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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STATISTICAL ANALYSIS PLAN
FOR CLINICAL STUDY REPORT

A PHASE 2 STUDY OF NIVOLUMAB IN COMBINATION WITH EITHER RUCAPARIB, DOCETAXEL, OR ENZALUTAMIDE IN MEN WITH CASTRATION-RESISTANT METASTATIC PROSTATE CANCER

PROTOCOL CA2099KD

VERSION # 2.1

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1 BACKGROUND AND RATIONALE

CA2099KD is a Phase 2 study of nivolumab in combination with either rucaparib, docetaxel, or enzalutamide in men with metastatic castration-resistant prostate cancer (mCRPC).

Prostate cancer is a leading cause of cancer mortality in men worldwide. Since 2010, six new therapeutic agents with diverse mechanisms of action have been added to the therapeutic armamentarium. While the availability of these new treatment options allows for tailoring therapy to patient characteristics such as presence or absence of symptoms, prior treatments, patient preferences and life expectancy, none of these therapies result in durable clinical responses. Despite high initial response rates, remissions following second-generation hormone therapies are temporary due to the occurrence of resistance mechanisms including androgen receptor reactivation. At this time, with judicious sequencing and use of available new therapies, participants with established mCRPC have a life expectancy in the range of 12 to 35 months. Thus mCRPC remains a disease with a lethal outcome with the urgent need for treatment options that will provide durable disease control and long term survival; see details in Section 3.2 of protocol.

Research Hypothesis:

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

Schedule of Analyses:

The final analysis of the co-primary endpoints of objective response rate per the Prostate Cancer Clinical Trials Working Group 3 (PCWG3) criteria and response rate of prostate-specific antigen (PSA) will occur after all the participants have been followed up for approximately 12 months since treatment initiation in a cohort.

In addition, the first safety interim will occur when approximately 15 participants in a cohort (A1, A2, B or C) or approximately 50 participants combined from all four cohorts, whichever occurs first, have been treated and evaluated for at least 8 weeks. Subsequent safety interim reviews will be held approximately every 6 months after the first interim review until the final analysis.

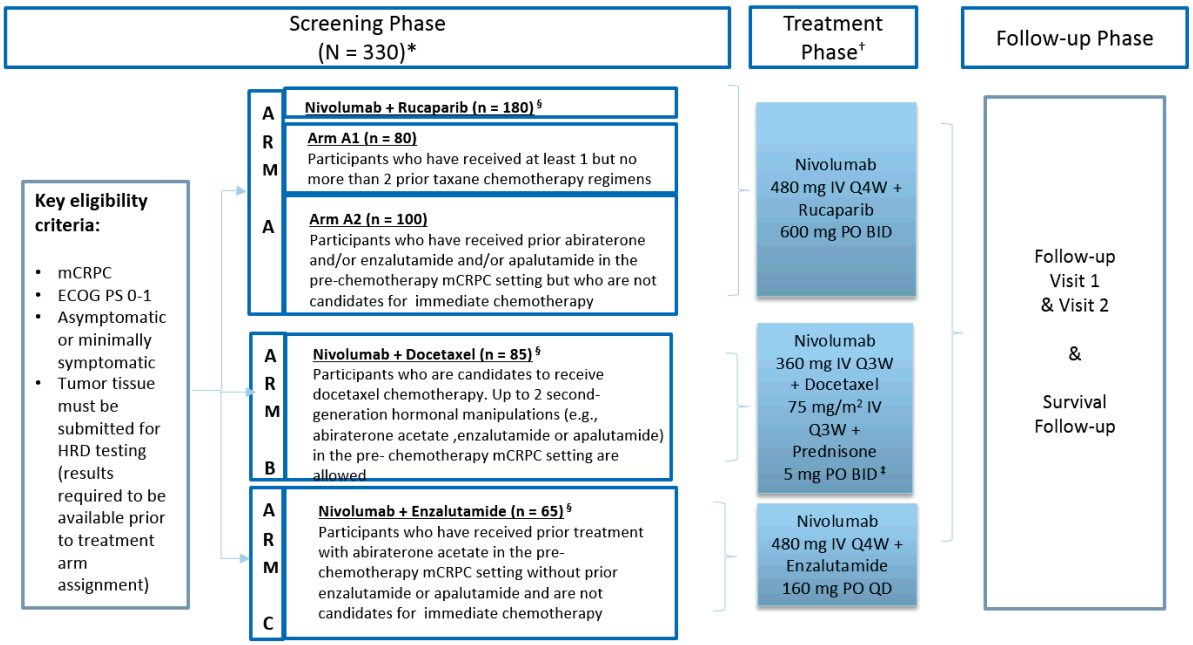
An interim analysis with efficacy data will be performed in each arm when at least 50% of planned participants have been treated with first dose at least 16 weeks prior to the cutoff date for the interim analysis database lock. All treated subjects whose first dose date is at least 16 weeks before the cutoff date for the interim analysis database lock will be included in the interim analysis.

2 STUDY DESCRIPTION

2.1 Study Design

This is a Phase 2 study of nivolumab in combination with either rucaparib, docetaxel, or enzalutamide in men with mCRPC. The study design schematic is presented in Figure 2.1-1.

Figure 2.1-1: 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.*

Three arms, including 4 parallel cohorts, are 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.
  - **Arm A2**: Chemotherapy-naive participants who 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): Chemotherapy-naive participants who 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): Chemotherapy-naive participants who 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.

Enrollment in any of the study arms may be terminated early due to poor accrual.

2.2 Treatment Assignment

All participants will be centrally assigned to a treatment arm using an Interactive Response Technology (IRT) system. 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 homologous recombination deficiency (HRD) testing of the submitted tumor sample by the central laboratory, will be ready for treatment arm assignment through the IRT. 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 one 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 of the protocol). 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.

The HRD status will be determined by central laboratory testing during screening. 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 at least one of the following homologous recombination deficiency genes: BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK2, FANCA, NBN, PALB2, RAD51, RAD51B, RAD51C, RAD51D, or RAD54L.

2.3 Blinding and Unblinding

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 of the protocol. 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 at the time of radiographic progression or discontinuation of study treatment of a participant, whichever occurs later, and at final analyses. In addition, only those Sponsor personnel not directly involved in the assessment of safety in the study will review HRD status up to discontinuation of study therapy or final analyses. During the Data Monitoring Committee (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 circulating tumor DNA [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 protocol Section 7.3, 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.

