivolumab	480 mg	Every 4 weeks	Intravenous
Rucaparib	600 mg	Twice daily (BID)	By mouth
Arm B			
Nivolumab[a]	360 mg	Every 3 weeks through Cycle 10	Intravenous
Docetaxel	75 mg/m^2	Every 3 weeks through Cycle 10	Intravenous
Prednisone	5 mg	Twice daily (BID) co-administered with docetaxel	By mouth
Dexamethasone	8 mg	At 12 hours, 3 hours and 1 hour before the docetaxel infusion	By mouth
Arm C			
Nivolumab	480 mg	Every 4 weeks	Intravenous
Enzalutamide	160 mg	Once daily (QD)	By mouth

[a] Nivolumab will be administered as monotherapy (480 mg Q4W) after 10 cycles of combination therapy with docetaxel, prednisone, and dexamethasone as of Cycle 11 until progression, unacceptable toxicity, withdrawal of consent, or completion of 24 months of nivolumab treatment, whichever occurs first.

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

Participants should be carefully monitored for infusion reactions during nivolumab or docetaxel administration. If an acute infusion reaction is noted, participants should be managed according to Section 7.1.4.

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 Injection, 100 mg/10 mL (10 mg/mL) and 40 mg/4 mL (10 mg/mL) Nivolumab injection is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding in-line filter at the protocol-specified doses. It is not to be administered as an IV push or bolus injection. When the dose is based on patient weight (ie, mg/kg), nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to protein concentrations as low as 0.35 mg/mL. When the dose is fixed (eg, 240 mg flat dose), nivolumab injection can be infused undiluted or diluted so as not to exceed a total infusion volume of 120 mL. Nivolumab infusion must be promptly followed by a flush of diluent to clear the line. Instructions for dilution and infusion of nivolumab injection may be provided in the clinical protocol, pharmacy binder, or pharmacy reference sheet. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

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

Nivolumab plus Rucaparib (Arm A)

Participants will receive nivolumab IV at a dose of 480 mg as a 30-minute infusion on Day 1 of each treatment cycle (Q4W) until progression, unacceptable toxicity, completion of 24 months of treatment, withdrawal of consent, or the study ends, whichever occurs first.

Participants will receive rucaparib at a dose of 600 mg orally with or without food twice daily every day of each treatment cycle until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first. Rucaparib will be administered on an out-patient basis, except on study days when PK samples are obtained (see Table 9.5.2-1). Participants should begin study treatment within 3 calendar days of treatment arm assignment.

Participants should take rucaparib doses as close to 12 hours apart as possible, preferably at the same times every day. If a patient misses a dose (ie, does not take it within 4 hours of the scheduled time), the patient should skip the missed dose and resume taking rucaparib with the next scheduled dose. Missed or vomited doses should not be made up.

Nivolumab plus Docetaxel (Arm B)

Participants will receive nivolumab 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 (or equivalent dose of another corticosteroid) s 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 infusion, there is a 30-minute delay before the start of the docetaxel infusion to monitor the participant for signs of possible infusion reactions. 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. After the completion of Cycle 10, nivolumab dosing will change to 480 mg, with the

Cycle 11 dose given 3 weeks (± 3 days) after the Cycle 10 dose. Nivolumab 480 mg will then continue to be given alone as maintenance therapy Q4W (± 3 days). The treatment with nivolumab will be given until progression, unacceptable toxicity, completion of 24 months of treatment, 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 treatment arm assignment.

Premedication:

There are no premedications recommended for nivolumab treatment.

For docetaxel, given the concurrent use of prednisone, the recommended premedication regimen is oral dexamethasone (or equivalent dose of another corticosteroid) 8 mg, 12 hours, 3 hours, and 1 hour before the docetaxel infusion, however other 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 7.1.4.

Nivolumab plus Enzalutamide (Arm C)

Participants will receive nivolumab at a dose of 480 mg as a 30-minute infusion on Day 1 of each treatment cycle (Q4W) until progression, unacceptable toxicity, completion of 24 months of treatment, withdrawal of consent, or the study ends, whichever occurs first.

Participants will receive enzalutamide at a dose of 160 mg orally once daily every day of each treatment cycle until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first. Enzalutamide will be administered on an out-patient basis, except on study days when PK samples are obtained (see Table 9.5.2-1).Participants should begin study treatment within 3 calendar days of treatment arm assignment.

If a participant misses taking Enzalutamide at the usual time, the prescribed dose should be taken as close as possible to the usual time. If a patient misses a dose for a whole day, treatment should be resumed the following day with the usual daily dose.

Please refer to Section 7.4.4 for enzalutamide dose reductions and increases for participants who are receiving concomitant strong CYP2C8 inhibitors or strong CYP3A4 inducers.

7.1.1 Dose Delay Criteria

Dose delay criteria for management of AEs during nivolumab, rucaparib, docetaxel, or enzalutamide treatment are outlined in this section.

For Arm A and Arm C, dosing of nivolumab may be delayed without delay of rucaparib or enzalutamide dosing if toxicity is felt to be related to only nivolumab and not related to rucaparib or enzalutamide. Conversely, treatment with rucaparib or enzalutamide may be delayed or the dose reduced without delay of nivolumab dosing if toxicity is felt to be related to only rucaparib or enzalutamide and not related to nivolumab. However, if toxicity is considered related to all study drugs or if the investigator is unable to determine which study drug is the cause of the AE, then all study drugs in the combination should be delayed and, if appropriate, the dose of rucaparib or enzalutamide should be reduced.

For Arm B, dosing for all drugs should be delayed if any criteria in Section 7.1.1.1 (for nivolumab) or Section 7.1.1.3 (for docetaxel) are met. That is, nivolumab should be delayed if criteria for delay of docetaxel are met, and docetaxel should be delayed if criteria for delay of nivolumab are met.

Participants who require dose delay should be re-evaluated weekly or more frequently if clinically indicated and resume dosing when re-treatment criteria are met (Section 7.1.2).

7.1.1.1 Nivolumab

Nivolumab administration should be delayed for the following:

- Grade 2 non-skin, drug-related AE, with the exception of fatigue
- Grade 2 drug-related creatinine, AST, ALT, and/or total bilirubin abnormalities*

  * Note for Arm A: Elevated creatinine is among the most frequently reported treatment-related AEs for rucaparib monotherapy. Rucaparib is a potent inhibitor of MATE1 and MATE2-K transporters, which are involved in active secretion of creatinine. Rucaparib-mediated creatinine elevation occurs early in treatment (Day 15 of Cycle 1), and is not typically accompanied by elevations in urea (blood urea nitrogen [BUN]). Creatinine elevation resolves with dose holds of rucaparib and recurs with re-challenge. Rucaparib associated creatinine elevation has not been associated with evidence or reports of permanent renal impairment.

- Grade 3 drug-related skin AE
- Grade 3 drug-related laboratory abnormality, with the following exceptions:
  - Grade 3 lymphopenia or asymptomatic amylase or lipase does not require dose delay
  - Grade ≥ 3 AST, ALT, and/or total bilirubin will require dose discontinuation (see Section 8.1.1)*

    * Note for Arm A: Elevated ALT/AST is among the most frequently reported treatment-related AEs for rucaparib monotherapy. Rucaparib-related ALT/AST elevations occur early in treatment (ie, during Cycle 1 or by Day 1 of Cycle 2) and then resolve or stabilize over time. Rucaparib-associated elevations in ALT/AST are generally not accompanied by a concomitant elevation in bilirubin. For participants with ≥ Grade 3 AST or ALT elevations with onset after Cycle 1 dosing, nivolumab dose discontinuation is not required

if AST and ALT elevations decline by Day 29 and toxicity, after the investigator discusses the case with the BMS Medical Monitor/designee, is considered to be mainly related to rucaparib.

- Any AE, laboratory abnormality, or intercurrent illness that, in the judgment of the investigator, warrants delaying the dose of study medication.

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

7.1.1.2 Rucaparib

Treatment with rucaparib should be delayed and dose reduction considered for the following drug-related AEs:

- Grade 3 or 4 hematologic toxicity
  - In addition, if Grade ≥ 3 hematologic toxicity persists for > 14 consecutive days, or a dependence upon blood transfusion occurs, then weekly complete blood counts (CBC) should be performed until resolution of the event.
  - If, after 42 days of interruption of rucaparib, the hematologic toxicity has not recovered to CTCAE Grade ≤ 1 then the participant should be referred to a hematologist and analysis of the bone marrow with cytogenetic studies are recommended according to standard hematologic practice.
    - The bone marrow analysis should include a bone marrow aspirate (for cellular morphology, cytogenetic analysis, and flow cytometry) and a core biopsy (for bone marrow cellularity).
- Grade 3 or 4 non-hematologic toxicity (except for alopecia, nausea, vomiting, or diarrhea adequately controlled with systemic antiemetic/antidiarrheal medication administered in standard doses according to the study center routine practice)
- Grade 2 ALT/AST elevations* that do not decline within 2 weeks or continue to rise
- Grade 3 ALT/AST elevations * that do not decline within 2 weeks or continue to rise
- Grade 4 ALT/AST elevations*

  * Note: Elevated ALT/AST is among the most frequently reported treatment-related AEs for rucaparib monotherapy. Rucaparib-related ALT/AST elevations occur early in treatment (ie, during Cycle 1 or by Day 1 of Cycle 2) and then resolve or stabilize over time. Elevations in ALT/AST are generally not accompanied by a concomitant elevation in bilirubin. Continuation of rucaparib with elevations of ALT/AST ≤ Grade 3 is permitted provided bilirubin is < ULN and there are no other signs of liver dysfunction.

- In addition, and at the discretion of the investigator, the dose of rucaparib could be held and/or reduced for Grade 2 toxicity not adequately controlled by concomitant medications and/or supportive care.

Treatment with rucaparib must be delayed until the toxicity resolved to ≤ CTCAE Grade 2. Twice daily (BID) dosing can then be resumed at either the same dose or a lower dose, per investigator discretion. If treatment is resumed at the same dose, and the participant experiences the same toxicity, the dose is to be reduced following resolution of the event to ≤ CTCAE Grade 2. If the participant continues to experience toxicity, additional dose reduction steps are permitted.

Rucaparib is a potent inhibitor of MATE1 and MATE2-K transporters, which are involved in active secretion of creatinine. Rucaparib-mediated creatinine elevation occurs early in treatment (Day 15 of Cycle 1) and then stabilizes with continued rucaparib treatment. Creatinine elevation is not typically accompanied by elevations in urea (BUN). Creatinine elevation resolves with dose holds of rucaparib and recurs with re-challenge. Creatinine elevation has not been associated with evidence or reports of permanent renal impairment.

Dose reduction guidelines for rucaparib are presented in Section 7.4.2.

7.1.1.3 Docetaxel

Docetaxel administration should be delayed for the following on the day of planned dosing:

- Any Grade ≥ 2 non-skin, drug-related AEs, with the following exceptions:
  - Grade 2 drug-related fatigue or laboratory abnormalities do not require dose delay
  - Grade 3 docetaxel-related enterocolitis of any duration requires discontinuation*
- Any Grade 3 skin, drug-related AEAny Grade ≥ 3 drug-related laboratory abnormality, with the following exceptions for lymphopenia, neutrophil count, AST, ALT, or total bilirubin:
  - Grade 3 lymphopenia does not require dose delay
  - Should not be given if neutrophil counts are < 1500 cells/mm3
  - Should not be given if total bilirubin > upper limit of normal (ULN), or if AST and/or ALT > 1.5xULN concomitant with alkaline phosphatase > 2.5x ULN
- Any AE, laboratory abnormality or inter-current illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Subsequent dose reductions may be required as per Section 7.4.3.

*Note: 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 (i.e. gastroenterologist) for assessment and full details of the participant's exposure to docetaxel should be provided.

Participants receiving docetaxel may receive growth factors (including G-CSF and erythropoietin) at the discretion of the investigator and following local guidelines.

7.1.1.4 Enzalutamide

If a participant experiences a Grade 2 drug-related AE or laboratory abnormality, dosing may continue but supportive care and more frequent monitoring should be implemented. For a

≥ Grade 3 drug-related AE, laboratory abnormalities, or any intolerable adverse reactions, dosing should be withheld for at least 1 week and until symptoms improve to ≤ Grade 2, then resumed at the same or a reduced dose (120 mg or 80 mg) if warranted. Dose reductions for enzalutamide are discussed in Section 7.4.4.

7.1.2 Criteria to Resume Study Treatment

For Arm A and Arm C, if dosing of both nivolumab and the combination agent (rucaparib or enzalutamide) have been delayed per the criteria specified in Section 7.1.1 above, and toxicity is felt to be related to both study drugs or it is not clear which study drug is the cause of toxicity, then participants may resume dosing when resuming criteria for BOTH nivolumab and the combination agent are met. The only exception is toxicities that are treated with a prolonged corticosteroid taper. In such cases, dosing with the combination agent may resume prior to nivolumab, when the criteria to resume dosing for the combination agent have been met. Nivolumab dosing may be resumed later, after completion of the corticosteroid taper and when criteria to resume nivolumab dosing have been met.

If dosing of both nivolumab and the combination agent (rucaparib or enzalutamide) have been delayed, and toxicity is later assessed by the investigator to be related to only one study drug, then dosing with the study drug which is not related to toxicity may resume prior to resuming the dosing of the study drug which is related to toxicity, at the investigator's discretion.

For Arm B, participants may resume dosing when resuming criteria for BOTH nivolumab and docetaxel are met. That is, nivolumab and docetaxel must be administered together until completion of Cycle 10 or until treatment discontinuation. The only exception is toxicities that are 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 dosing may be resumed later, after completion of the corticosteroid taper and when criteria to resume nivolumab dosing have been met. It is allowed to administer either nivolumab or docetaxel if the other is discontinued due to toxicity, judging by the treating investigator if it is the best interest of the participants (see Section 8.1).

7.1.2.1 Nivolumab

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

- Participants may resume treatment in the presence of Grade 2 fatigue.
- Participants who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- For participants with Grade 2 AST, ALT, or total bilirubin elevations, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, is complete.
- Participants with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (Section 8.1.1) should have treatment permanently discontinued.

- Drug-related pulmonary toxicity, diarrhea or colitis must have resolved to baseline before treatment is resumed. Participants with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by the BMS Medical Monitor/designee.

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

7.1.2.2 Rucaparib

Treatment with rucaparib may be resumed, when the toxicity resolves to ≤ CTCAE Grade 2, at the same dose or a reduced dose at the investigator's discretion. If the same dose is resumed and the toxicity recurs, then the dose should be reduced. See Section 7.4.2 for dose reduction instructions.

Rucaparib administration is permitted with elevations of ALT/AST ≤ Grade 3, provided bilirubin is < ULN and there are no other signs of liver dysfunction.

For prolonged hematological toxicities, rucaparib administration should be interrupted and blood counts monitored weekly until recovery. If the levels have not recovered to Grade 1 or less after 4 weeks, the participant should be referred to a hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics. If Myelodysplastic Syndrome/Acute Myeloid Leukemia is confirmed, treatment with rucaparib must be discontinued.

7.1.2.3 Docetaxel

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

- Participants may resume treatment in the presence of ANC ≥ 1500 / mm^3
- Participants may resume treatment in the presence of Grade 2 fatigue
- Participants who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- Participants with decreased neutrophil counts, or with elevations in total bilirubin, AST or ALT must meet criteria for resuming treatment according to the boxed warning contained within the docetaxel prescribing information
- Participants with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (Section 8.1.3) should have treatment permanently discontinued

When resuming docetaxel treatment, please follow the dose reduction recommendations noted in Section 7.4.3.

If treatment is delayed > 8 weeks, docetaxel treatment must be permanently discontinued, except as specified in Section 8.1.3.

7.1.2.4 Enzalutamide

Participants may resume treatment with enzalutamide when the drug-related AE(s) resolve(s) to Grade 2 or lower severity.

7.1.3 Management Algorithms for Immuno-Oncology Agents

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

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

The above algorithms are found in the Appendix 6 of this protocol.

7.1.4 Treatment of Infusion-related Reactions (Nivolumab or Docetaxel)

Nivolumab

Since nivolumab contains only human immunoglobulin protein sequences, these sequences are unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the BMS Medical Monitor/designee and reported as SAEs if they meet the criteria. Infusion reactions should be graded according to NCI CTCAE (Version 4.03) guidelines.

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

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

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

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

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

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

- Immediately discontinue infusion of study 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. Participant should be monitored until the investigator is comfortable that the symptoms will not recur. Study drug will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor participant until recovery of the symptoms.

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

Docetaxel

Participants 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, such as severe hypotension, bronchospasm or generalized rash/erythema require

immediate discontinuation of docetaxel and appropriate therapy. Participants who have developed severe hypersensitivity reactions should not be re-challenged with docetaxel.

7.1.5 Treatment of Hypersensitivity or Allergic Reactions (Rucaparib or Enzalutamide)

Hypersensitivity or allergic reactions associated with treatment with rucaparib or enzalutamide should be managed per local SOC.

7.2 Method of Treatment Assignment

All participants will be centrally assigned to a treatment arm using an Interactive Response Technology (IRT) system. Before the study is initiated, each site will receive log-in information and directions on how to access the IRT.

After obtaining informed consent from the participant, the investigator or designee will register the participant for enrollment in IRT by following the enrollment procedures established by BMS.

Once enrolled in IRT, enrolled participants who have met all eligibility criteria, including completion of HRD testing of the submitted plasma and/or tumor sample by the central laboratory, will be ready for treatment arm assignment through the IRT. As approximately 20-25% of BRCA homozygous deletions are not detected by plasma analysis, the study will allow for the testing of both plasma and tissue samples to capture all possible HRD mutations.

For participants with local HRD test results obtained prior to enrollment, an unblinded Sponsor reviewer will confirm that they are acceptable for treatment arm assignment (refer to Section 5.1 for definition of acceptable local results). Although completion of central HRD testing is not required for subjects with acceptable local HRD results, central laboratory must confirm receipt of plasma and tumor samples prior to IRT treatment arm assignment. Based on prior treatment history, presence or absence of measurable disease, eligibility for chemotherapy and HRD status, IRT will assign the participant to a treatment arm that has available spots. If more than 1 treatment arm has available spots, the investigator or designee will be able to choose the treatment arm for the participant (for guidance, refer to Figure 5.1-2). If there are no available spots in any of the treatment arms, the participant will be a screen failure. The BMS study team will update sites when enrollment in a treatment arm is nearing completion.

