PARKER INSTITUTE FOR CANCER IMMUNOTHERAPY

Statistical Analysis Plan for

Protocol Number: PICI0033

Protocol Title: A Multicenter, Open-Label, Exploratory Platform Study to Evaluate Biomarkers and Immunotherapy Combinations for the Treatment of Patients with Metastatic Castration-resistant Prostate Cancer

IND Number:	139269
Sponsor:	Parker Institute for Cancer Immunotherapy 1 Letterman Drive Suite D3500 San Francisco, CA 94129
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2 INTRODUCTION

The purpose of this document is to provide details of the planned analyses for PICI0033. The analyses specified in this document supersede the high-level analysis plan described in the protocol and its appendices. Statistical analyses will be performed consistent with the principles of the ICH/FDA Guidance for Industry E9 Statistical Principles for Clinical Trials.

3 STUDY DESIGN

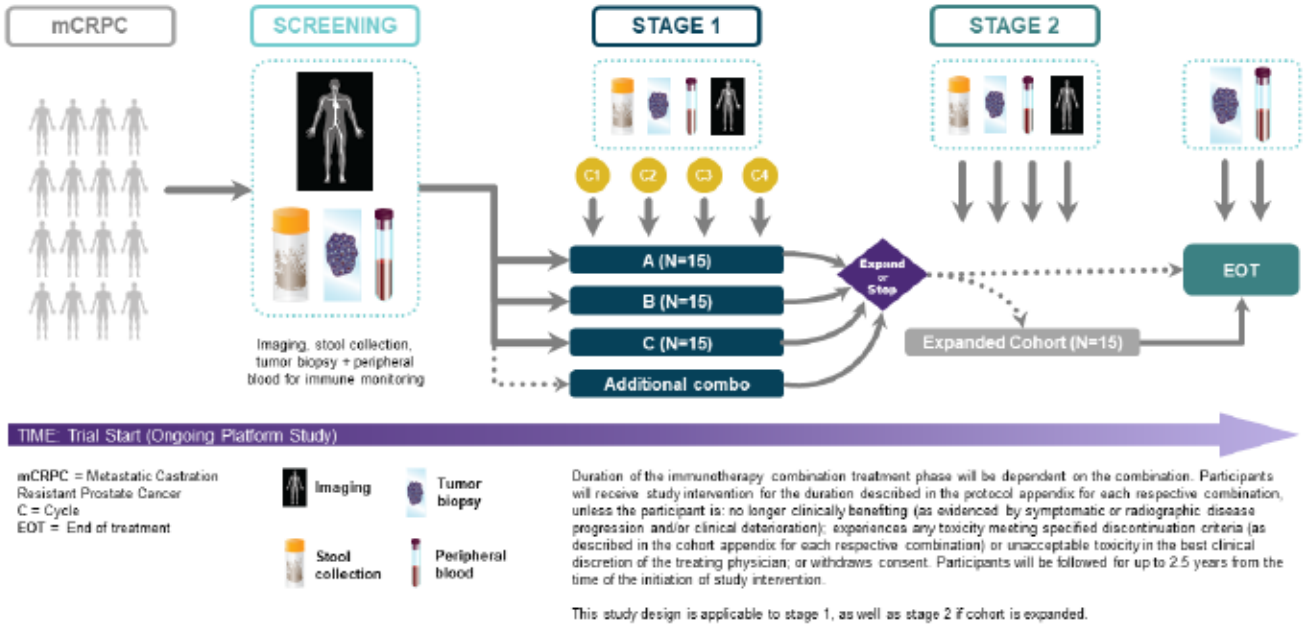
PICI0033 is an open-label, non-randomized, exploratory platform protocol designed to assess the safety and antitumor activity of multiple immunotherapy combinations in participants with metastatic castration-resistant prostate cancer (mCRPC) who have received prior therapy. Each cohort of the platform study will consist of up to 2 stages: Stage 1, an initial stage to evaluate safety, biomarkers, and clinical activity of a combination and Stage 2, an expanded cohort, when warranted, based on the safety, clinical activity, and/or biomarker results from Stage 1. The Sponsor intends to modify and/or add new combinations to the protocol as data emerge from this and other trials.