2.4 Protocol Amendments

This SAP incorporates the following amendment:

Table 2.4-1: Protocol Amendments

Amendment	Date of Issue	Summary of Major Changes
Revised Protocol 01 (Incorporate Amendment 01)	22-Mar-2018	PSA testing is to be performed locally, not centrally; [redacted] Guidance added that participants who have initial PSA decline during treatment, must have confirmation with a second consecutive value 3 or more weeks later; Enzalutamide pharmacokinetics will be assessed in the study.
Revised Protocol 02	10-Sep-2018	Clarifies procedure requirement in the Schedule of Activities; Clarifies requirements for inclusion and exclusion criteria; Updates 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
Revised Protocol 03	31-Jan-2019	Introduces an interim analysis in each arm when at least 50% of planned participants have been treated with first dose at least 16 weeks prior to the cutoff date for the interim analysis database lock; Clarifies the timing of the final analysis for each arm, incorporates changes from administrative letters, Incorporates updated nivolumab clinical program protocol standards.
Revised Protocol 04	TBD	Changed NCI CTCAE v 5.0 back to v.4.03

Table 2.4-1: Protocol Amendments

Amendment	Date of Issue	Summary of Major Changes
		Clarified that enrollment in any study arm may be terminated early due to poor accrual 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 Clarified that the immediate study team members will remain blinded to Homologous recombination deficiency (HRD) status of individual study participants

2.5 Data Monitoring Committee

An independent DMC will be instituted and 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.

3 OBJECTIVES

3.1 Primary

- To evaluate the objective response rate per PCWG3 (ORR-PCWG3) in HRD+ participants and in all treated participants.
- To evaluate PSA response rate (RR-PSA) in HRD+ participants and in all treated participants.

3.2 Secondary

- To evaluate radiographic progression-free survival (rPFS) in HRD+ participants and in all treated participants.
- 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
- To estimate time to PSA progression (TTP-PSA) in HRD+ participants and in all treated participants
- To assess overall survival (OS) in HRD+ participants and in all treated participants
- To evaluate overall safety and tolerability

[redacted]

4 ENDPOINTS

4.1 Primary Efficacy Endpoints

4.1.1 Objective Response Rate

Objective response rate per PCWG3 (ORR-PCWG3) is the proportion of participants who have confirmed complete or partial best overall response (BOR) per PCWG3 among treated participants with measurable disease at baseline. The BOR is assessed per investigator per PCWG3 and is recorded between treatment initiation and the date of objectively documented progression per PCWG3 or the date of start of subsequent cancer therapies (as recorded in the Subsequent Cancer Therapy Case Report Form [CRF] pages), whichever occurs first. For participants without documented progression or subsequent cancer therapy, all available response assessments will contribute to the BOR assessment. Tumor assessments are scheduled to be performed every 8 weeks for 24 weeks following treatment initiation and thereafter every 12 weeks until documented radiographic progression per PCWG3.

If BOR per the Blinded Independent Central Review (BICR) is available, ORR per BICR will be defined in the same way as for ORR per the investigator.

4.1.2 PSA Response Rate

Response rate of PSA (RR-PSA) is defined as the proportion of subjects with 50% or greater decrease in PSA from baseline to the lowest post-baseline PSA result within each randomized arm, confirmed by a second value obtained 3 or more weeks later that occurs prior to PSA progression.

4.2 Secondary Efficacy Endpoints

Secondary endpoints will be analyzed at the time of the co-primary endpoint analysis.

4.2.1 Radiographic Progression Free Survival

Radiographic progression-free survival (rPFS) is the time from treatment initiation to the first date of documented radiographic progressions per PCWG3 or death due to any cause, whichever occurs first.

The following radiographic progressive diseases will be collected and documented as assessed by the investigator. The date of progression for each type is defined in Table 9.1.2-1 of the protocol.

- Soft tissue disease progression by RECIST v1.1 modified per PCWG3. Date of first unequivocal progression of soft tissue lesion will be recorded in the Disease Progression CRF page.
- Bone disease progression per PCWG3. Date of bone progression will be recorded in the Disease Progression CRF page.

The following censoring rules will be used to define rPFS endpoint for primary analysis.

- Participants who did not progress or die will be censored on the date of their last evaluable tumor and/or bone assessment.
- Participants who did not have any post-treatment tumor and bone assessments and did not die will be censored on the date of first treatment.
- Participants who receive subsequent cancer therapy prior to progression or death will be censored at date of last evaluable tumor or bone assessment up to start of any subsequent systemic cancer therapy.
- Participants without baseline tumor assessment for soft tissues or bone lesions and who are not known to have died will be censored at the date of first treatment.

If rPFS per BICR is available, rPFS per BICR will be defined in the same way as for rPFS per the investigator.

4.2.2 Time to Objective Response and Duration of Response

Time to objective response (TTR) per PCWG3 is the time from treatment initiation to the date of the first documented CR or PR per PCWG3.

Duration of response (DOR) per PCWG3 is the time from 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.

If TTR/DOR per BICR are available, TTR/DOR per BICR will be defined in the same way as for TTR/DOR per the investigator.

4.2.3 Time to PSA Progression

Time to progression by PSA (TTP-PSA) is the time from treatment initiation to the date of first confirmed progression in PSA per PCWG3 in treated participants. Date of disease progression by PSA will be recorded in the Disease Progression CRF page.

PSA progression is defined as:

- If there is a decline from baseline in PSA, a PSA progression is recorded at the time when the first PSA increase is ≥ 25% and ≥ 2 ng/mL above the nadir from start of therapy, which is confirmed by a second value 3 or more weeks later (i.e., a confirmed rising trend à PSA progression holds even if the confirmatory second value is lower than the first, providing both values show a 25% increase from the nadir – only values on or after week 12 are used when determining PSA progression);
- If there is no decline from baseline in PSA, PSA progression is recorded at the time when a PSA increase is ≥ 25% and ≥ 2 ng/mL above the baseline after 12 weeks from start of therapy.

For participants who have no confirmed progression by PSA, the time will be censored at the date of last PSA evaluation or at the date of treatment initiation for participants with no PSA evaluation.