Retrospective plasma HRD testing will be performed in all subjects who were enrolled prior to global revised protocol 02. Participants initially assigned to an HRD-negative or not evaluable spot based on tumor testing who are found to be HRD positive on retrospective plasma testing will be re-assigned to the HRD positive group. As a result of re-assignment of HRD not-evaluable patients, additional slots may become available in the HRD negative/not-evaluable group and will be released to the sites. Study treatment will be dispensed at the study visits as listed in Schedule of Activities (Section 2).

7.3 Blinding

Blinding is not applicable, as this is an open-label study; however, the specific treatment to be taken by a participant will be assigned using an IRT, as specified in Section 7.2. Treatment arm

assignments will be released to the bioanalytical laboratory in order to minimize unnecessary analysis of samples.

The HRD status as determined by the central laboratory will be masked to investigator sites and participants and can be unmasked if requested by investigator sites at the time of radiographic progression or discontinuation of study treatment of a participant, whichever occurs later, and at final analyses. HRD status based on central laboratory testing may also be unmasked if requested by the investigator for participants who screen fail due to lack of available HRD negative of slots at the time of treatment arm assignment. The HRD status determined by a local laboratory will be masked to BMS study team. Only those Sponsor personnel not directly involved in the assessment of safety and efficacy in the study will review local and central HRD status up to discontinuation of study therapy or final analyses. During the DMC review, the HRD status will be transferred to an independent data center to perform analyses as needed.

In the event that a germline mutation is suspected based on the results from central analyses of tumor tissue (or ctDNA), these results will be provided to the treating physician and the participant may be referred by the investigator for confirmation and genetic counseling per institutional guidelines.

As specified in Section 10.3.4, interim analyses by HRD status may be unblinded to a small BMS team outside the immediate CA2099KD study team to inform internal decision making on further clinical development in prostate cancer and determine if any arm in the study should be expanded to generate additional data that may support a regulatory filing.

Members of the immediate study team (site-facing BMS team members) will remain blinded to the HRD status of individual study participants in order to maintain study integrity until the final analysis.

7.4 Dosage Modification

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

- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids (except as stated in Section 7.7.2)
- Any concurrent non-protocol-specified anti-neoplastic therapy (ie, chemotherapy, hormonal therapy other than ADT, immunotherapy, extensive or non-palliative radiotherapy, standard or investigational agents for CRPC)

7.4.1 Nivolumab

There will be no dose modifications permitted for nivolumab.

7.4.2 Rucaparib

Rucaparib dose reduction steps are provided in Table 7.4.2-1.

Table 7.4.2-1: Dose Reduction for Rucaparib

Dose Reduction	Dose
Starting Dose	600 mg twice daily
First Dose Reduction	500 mg twice daily
Second Dose Reduction	400 mg twice daily
Third Dose Reduction	300 mg twice daily

*Consultation with the BMS Medical Monitor/designee is required before reducing to the Third Dose Reduction Level.

After 3 dose reductions, if a participant continues to experience toxicity, or if dosing is interrupted for more than 14 consecutive days due to toxicity, treatment should be discontinued unless otherwise agreed between the investigator and the Sponsor (see Section 8.1.2). Dose re-escalation upon resolution of toxicity to ≤ CTCAE Grade 1 is permitted at the discretion of the investigator.

7.4.3 Docetaxel

Dose reductions of docetaxel may be required[114] and will be performed according to Table 7.4.3-1.

Table 7.4.3-1: Dose Reductions for Docetaxel

Dose Level	Docetaxel
Starting dose	75 mg/m²
First dose reduction	60 mg/m²
Second dose reduction	45 mg/m²
Third dose reduction	Discontinue docetaxel

Doses of docetaxel will be modified for participants who experience any of the following conditions during docetaxel treatment:

- Febrile neutropenia (body temperature ≥ 38.5°C and neutrophils < 1,000 cell/mm^3)
- Neutrophils < 500 cell/mm³ for more than one week despite growth factor support
- Severe or cumulative cutaneous reactions
- Other Grade 3/4 non-hematological toxicities.

Participants should have treatment delayed according to Section 7.1.1.3, and then resumed at 1 dose level reduction (60 mg/m^2). Should these AEs occur after the first dose reduction, then a second dose reduction to 45 mg/m^2 is permitted. If a third dose reduction is required, then the

participant should discontinue docetaxel treatment and enter the follow-up phase. The dose which has been reduced for toxicity must not be re-escalated.

Participants who develop Grade ≥ 3 peripheral neuropathy, or who otherwise meet criteria specified in Section 8.1.3, should discontinue docetaxel treatment and enter the follow-up phase.

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 patient will continue docetaxel treatment in the absence of major toxicity, disease progression or any other discontinuation criteria as defined in Section 8.1.3.

7.4.4 Enzalutamide

Participants who experience a Grade 3 or greater toxicity that cannot be ameliorated by the use of adequate medical intervention should have their treatment interrupted until the toxicity improves to a Grade 2 or lower severity. Participants may subsequently be re-started on study drug, at the same dose or at a reduced dose (120 mg or 80 mg) if warranted, at the investigator's discretion. Enzalutamide doses will not be re-escalated once reduced, unless a concomitant strong CYP3A4 inducer is started or a strong CYP2C8 inhibitor is discontinued (see below).

As stated in the prescribing information for enzalutamide, strong inhibitors (eg, gemfibrozil) of CYP2C8 are to be avoided or used with caution during enzalutamide treatment. If participants must be co-administered a strong CYP2C8 inhibitor, the dose of enzalutamide should be reduced to 80 mg once daily. If co-administration of the strong CYP2C8 inhibitor is discontinued, the enzalutamide dose should be returned to the dose used prior to initiation of the strong CYP2C8 inhibitor.

The concomitant use of strong CYP3A4 inducers (eg, phenytoin) should be avoided if possible. If a strong CYP3A4 inducer must be co-administered, the enzalutamide dose should be increased from 160 mg to 240 mg once daily. If co-administration of the strong CYP3A4 inducer is discontinued, the enzalutamide dose should be returned to the dose used prior to initiation of the strong CYP3A4 inducer.

7.5 Preparation/Handling/Storage/Accountability

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

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

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

The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to

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

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

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

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

- 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

Not applicable.

7.6 Treatment Compliance

Treatment compliance will be monitored by drug accountability as well as the participant's medical record and eCRF. Participants will be provided with a medication diary in which to record study drug doses taken by mouth and will be instructed to bring this diary and study drug containers (rucaparib, prednisone, dexamethasone and enzalutamide) to clinic visits.

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

All Arms

For all participants, 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 botanical preparation (eg, herbal supplements or traditional Chinese medicines) intended to treat the disease under study or provide supportive care. Use of marijuana and its derivatives for treatment of symptoms related to cancer or cancer treatment are permitted if obtained by

medical prescription or if its use (even without a medical prescription) has been legalized locally

- 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

Arm A

For participants in Arm A (nivolumab plus rucaparib), rucaparib is a moderate inhibitor of CYP1A2 and a weak inhibitor of CYP2C9, CYP2C19, and CYP3A4 in vivo. Caution should be used for concomitant substrate medications with narrow therapeutic windows. Examples of such medications are listed below:

- CYP1A2 substrates: tizanidine, theophylline
- CYP2C9 substrates: warfarin, phenytoin
- CYP2C19 substrates: S-mephenytoin
- CYP3A: alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine

Dose adjustment maybe considered for these medications, if clinically indicated. Participants taking warfarin should have their international normalized ratios (INRs) monitored regularly per standard clinical practice.

In vitro, rucaparib is a potent inhibitor of MATE 1 and MATE2-K, a moderate inhibitor of OCT1, and a weak inhibitor of OCT2. As inhibition of these transporters could increase renal elimination of metformin and decrease liver uptake of metformin, caution is advised when metformin is co-administered with rucaparib. In addition, rucaparib is an inhibitor of BCRP with an IC50 value suggesting potential BCRP inhibition and increased exposures of medicinal products that are BCRP substrates (eg, rosuvastatin).

Therapies considered necessary for the participant's well-being may be given at the discretion of the investigator and should be documented on the eCRF. Other concomitant medications, except for analgesics, chronic treatments for concomitant medical conditions, or agents required for life-threatening medical problems, should be avoided. Herbal and complementary therapies should not be encouraged because of unknown side effects and potential drug interactions, but any taken by the participant should be documented appropriately on the eCRF.

Because rucaparib is a moderate inhibitor of P-gp in vitro, caution should be exercised for participants receiving study drug and requiring concomitant medication with digoxin. Participants taking digoxin should have their digoxin levels monitored after starting study treatment and then regularly per standard clinical practice. Caution should also be exercised for concomitant use of certain statin drugs (eg, rosuvastatin and fluvastatin) due to potential increase in exposure from inhibition of BCRP and CYP2C9.

Arm B

For participants in Arm B (nivolumab plus docetaxel), strong CYP3A4 inhibitors should be avoided during the treatment with docetaxel. This includes, but is not limited to:

- Ketoconazole
- Itraconazole
- Clarithromycin
- Atazanavir
- Indinavir
- Nefazodone
- Nelfinavir
- Ritonavir
- Saquinavir
- Teithromycin
- Voriconazole

Arm C

For participants in Arm C (nivolumab plus enzalutamide), enzalutamide is an inducer and inhibitor of several CYP isoenzymes and susceptible to many drug interactions. Since the half-life of enzalutamide is 5.8 days, the effects on enzymes may persist for ≥ 1 month after stopping the drug.

Co-administration with warfarin and coumarin-like anticoagulants should be avoided. If enzalutamide (Xtandi) is co-administered with an anticoagulant metabolised by CYP2C9 (such as warfarin or acenocoumarol), additional International Normalised Ratio (INR) monitoring should be conducted.

CYP3A4 inhibitors may increase enzalutamide exposure, but the clinical significance is unclear and no dosage adjustment is recommended. Enzalutamide is a substrate of CYP2C8 and an inducer/inhibitor of CYP2B6. Per the enzalutamide current prescribing information, strong inhibitors of CYP2C8 should be avoided. See Section 7.4.4 for more information on dose reductions for enzalutamide.

7.7.2 Other Restrictions and Precautions

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

7.7.2.1 Imaging Restriction and Precautions

It is the local imaging facility's responsibility to determine, based on participant attributes (eg, allergy history, diabetic history and renal status), the appropriate imaging modality and contrast regimen for each participant. Imaging contraindications and contrast risks should be

considered in this assessment. Participants with renal insufficiency should be assessed as to whether or not they should receive contrast and, if so, what type and dose of contrast is appropriate. Specific to MRI, participants with severe renal insufficiency (ie, estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2) are at increased risk of nephrogenic systemic fibrosis. MRI contrast should not be given to this participant population. In addition, participants are excluded from MRI if they have tattoos, metallic implants, pacemakers, etc.

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

7.7.3 Permitted Therapy

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

7.7.3.1 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 8.1.5) 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.

Treatment with rucaparib should be held prior to initiation of radiation therapy and until the patient has recovered from any radiation-related toxicity.

For docetaxel and enzalutamide local standard of care guidelines should be followed.

7.8 Treatment After the End of the Study

At the conclusion of the study, participants who continue to demonstrate clinical benefit will be eligible to receive BMS supplied study treatment for the maximum treatment duration specified in protocol Section 7.1. 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

General Information on Study Treatment Discontinuation

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

- Participant's request to stop study treatment. Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information
- Any clinical AE, laboratory abnormality, or intercurrent illness that, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant
- Termination of the study by BMS
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness. (Note: Under specific circumstances, and only in countries where local regulations permit, a participant who has been imprisoned may be permitted to continue as a participant. Strict conditions apply and BMS approval is required.)
- Participant meets criteria for radiographic progression per PCWG3 criteria or clinical progression (as defined in Section 9.1.2) unless criteria for treatment beyond progression have been met (see Section 8.1.5).

All participants who discontinue study treatment should comply with protocol specified follow-up procedures as outlined in Table 2-2 and Table 2-3. 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 drug 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.

Discontinuation of Specific Study Treatments (Nivolumab, Rucaparib, Docetaxel, or Enzalutamide)

The assessment for discontinuation of nivolumab and the combination agent (rucaparib, docetaxel, or enzalutamide) 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.

8.1.1 Nivolumab Dose Discontinuation

Nivolumab treatment should be permanently discontinued for any of the following:

- Any Grade 2 drug-related uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Any Grade 3 non-skin, drug-related AE lasting >7 days or that recurs, with the following exceptions: laboratory abnormalities, drug-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, hypersensitivity reactions, infusion reactions, and endocrinopathies
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, myocarditis, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
  - Grade 3 drug-related endocrinopathies, adequately controlled with only physiologic hormone replacement do not require discontinuation. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia >7 days or associated with bleeding requires discontinuation
    - Grade ≥3 drug-related AST, ALT, or total bilirubin requires discontinuation*

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

      * Note for Arm A: Elevated ALT/AST is among the most frequently reported treatment-related AEs for rucaparib monotherapy. Rucaparib-related ALT/AST elevations occur early in treatment (ie, in Cycle 1 or by Day 1 of Cycle 2) and then resolve or stabilize over time. Rucaparib associated elevations in ALT/AST are generally not accompanied by a concomitant elevation in bilirubin.
    - Concurrent AST or ALT >3× ULN and total bilirubin >2× ULN
- Any Grade 4 drug-related AE or laboratory abnormality (including but not limited to creatinine, AST, ALT, or total bilirubin), except for the following events that do not require discontinuation:
  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia or leukopenia or asymptomatic amylase or lipase

  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
  - Grade 4 drug-related endocrinopathy AEs, such as, hyper- or hypothyroidism, or glucose intolerance, that resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the BMS Medical Monitor/designee. Grade 4 drug-related adrenal insufficiency or hypophysitis requires discontinuation regardless of control with hormone replacement.
- Any event that leads to delay in dosing lasting > 8 weeks (Q3W cycle) or > 10 weeks (Q4W cycle) from the previous dose requires discontinuation, with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related AEs are allowed.
  - 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 BMS Medical Monitor/designee.

Prior to re-initiating treatment in a participant with a dosing delay lasting > 8 weeks (Q3W cycle) or > 10 weeks (Q4W cycle), the BMS Medical Monitor/designee must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.

- Any AE, laboratory abnormality, or intercurrent illness that, in the judgment of the investigator, presents a substantial clinical risk to the participant with continued nivolumab dosing

Note for Arm A: Elevated creatinine is among the most frequently reported treatment-related AEs for rucaparib monotherapy. Rucaparib is a potent inhibitor of MATE1 and MATE2-K transporters, which are involved in active secretion of creatinine. Rucaparib-mediated creatinine elevation occurs early in treatment (Day 15 of Cycle 1), and is not typically accompanied by elevations in urea (BUN). Creatinine elevation resolves with dose holds of rucaparib and recurs with re-challenge. Rucaparib associated creatinine elevation has not been associated with evidence or reports of permanent renal impairment.

8.1.2 Rucaparib Discontinuation

- If a participant continues to experience toxicity despite multiple dose reduction steps as per Section 7.4.2, or if dosing with rucaparib is interrupted for > 14 consecutive days due to toxicity, treatment should be discontinued, unless otherwise agreed between the investigator and the Sponsor on a case-by-case basis. Prior to re-initiating treatment in a participant with a dosing delay lasting > 14 days, the BMS Medical Monitor/designee must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed.

- Rucaparib treatment must be discontinued if Myelodysplastic Syndrome (MDS)/Acute Myeloid Leukemia (AML) is confirmed.
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the participant with continued rucaparib dosing.

8.1.3 Docetaxel Discontinuation

Docetaxel treatment should be permanently discontinued for the following:

- Any Grade ≥ 3 peripheral neuropathy
- Any Grade 3 non-skin drug-related AE lasting > 7 days, with the following exceptions:
  - Grade 3 docetaxel-related enterocolitis of any duration requires discontinuation*
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia associated with bleeding requires discontinuation
    - Any drug-related liver function test (LFT) abnormality that meets the following criteria requires discontinuation:
      - AST or ALT > 5~10x ULN for > 2 weeks
      - AST or ALT > 10x ULN
      - Total bilirubin > 5x ULN
      - Concurrent AST or ALT > 3x ULN and total bilirubin > 2x ULN
- Any Grade 4 drug-related AE or laboratory abnormality, except for the following events which do not require discontinuation:
  - Grade 4 neutropenia
  - Grade 4 lymphopenia or leukopenia
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
- Any dosing delay lasting > 8 weeks with the following exceptions:
  - Dosing delays > 8 weeks that occur for non-drug-related reasons may be allowed if approved by the BMS Medical Monitor/designee. Prior to re-initiating treatment in a participant with a dosing delay lasting > 8 weeks, the BMS Medical Monitor/designee must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed.
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the participant with continued docetaxel dosing.

*Note: 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 (i.e. gastroenterologist) for assessment and full details of the participant's exposure to docetaxel should be provided.

8.1.4 Enzalutamide Discontinuation

Treatment with enzalutamide should be discontinued for any of the following:

- Seizure or posterior reversible encephalopathy syndrome (PRES)
- Creatinine > 305 µmol/L (4.0 mg/dL)
- Liver function tests (AST, ALT, or total bilirubin) > 5x ULN
- An absolute neutrophil count of ≤ 750/µL
- A platelet count of < 50,000/µL
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the participant with continued enzalutamide dosing.
- Any dose delays lasting > 10 weeks with the following exceptions:
  - Dosing delays > 10 weeks that occur for non-drug-related reasons may be allowed if approved by the BMS Medical Monitor/designee. Prior to re-initiating treatment in a participant with a dosing delay lasting > 10 weeks, the BMS Medical Monitor/designee must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed.