This is not a randomized study. Assignment to one of the immunotherapy combinations will be made by the Investigator using his/her best clinical discretion based on the participant's medical history and disease status and knowledge of the available immunotherapy combination cohorts open for enrollment. The dose and schedule selected will be described in the protocol cohort appendix for each respective combination (eg, Appendix Cohort A, Appendix Cohort B, etc.). The duration of immunotherapy combination study intervention will be dependent on the combination administered. Participants will be followed for up to 2.5 years from the time of the initiation of study intervention.

The study is not intended or powered for hypothesis testing or comparison between cohorts. The study is intended to provide preliminary estimates of adverse event (AE) rates, response rates, effect sizes, and confidence intervals (CIs) to aid the design of later studies. Approximately 15 participants, including a minimum of 7 with a non-bone metastatic lesion that can be biopsied, will be enrolled in each immunotherapy combination cohort in Stage 1. An additional approximately 15 participants, including a minimum of 7 with a non-bone metastatic lesion, will be enrolled in Stage 2 if the cohort is expanded.

The general study schema is depicted in Figure 1.

Figure 1: Study Schema



3.1 Protocol Synopsis

Due to the platform design of this trial, there are multiple protocol levels. The Core Protocol contains information on study conduct that is uniform across all cohorts. Each cohort has a unique protocol appendix that describes study conduct and procedures that are unique to that particular immunotherapy combination. The Core Protocol and cohort-specific appendix should be used in conjunction with each other.

The Core Protocol Synopsis is included in Section 8.1.

3.2 Study Objectives and Endpoints

The study objectives and endpoints for the Core Protocol are listed in Table 1. Any cohort-specific endpoints will be captured in an appendix to this SAP.

Table 1: Objectives and Corresponding Endpoints

Objectives	Endpoints
Primary	
• To determine the safety of each immunotherapy combination in participants with mCRPC.	• Incidence and severity of AEs.
Secondary	
• To determine the CRR of each immunotherapy combination in participants with measurable mCRPC.	• Composite Response Rate (CRR): A composite endpoint where response is defined as a participant meeting at least one of the following:

• To determine the DCR of each immunotherapy combination in participants with measurable mCRPC. • To evaluate the rPFS of each immunotherapy combination in participants with mCRPC. • To estimate the OS of each immunotherapy combination in participants with mCRPC.	○ CTC response: Change from unfavorable (≥ 5 cells/7.5 mL of blood) to favorable (≤ 4 cells/7.5 mL of blood). Participants with a baseline CTC value < 5 cells/7.5 mL of blood will not be evaluated for this criterion. ○ PSA response: Confirmed PSA response is defined as ≥ 50% reduction in PSA from baseline, with a repeat assessment confirming the result at least 3 weeks later. Participants without a baseline PSA assessment will not be evaluated for this criterion. ○ Objective response rate (ORR): Confirmed response of CR or PR by objective radiographic disease assessment using PCWG3-modified RECIST version 1.1 (ie, CR or PR and no progression in bone per the PCWG3; Scher et al., 2016). Per RECIST, to be assigned a best overall response of CR or PR, changes in tumor measurements must be confirmed by repeat radiographic assessments that should be performed no less than 4 weeks after the criteria for response are first met. Participants with measurable disease at baseline who received at least 1 dose of any component of the combination study intervention but do not have radiographic disease assessments for any reason will be counted as not responding. Participants without measurable disease at baseline will not be evaluated for this criterion. • DCR: Defined as the proportion of participants with CR, PR, or SD for 6 months as best response by PCWG3-modified RECIST v1.1. Participants with measurable disease at baseline who received at least 1 dose of any component of the study intervention combination but do not have RECIST assessment for any reason will be counted as not responding. Participants without measurable disease at baseline will not be evaluated for this endpoint. • rPFS: Defined as the time from initiation of study intervention to the first objective evidence of radiographic progression per PCWG3-modified RECIST v1.1 or death due to any cause (whichever occurs first). • OS: Defined as the time from initiation of study invention until death due to any cause. • OS rate at 12 months.