4.2.4 Overall Survival

Overall survival (OS) is the time from treatment initiation to the date of death from any cause. For participants who are alive, their survival time will be censored at the last known alive date. OS will be censored for participants at the date of first treatment if they had no follow up.

[redacted]

4.4 Safety Endpoints

Safety and tolerability of nivolumab combined with rucaparib, docetaxel, or enzalutamide is one of secondary study objectives. Overall safety and tolerability will be measured by the incidence of adverse events, serious adverse events, adverse events leading to discontinuation, deaths, specific laboratory abnormalities (worst grade) and changes from baseline. Toxicities will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. See details in the Core Safety SAP[1].

4.5 Pharmacokinetics

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

5 SAMPLE SIZE AND POWER

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

Planned sample size is summarized in Table 5-1 by arm and cohort, which is further divided into smaller subgroups by prior treatment, measurable disease at baseline and the HRD test results.

Table 5-1: 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	Any	Any[b]	Positive	100
A-HRD- for RR-PSA	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	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 a cohort, and RR-PSA among treated participants in a cohort. Table 5-2 provides the precision for potential response rates. For example, if 6 or more responders are observed among 30 participants in a cohort, then the lower limit of the 95% CI for the response rate is above 7.7%.

Table 5-2: 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 cohort in this study; see Table 5.4.3-1 of the protocol. A target ORR for a promising combination treatment is assumed as an increase of 15% or more compared to the current SOC in a cohort. As shown in Table 5-3, powers are assessed at a 1-sided alpha of 10% using the method from Fleiss (1981).[2] 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 cohort.

Table 5-3: 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 a cohort and the final analysis of a cohort/arm 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.

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

This study consists of three periods used for analyses: pre-treatment, on-treatment (i.e., combination therapy and monotherapy), and post-treatment.

6.1.1 Baseline (Pre-Treatment) Period

Baseline evaluations or events will be defined as evaluations or events that occur before the date and time of the first dose of study treatment. Evaluations on the same date and time of the first dose of study treatment will be considered as baseline evaluations.

In cases where the time (onset time of event or evaluation time and dosing time) is missing or not collected, the following definitions will apply:

- Pre-treatment adverse events will be defined as adverse events with an onset date prior to but not including the day of the first dose of study treatment
- Baseline evaluations (laboratory tests, pulse oximetry and vital signs) will be defined as evaluations with a date on or prior to the day of first dose of study treatment

If there are multiple valid assessments, the assessment that is closest to day (and time if collected) of the first dose of study treatment will be used as the baseline in the analyses. If multiple assessments are collected at the same date (and time if collected), the assessment with the latest database entry date (and time if collected) will be considered as baseline.

If more than one tumor biopsy specimen is available, baseline [redacted] will be determined from the most recently collected specimen (prior to first dose of study treatment) with

a measurable result. If all specimens for a given participant are either indeterminate or unknown, then the [redacted] will be considered indeterminate as long as at least one specimen is indeterminate. Otherwise, [redacted] will be considered unknown. Other biomarker results at baseline, including the HRD status [redacted], will be determined in the same way as for baseline [redacted].

- **Baseline for Nivolumab Monotherapy Period in Arm B**

Baseline evaluations or events for the nivolumab monotherapy period will be defined as evaluations or events that occur before the date and time of the first dose of nivolumab 480 mg flat dose and after the last combination dose date. Evaluations on the same date and time of the first dose of nivolumab 480 mg will be considered as baseline evaluations. Conventions for handling missing or not collected time and multiple assessments will be as described above except that the nivolumab 480 mg dosing date will replace the study dosing date.

6.1.2 On-Study (On-Treatment) Period

On-treatment adverse events will be defined as adverse events with an onset date-time on or after the date-time of the first dose of study treatment (or with an onset date on or after the day of first dose of study treatment if time is not collected or is missing). An adverse event will be counted as on-treatment if the event occurred within 30 days (or 100 days depending on analysis) of the last dose of study treatment.

On-treatment evaluations (laboratory tests, pulse oximetry and vital signs) will be defined as evaluations taken after the day (and time, if collected and not missing) of first dose of study treatment. An evaluation will be counted as on-treatment if it occurred within 30 days (or 100 days depending on analysis) of the last dose of study treatment.

The on-treatment period may be further divided into the following sub-periods in Arm B.

- **Combination Treatment Period in Arm B**

Combination dosing is defined as any medication recorded on 'Record of Study Medication' CRF page with a visit label containing the text 'nivolumab 360 mg' and with total volume infused > 0 mL.

On-treatment adverse events during the combination period will be defined as adverse events with an onset date-time on or after the date-time of the first dose of combination study treatment (or with an onset date on or after the day of first dose of combination study treatment if time is not collected or is missing). An adverse event will be counted as on-treatment during combination therapy if the event occurred within 30 days (or 100 days depending on analysis) of the last dose of combination study treatment for treated participants who do not continue nivolumab 480 monotherapy and if the event occurred within 30 days of the last dose of combination study treatment and prior to start of nivolumab 480 mg monotherapy.

On-treatment evaluations (laboratory tests) during combination will be defined as evaluations taken after the day (and time, if collected and not missing) of first dose of combination study treatment. An evaluation will be counted as on-treatment during combination if it occurred within

30 days (or 100 days depending on analysis) of the last dose of combination study treatment for treated participants who do not continue nivolumab 480 mg monotherapy or if it occurred within 30 days of the last dose of combination study treatment and prior to start of nivolumab 480 mg monotherapy.

- **Nivolumab Monotherapy Treatment Period in Arm B**

Nivolumab 480 mg dosing is defined as any medication recorded on 'Record of Study Medication' CRF page with a visit label containing the text 'Nivolumab 480' and with total dose delivered > 0 mg.

On-treatment adverse events during the nivolumab 480 mg monotherapy period will be defined as AEs with an onset date-time on or after the date-time of the first dose of nivolumab 480 mg study treatment (or with an onset date on or after the day of first dose of nivolumab 480 mg study treatment if time is not collected or is missing). An AE will be counted as on-treatment if the event occurred within 30 days (or 100 days depending on analysis) of the last dose of nivolumab 480 mg study treatment.