8.1.5 Nivolumab Treatment Beyond Disease Progression

Accumulating evidence indicates a minority of participants treated with immunotherapy may derive clinical benefit despite initial evidence of PD.[29]

Participants treated with nivolumab will be permitted to continue nivolumab treatment beyond initial PCWG3-defined PD, assessed by the investigator (see Table 9.1.2-1 and Appendix 5) up to a maximum of 24 months from date of first dose, as long as they meet the following criteria:

- Investigator-assessed clinical benefit
- Tolerance of study drug
- Stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases)
- Participant provides written informed consent prior to receiving additional nivolumab treatment. All other elements of the main consent including description of reasonably foreseeable risks or discomforts, or other alternative treatment options will still apply.
- At the discretion of the investigator, rucaparib (Arm A1 or A2) and enzalutamide (Arm C) may also be continued beyond progression with nivolumab. Docetaxel (Arm B) may be continued beyond progression with nivolumab but docetaxel may not continue beyond Cycle 10.

Re-assessment Following Initial Assessment of Progression

A radiographic assessment/ scan should be performed within 6 weeks (if progression is based on soft-tissue lesions [identified on CT or MRI]) or within 8 weeks (if progression is based only on bone lesions identified on bone scan) of initial investigator-assessed progression. 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.

If the investigator feels that the participant continues to achieve clinical benefit by continuing treatment, the participant should remain on the trial and continue to receive monitoring according to the Schedule of Activities (Section 2).

For the participants who continue study therapy beyond progression, further progression is defined as per RECIST v1.1 (for soft tissue progression) or PCWG3 criteria (for bone progression, see Appendix 5), whichever occurs first as follows:

Further disease progression by RECIST v1.1 is defined as an additional 10% increase in tumor burden with a minimum 5 mm absolute increase from time of initial PD. This includes an increase in the sum of diameters of all target lesions and/ or the diameters of new measurable lesions compared to the time of initial PD.

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

Further bone disease progression is defined as additional two or more new bone lesions noted on bone scans compared to the time of PCWG3-defined progression of bone disease.

Study treatment should be discontinued permanently upon documentation of further progression.

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

8.1.6 Post Study Treatment Follow-up

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

BMS may request that survival data be collected on all treated participants outside of the protocol-defined window (see 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 or is lost to follow-up, including information of subsequent therapy.

8.2 Discontinuation from the Study

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

Participants who discontinue treatment for reasons other than radiographic disease progression will stay on study and continue study-related disease assessments until radiographic disease progression (see Section 9.1.2 below), subject withdrawal from the trial, or becoming lost to follow-up. All participants will be followed for survival.

8.3 Lost to Follow-Up

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

- If after all attempts, the participant remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the participant's medical records.

9 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in the Schedule of Activities (Section 2).
- Protocol waivers or exemptions are not allowed.
- All immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue treatment.
- Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before treatment arm assignment. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Schedule of Activities.

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

If a participant shows pulmonary-related signs (hypoxia, fever) or symptoms (eg. dyspnea, cough, and fever) consistent with possible pulmonary AEs, the participant should be immediately evaluated to rule out pulmonary toxicity, according to the suspected pulmonary toxicity management algorithm in Appendix 6.

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

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

Radiographic tumor response will be assessed at 8 weeks after first dose (± 7 days), then every 8 weeks (± 7 days) for the first 24 weeks (until Week 25 ± 7 days) and every 12 weeks (± 7 days) thereafter, until disease progression is documented (and confirmed if confirmation is required) or treatment is discontinued (whichever occurs later). This tumor assessment schedule should be

followed regardless of treatment schedule or dose delays. Additional scans at other time points may be performed if clinically indicated.

9.1.1 Imaging Assessment for the Study

Images will be submitted to an imaging core laboratory for storage and potential future blinded independent central review (BICR) per Sponsor request. Sites should be trained prior to scanning the first study participant. Image acquisition guidelines and submission process will be outlined in the CA2099KD Imaging Manual to be provided by the core lab.

Bone lesions will be assessed using Technetium-99m (Tc-99m) based radionuclide bone scans. Anterior and posterior whole body planar images should be acquired. Additional (including spot views and SPECT) images should also be submitted if acquired.

Soft tissue lesions will be preferably assessed with contrast-enhanced computed tomography (CT) scans acquired on dedicated CT equipment (preferred for this study). Contrast-enhanced CT of the chest, abdomen, pelvis, and other known/suspected sites of soft tissue disease should be performed for tumor assessments.

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

Should a participant have contraindication for both MRI and CT intravenous contrasts, a non-contrast CT of the chest and a non-contrast MRI of the abdomen, pelvis, and other known/suspected sites of soft tissue disease should be obtained.

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

CT and MRI scans 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 time points.

Use of CT component of a PET/CT scanner: Combined modality scanning such as with FDG-PET/CT is increasingly used in clinical care, and is a modality/technology that is in rapid evolution; therefore, the recommendations outlined here may change quickly with time. At present, low dose or attenuation correction CT portions of a combined FDG-PET/CT are of limited use in anatomically-based efficacy assessments and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for anatomically-based RECIST measurements. However, if a site can document that the CT performed as part of a FDG-PET/CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the FDG-PET/CT can be used for tumor measurements. Note, however, that the FDG-PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Assessments will be performed at baseline and at the time points described per PCWG3 criteria until disease progression per PCWG3 criteria (Appendix 5), or discontinuation of study treatment, whichever occurs later. Tumor assessments at other time points may be performed if clinically indicated and should be submitted to the central imaging vendor. Assessments of PR and CR must be confirmed at least 4 weeks after initial response. A BOR of stable disease can only be made after the participant is on-study for a minimum of 49 days from the date of treatment initiation (ie, first dose). Changes in tumor measurements and tumor responses will be assessed by the investigator per study design using PCWG3 criteria. Investigators will also report the number and size of new lesions that appear while on study. The time point of tumor assessments will be reported on the eCRF based on the investigator's assessment

For participants who are treated beyond PCWG3-defined progression, tumor assessments will continue to be performed until discontinuation of study treatment (typically upon evidence of further progression, as defined in Section 8.1.5).

Any additional imaging that may demonstrate tumor response or progression (including scans performed at unscheduled time points and/or at an outside institution) should be collected for PCWG3 tumor assessment and submitted to the BICR.

9.1.2 Disease Response Evaluation

The consensus guidelines of the PCWG3 have been taken into consideration for the determination of radiographic disease progression assessment.

All target and non-target sites of disease identified on the baseline assessment should be reassessed with the same imaging modality at subsequent assessments. Bone lesions should be assessed with Tc-99m based bone scans.

Disease Progression Criteria

At each disease assessment, PD will be determined using the criteria based on PCWG3.

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 5 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, confirmed on the next scan (performed at least 6 weeks later) AND with at least 2 additional lesions 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. In addition, participants must also meet progression criteria per PCWG3 for measurable disease and/or bone disease (Table 9.1.2-1 above).

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

9.2 Adverse Events

The definitions of an AE or serious SAE can be found in Appendix 3.

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

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

Contacts for SAE reporting are specified in Appendix 3.

Immune-mediated AEs 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 that were exacerbated by the induction of autoimmunity. Information supporting the assessment will be collected on the participant's eCRF.

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

The collection of non-serious AE information should begin at initiation of study treatment until the time points specified in the Schedule of Activities (Section 2).

Section 5.6 in the nivolumab IB and Section 6.6 in the rucaparib IB present the Reference Safety Information to determine expectedness of SAEs for expedited reporting. Following the participant's written consent to participate in the study, all SAEs, whether related or not related to study treatment, must be collected, including those thought to be associated with protocol-specified procedures.

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

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

The investigator must report any SAE that occurs after these time periods and that is believed to be related to study drug or a protocol-specified procedure.

- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the appropriate section of the eCRF.
- All SAEs will be recorded and reported to Sponsor or designee within 24 hours, as indicated in Appendix 3.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of these data being available.

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

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

9.2.2 Method of Detecting AEs and SAEs

AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a participant. Care should be taken not to introduce bias when collecting AE and/or

SAEs. Inquiry about specific AEs should be guided by clinical judgment in the context of known adverse events, when appropriate for the program or protocol.

All nonserious 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.

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

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

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

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

9.2.4 Regulatory Reporting Requirements for SAEs

- Prompt notification of SAEs by the investigator to the Sponsor 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 IBs and will notify the IRB/IEC, if appropriate according to local requirements.

Sponsor or designee will be reporting AEs to regulatory authorities and ethics committees according to local applicable laws including European Directive 2001/20/EC and FDA Title 21 Code of Federal Regulations (CFR) Parts 312 and 320. A suspected unexpected serious adverse reaction (SUSAR) 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

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

9.2.6 Laboratory Test Result Abnormalities

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

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

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

9.2.7 Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 9.2.4 for reporting details).

Potential drug induced liver injury is defined as:

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

AND

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

AND

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

9.2.8 Other Safety Considerations

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

9.3 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see Section 9.2.4).

There is no specific treatment in the event of rucaparib overdose, and symptoms of overdose are not established. In the event of suspected overdose, physicians should follow general supportive measures and should treat symptomatically.

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.

There is no antidote for enzalutamide overdose. In the event of an overdose, treatment with enzalutamide should be stopped and general supportive measures initiated taking into consideration the half-life of 5.8 days. Participants may be at increased risk of seizures following an overdose.

9.4 Safety

Planned time points for all safety assessments are listed in the Schedule of Activities (Section 2). Some of the assessments referred to in this protocol may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

9.4.1 Clinical Safety Laboratory Assessments

Investigators must document their review of each laboratory safety report. Please refer to the Schedule of Activities in Section 2 and Table 9.4.1-1 for details regarding required laboratory tests.

Table 9.4.1-1: Laboratory Assessments for Study CA2099KD

Hematology	
Hemoglobin	
Hematocrit	
Total leukocyte count, including differential	
Platelet count	
Serum Chemistry	
Aspartate aminotransferase (AST)	Albumin at screening and as clinically indicated
Alanine aminotransferase (ALT)	ACTH at screening and as clinically indicated
Total bilirubin	Cortisol at screening and as clinically indicated
Alkaline phosphatase	Sodium
Lactate dehydrogenase (LDH)	Potassium
Creatinine	Chloride
Blood Urea Nitrogen (BUN)	Calcium
Glucose (fasting) (at screening only)	Phosphate
TSH, Free T3, Free T4	Magnesium
TSH, with reflexive fT3 and fT4 if TSH is abnormal - on treatment	
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	
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)	
HRD Status	

9.4.2 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

9.5.1 Background

Nivolumab

The pharmacokinetics (PK) of nivolumab were studied in participants over a dose range of 0.1 to 10 mg/kg administered as a single dose or as multiple doses of nivolumab every 2 or 3 weeks. Nivolumab clearance (CL) decreases over time, with a mean maximal reduction (% coefficient of variation [CV%]) from baseline values of approximately 24.5% (47.6%), resulting in a geometric mean steady state clearance (CLss) (CV%) of 8.2 mL/h (53.9%). The decrease in CLss is not considered clinically relevant. The geometric mean volume of distribution at steady state (Vss) was 6.8 L (27.3%), and geometric mean elimination half-life (t1/2) was 25 days (77.5%). Steady state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg Q2W, and systemic accumulation was approximately 3.7-fold. The exposure to nivolumab increased dose-proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks. The clearance of nivolumab increased with increasing body weight. The PPK analysis suggested that the following factors had no clinically important effect on the CL of nivolumab: age (29 to 87 years), gender, race, baseline LDH, PD-L1. A PPK analysis suggested no difference in CL of nivolumab based on age, gender, race, tumor type, baseline tumor size, and hepatic impairment.

Although ECOG status, baseline GFR, albumin and body weight had an effect on nivolumab CL, the effect was not clinically meaningful. PPK and exposure response analyses have been performed to support use of nivolumab 240 mg Q2W, 360 mg Q3W, and 480 mg Q4W dosing regimens in addition to the 3 mg/kg Q2W regimen. A flat dose of nivolumab 240 mg Q2W was selected since it is identical to a dose of 3 mg/kg for subjects weighing 80 kg, the observed median body weight in nivolumab-treated cancer patients, while the nivolumab 360 mg Q3W and 480 mg Q4W regimens allow flexibility of dosing with less frequent visits and in combination with other agents using alternative dosing schedules to Q2W. Using a PPK model, the overall distributions of nivolumab exposures (Cavgss, Cminss, Cmaxss, and Cmin1) are comparable after treatment with either nivolumab 3 mg/kg or 240 mg Q2W. Following nivolumab 360 mg Q3W and 480 mg Q4W, Cavgss are expected to be similar to those following nivolumab 3 mg/kg or 240 mg Q2W, while Cminss are predicted to be, respectively, 6% and ~16% lower and are not considered to be clinically relevant. Following nivolumab 360 mg Q3W and 480 mg Q4W, Cmaxss are predicted to be approximately ~23% and ~43% greater, respectively, relative to that following nivolumab 3 mg/kg Q2W dosing. However, the range of nivolumab exposures (median and 90% prediction intervals) following administration of 240 mg flat Q2W, 360 mg Q3W, and 480 mg Q4W regimens across a wide 35 to 160 kg weight range are predicted to be maintained well below the corresponding exposures observed with the well-tolerated 10 mg/kg nivolumab Q2W dosing regimen.

Additional information on the clinical pharmacology of nivolumab can be found in the nivolumab IB.

Rucaparib

The mean oral bioavailability following a single oral dose of 12 to 120 mg rucaparib was 36%. Following oral administration of rucaparib of 40 to 500 mg and 240 mg to 840 mg BID, rucaparib exposures, as measure by Cmax and AUC, increased approximately dose proportionally. The steady-state accumulation following QD dosing was 1.06 to 1.8 for Cmax, and 1.6 to 2.33 for AUC0-24. And the steady-state accumulation following BID dosing was in the range of 2.6 to 4.9 for Cmax, and 1.47 to 5.44 for AUC0-12. The mean Tmax and t1/2 were approximately 4 hours and 17 hours, respectively. A potential food effect was evaluated at 600 mg. A high-fat meal increased Cmax and AUC0-24 by 20% and 38%, respectively, and delayed Tmax by 2.5 hours as compared to that under fasted conditions. A high-fat meal did not change PK variability, and the food effect is not considered clinically meaningful based on collective clinical efficacy and safety data. Thus, rucaparib can be taken with or without food.

In this study, trough plasma concentrations of rucaparib will be determined for all participants receiving rucaparib as described in Table 9.5.2-1. Details of plasma rucaparib PK sample collection and processing procedures will be provided to the study sites in the laboratorymanual. Plasma concentrations for rucaparib will be determined using a validated HPLC-MS/MS method.

Additional information on the clinical pharmacology of rucaparib can be found in the rucaparib IB.

Enzalutamide

The pharmacokinetics of enzalutamide have been evaluated in prostate cancer patients and in healthy male subjects. The mean terminal half-life ($t_{1/2}$) for enzalutamide in patients after a single oral dose is 5.8 days (range 2.8 to 10.2 days), and steady state is achieved in approximately one month. Maximum plasma concentrations (C_{max}) of enzalutamide in patients are observed 1 to 2 hours after administration. Daily fluctuations in plasma concentrations are low (peak-to-trough ratio of 1.25). Based on a mass balance study in humans, oral absorption of enzalutamide is estimated to be at least 84.2%. With daily oral administration, enzalutamide accumulates approximately 8.3-fold relative to a single dose. Daily fluctuations in plasma concentrations are low (peak-to-trough ratio of 1.25).

Clearance of enzalutamide is primarily via hepatic metabolism, producing an active metabolite that is equally as active as enzalutamide and circulates at approximately the same plasma concentration as enzalutamide. Enzalutamide is not a substrate of the efflux transporters P-gp or BCRP. At steady state, the mean C_{max} values for enzalutamide and its active metabolite are 16.6 µg/mL (23% coefficient of variation [CV]) and 12.7 µg/mL (30 %CV), respectively.

Food has no clinically significant effect on the extent of absorption. In clinical trials, enzalutamide (Xtandi) was administered without regard to food.

The mean apparent volume of distribution (V/F) of enzalutamide in patients after a single oral dose is 110 L (29% CV). The volume of distribution of enzalutamide is greater than the volume of total body water, indicative of extensive extravascular distribution.

Enzalutamide is 97% to 98% bound to plasma proteins, primarily albumin. The active metabolite is 95% bound to plasma proteins. There was no protein binding displacement between enzalutamide and other highly bound drugs (warfarin, ibuprofen and salicylic acid) *in vitro*.

Enzalutamide is metabolised by CYP2C8 and to a lesser extent by CYP3A4/5, both of which play a role in the formation of the active metabolite. *In vitro*, N-desmethyl enzalutamide (active) is metabolised to the carboxylic acid metabolite (inactive) by carboxylesterase 1, which also plays a minor role in the metabolism of enzalutamide to the carboxylic acid metabolite. N-desmethyl enzalutamide was not metabolised by CYPs *in vitro*.

In this study, predose plasma concentrations of enzalutamide will be determined for all participants receiving enzalutamide as described in Table 9.5.2-1. Details of plasma enzalutamide PK sample collection and processing procedures will be provided to the study sites in the laboratory manual. Plasma concentrations for enzalutamide will be determined using a validated HPLC-MS/MS method. Additional information on the clinical pharmacology of enzalutamide can be found in the enzalutamide prescribing information.

9.5.2 Pharmacokinetics Assessments

This study evaluates the effect of nivolumab combined with rucaparib, docetaxel, or enzalutamide in participants with mCRPC and affords the opportunity to assess the pharmacokinetics of nivolumab. Given that the hypothesis is that nivolumab plus each of these combination therapies will improve efficacy compared to any agent alone, nivolumab PK [redacted] will be collected in the study. In addition, rucaparib and enzalutamide PK will be assessed in the study.

Samples for PK (nivolumab, rucaparib and enzalutamide) assessment will be collected for all participants receiving nivolumab or nivolumab/rucaprib or nivolumab/enzalutamide as described in Table 9.5.2-1. All time points are relative to the start of study treatment administration. All on-treatment 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.

Blood samples should be drawn from a site other than the nivolumab infusion site (ie, contralateral arm) on days of infusion. All samples collected pre-dose should be taken just prior to the administration from the contralateral arm (ie, the arm not used for the infusion). A pretreatment PK sample before C1D1 can be collected from the same site as where the infusion will be administered. All nivolumab PK samples after C1D1 should be collected from contralateral arm to prevent sample contamination at the collection site. If the nivolumab infusion was interrupted, the interruption details will also be documented on the CRF. Blood samples will be processed to collect serum and stored preferably at -70°C (samples may be stored at -20°C up to 2 months). Further details of pharmacokinetic [redacted] sample collection and processing will be provided to the site in the laboratory manual. Serum concentration analyses for nivolumab and plasma concentration analyses for rucaparib and enzalutamide will be performed by validated bioanalytical methods(s).

Table 9.5.2-1: Pharmacokinetic [redacted] Sample Collections (CA2099KD)

Study Day (Cycle, Day)[a] (1 Cycle = 4 Weeks for Arms A and C 1 Cycle = 3 Weeks for Arm B up to Cycle 10 then 4 weeks at Cycle 11 and thereafter)	Time (Event)	Time (Relative to Start of Infusion)	Pharmacokinetic Blood Sample for Nivolumab	[redacted]	Pharmacokinetic Blood Sample for Rucaparib	Pharmacokinetic Blood Sample for Enzalutamide
C1D1	(Predose)[b]	00:00	X			
	(EOI nivo)[c]	00:30	X			
C2D1	(Predose)[b]	00:00	X		X	X
	(EOI nivo)[c]	00:30	X			
C3D1	(Predose)[b]	00:00	X		X	X
C4D1	(Predose)[b]	00:00			X	X
C5D1	(Predose)[b]	00:00				
C10D1	(Predose)[b]	00:00				
CXD1: Every 4 cycles after C10 D1 (ie, C14D1, C18D1, etc.)	(Predose)[b]	00:00	X			

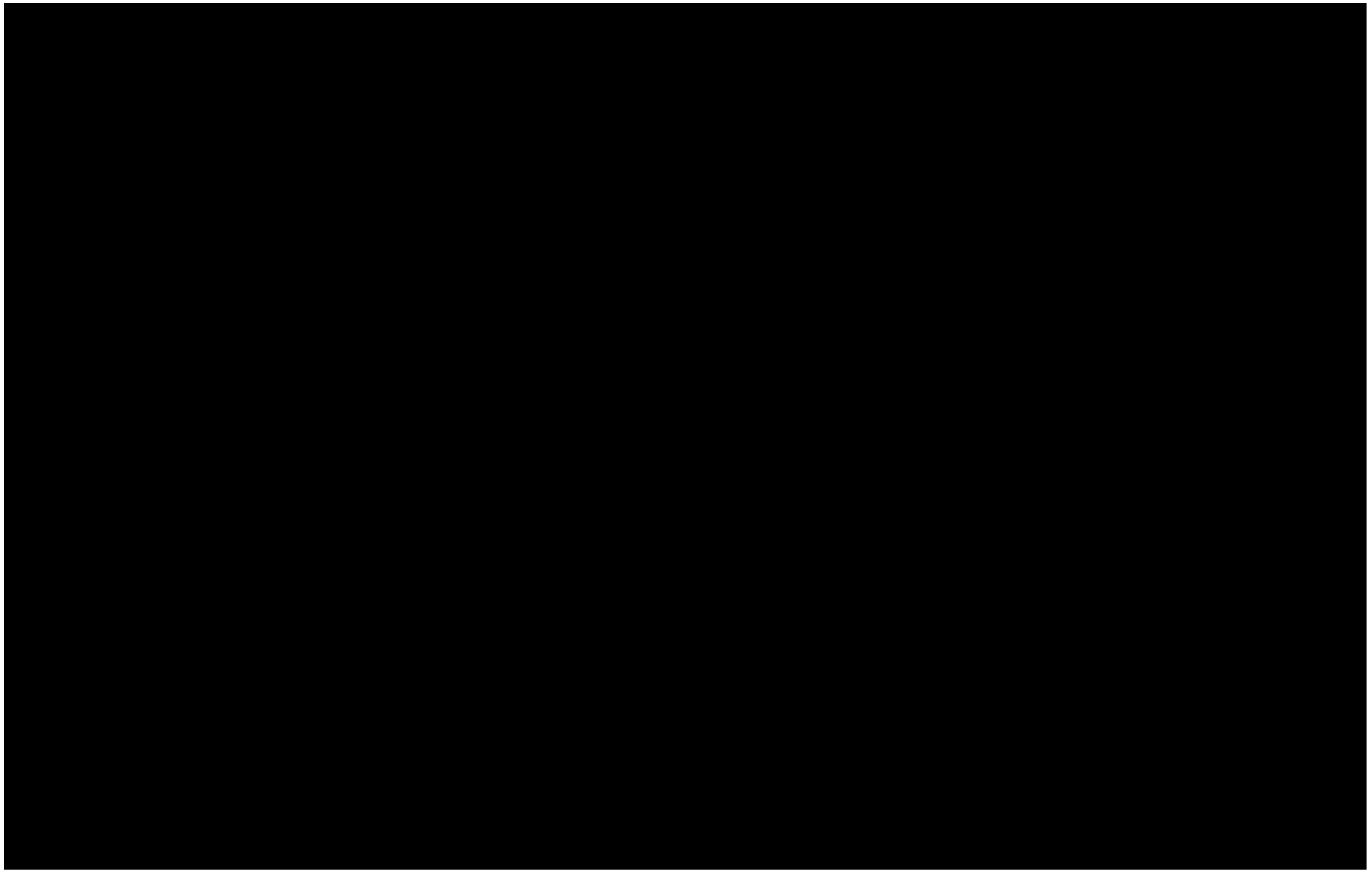
Table 9.5.2-1: Pharmacokinetic [redacted] Sample Collections (CA2099KD)

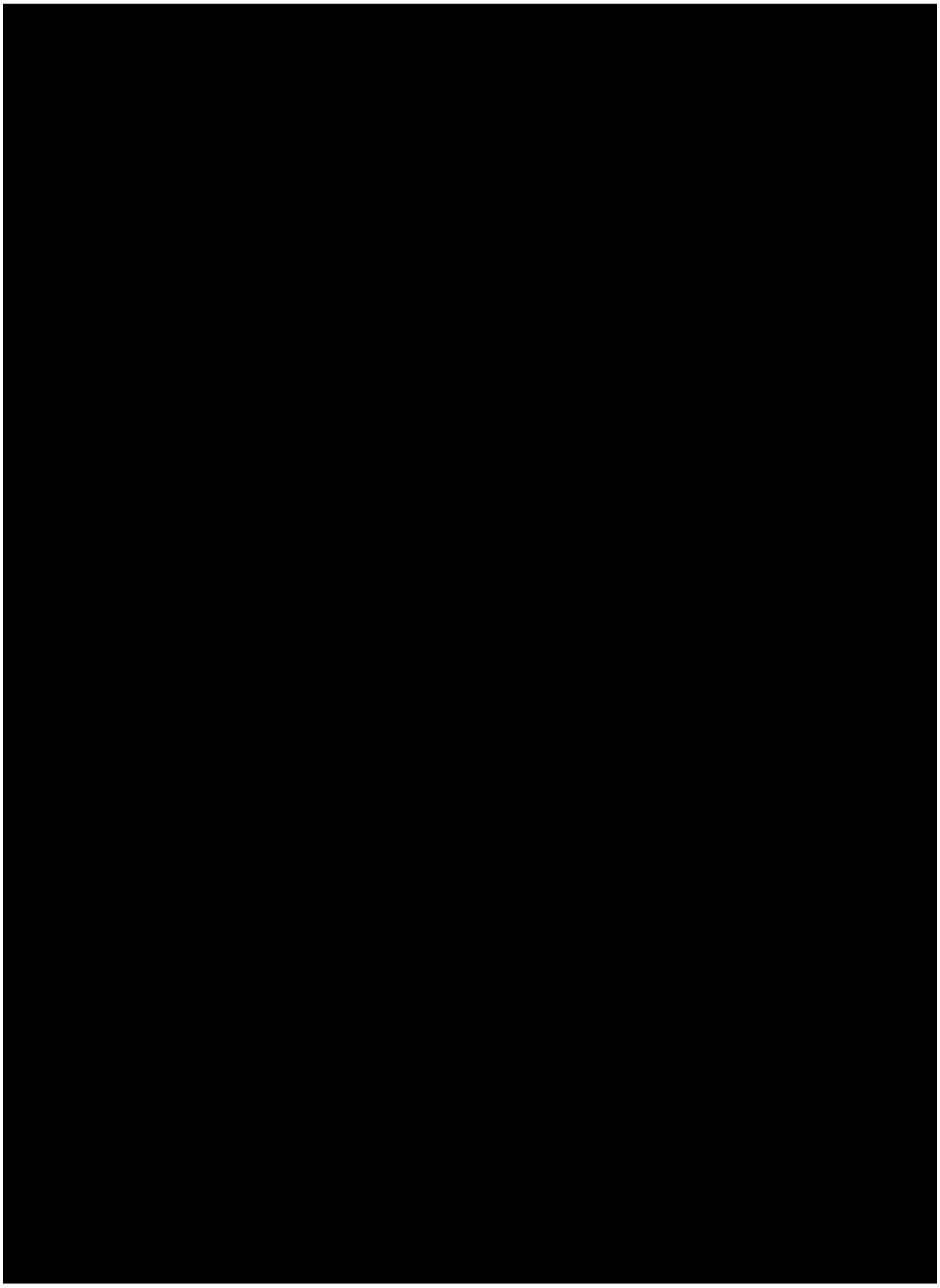
Study Day (Cycle, Day)[a] (1 Cycle = 4 Weeks for Arms A and C 1 Cycle = 3 Weeks for Arm B up to Cycle 10 then 4 weeks at Cycle 11 and thereafter)	Time (Event)	Time (Relative to Start of Infusion)	Pharmacokinetic Blood Sample for Nivolumab	[redacted]	Pharmacokinetic Blood Sample for Rucaparib	Pharmacokinetic Blood Sample for Enzalutamide
Safety Follow-up Visits 1 (Approximately 30 days) & 2 (Approximately 100 Days) from the Discontinuation of Nivolumab during sampling period or at 2 yrs.	NA		X			

[a] If a participant discontinues nivolumab treatment during the sampling period (ie, prior to 2 yrs.), they will move to sampling at the follow-up visits

[b] All predose samples for nivolumab should be taken (preferably within 30 minutes) prior to the start of nivolumab infusion. All nivolumab PK samples after C1D1 should be collected from contralateral arm to prevent sample contamination at the collection site. All predose samples for rucaparib and enzalutamide should be taken prior to the morning dose. 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] EOI-nivo: End of Infusion samples for nivolumab. **EOI samples should be collected immediately (preferably within 2 - 5 minutes) prior to the end of the 30 minute nivolumab infusion**. If the end of infusion is delayed, the collection of the EOI samples should be delayed accordingly. Please ensure accurate collection of time/date of sample collection. EOI samples may not be collected from the same IV access as drug was administered





[redacted]

9.8.2 Tumor Tissue Specimens

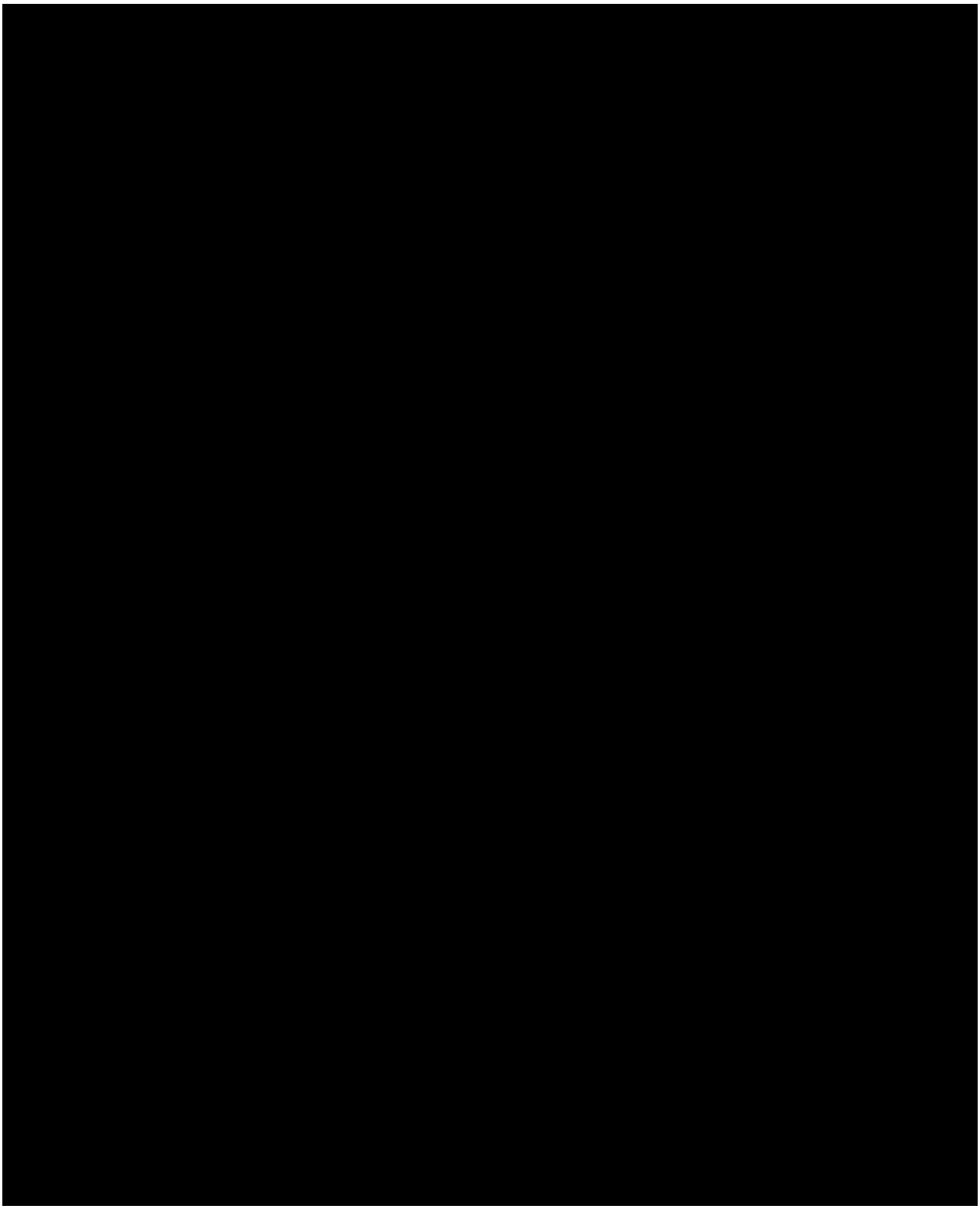
Pre-treatment tumor tissue is mandatory, and defined as a biopsy or surgical specimen obtained within 5 years prior to enrollment from a metastatic soft tissue tumor lesion or from a primary tumor lesion that has not been previously irradiated. [redacted] Submission of fewer than 15 unstained slides may be acceptable in some circumstances following discussion with the BMS Medical Monitor/designee. An associated pathology report should accompany each submitted tumor sample specimen.

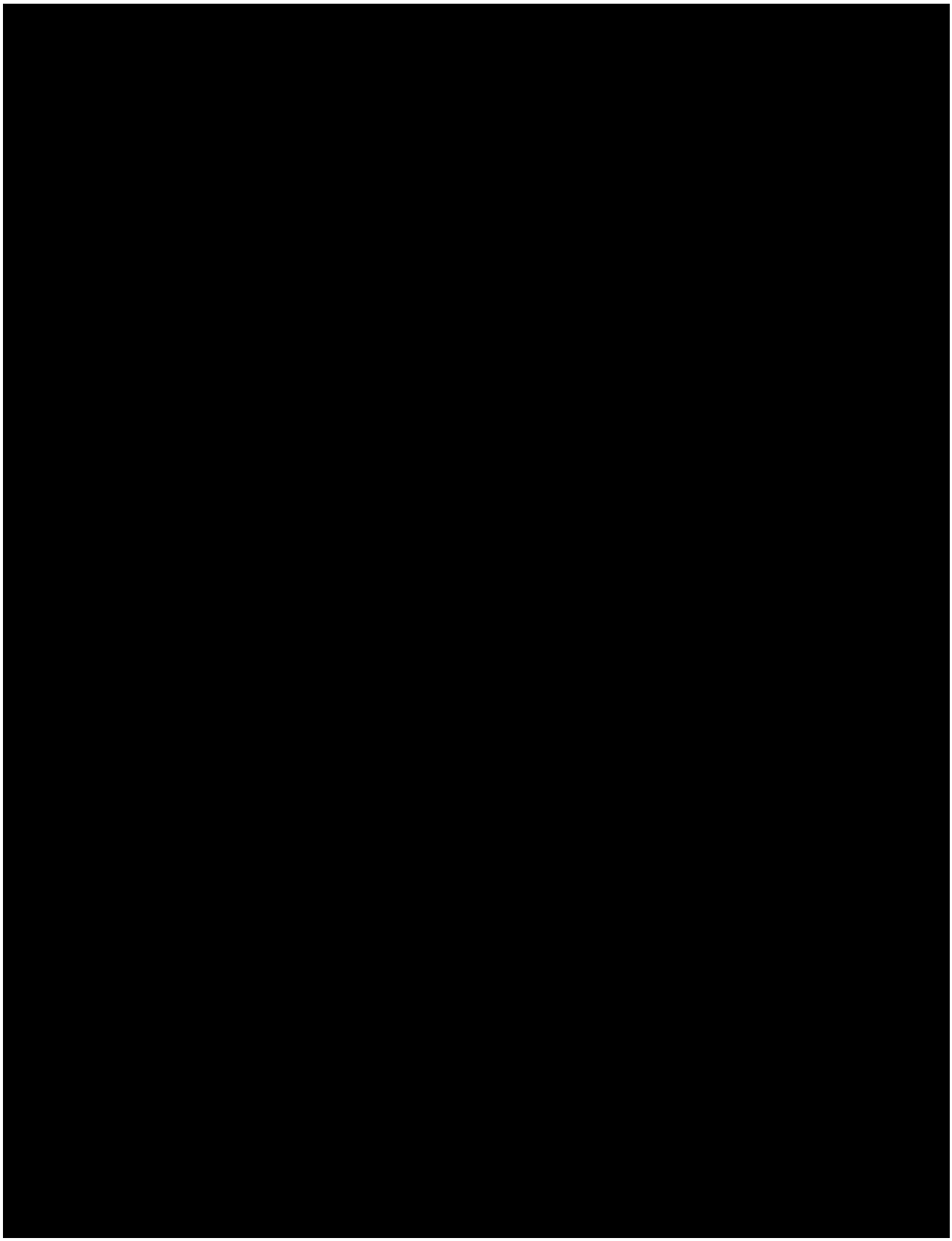
Tumor tissue samples obtained within 5 years prior to enrollment must be submitted during screening. The submitted tumor sample must undergo central HRD testing in order to prospectively assess each participant's HRD tumor status, which is required for treatment arm assignment in IRT, unless local HRD test results obtained prior to enrollment are provided to the Sponsor and confirmed to be acceptable for treatment assignment. Plasma HRD test results will be also used to characterize patients, and transmitted to IRT system prior to treatment assignment.