On-treatment evaluations (laboratory tests) during nivolumab 480 mg monotherapy will be defined as evaluations taken after the day (and time, if collected and not missing) of first dose of nivolumab 480 mg study treatment. An evaluation will be counted as on-treatment if it occurred within 30 days (or 100 days depending on analysis) of the last dose of nivolumab 480 mg study treatment.

6.1.3 Follow-up (Post-Treatment) Period

The post-treatment period is defined as 30 days after last dose of study therapy.

6.2 Treatment Regimens

Participants eligible will be given up to 24 months of nivolumab in combination with either rucaparib, docetaxel, or enzalutamide until recurrence of disease, unacceptable toxicity, or participant withdrawal of consent. Treatment administration in each arm is as follows:

- **Arm A dosing**: nivolumab 480 mg IV Q4W plus rucaparib 600 mg PO BID
- **Arm B dosing**: nivolumab 360 mg Q3W plus docetaxel 75 mg/m2 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. Docetaxel is given up to a maximum of 10 cycles. Nivolumab 480 mg Q4W will be administered as monotherapy after Cycle 10.
- **Arm C dosing**: nivolumab 480 mg Q4W plus enzalutamide 160 mg PO QD

An analysis by the HRD status and cohort will performed for 4 cohorts: A1, A2, B, and C, and within each cohort for HRD+ and HRD-/Not evaluable, respectively. The HRD status will be determined by the central laboratory as recorded in IRT. Additional sensitivity analyses by the HRD status per CRF will be performed if the concordance rate of the HRD status between IRT and CRF is less than 90%.

6.3 Populations for Analyses

- **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 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.

[redacted]

7 STATISTICAL ANALYSIS

7.1 General Methods

Unless otherwise noted, the following subsections describe tabulations of discrete variables, by the frequency and proportion of participants falling into each category, grouped by cohort (with total). Percentages given in these tables will be rounded and, therefore, may not always sum to 100%. Continuous variables will be summarized by the HRD status and cohort using the mean, standard deviation, median, minimum and maximum values. If a missing category is not being presented in the data display, only those participants with non-missing values for the parameter being assessed are included in the percentage calculation.

Time to event distribution will be estimated using Kaplan Meier techniques. This will be done for endpoints progression free survival(s), overall survival and duration of response. Median survival time along with 95% CI will be constructed based on a log-log transformed CI for the survivor function.[3,4] Rates at fixed time points will be derived from the Kaplan Meier estimate and corresponding CI will be derived based on Greenwood formula[5] for variance derivation and on log-log transformation applied on the survivor function.[6]

CIs for binomial proportions will be derived using the Clopper-Pearson method. [7]

There are no statistical hypotheses in this study.

7.2 Study Conduct

7.2.1 Accrual

The accrual pattern will be summarized per country, investigational site, and per month for all enrolled participants and for all treated participants. The informed consent date, the first dosing date, country, investigational site will be presented in a by-participant listing of accrual.

7.2.2 Relevant Protocol Deviations

The following programmable deviations are considered as relevant deviations that may affect the interpretability of the study results. Non-programmable related eligibility and on-treatment protocol deviations as well as significant (both programmable and non-programmable) eligibility and on-treatment protocol deviations will be reported through ClinSIGHT listings.

The following relevant deviations will be summarized by the HRD status and cohort and combined and listed for all treated participants:

- Relevant eligibility deviations:
  - Did not sign informed consent (Inclusion Criteria 1a)
  - Had ECOG performance status of 2 or higher (Inclusion Criteria 2e)
  - Did not have metastatic M1 disease (Inclusion Criteria 2b)
  - Baseline testosterone level > 50 ng/dL (Inclusion Criteria 2c)
  - Received prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways (Exclusion Criteria 2b)
  - Received pelvic-targeted radiotherapy within 3 months prior to the start of study therapy (Exclusion Criteria 2c)
  - Received prior PARP inhibitor treatment, mitoxantrone, cyclophosphamide, or platinumbased chemotherapy (Exclusion Criteria 2ei), applied to Arm A only
  - Subjects who did not receive prior taxanes chemotherapy for mCRPC, Inclusion Criteria 1fi1), applied to Arm A1 only
  - Received prior chemotherapy for mCRPC. Prior docetaxel for metastatic hormone-sensitive prostate cancer is allowed if ≥ 4 weeks elapsed from last dose of docetaxel (Exclusion Criteria 2eii), applied to Arm A2 only
  - Received prior treatment with docetaxel or another chemotherapy agent for metastatic prostate cancer (Exclusion Criteria 2fi),, applied to Arm B only
  - Subjects who did not receive prior abiraterone acetate and/or enzalutamide (Inclusion Criteria 2fii),, applied to Arm B only
  - Received i) prior chemotherapy for mCRPC. Prior docetaxel for metastatic hormone-sensitive prostate cancer is allowed if ≥ 4 weeks elapsed from last dose of docetaxel, ii) prior treatment with enzalutamide, and/or iii) Treatment with 5-α reductase inhibitors (eg, finasteride, dutasteride), estrogens, and/or cyproterone within 4 weeks of the screening visit (Exclusion Criteria 2g), applied to Arm C only
  - Subjects who did not receive prior abiraterone acetate and/or enzalutamide (Inclusion Criteria 2fiii), applied to Arm C only
  - Had BPI-SF item # 3 score of 5 or higher (Inclusion Criteria 2i)
- Relevant on-study deviations:
  - Received prohibited and/or restricted treatments (see Section of 7.7.1 of the protocol), while receiving study treatment.

[redacted]

7.3 Study Population

7.3.1 Participant Disposition and Discontinuation of Study Therapy

- Number of participants treated, not treated and reasons for not being treated will be summarized for enrolled participants.
- Number of participants who discontinued study therapy and reason for discontinuation will be summarized by the HRD status and cohort and combined for all treated participants.

By-participant listing of first dosing date in respective treatment phase or reasons for being not treated will be provided.

7.3.2 Demography and Participant Characteristics

The following demographics and baseline characteristics will be summarized by the HRD status and cohort and combined for all treated participants. The corresponding by-participant listing will be provided.