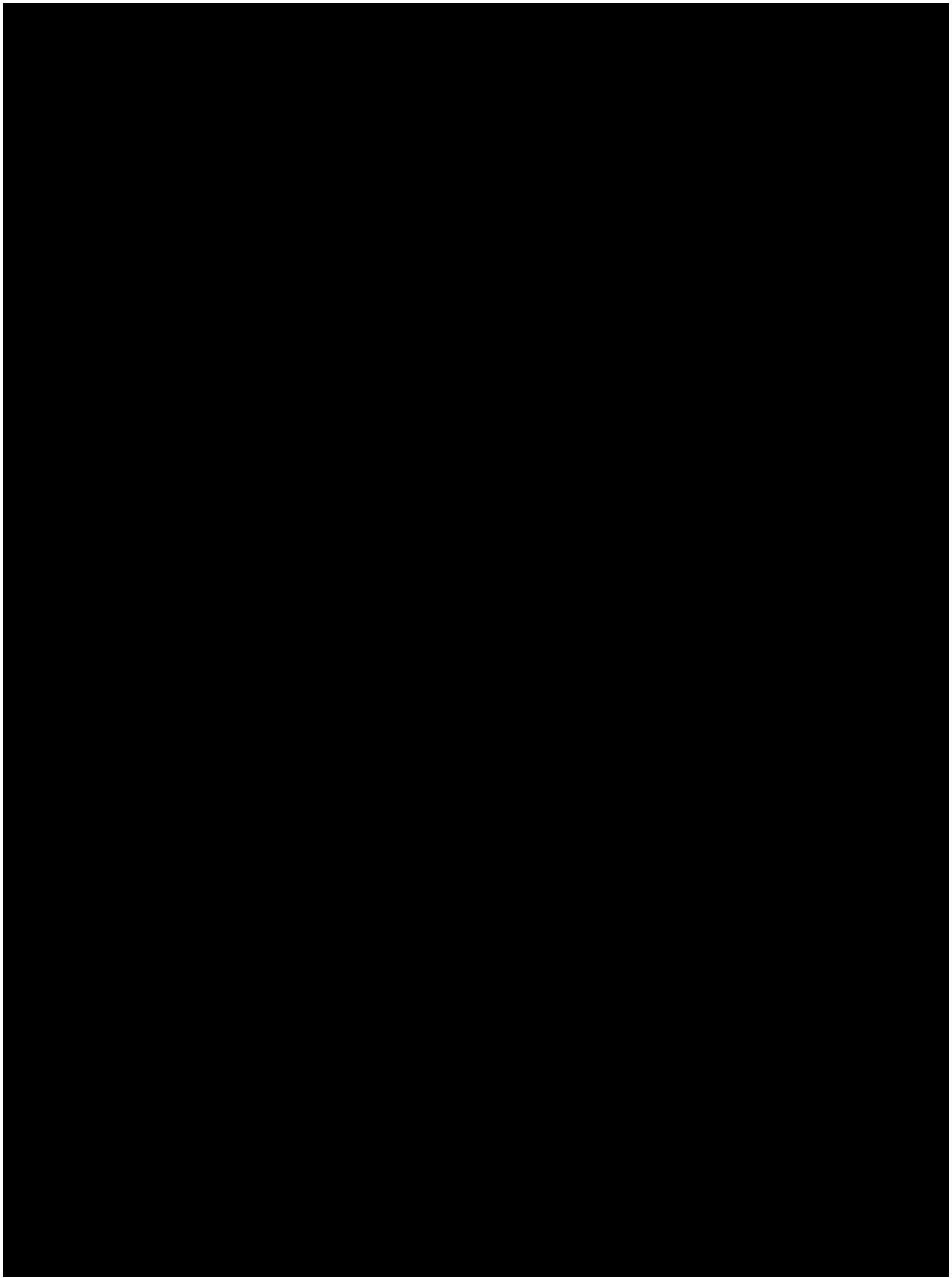
The results of central HRD testing will be submitted by the core laboratory to the IRT. Sites and the BMS study team will remain blinded to each participant's HRD status if determined by the central core laboratory. Sites may be provided with the results of a participant's HRD screening test at the time of radiographic progression or study treatment discontinuation, whichever occurs later. In the event that a germline mutation is identified from central analyses of tumor tissue (or ctDNA), these results will be provided to the treating physician and the participant may be referred by the investigator for genetic counseling per institutional guidelines.

For participants with bone-only disease or inaccessible soft tissue lesions; a minimum of 3 fresh core bone biopsies must be obtained during screening if archival SOFT tissue (less than 5 years old) is unavailable. The first 2 samples should be used to (1) confirm disease and presence of tumor cells by local pathology review and [redacted]

[redacted]







10 STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

Approximately 330 participants with mCRPC will be enrolled and treated in 3 arms.

Planned sample size is summarized in Table 10.1-1 by arm and analysis cohort, which is further divided into smaller subgroups by prior treatment, measurable disease at baseline and the HRD test results.

Table 10.1-1: Sample Size by Arm/Analysis Cohort

Arm/Cohort	Prior Therapy	Measurable Disease	HRD	Size
Arm A (Nivolumab + Rucaparib)				
A1: HRD+	Taxane	Any[b]	Positive	40
A1: HRD-	Taxane	Any[b]	Negative	40
A2: HRD+	Abi and/or Enza[a]	Any[b]	Positive	60
A2: HRD-	Abi and/or Enza[a]	Any[b]	Negative	40
A1 for ORR	Taxane	Yes	Any	48
A2 for ORR	Abi and/or Enza[a]	Yes	Any	60
A1 for RR-PSA/PFS	Taxane	Any[b]	Any	80
A2 for RR-PSA/PFS	Abi and/or Enza[a]	Any[b]	Any	100
A-HRD+ for ORR	Any	Yes	Positive	60
A-HRD- for ORR	Any	Yes	Negative	48
A-HRD+ for RR-PSA/PFS	Any	Any[b]	Positive	100
A-HRD- for RR-PSA/PFS	Any	Any[b]	Negative	80
Arm B (Nivolumab + Docetaxel)				
B: HRD+ [b]	Abi and/or Enza[c]	Any[b]	Positive	25
B: HRD- [b]	Abi and/or Enza[c]	Any[b]	Negative	60
B for ORR	Abi and/or Enza[c]	Yes[b]	Any	51
B for RR-PSA/PFS	Abi and/or Enza[c]	Any[b]	Any	85
Arm C (Nivolumab + Enzalutamide)				
C: HRD+ [b]	Abi only[a]	Any[b]	Positive	25
C: HRD- [b]	Abi only[a]	Any[b]	Negative	40
C for ORR	Abi only[a]	Yes	Any	39
C for RR-PSA/PFS	Abi only[a]	Any[b]	Any	65

[a] No immediate chemotherapy

[b] 60% of participants in each treatment arm are required to have measurable disease

[c] Need immediate chemotherapy

The sample size is calculated using the precision approach for the co-primary endpoints, ie, ORR, as assessed by investigator per PCWG3, among treated participants with measurable disease at baseline in an analysis cohort, and RR-PSA among treated participants in an analysis cohort. Table 10.1-2 provides the precision for potential response rates. For example, if 6 or more responders are observed among 30 participants in an analysis cohort, then the lower limit of the 95% CI for the response rate is above 7.7%.

Table 10.1-2: Exact 95% CI for ORR and RR-PSA

Participants	Responders	Observed Rate	Lower Limit	Upper Limit
30	6	20.0%	7.7%	38.6%
30	11	36.7%	19.9%	56.1%
39	10	25.6%	13.0%	42.1%
39	15	38.5%	23.4%	55.4%
50	10	20.0%	10.0%	33.7%
50	15	30.0%	17.9%	44.6%
51	18	35.3%	22.4%	44.9%
51	23	45.1%	31.1%	59.7%
60	43	71.7%	58.6%	81.5%
60	48	80.0%	67.7%	89.2%
65	26	40.0%	28.0%	52.9%
65	31	47.7%	35.1%	60.5%
85	53	62.4%	51.2%	72.6%
85	58	68.2%	57.2%	77.9%
100	78	78.0%	68.6%	85.7%
100	83	83.0%	74.2%	89.8%

Powers are assessed for ORR and RR-PSA, using the one-arm binomial test. Estimates of reference ORR and RR-PSA are based on the current SOC for the target populations for each analysis cohort in this study; see Table 5.4.3-1. A target ORR for a promising combination treatment is assumed as an increase of 15% or more compared to the current SOC in an analysis cohort. As shown in Table 10.1-3, powers are assessed at a 1-sided alpha of 10% using the method from Fleiss (1981).[128] In addition, the planned number of treated participants will also provide an adequate power for detecting a 10% absolute increase in RR-PSA for the combination compared to SOC and provide a stable estimate of median rPFS for each analysis cohort.

Table 10.1-3: Power for ORR in Participants with Measurable Disease at Baseline

Analysis Cohort/Arm	Participants	Null ORR	Target ORR	Power
A1	48	10%	25%	94%
A2	60	21%	36%	91%
B	51	21%	36%	87%
C	39	10%	25%	89%

The accrual duration is approximately 15 months, based on a monthly enrollment rate of 22 participants, and the follow-up period will be 12 months. The final analysis of the co-primary endpoints of ORR and RR-PSA will occur approximately 2.5 years after the first participant is treated in an analysis cohort/arm and may be performed independently from other cohorts/arms if enrollment is completed at different times across the cohorts/arms. This will allow sufficient follow-up for a stable estimate of BOR and DOR, and an adequate safety assessment. Additional survival analyses may be conducted for up to 5 years after treatment initiation following the updated analysis of the co-primary endpoints.

10.2 Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign an informed consent form and are registered into the IRT
Treated	All enrolled participants who receive any dose of study therapy (ie, any component therapy in the combination for each analysis cohort). This is the primary dataset for the analyses of study conduct, study population, efficacy, exposure, safety, and outcome research.
Response evaluable	All treated participants who have measurable disease at baseline as assessed by investigator per PCWG3
HRD+ and Response evaluable	All response-evaluable participants who had HRD+ status at baseline
HRD-/Not evaluable and Response evaluable	All response evaluable participants who had HRD- status or not evaluable status at baseline
Pharmacokinetic	All treated participants with available serum concentration vs time data for nivolumab All treated participants with available plasma concentration vs time data for rucaparib

Population	Description
	All treated participants with available plasma concentration vs time data for enzalutamide
[redacted]	

10.3 Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock and will describe the selection of participants to be included in the analyses and procedures for accounting for missing, 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 the statistical output reported, including subgroups of age, gender, and race.

10.3.1 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Co-Primary	
• ORR-PCWG3	• Estimate of ORR-PCWG3 and corresponding 2-sided exact 95% CI using the Clopper-Pearson method by the HRD status and analysis cohort for all response evaluable participants.
• RR-PSA	• RR-PSA will be analyzed by the HRD status and analysis cohort for all treated participants in the same way as for ORR-PCWG3.
Secondary	
• rPFS • TTR and DOR per PCWG3 • TTP-PSA • OS	Time to event distribution (rPFS, DOR-PCWG3 for responders, TTR-PCWG3 for responders, TTP-PSA, OS) will be estimated by the HRD status and analysis cohort for treated participants using Kaplan Meier techniques. This will be performed for PFS(s), OS and DOR. Median survival time along with 95% CI will be constructed by analysis cohort based on a log-log transformed CI for the survivor function. Rates at fixed time points will be derived from the Kaplan Meier estimate and corresponding CI will be derived by analysis cohort based on Greenwood formula for variance derivation and on log-log transformation applied on the survivor function.

Endpoint	Statistical Analysis Methods
[redacted]	

10.3.2 Safety Analyses

Endpoint	Statistical Analysis Methods
Incidence of AEs, SAEs, AEs leading to discontinuation, deaths AEs will be graded according to CTCAE Version 4.03	Frequency distribution of treated participants with AE using the worst common terminology criteria grade on treatment. Participants will be counted once at the preferred term (PT) level, once at the system organ class (SOC) level, and once in the "Total participant" row at their worst common terminology criteria grade, regardless of SOC or PT.
Laboratory abnormalities Laboratory values will be graded according to CTCAE Version 4.03	Laboratory shift table using worst common terminology criteria grade on treatment per participant.

10.3.3 Other Analyses

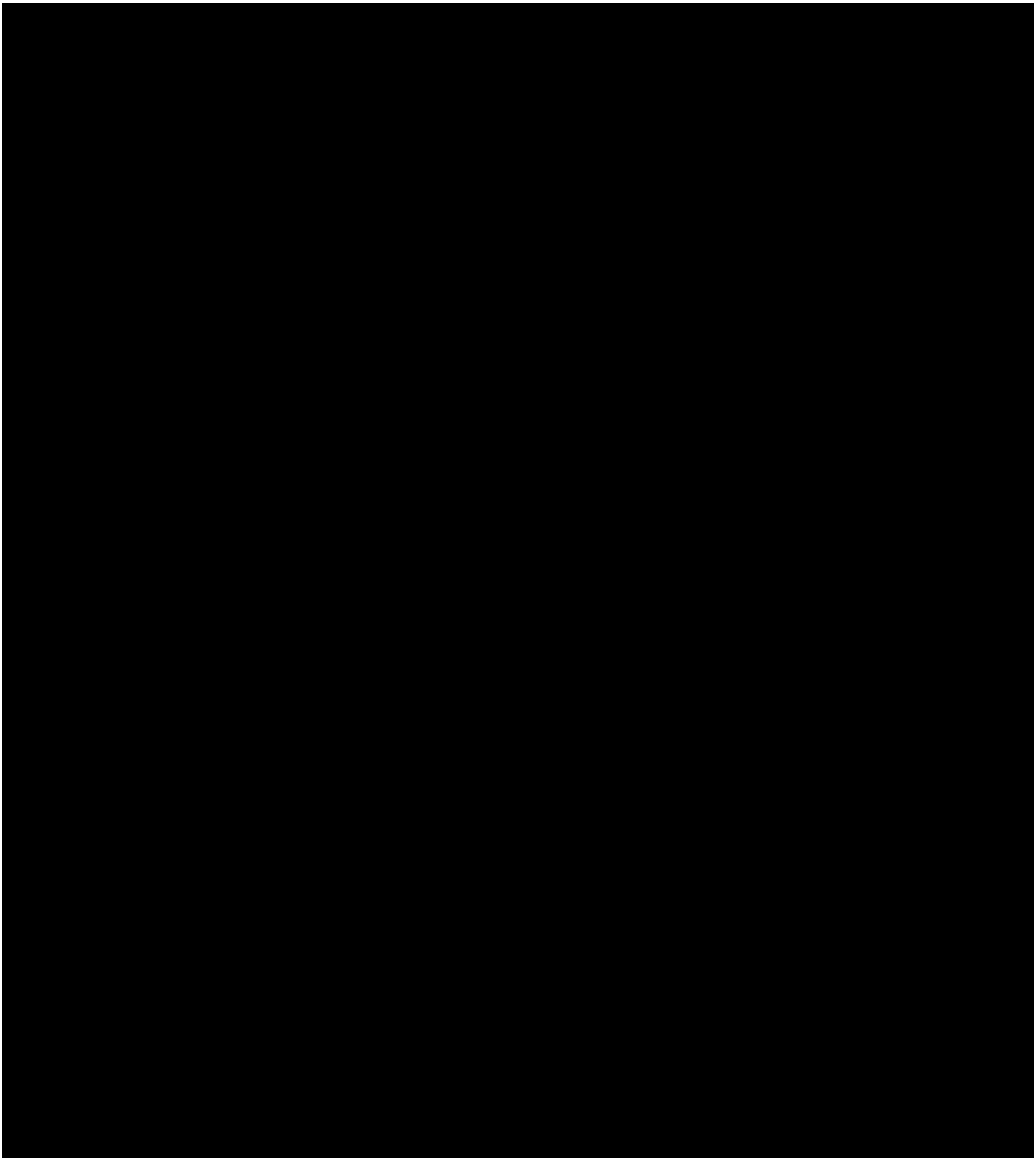
[redacted]

Pharmacokinetic Analyses

The nivolumab concentration versus time data obtained in this study will be combined with data from other studies in the clinical development program to develop a PPK model. This model will be used to evaluate the effects of intrinsic and extrinsic covariates on the PK of nivolumab to determine measures of individual exposure (such as steady state peak, trough and time-averaged concentration). Pharmacokinetic drug-drug interaction between nivolumab and other component drugs will be studied by a PPK approach. Model-determined exposures will be used for exposure-

response analyses of selected efficacy and safety endpoints if the data permit. The PPK analysis will be presented separately from the main clinical study report.

The trough plasma concentrations of rucaparib and enzalutamide versus time data will be analyzed, including summary statistics and plotting. Post hoc estimates of PK parameters and exposures will be estimated for each participant using the existing or updated PPK model. The estimated exposures will be used for exposure-response analyses of selected efficacy and safety endpoints if the data permit. The PPK analysis may be presented separately from the main clinical study report.



10.3.4 Interim Analyses

An interim analysis will be performed in each arm when at least 50% of planned participants have been treated, with at least 16 weeks of follow-up after first dose. The purpose of the interim analysis is to generate preliminary data that will inform decisions related to external studies, as well as determine if any of the study arms should be expanded to generate additional data that may support a regulatory filing. If the data from the initial interim analysis appear to be immature to support decision-making on the expansion of a specific study arm, a second interim analysis of that arm may be performed after enrollment has been completed and all treated patients have been followed for at least 16 weeks after first dose.

After the interim analysis, an expansion for each arm may be triggered based on review of the totality of available data by a small unblinded BMS team outside of the CA2099KD team (see Section 7.3) if a clinically meaningful response compared to the historical standard of care [SOC] for the population in that arm or subgroup is observed.. Table 10.3.4-1 provides some examples of potential response rates observed at the interim analysis and the precision for potential sample

sizes to be expanded to for each arm or HRD subgroup, if applicable, based on the historical ORR for SOC in that arm or HRD subgroup. (See Rationale for Interim Analysis in Section 5.4.9 for more details regarding the historical ORR assumptions for each arm/subgroup.) For example, if an interim ORR of 43% is observed for HRD+ participants in Arm A1 (15% improvement over the historical ORR for SOC in this subgroup), the sample size of HRD+ in Arm A1 could be expanded up to ~ 46 participants measurable disease. Summaries and listings of efficacy and safety for treated participants with at least 16 weeks of follow-up and by HRD status will be shared with the DMC after the interim analysis in each arm. In any arm or subgroup that is expanded, interim analyses in the additional participants treated in the expansion with at least 16 weeks of follow-up after first dose may be performed if needed to determine if the data may be sufficient to support a regulatory filing.

Table 10.3.4-1: Exact 95% CI for Potential Observed ORR and Potential Sample Size

Arm/subgroup	SOC Historical ORR	Observed ORR	N (meas disease)	Lower Limit (%)	Upper Limit (%)
A1 or A2 HRD+	28%	43%	46	28.9	58.9
		48%	29	29.4	67.5
A1 HRD-	14%	29%	34	15.1	47.5
		34%	20	15.4	59.2
A2 HRD-	21%	36%	41	22.1	53.1
		41%	24	22.1	63.3
B or C All-Comers	21%	36%	41	22.1	53.1
		41%	24	22.1	63.3

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12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
ACTH	adrenocorticotropic hormone
[redacted]	
ADT	androgen deprivation therapy
AE	adverse event
AIDS	Acquired Immunodeficiency Syndrome
AJCC	American Joint Committee on Cancer
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	Acute myeloid leukemia
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BICR	Blinded Independent Central Review
BID, bid	bis in die, twice daily
BMS	Bristol-Myers Squibb
BOR	best overall response
BPI-SF	Brief Pain Inventory - Short Form
BP	blood pressure
BRCA	breast cancer susceptibility gene
BUN	blood urea nitrogen
Ca^{++}	calcium
Cavgss	average concentration at steady state
CBC	complete blood count
cHL	Classical Hodgkin Lymphoma
CI	confidence interval
$C1^{-}$	chloride
[redacted]	
Cmaxss	maximum observed concentration at steady state
Cminss	minimum observed concentration at steady state
CNS	Central Nervous System

Term	Definition
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form, paper or electronic
CRPC	castration-resistant prostate cancer
crPFS	clinical/radiographic progression-free survival
CT	Computed tomography
CTAg	clinical trial agreement
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	
CYP	cytochrome p-450
DDI	drug-drug interaction
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
[redacted]	
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
[redacted]	
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
FU	Follow-up
GnHR	gonadotropin releasing hormone
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HBVsAG	Hepatitis b virus surface antigen
HCV	hepatitis C virus
Hep B/C	Hepatitis B or Hepatitis C
HIV	Human Immunodeficiency Virus

Term	Definition
HR	homologous recombination
HRD	Homologous Recombination Deficiency
HSPC	hormone-sensitive prostate cancer
IB	Investigator Brochure
ICF	Informed Consent Form
IEC	Independent Ethics Committee
[redacted]	
IMAE	immune-mediated adverse event
[redacted]	
IMP	investigational medicinal products
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	intravenous
K^+	potassium
LDH	lactate dehydrogenase
LFT	liver function test
LHRH	luteinizing hormone releasing hormone
mCRPC	metastatic castration-resistant prostate cancer
MDS	myelodysplastic syndrome
[redacted]	
MHC	major histocompatibility complex
MRI	Magnetic Resonance Imaging
[redacted]	
MTD	maximum tolerated dose
Na^+	sodium
N/A	not applicable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
[redacted]	
NSCLC	non-small cell lung cancer

Term	Definition
ORR	objective response rate
OS	overall survival
PAP	Prostatic acid phosphatase
PARP	Poly (ADP-ribose) polymerase
PAPRi	PARP inhibitor
[redacted]	
PCWG3	Prostate Cancer Clinical Trials Working Group 3
PD	progressive disease
PD-L1	programmed death ligand no. 1
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetics
PO	By mouth
PPK	population pharmacokinetics
PSA	prostate-specific antigen
PSMA	prostate-specific membrane antigen
PT	Preferred Term
QXW	every x weeks
QD, qd	quaque die, once daily
QoL	quality of life
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
rPFS	radiographic progression-free survival
RR	respiration rate
RR-PSA	PSA response rate
SAE	serious adverse event
SmPC	Summary of Product Characteristics
SNP	single nucleotide polymorphism
SOC	Standard of Care

Term	Definition
SSBD/DSB	Single/double strand breaks
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAA	tumor-associated antigen
T. Bili	total bilirubin
TCR	T cell receptor
TIL	tumor infiltrating lymphocytes
Treg	regulatory T-cells
TSH	thyroid stimulating hormone
TTR	time to response
[redacted]	
ULN	upper limit of normal
USP	United States Pharmacopoeia
USPI	United States Prescribing Information
WOCBP	women of childbearing potential
WNOCBP	women **not** of childbearing potential

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

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

REGULATORY AND ETHICAL CONSIDERATIONS

GOOD CLINICAL PRACTICE

This study will be conducted in accordance with:

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

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

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

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

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., 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. 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 to 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 (i.e., 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 nivolumab, rucaparib, docetaxel, and enzalutamide (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 (e.g., lost, wasted) • amount destroyed at study site, if applicable • amount returned to BMS [redacted] • 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 drug integrity in accordance with requirements applicable under law and the SOPs/standards of the sourcing pharmacy. •

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

CASE REPORT FORMS

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

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

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

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

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

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

MONITORING

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

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

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

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

RECORDS RETENTION

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

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

If the investigator withdraws from the study (e.g., relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g., 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 (e.g., 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, i.e., incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

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

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

CLINICAL STUDY REPORT

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

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

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

SCIENTIFIC PUBLICATIONS

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

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

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

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

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

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

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

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

ADVERSE EVENTS

Adverse Event Definition:
An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study treatment and that does not necessarily have a causal relationship with this treatment.
An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study treatment, whether or not considered related to the study treatment.
Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or results from other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Note that abnormal lab tests or other safety assessments should only be reported as AEs if the final diagnosis is not available. Once the final diagnosis is known, the reported term should be updated to be the diagnosis. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose, as a verbatim term (as reported by the investigator), should not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae and should specify "intentional overdose" as the verbatim term
Events <u>NOT</u> Meeting the AE Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

DEFINITION OF SAE

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

SERIOUS ADVERSE EVENTS

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
Requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below) NOTE: The following hospitalizations are not considered SAEs in BMS clinical studies: • a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event) • elective surgery, planned prior to signing consent • admissions as per protocol for a planned medical/surgical procedure • routine health assessment requiring admission for baseline/trending of health status (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 (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason) • admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)
Results in persistent or significant disability/incapacity
Is a congenital anomaly/birth defect

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
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 9.2.7 for the definition of potential DILI.)

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

EVALUATING AES AND SAES

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

Follow-up of AEs and SAEs
If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports must include the same investigator term(s) initially reported.) If an ongoing SAE changes in its intensity or relationship to study treatment or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report. All SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

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

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

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

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

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

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

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

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

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

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

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

Unacceptable Methods of Contraception*
• Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously • Diaphragm with spermicide • Cervical cap with spermicide • Vaginal Sponge with spermicide

Unacceptable Methods of Contraception*
• Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action • Periodic abstinence (calendar, symptothermal, post-ovulation methods) • Withdrawal (coitus interruptus). • Spermicide only • Lactation amenorrhea method (LAM)

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

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

Male participants with female partners of childbearing potential are eligible to participate if they agree to the following during the treatment and until the end of relevant systemic exposure.

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- Male participants are required to use a condom for study duration and until end of relevant systemic exposure defined as 7 months after the end of study treatment.
- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 7 months after the end of treatment in the male participant.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 7 months after the end of study treatment.
- Refrain from donating sperm for the duration of the study treatment and until 7 months after the end of study treatment.

COLLECTION OF PREGNANCY INFORMATION

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

APPENDIX 5 PCWG3 GUIDELINES (WITH MODIFIED RECIST V1.1 CRITERIA FOR SOFT TISSUE LESION ASSESSMENT)

Participants with metastatic castration-resistant prostate cancer may have only soft tissue lesions, only bone lesions, or both soft tissue lesions and bone lesions. PCWG3 guidelines use modified RECIST 1.1 criteria for evaluation of soft tissue lesions, including lymph nodes, but have special rules for evaluation of metastatic bone lesions.[1] Each section below will specify the guidelines for assessment of soft tissue lesions and bone lesions separately.

1 EVALUATION OF BASELINE LESIONS

1.1 Soft Tissue Lesions

At baseline, soft tissue lesions, including lymph nodes, should be evaluated by CT or MRI and will be categorized as measurable or non-measurable as follows.

1.1.1 Measurable

Measurable disease is defined by presence of at least one measurable tumor lesion. Measurable 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 5mm.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be≥ 15 mm in short axis when assessed by CT/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.

1.1.2 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.

Tumor lesions situated in a previously irradiated area are usually not considered measurable unless there has been demonstrated progression in the lesion.

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

1.1.3 Baseline Documentation Of 'Target' And 'Non-Target' Soft Tissue 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 target lesions can be selected per organ system. For example, a maximum of 5 lung lesions can be selected. A maximum of 5 lymph node lesions 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 of 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 of diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other soft tissue 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. 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').

1.2 Bone Lesions

Bone lesions should only be evaluated with Technecium-99m based radionuclide bone scan as per PCWG3. The number of bone lesions identified on the baseline radionuclide bone scan, as well as the anatomic location of each bone lesion, should be noted. In this study, bone lesions should be reported and followed separately from soft tissue non-target lesions.

2 POST-BASELINE DISEASE ASSESSMENT

Participants with any soft tissue lesions at baseline that can be followed as target and/or non-target lesions on CT or MRI scans should be evaluated per the rules described Section 2.1. Participants with only bone lesions at baseline should be evaluated per the rules described in Section 2.1.2.

2.1 Post-Baseline Evaluation in Participants with Baseline Soft Tissue Lesions

2.1.1 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 PD as defined above.

2.1.1.1 Special Notes on the Assessment of Target Lesions

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.

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.

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'.

2.1.2 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.

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

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

When the participant 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.

When the participant 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 participants for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include, an increase in lymphangitic disease from localized to widespread, or may be described as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the participant 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.

2.1.3 New Lesions

2.1.3.1 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 posttreatment 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 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.

2.1.3.2 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 participant'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 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 participant who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The participant'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 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. Response Assessment.

2.1.3.3 Participants with New Bone Lesions and New Soft Tissue Lesions

Participants may develop new bone lesions (identified on radionuclide bone scans) at a different time point than new soft tissue lesions (identified on CT or MRI). If progression is based solely on the identification of new lesions and new bone lesions and new soft tissue lesions are identified at different time points, then the time point at which any new lesion (bone or soft tissue) was first identified should be the date of progression (taking into account the need for subsequent confirmatory bone scan for new bone lesions, as mentioned above).

2.1.4 Time Point Response

At each protocol specified time point, a response assessment occurs. Table 2.1.4-1 provides a summary of the overall response status calculation at each time point for participants who have measurable disease at baseline. When participants have non-measurable (therefore non-target) soft tissue disease only, Table 2.1.4-2 is to be used.

Table 2.1.4-1: Time Point Response: Participants With Target (± Non-Target) Disease

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

Table 2.1.4-2: Time Point Response: Participants with Non-target Soft Tissue Disease Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

[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.

2.1.5 Best Overall Response

The best overall response (BOR) 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 participant'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.

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 2.1.5-1. In this study, a BOR of SD can only be made if a tumor assessment meeting SD criteria was performed at least 49 days after the date of first treatment.

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 participants with CR may not have a total sum of 'zero' on the case report form (CRF).

Table 2.1.5-1: 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

Table 2.1.5-1: Best Overall Response (Confirmation of CR&PR Required)

Overall Response First Time Point	Overall Response Subsequent Time Point	BEST Overall Response
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

[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 participant 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.

2.1.6 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: New bone lesions identified on radionuclide bone scan must be confirmed, as specified in Section 2.1.5. Progression of disease should also be verified in cases where progression is suspected based solely on an equivocal new lesion. If repeat scans confirm that the new lesion is an unequivocal tumor lesion, 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 PD.

2.2 Post-Baseline Evaluation in Participants with Baseline Bone-Only Disease

Complete or partial response in bone lesions cannot be accurately assessed on radionuclide bone scan. Progression in participants who only have bone lesions at baseline is based only on the

identification of new lesions (either bone or soft tissue) that meet the criteria specified in Section 2.1.3. Therefore, participants who have bone-only disease at baseline should have an overall response of stable disease for any time point that does not document new lesions according to the criteria specified in Section 2.1.3. If new lesions meeting the criteria specified in Section 2.1.3 are identified at any time point (with a subsequent confirmatory bone scan for new bone lesions), then the overall response for that time point is progression. The first time point documenting new lesions should be the date of progression in participants with bone-only disease at baseline.

[1] Scher HL, 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;34:1402-18.

APPENDIX 6 MANAGEMENT ALGORITHMS

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

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

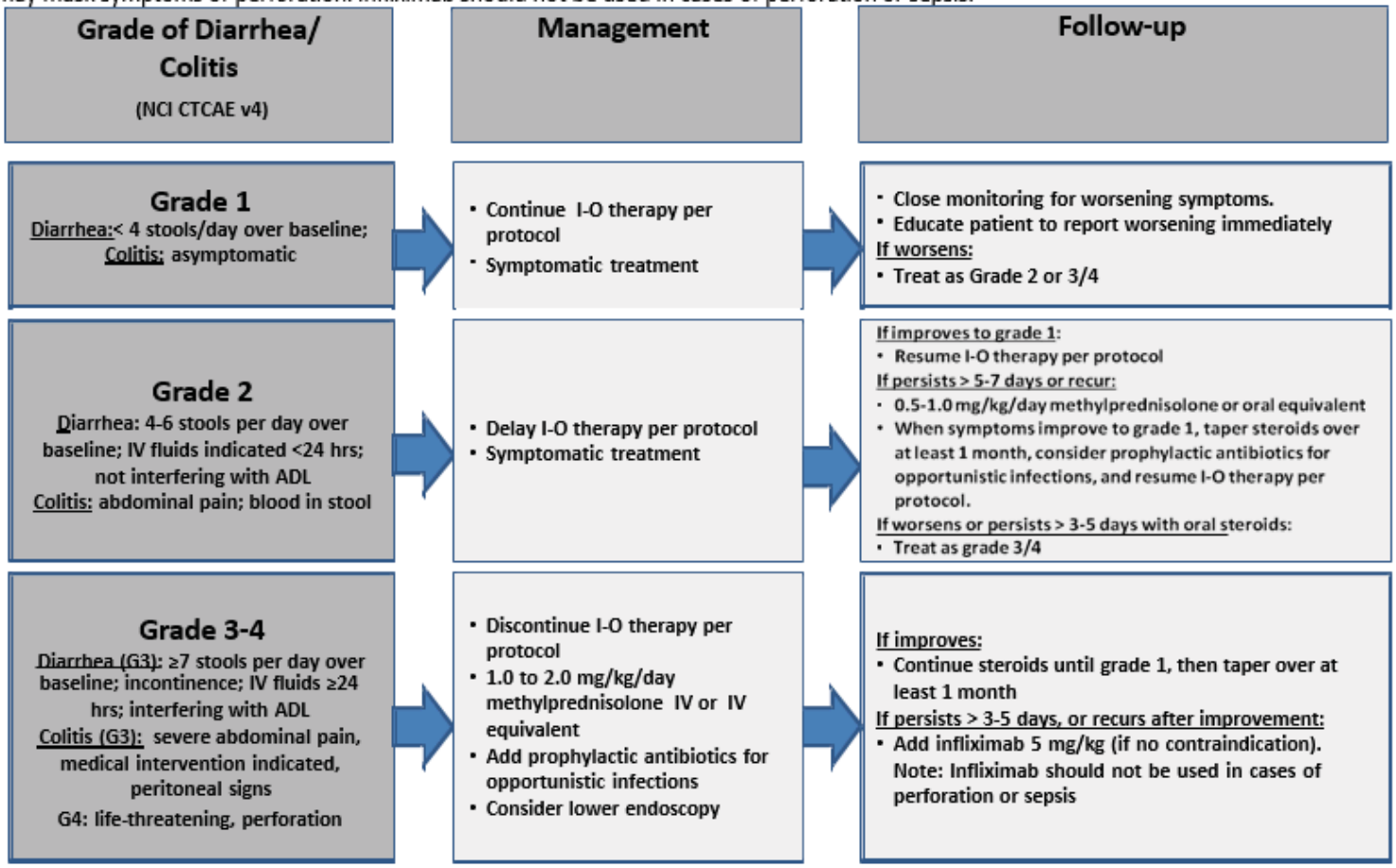
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the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