- Age in years
- Age category I (< 70, ≥ 70)
- Age category II (< 65, ≥ 65-<75, ≥ 75)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other)
- Region (US, EU, Rest of World [ROW])

The following baseline disease characteristics will be summarized by the HRD status and cohort and combined for all treated participants. The corresponding by-participant listing will be provided.

- Time from initial disease diagnosis to initiation of study therapy, including summary statistics and frequencies (<1, 1-<2, 2-<3, 3-<4, 4-<5, ≥5 years)
- Disease stage at initial diagnosis (Stage I, IIA, IIB, III, IV)
- M status at initial disease diagnosis (M0, M1, unknown, not reported)
- Cell type at initial disease diagnosis (adenocarcinoma, other, unknown, not reported)

- Gleason score (≤ 7, > 7, not reported)
- Disease stage at study entry (Stage IV, not reported)
- M status at study entry (M1, not reported)
- Cell type at study entry (adenocarcinoma, other, not reported)
- History of brain metastasis (yes, no)
- Height (cm)
- Baseline Weight (kg)
- Baseline ECOG performance status (0, 1)
- Number of bone lesions at baseline (0, <4, ≥4)

[redacted]

- PSA (summary statistics and ≥ median of PSA from all treated participants in 4 cohorts, < median)

[redacted]

- The HRD Status per IRT (Positive, Negative, Not evaluable)
- The HRD Status per CRF (Positive, Negative, Not evaluable)
- LDH (≤ULN, >ULN)
- LDH (≤ 2*ULN, > 2*ULN)
- Hemoglobin (< 11 g/dl, ≥ 11 g/dl, not reported)
- Alkaline phosphatase (< 1.5 x ULN, ≥ 1.5 x ULN, not reported)
- Lactate dehydrogenase (< 200 IU/L, ≥ 200 IU/L, not reported)
- Visceral metastases in soft tissue (yes, no) from lung, adrenal and other sites
- Presence of measurable disease per IRT (yes, no)
- Baseline bisphosphonate use (yes vs no)
- Smoking status (current/former, never smoked, not reported, unknown)

The following tumor lesions from both CT and bone scans and as assessed per investigator at baseline will be also summarized by the HRD status and cohort and combined for all treated participants: The corresponding by-participant listing will be provided.

- All lesions per investigator tumor assessment at baseline: sites of disease, number of disease sites per participant
- Target lesions per investigator tumor assessment at baseline: presence of target lesions, site of target lesion, sum of longest diameter of target lesion
- Investigator's tumor assessment and disease sites (all lesions, index lesions)

The concordance rate, defined as the percentage of the HRD status that agree (positive, negative, not evaluable [including not reported]) between the IRT and CRF of the total number of results (positive, negative, not evaluable [including not reported]) will be summarized by the HRD status

and cohort and combined for all treated participants: The corresponding by-participant listing will be provided.

7.3.3 Medical History

By-participant listing of general medical history will be produced.

7.3.4 Prior Therapy

The following prior therapy will be summarized by the HRD status and cohort and combined for all treated participants.

- Prior systemic therapy
- Prior cancer hormonal therapy (yes, no) by the following category
  - Anti-androgens (e.g., enzalutamide, bicalutamide, flutamide, nilutamide) or
  - Androgen synthesis inhibitors (e.g., abiraterone, aminoglutethamide, ketoconazole),
  - LHRH]/GnRH analogues
- Prior surgery related to cancer (yes, no)
- Prior radiotherapy (yes, no)

By-participant listings of prior systemic therapy and prior anti-cancer hormonal therapies will be produced.

7.3.5 Baseline Examinations

Participants with abnormal baseline physical exam results will be tabulated by examination criteria (e.g., neck, cardiovascular, lungs, etc.) and by the HRD status and cohort and combined for all treated participants.

7.4 Extent of Exposure

The exposure data will be summarized by the HRD status and cohort for all treated participants across the entire treatment period. In addition, the exposure data will also be summarized respectively for the combination and nivolumab 480 mg monotherapy period in Arm B. By-participant listing of dosing information as well as batch/label information will be provided. Listing of participants who received prednisone and dexamethasone in Arm B will be produced.

7.4.1 Administration of Study Therapy

Duration of study therapy (nivolumab, rucaparib, docetaxel, and enzalutamide) will be presented by the HRD status and cohort for the combination and component therapy, respectively. Duration of combination therapy is defined as the time from the first dosing date of any component therapies of the combination to the last dosing date of any component therapies of the combination. In addition, duration of the combination and nivolumab monotherapy will be presented for participants treated in nivolumab monotherapy in Arm B.

Duration of study therapy will be presented using a Kaplan-Meier curve whereby the last dose date will be the event date for those participants who are off study therapy. Median duration of study therapy and associated 95% CI will be provided. Participants who are still on study therapy will be censored on their last dose date. In addition, duration of study therapy will be summarized in

a table with descriptive statistics (mean, minimum, and maximum). The percentage of participants with study therapy duration > 3 months, > 6 months, > 9 months, and > 12 months will be tabulated.

The following parameters will be summarized by the HRD status and cohort for each component therapy in the combination (and by treatment period in Arm B, i.e., the combination phase and nivolumab monotherapy phase) for all treated participants; see Table 7.4.1-1 and Table 7.4.1-2.

- Number of doses received
- Cumulative dose in mg/kg
- Relative dose intensity (%) (< 50%; 50 - < 70%; 70 - < 90%; 90 - < 110%; ≥ 110%)
- Infusion duration in minutes, applicable to nivolumab and docetaxel
- Duration of study therapy

Table 7.4.1-1: Study Therapy Parameters

	Nivolumab (Arm A, C)	Docetaxel
Dosing Schedule per Protocol	Arm A and C: 480 mg IV Q4W Arm B: 360 mg IV Q3W	75 mg/m^2 IV Q3W
Dose	Dose (mg) = total dose delivered as recorded on Record of Study Medication CRF	Dose (mg/m2) = total dose administered in mg at each dosing date is collected on the CRF and BSA is derived from baseline weight and height also collected on the CRF
Cumulative Dose	Cum Dose (mg) is the sum of the doses administered to a participant	Cum Dose (mg/m^2) is the sum of the doses (mg/m^2) administered to a participant
Relative Dose Intensity (%)	Arm A and C: [Cumulative dose (mg)/((Last dose date – first dose date + 28) × 480/28)] × 100	[Cumulative dose (mg/m2) /((Last dose date – first dose date + 21) × 75/21)] × 100
Infusion Duration (mins)	Each infusion duration is calculated as infusion stop date/time - infusion start date/time.	Each infusion duration is calculated as infusion stop date/time - infusion start date/time.
Duration of Treatment	last dose date - first dose date + 1	last dose date - first dose date + 1

Table 7.4.1-2: Study Therapy Parameters (Rucaparib and Enzalutamide)

	Rucaparib	Enzalutamide
Dosing Schedule per Protocol	600 mg PO BID	160 mg PO QD
Dose	Dose (mg) = total dose delivered as recorded on Record of Study Medication CRF	Dose (mg) = total dose delivered as recorded on Record of Study Medication CRF
Cumulative Dose	Cum Dose (mg) is the sum of the doses administered to a participant	Dose (mg) = total dose delivered as recorded on Record of Study Medication CRF
Relative Dose Intensity (%)	[Cumulative dose (mg) /((Last dose date – first dose date + 1) × 600*2)] × 100	[Cumulative dose (mg) /((Last dose date – first dose date + 1) × 160)] × 100
Duration of Treatment	Last dose date - Start dose date +1	Last dose date - Start dose date +1

7.4.2 Modifications of Study Therapy

Dose escalations, reductions and omissions are not permitted for nivolumab in this study. Dose delays will be summarized.

7.4.2.1 Dose Delays

Each nivolumab and docetaxel infusion may be delayed per the Dose Changes CRF pages. All study drugs must be delayed until treatment can resume. Reason for dose delay will be retrieved from the Dose Changes CRF pages.

- Number of participants with at least one dose delayed, reason for first delay, number of dose delays, and length of delay will be summarized by cohort.

By-participant listing of all dose delays and reasons will be provided.

7.4.2.2 Infusion Interrupted and Rate Reduced

The infusion interruptions and the IV infusion reduction rates will be summarized by study drug (nivolumab and docetaxel) and by the HRD status will be summarized for all treated participants.

- Number of participants with at least one dose infusion interruption, the reason for the first interruption, and the number of infusion interruptions.
- Number of participants with at least one rate of infusion reduced, the reason for first reduction, and number of rate reductions

By-participant listing of all infusion interruptions and rate reductions and all the corresponding reasons and will be provided.

7.4.2.3 Dose Reduction

Dose reduction of docetaxel from last cycle will be recorded in the Dose Changes CRF pages, and will be summarized by the HRD status for all treated participants in Arm B.

- Number of participants with at least one dose reduction, reason for first reduction, and number of dose reductions will be summarized by cohort.

In addition, dose reduction of rucaparib will be recorded in the Study Medication CRF pages, and will be summarized by the HRD status and cohort in Arm A.

By-participant listing of all dose reduction and reasons will be provided.

7.4.3 Concomitant Medications

Concomitant medications, defined as medications other than study medications which are taken at any time on-treatment (i.e., on or after the first day of study therapy and within 100 days following the last dose of study therapy), will be coded using the WHO Drug Dictionary.

- Concomitant medications (participants with any concomitant medication, participants by medication class and generic term)

By-participant listing of concomitant medications will be produced. In addition, listings of participants who received immunosuppressive agents and steroids will be produced.

7.4.4 Treatment Beyond Disease Progression

A participant listing of participants who received study treatment beyond progression will be provided.

7.4.5 Subsequent Cancer Therapy

Therapies received subsequent to discontinuation of study therapy will be summarized by the HRD status and cohort and combined for all treated participants.

- Frequency of participants with subsequent systemic cancer therapy as recorded in subsequent therapy CRF pages by type (any, immunotherapy only, chemotherapy only, hormonal only, immunotherapy and chemotherapy, immunotherapy and hormonal, hormonal and chemotherapy, immunotherapy, hormonal and chemotherapy, other)
- Time from initiation of study therapy to first systemic cancer subsequent therapy (median, range)

By-participant listing of subsequent systemic cancer therapies (including dates of therapy) will be produced.

7.5 Efficacy

All efficacy analyses will be performed by the HRD status and cohort as applicable to either (i) treated participants with measurable disease by RECIST v1.1 and/or (ii) all treated participants in a cohort.

To assess consistency of treatment effects in an efficacy endpoint across subgroups, the following pre-defined subsets will be used in the corresponding subgroup analyses, if there are more than 10 participants in the subset.

- Age category I (< 70, ≥ 70)
- Age category II (< 65, ≥ 65-<75, ≥ 75)

- Race (White, Black or African American, Others)
- Region (US, EU, ROW)
- Gleason score (≤ 7, > 7, not reported)
- Cell type at study entry (adenocarcinoma, other, not reported)
- History of brain metastasis (yes, no)
- Baseline ECOG performance status (0, 1)
- Number of bone lesions at baseline (0, <4, ≥4)

[redacted]

- PSA (summary statistics and ≥ median of PSA from all treated participants in 4 cohorts, < median)

[redacted]

- HRD Status per IRT
- HRD Status per CRF
- LDH (≤ULN, >ULN)
- LDH (≤ 2*ULN, > 2*ULN)f
- Visceral metastases in soft tissue (yes, no) from lung, adrenal and other sites
- Presence of measurable disease per IRT (yes, no)
- Baseline bisphosphonate use (yes, no)

7.5.1 Objective Response Rate per PCWG3

For co-primary endpoint of ORR per PCWG3, estimated rates and corresponding 2-sided exact 95% CIs will be calculated using the Clopper-Pearson method by the HRD status and cohort for all response evaluable participants.

To assess consistency of treatment effects in ORR in different subsets, a forest plot of the ORRs and corresponding 2-sided exact 95% CIs will be produced for the following subgroups in a stratum, if a stratum has more than 10 participants.

ORR per PCWG3 per BICR, if available, will be analyzed in the same way as for ORR per PCWG3 per investigator.

7.5.2 PSA Response Rate

RR-PSA will be analyzed by the HRD status and cohort for all treated participants in the same way as for ORR per PCWG3.

7.5.3 Radiographic Progression-Free Survival

For secondary endpoint of radiographic progression free survival (rPFS) per investigator, Kaplan-Meier plots will be presented. The estimates of the median and corresponding log-log transformed

two-sided 95% confidence intervals will be calculated.[8] The rates at months 6 and 12 and corresponding 95% CIs will be estimated via the Kaplan-Meier methodology.