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

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

GI Adverse Event Management Algorithm

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



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

27-Jun-2019

Renal Adverse Event Management Algorithm

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

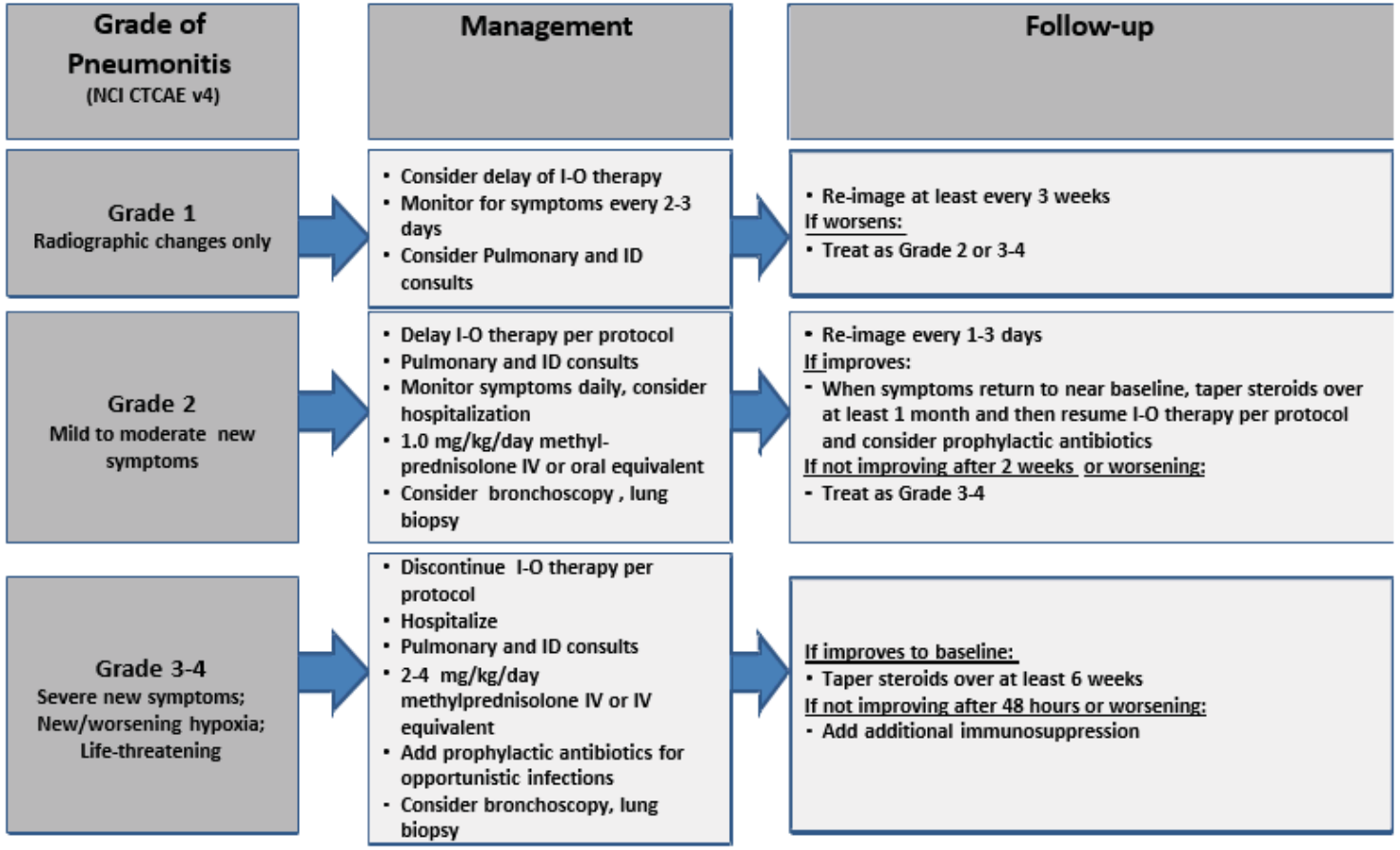
Grade of Creatinine Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 Creatinine > ULN and > than baseline but ≤ 1.5x baseline	• Continue I-O therapy per protocol • Monitor creatinine weekly	If returns to baseline: •Resume routine creatinine monitoring per protocol If worsens: •Treat as Grade 2 or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

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

27-Jun-2019

Pulmonary Adverse Event Management Algorithm

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



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

27-Jun-2019

Hepatic Adverse Event Management Algorithm

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

Grade of Liver Test Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 AST or ALT > ULN to 3.0 x ULN and/or T. bili > ULN to 1.5 x ULN	• Continue I-O therapy per protocol	• Continue LFT monitoring per protocol If worsens: • Treat as Grade 2 or 3-4
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and/or T. bili > 1.5 to ≤ 3 x ULN	• Delay I-O therapy per protocol • Increase frequency of monitoring to every 3 days	If returns to baseline: •Resume routine monitoring, resume I-O therapy per protocol If elevations persist > 5-7 days or worsen : • 0.5-1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol
Grade 3-4 AST or ALT > 5 x ULN or T.bili >3 x ULN	• Discontinue I-O therapy* • Increase frequency of monitoring to every 1-2 days • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent* • Add prophylactic antibiotics for opportunistic infections • Consult gastroenterologist	If returns to grade 2: • Taper steroids over at least 1 month If does not improve in >3-5 days, worsens or rebounds: • Add mycophenolate mofetil 1 g BID • If no response within an additional 3-5 days, consider other immunosuppressants per local guidelines

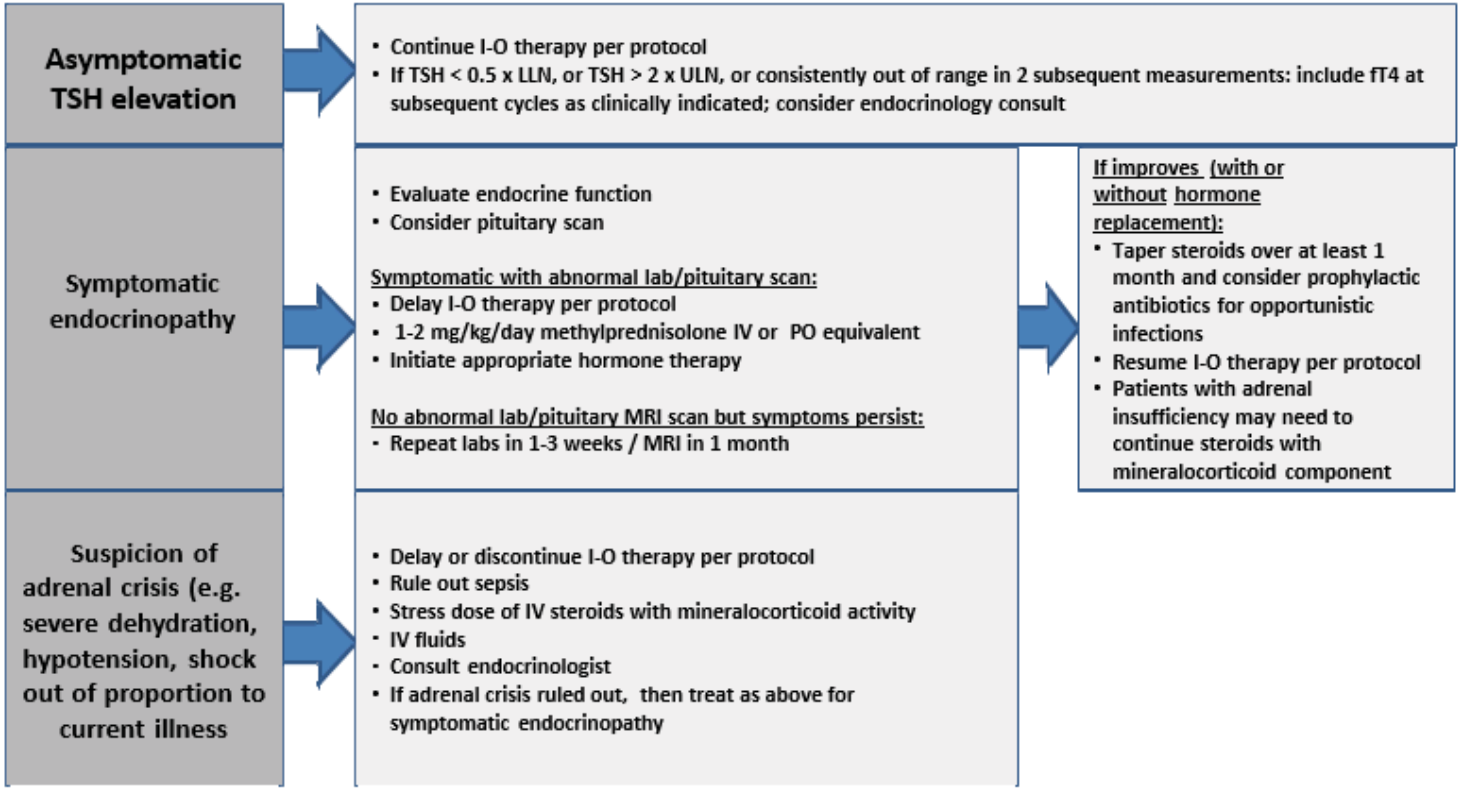
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

27-Jun-2019

Endocrinopathy Adverse Event Management Algorithm

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

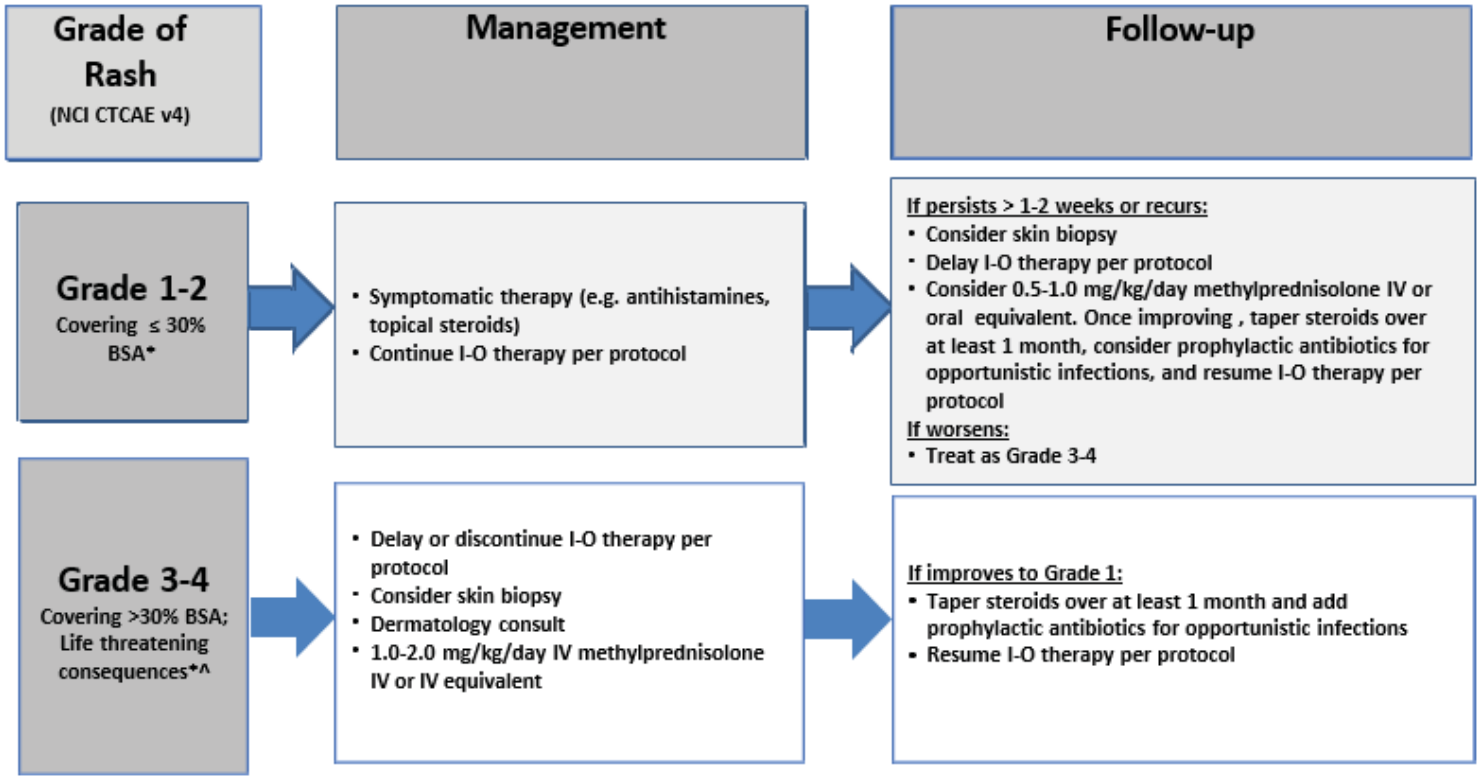


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

27-Jun-2019

Skin Adverse Event Management Algorithm

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



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

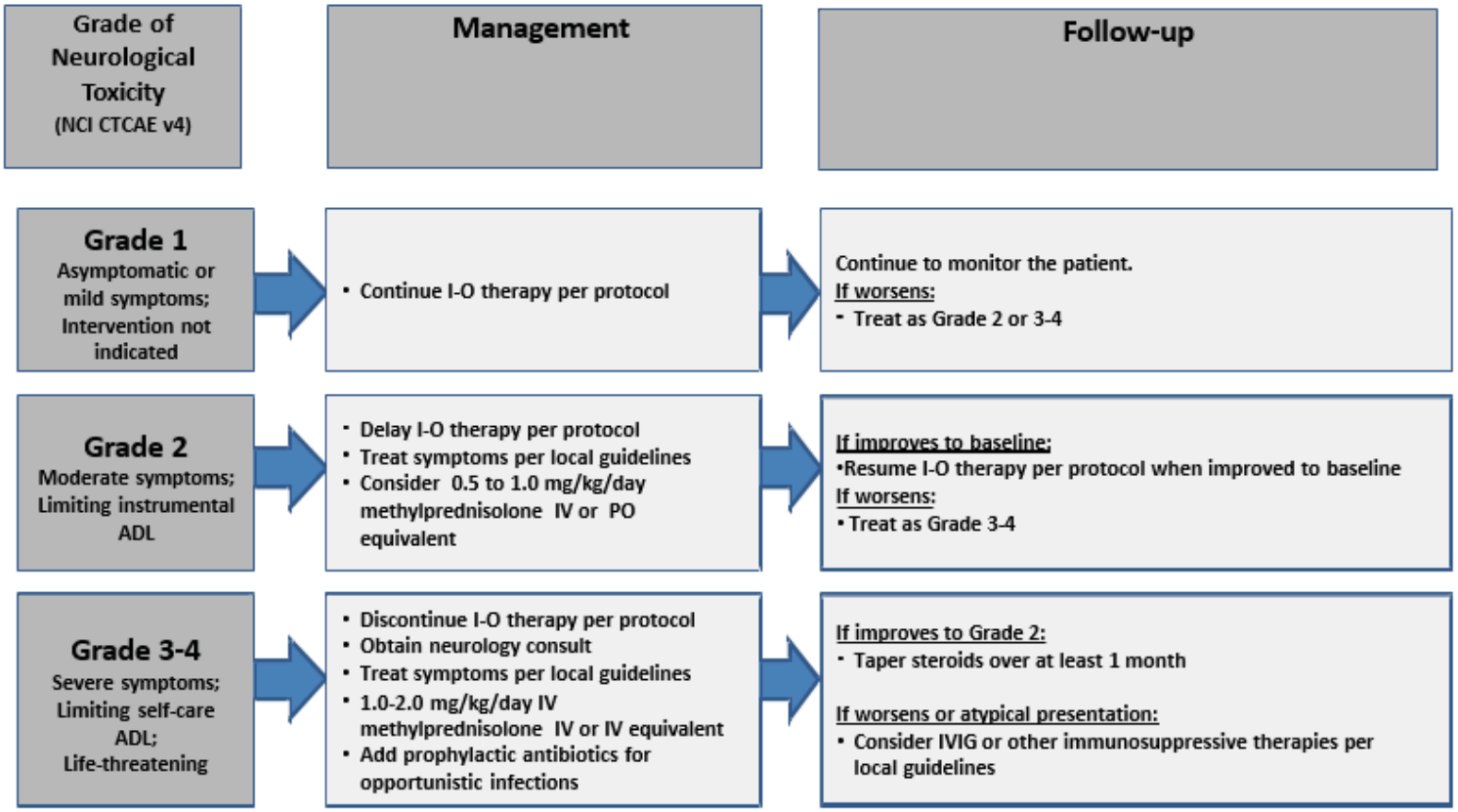
*Refer to NCI CTCAE v4 for term-specific grading criteria.

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

27-Jun-2019

Neurological Adverse Event Management Algorithm

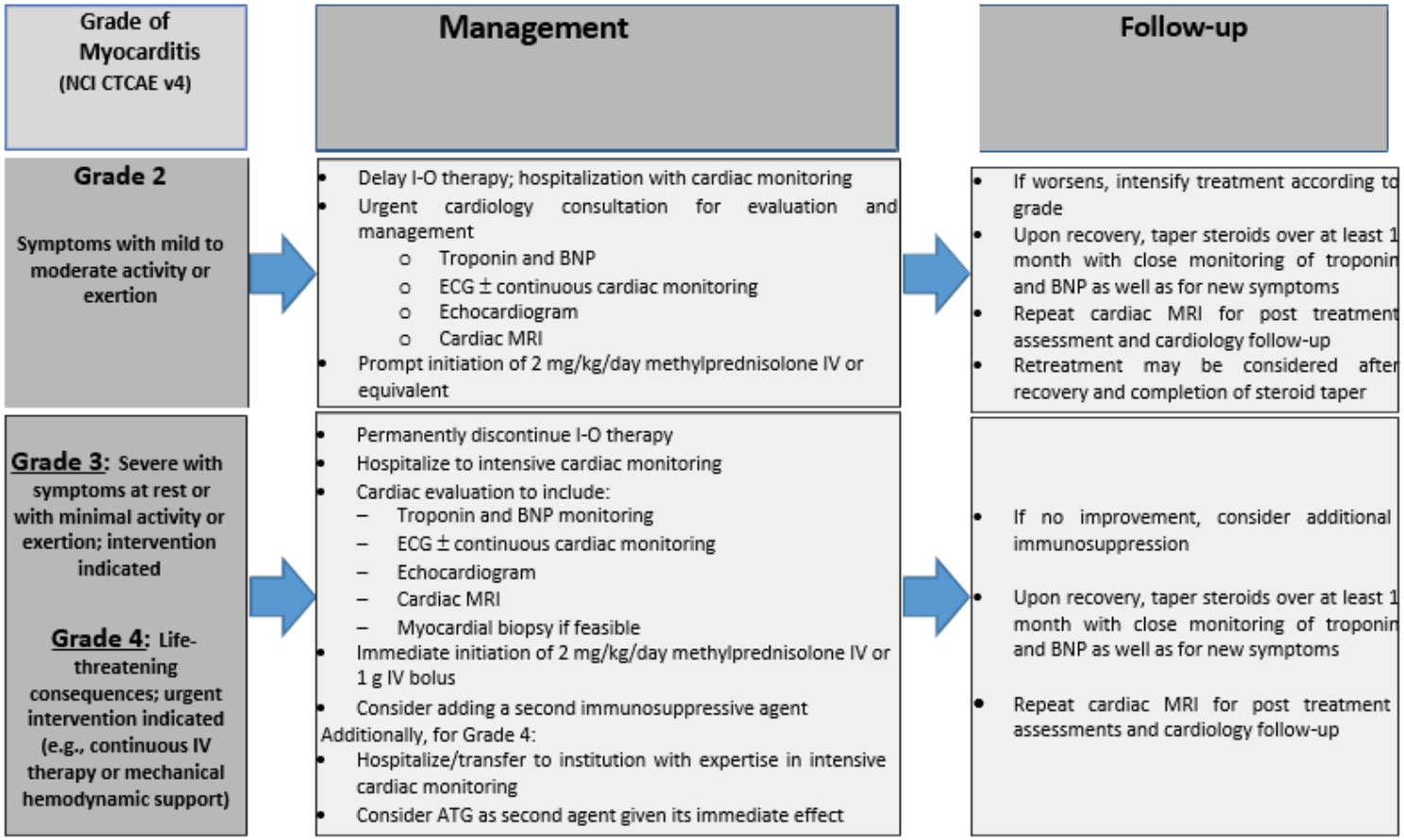
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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

27-Jun-2019

Myocarditis Adverse Event Management Algorithm



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

Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression.

ATG = anti-thymocyte globulin; BNP = B-type natriuretic peptide; ECG = electrocardiogram; IV = intravenous; MRI = magnetic resonance imaging

27-Jun-2019

APPENDIX 7 PERFORMANCE STATUS SCALES - ECOG

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

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

APPENDIX 8 COUNTRY SPECIFIC REQUIREMENTS

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

	Country-specific language
Section 2 Schedule of Activities, Table 2-1: Screening Procedural Outline - Laboratory Tests	Add "HIV" to the list of laboratory tests
Section 6.2 Exclusion Criteria, Exclusion criterion 2h	"Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)"to be replaced with "Positive test for HIV".
Section 9.4 Safety Assessments (baseline laboratory assessments)	Add "HIV" test to Baseline local laboratory assessments to be done within 14 days prior to first dose.

APPENDIX 9 REVISED PROTOCOL SUMMARY OF CHANGE HISTORY

Overall Rationale for the Revised Protocol 03, 31-Jan-2019

This Global Revised Protocol 03 introduces an interim analysis in each arm when at least 50% of planned participants have been treated with at least 16 weeks of follow-up from first dose. The purpose of the interim analysis is to generate preliminary data that will inform internal decision-making related to external studies being planned or conducted by the Sponsor, as well as to determine if any of the arms should be expanded to generate additional data that may support regulatory filing. In addition, this revised protocol clarifies the timing of the final analysis for each arm, incorporates changes from administrative letters, incorporates updated nivolumab clinical program protocol standards, and makes minor clarifications for consistency throughout the protocol document.

This Revised Protocol 03 applies in all countries, at all sites, to all future participants enrolled in the study and, where applicable, to all participants currently enrolled in the study.

Summary of key changes of Revised Protocol 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Synopsis, Section 5.2 Number of Participants	Arm A divided into Arms A1 and A2	To clarify each sub arm enrollment/assignment goal within Arm A
[redacted]		
Section 5.1 Overall Design	Updated percentage of available spots designated for participants who are HRD positive, HRD negative, or HRD not evaluable	To clarify the overall percentage of treated participants by HRD status
Section 5.4.6 Rationale for Duration of Treatment	Updated language describing optimal duration of immunotherapy with nivolumab	To meet current standards
Section 5.4.9 Rationale for Interim Analysis	Added rationale for interim analysis	To clarify the inclusion of interim analysis to generate preliminary data that will inform internal decision-making related to external studies and for potential cohort expansion to generate additional data that may support a regulatory filing
Section 5.5.1.1 Dose Justification for Nivolumab 480 mg IV Q4W	Updated language justifying nivolumab dosage of 480 mg IV Q4W	To meet current standards

Summary of key changes of Revised Protocol 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 6.2 Exclusion Criteria	Added language defining superscan	To clarify exclusion criterion for participants who have undergone a superscan on Technecium-99m radionuclide bone scans
Section 7.1 Treatments Administered	Updated language specifying ± 3 day dosing window and a recommendation against premedications for the first dose of nivolumab	To meet current standards
Section 7.3 Blinding	Included text describing unblinding of a small BMS team outside the CA2099KD study team to interim analyses by HRD status	To clarify that the CA2099KD study team will remain blinded to central HRD status of participants in order to maintain study integrity
Section 7.4.3 Docetaxel	Added text providing instructions regarding changes in or stoppage of prednisone or prednisolone	To clarify the use of prednisone and prednisolone in Arm B
Section 7.7.1 Prohibited and/or Restricted Treatments	Revised text regarding prohibition of immunosuppressive agents and immunosuppressive doses of systemic corticosteroids during treatment with nivolumab	To clarify the use of systemic corticosteroids is prohibited during treatment with nivolumab
	Updated text regarding use of live / attenuated vaccines	To meet current standards
Section 8.1.1 Nivolumab Dose Discontinuation	Added Grade 3 myocarditis to list of events necessitating discontinuation from nivolumab	To meet current standards
Section 8.1.6 Post Study Treatment Follow-up	Updated post-study follow-up text	To meet current standards
Section 9.2.2 Method of Detecting AEs and SAEs	Updated collection period for nonserious AEs to specify a minimum of 100 days following discontinuation of study treatment	To meet current standards
[redacted]		
Section 10.1 Sample Size Determination	Modified text regarding the final analysis of the co-primary endpoints of ORR and RR-PSA	To clarify that the final analysis may be performed independently from other cohorts/arms if enrollment is completed at different times across the cohorts/arms
[redacted]		

Summary of key changes of Revised Protocol 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 10.3.4 Interim Analyses	Added section detailing performance of an interim statistical analysis when at least 50% of planned participants have been treated with at least 16 weeks of follow-up after first dose	To generate preliminary data that will inform decisions related to external studies, as well as determine if any of the study arms should be expanded to generate additional data that may support a regulatory filing
Appendix 6, IO Management	Updated treatment algorithms Hepatic AE, Grade 3-4, an asterisk was removed from "Discontinue I-0 therapy"	To meet current standards Corrected typographical error
Various	Updated NCI CTCAE v 4.03 to .5.0	To meet current standards
ALL	Minor edits made throughout document to align sections for consistency	Minor, therefore have not been summarized

Overall Rationale for the Revised Protocol 02, 10-Sep-2018

This Global Revised Protocol 02 clarifies content in the Schedule of Activities, including updates for PSA [redacted] testing and plasma testing, clarifies requirements for inclusion and exclusion criteria, increases patient number in Arm A, provides further guidance for tumor sample collection in case of bone only disease,clarifies method of treatment assignment,incorporates language to define disease progression by PSA, incorporates updated nivolumab clinical program protocol standards, and makes minor clarifications for consistency throughout document.

This Revised Protocol 02 applies in all countries, at all sites, to all future participants enrolled in the study, and where applicable, to all participants currently enrolled in the study.

Summary of key changes of Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Synopsis, Key Inclusion Criteria Section 6.1, Inclusion Criteria	Central blood plasma added. Local HRD test results wording added Clarification about radiographic progression added Wording for previous treatment has been added to Arm A1 : Up to 2 second generation hormonal manipulations for castration resistant disease are allowed. Arm A2: at least 1 , not more than 2. Apalutamide added Arm B : added Apalutamide Added wording about superscans not allowed	Please see sections below
Section 2 Schedule of Activities	1) Central blood plasma testing added 2) Local HRD results wording added 3) Clarification of PSA testing after discontinuation added [redacted]	1) Central blood plasma testing added to facilitate patient inclusion The addition of prospective plasma HRD testing will increase the chances of identifying the HRD status in a higher number of patients than using tumor samples only. 2) Inclusion of patients based on local HRD status will shorten their screening time as they will not be required to wait for central HRD results. 3) Clarification PSA testing added to align with co- primary end point analysis and PCWG3 definition.
Section 4 - Objectives and end points. Table 4-1 Co-primary, Secondary [redacted]	PSA response wording clarified TTP- PSA wording added [redacted]	**Clarification PSA testing added to align with co- primary end point analysis and PCWG3 definition.**
Study design 5.1 Figure 5.1-1 Section 5.2 Number of participants	Updates patient number Apalutamide in Arm A2 . Arm B and Arm C added. Clarification about HRD + ve definition added Clarification about screening added	To clarify previous treatment allowed as Apalutamide is being used more widely in prostate cancer patients following positive results of SPARTAN study
Section 5.4.3 Rationale for sample size	Rationale for Increasing the number of HRD negative/not evaluable participants in Arm A	As described in section 5.4.3, the sample size was revised to extend the potential clinical benefit of PARPi combinations to additional HRD negative/not evaluable mCRPC patients, following

Summary of key changes of Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
		recently reported benefit of PARPi combinations regardless of HRD status.
Section 6.1 Inclusion criteria	1) Inclusion criteria 2b updated , M1 metastatic wording updated 2) Inclusion criteria 2d) ii) updated to include clarification about (N1) measuring at least 2 cm in short axis 3) Inclusion criteria 2f)i)(2) wording to include at least 1 but not more than 2 second-generation hormonal manipulations and apalutamide Inclusion criteria 2f)ii) Arm B to include apalutamide Inclusion criteria 2f)iii) Arm C to include apalutamide 4) Inclusion criteria 2j) to include plasma and/fresh or archival tumor tissue. To clarify that central laboratory must confirm receipt of plasma and tumor samples prior to IRT treatment arm assignment	1) "M1 metastatic" wording contradicted with inclusion criterion 2d) ii) and was therefore replaced by "Stage IV", so both criteria are now aligned to allow patients with pelvic lymph nodes metastases in the study. 2) To ensure adequate disease volume to evaluate co-primary ORR endpoint. 3) To clarify previous treatment allowed as Apalutamide is being used more widely in prostate cancer patients following positive results of SPARTAN study 4) To mandate plasma HRD testing and clarify process for accepting local HRD results.
Section 6.2 Exclusion criteria	Exclusion criteria 1k) has been added to prohibited patients with superscan or technecium-99mm radionuclide bone scans participation Exclusion criteria 2g) ii) has been added to exclude patients with Prior treatment with enzalutamide, apalutamide, or other novel androgen receptor inhibitor to be eligible for Arm C	To exclude patients with superscans since they are not evaluable for response and progression endpoints. To clarify criteria of entry for Arm C
Section 7.1 Treatment Administered. Table 7-1 Study treatments for CA2099KD	1) Footnote table 7.1,. b) wording has been updated to include clarification about Prednisone and Dexamethasone required as premedication to Docetaxel infusion. Wording allowing other corticosteroids has been added. 2) Added languages regarding Rucaparib doses window for Arm A 3) Added language to allow IV dexamethasone and other corticosteroids for Arm B Added language regarding Enzalutamide window for Arm C	1) To clarify use of prednisone and dexamethasone and allowing other corticosteroids as per local standards. 2) To Clarify Rucaparib doses window. 3) Ref To clarify use of corticosteroids in Arm B To clarify Enzalutamide window
Section 7.1.1 Dose delay criteria 7.1.1.2 and 7.1.2.2 Rucaparib	Delete wording about alkaline phosphatase < 3 xULN	To avoid unnecessary dose delays, as alkaline phosphatase is often elevated in prostate cancer and cannot be used reliably as a measure of hepatic function.

Summary of key changes of Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 7.2 Method of treatment assignment	Added wording to allow HRD plasma testing, previous local HRD test results, and retrospective plasma HRD testing.	Refer to previous rationale regarding HRD
Section 7.3 Blinding	Added language regarding HRD results release and masking local HRD test results to BMS study team	To clarify HRD test results blinding and masking.
Section 7.1.2.2 palliative Local Therapy	Added clarification regarding holding Rucaparib treatment prior to initiation of radiation therapy and until patient has recovered from radioation-related toxicities	To ensure radiotherapy and rucaparib are administered safely in ARM A patients.
Section 9.1.1 Imaging assessment for the study Section 9.1.2 Disease response evaluation	Added wording regarding disease progression by PSA (PSA progression0	Please refer to rationale above
[redacted]		
Section 10 Statistical Consideration Table 10.1-1 and Table 10.1-3	Update participant number and power	The sample size was revised to extend the potential clinical benefit of PARPi combinations to additional HRD negative/not evaluable mCRPC patients, following recently reported benefit of PARPi combinations regardless of HRD status.
Reference	Updated to include new references	To include new references

Overall Rationale for the Revised Protocol 01, 22-Mar-2018

This Global Revised Protocol 01 clarifies content in the Schedule of Activities, including updates for PSA [redacted] testing [redacted], clarifies requirements for inclusion and exclusion criteria, provides further guidance for Docetaxel discontinuation criteria, adds language to Prohibited and/or Restricted Treatments section for Arm C, adds enzalutamide background information, provides additional guidance for PK sampling including addition of an enzalutamide PK sample collection, incorporates updated nivolumab clinical program protocol standards, updates Study Director information and makes minor clarifications for consistency throughout document.

This Revised Protocol 01 applies in all countries, at all sites, to all future participants enrolled in the study, and where applicable, to all participants currently enrolled in the study.

Summary of key changes of Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	Added new Study Director contact information	Study Director has been added to study.
Synopsis, Key Inclusion Criteria Section 6.1, Inclusion Criteria	Further guidance provided for histologic confirmation of adenocarcinoma of the prostate Details added for participants who have not had an orchiectomy Clarifications and further guidance added regarding documented prostate cancer progression Language ("for mCRPC") added for chemotherapy-naive participants Language "for Arm A2 and Arm C" added to clarify requirement for participants who are asymptomatic or minimally symptomatic according to Brief Pain Inventory - Short Form (BPI-SF)	Language added to provide further detail. Language revised to clarify that radiographic progression is required for inclusion, since PSA progression alone does not meet criteria requirement. Language added to define participant population for Arm A, B and C as chemotherapy-naive in the context of castration resistant disease. Language updated to clarify that asymptomatic or minimally symptomatic mCRPC participants will not be enrolled into Treatment Arm B
Section 2 Schedule of Activities	The header language designating cycles was updated to remove reference to "C24" and instead refer to "subsequent cycles". PSA laboratory tests designated as "Local"	"C24" reference was misleading since Nivolumab program standards specify a maximum treatment period of 24 months from first dose. PSA testing is to be performed locally, not centrally.
[redacted]	[redacted]	[redacted]

Summary of key changes of Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 5.4.4 Rationale for Evaluating Asymptomatic or Minimally Symptomatic Metastatic CPRC Participants [redacted]	Language "for Arm A2 and Arm C" added to clarify requirement for participants who are asymptomatic or minimally symptomatic according to Brief Pain Inventory - Short Form (BPI-SF)	Language updated to clarify that asymptomatic or minimally symptomatic mCRPC participants will not be enrolled into Treatment Arm B
Section 6.2 Exclusion Criteria Section 7.7.1 Prohibited and/or Restricted Treatments	Language added as Exclusion criteria 2)i) prohibiting live/attenuated vaccine within 30 days of first treatment and prohibiting live/attenuated vaccines during the study	Criteria added to satisfy health authority request.
Section 7.1.1.3 Docetaxel	Added language that Grade 3 docetaxel-related enterocolitis requires discontinuation and provided additional guidance for rare cases.	Language incorporates recommendations issued by the INCA (National Cancer Institute of France)
Section 7.7.1 Prohibited and/or Restricted Treatments	For All Arms section, language was added regarding use of marijuana. For Arm C section, language was added regarding co-administration with warfarin and coumarin-like anticoagulants and co-administration of Xtandi with an anticoagulant metabolised by CYP2C9 (such as warfarin or acenocoumarol)	Clarifies marijuana as treatment for cancer or its symptoms, as permitted if obtained by medical prescription or without a medical prescription where has been legalized locally Language added to align with prescription information per enzalutamide SmPC
Section 8.1.3 Docetaxel Discontinuation	Added language that Grade 3 docetaxel-related enterocolitis requires discontinuation and provided additional guidance for rare cases.	Language incorporates recommendations issued by the INCA (National Cancer Institute of France)
Section 9.1.2 Disease Response Evaluation	Guidance added that participants who have initial PSA decline during treatment, must have confirmation with a second consecutive value 3 or more weeks later	Language added to clarify requirements when determining PSA progression
Section 9.5 Pharmacokinetics	Added background information for Enzalutamide	Language incorporates enzalutamide SmPC
Section 9.5.2 Pharmacokinetics Assessments	Guidance added that all nivolumab PK samples after C1D1 should be collected from contralateral arm Table 9.5.2-1 was updated to add PK blood sample for Enzalutamide	Language revised to prevent sample contamination at the collection site Enzalutamide PK will be assesses in the study

Summary of key changes of Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
All	Minor clarifications across sections for consistency	Language updated for consistency throughout document
	Updates per nivolumab program standardized language, including rationale for maximum duration of nivolumab treatment of 2 years	Language updated to align with nivolumab program standards. Accumulating data suggest that treatment beyond 2 years is unlikely to confer additional clinically meaningful benefit, risk of progression after discontinuing treatment at 2 years is low and although immunotherapy is well tolerated, participants will be at risk for additional toxicity with longer term treatment.