The 1-year rPFS rate, median and corresponding two-sided log-log transformed 95% CIs will be calculated for the pre-defined subsets in a stratum, if a stratum has more than 10 participants.

rPFS per BICR, if available, will be analyzed in the same way as for rPFS per investigator.

7.5.4 Time to Objective Response and Duration of Response per PCWG3

Summary statistics of time to objective response (TTR) will be provided by the HRD status and cohort for treated participants with a BOR of CR or PR. TTR curves will be estimated using the Kaplan-Meier methodology by the HRD status and cohort for all treated participants. Due to small sizes for each stratum, spider plots will be provided by the HRD status and cohort for all treated participants.

Duration of response (DOR) will be summarized for participants with a BOR of PR or CR per investigator using the Kaplan-Meier methodology. Median values, along with two-sided 95% CIs will also be calculated.

TTR/DOR per BIRC, if available, will be analyzed in the same way as for TTR/DOR per investigator.

7.5.5 Time to PSA Progression

For time to PSA progression, Kaplan-Meier plots will be presented by the HRD status and cohort for all treated participants. The estimates of the median and corresponding log-log transformed two-sided 95% CIs will be calculated. The rates at months 3, 6, 9 and 12 and corresponding 95% CIs will be estimated via the Kaplan-Meier methodology.

7.5.6 Overall Survival

For overall survival, Kaplan-Meier plots will be presented by the HRD status and cohort for all treated participants. The estimates of the median and corresponding log-log transformed two-sided 95% CIs will be calculated. The rates at months 6 and 12 and corresponding 95% CIs will be estimated via the Kaplan-Meier methodology. The extent of follow-up, defined as the time from treatment initiation to last OS contact (whether status is alive or dead), will be summarized by the HRD status and cohort for all treated participants.

[redacted]

7.6 Safety

All the safety analyses will be performed by the HRD status and cohort and total for all treated participants. Descriptive statistics of safety will be presented using the NCI CTCAE v4.03 by the HRD status and cohort and combined. All AEs, drug-related adverse events, serious adverse events (SAEs) and drug-related SAEs will be tabulated using the worst grade per NCI CTCAE v4.03 by system organ class and preferred term. On-study lab parameters including hematology, coagulation, chemistry, liver function, thyroid, adrenal and renal function will be summarized using worse grade by NCI CTCAE v4.03. In addition, immune mediated adverse events incident rate is defined as the proportion participants with any grade adverse events among participants treated by each cohort and total. Events reported from the first dose and up to and including 100 days following the last dose of study treatment could be included in estimating this incidence rate. Details are in the Core Safety SAP. [1]

7.6.1 Deaths

Refer to Core Safety SAP.

7.6.2 Serious Adverse Events

Refer to Core Safety SAP.

Summaries of SAEs and drug-related SAEs with onset during the nivolumab monotherapy period in Arm B (using the 30-day safety window only) will also be provided for all participants treated in the nivolumab monotherapy period.

7.6.3 Adverse Events Leading to Discontinuation of Study Therapy

See Core Safety SAP.

Summaries of adverse events leading to discontinuation and drug-related adverse events leading to discontinuation with onset during the nivolumab monotherapy period in Arm B (using the 30-day safety window) will also be provided for all participants treated in the nivolumab monotherapy.

7.6.4 Adverse Events Leading to Dose Modification

See Core Safety SAP.

7.6.5 Adverse Events

Refer to Core Safety SAP.

Summaries of adverse events and drug-related adverse events will also be provided separately for events with onset during the combination therapy for all treated participants in Arm B and for events with onset during the monotherapy period for all participants treated in nivolumab 480 mg monotherapy in Arm B. These additional summaries by treatment period will be performed using the 30-day safety window only.

7.6.6 Select Adverse Events

Refer to Core Safety SAP.

7.6.7 Immune Modulating Medication

Refer to Core Safety SAP.

7.6.8 Multiple Events

Refer to Core Safety SAP.

[redacted]

7.6.10 Immune-Mediated Adverse Events

Refer to Core Safety SAP.

7.6.11 Laboratory Parameters

Refer to Core Safety SAP.

Lipase and Amylase will be added to the list of lab parameters to be summarized.

7.6.12 Vital Signs and Pulse Oximetry

Refer to Core Safety SAP.

[redacted]

7.6.14 Adverse Events by Subgroup

Refer to Core Safety SAP.

Categories for region will be US, EU and ROW.

[redacted]

[redacted]

[redacted]

7.8 Pharmacokinetics

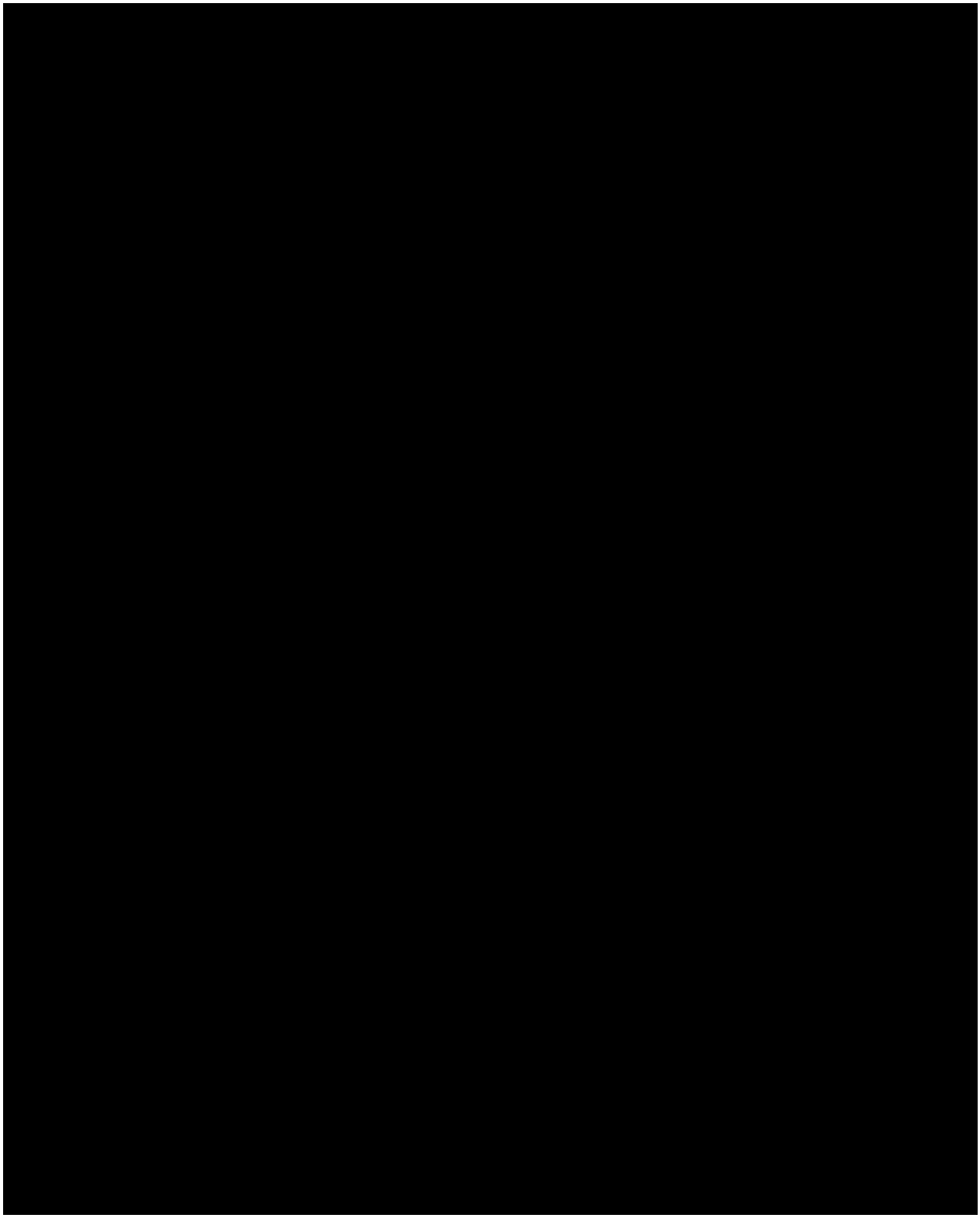
7.8.1 Pharmacokinetics of Nivolumab

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 Clinical Study Report (CSR).

7.8.2 Pharmacokinetics of Rucaparib/ Enzalutamide

The trough plasma concentrations of rucaparib and enzalutamide data will be analyzed, respectively, 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 CSR.

[redacted]



7.10 Interim Analysis

An interim analysis may be performed in each arm when at least 50% of planned participants have been treated with first dose at least 16 weeks prior to the cutoff date for the interim analysis

database lock. 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 7.12-1 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 in protocol 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 with measurable disease. For the interim analysis, the analysis population is defined as all treated subjects whose first dose date is at least 16 weeks before the cutoff date for the interim analysis database lock, and analysis will also be performed by HRD status. Summaries and listings of efficacy and safety will be produced at the interim, and the interim results 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 7.10-1: 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

8 CONVENTIONS

Unless otherwise noted, the following conventions should be understood to apply. Further conventions may be detailed in the Data Presentation Plan (DPP).

The duration between two dates will be calculated as difference between the two dates. Study Day 1 or first dose date is the date of first dose of study therapy.

- if the assessment is before the first dose then the study day associated with an assessment will be calculated as [assessment date] - [first dose date]
- if the assessment is on or after first dose then the study day will be calculated as [assessment date] - [first dose date]+1.

In the absence of evidence of discontinuation of therapy, participants will be assumed still to be on-study.

Events with an onset prior to Day 1 (or to the first dosing date, for non-treated participants) will constitute pretreatment events.

Events will be considered as occurring within X days (e.g. deaths within 30 days, deaths and adverse events within 100 days) of last dose of study medication if [event date] minus [last dosing date] ≤ X. The following factors will convert days to months or years: 1 month = 30.4375 days, 1 year = 365.25 days.

8.1 Conventions for Partial or Missing Dates

See Core Safety SAP.

For death dates, the following conventions will be used for imputing partial dates:

- If only the day of the month is missing, the first of the month will be used to replace the missing day. The imputed date will be compared to the last known date alive and the maximum will be considered as the death date.
- If the month or the year is missing, the death date will be imputed as the last known date alive.
- If the date is completely missing but the reason for death is present the death date will be imputed as the last known date alive.

For date of progression, the following conventions will be used for imputing partial dates:

- If only the day of the month is missing, the first of the month will be used to replace the missing day*.
- If the day and month are missing or a date is completely missing, it will be considered as missing.

* In cases where the date of death is present and complete, the imputed progression date will be compared to the date of death. The minimum of the imputed progression date and date of death will be considered as the date of progression.

For other partial/missing dates not covered by Core Safety SAP, the following conventions may be used:

- If only the day of the month is missing, the 15th of the month will be used to replace the missing day.
- If both the day and the month are missing, "July 1" will be used to replace the missing information.
- If a date is completely missing, it will be considered as missing.

9 CONTENT OF REPORTS

The table, figure and listing outputs that will be produced will be described in DPP for this study.

10 REFERENCES

1 Core Safety Statistical Analysis Plan for Nivolumab Program v5.0.

2 Fleiss JL, Levin B, Paik MC. Statistical Methods for Rates and Proportions, Second Edition. John Wiley & Sons (1981).

3 Brookmeyer R. and Crowley J. A confidence interval for the median survival time. Biometrics 38:29-41, 1982

4 Klein, J. P. and Moeschberger, M. L. (1997), Survival Analysis: Techniques for Censored and Truncated Data, New York: Springer-Verlag.

5 Greenwood, M. The errors of sampling of the survivorship tables, Reports on Public Health and Statistical Subjects, 33, Appendix 1, HMSO, London, 1926

6 Kalbfleisch, J. D. and Prentice, R. L. (1980), The Statistical Analysis of Failure Time Data, New York: John Wiley & Sons.

7 Clopper, CJ and Pearson, ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 26: 404-413, 1934

8 Kalbfleisch RL. The Statistical Analysis of Failure Time Data. Wiley-Interscience 2002.

[redacted]