Exploratory	
• To evaluate tumor and immune biomarkers and their association with treatment outcome (antitumor activity and/or safety). • To estimate the radiographic DOR of each immunotherapy combination in participants with mCRPC. • To evaluate the PK of the components of the immunotherapy combination. • To evaluate the immunogenicity of the components of the immunotherapy combination.	• Association of tumor and immune biomarkers from tissue, blood, and/or stool with clinical outcomes, including ORR, DCR, rPFS, and tolerability. Biomarkers to be studied will be chosen based on the immunotherapy combination. • Molecular characterization of CTC and evaluation of percent change from baseline. • Enumeration of CTC ≥ 1 at baseline with conversion to CTC0 on treatment. • PSA: o Percent change in PSA from baseline at 12 weeks. o Maximum change in PSA at any point after initiation of study intervention. o Time to PSA progression, defined as the time from study treatment initiation to the date that a $\geq 25\%$ increase and absolute increase of ≥ 2 ng/mL above the nadir (or baseline value for participants who did not have a decline in PSA) in PSA. The increase must be confirmed by a second consecutive assessment conducted at least 3 weeks later. • DOR: Defined as time from the first tumor assessment that documents radiographic response (CR or PR) to the first documentation of radiographic progression per PCWG3-modified RECIST v1.1 or death due to any cause (whichever occurs first). • Sparse PK analysis. • Presence of ADA against biologic components of each immunotherapy combination.

ADA = anti-drug antibodies; AE = adverse event(s); CR = complete response; CRR = composite response rate; CTC = circulating tumor cells; CTC0 = a measure of zero CTC; DCR = disease control rate; DOR = duration of response; mCRPC = metastatic castration-resistant prostate cancer; ORR = objective response rate; OS = overall survival; PCWG3 = Prostate Cancer Clinical Trials Working Group 3; PK = pharmacokinetics; PR = partial response; PSA = prostate-specific antigen; RECIST = Response Evaluation Criteria in Solid Tumors; rPFS = radiographic progression-free survival; SD = stable disease

3.3 Determination of Sample Size

The study is not intended or powered for hypothesis testing or comparison between cohorts. The study is intended to provide preliminary estimates of AE rates, response rates, effect sizes and CIs to aid the design of later studies. A sample size of approximately 15 participants per immunotherapy combination cohort will provide these preliminary estimates while limiting exposure.

Table 2 provides 95% exact confidence intervals for the proportion of participants experiencing a specific AE for sample sizes of 15 and 30 participants per cohort. These confidence intervals, along with the CRR (described below), provide information needed to assess the risk-benefit ratio of the immunotherapy combination for expanding the cohort to Stage 2 and for the design of further studies.

Table 2: Confidence Intervals for the True Proportion of Adverse Events

Observed AE rate	95% Confidence Interval (n = 15)	95% Confidence Interval (n = 30)
6.7% (1/15 or 2/30)	(0.2%, 31.9%)	(0.8%, 22.1%)
13.3% (2/15 or 4/30)	(1.7%, 40.5%)	(3.8%, 30.7%)
20.0% (3/15 or 6/30)	(4.3%, 48.1%)	(7.7%, 38.6%)
26.7% (4/15 or 8/30)	(7.8%, 55.1%)	(12.3%, 45.9%)
33.3% (5/15 or 10/30)	(11.8%, 61.6%)	(17.3%, 52.8%)
40.0% (6/15 or 12/30)	(16.3%, 67.7%)	(22.7%, 59.4%)

AE = adverse event

A Simon two-stage minimax design (Simon, 1989) will be implemented for each cohort. A CRR of at least 25% would provide sufficient evidence of clinical activity to warrant further investigation, while a CRR of 10% would not be of interest. In Stage 1, 15 participants will be enrolled. If the safety profile is acceptable and there are 2 or more responses in these 15 participants, 15 additional participants may be enrolled in Stage 2 for a total of 30 participants in the cohort. If there are 6 or more responses in these 30 participants, then the immunotherapy combination will be considered worthy of further investigation. This design yields a type I error rate of 0.07 and 77% power when the null hypothesis assumes the CRR is 10% and the alternative hypothesis assumes the CRR is 25%. Under the null hypothesis, the probability of terminating a cohort after Stage 1 is 55%.

3.4 Analysis Timing

The primary analyses described in the main body of this document will be performed for each immunotherapy combination cohort separately after all participants for a specific cohort have at least 6 months of follow-up from the date of first dose or have discontinued the study. Each cohort will be assessed independently of the other cohorts, and the data from each cohort will be analyzed separately. Study conduct of one or more cohorts may be ongoing at the time of final analysis for a given cohort.

Any cohort-specific modifications to the statistical methods, including any additional cohort-specific endpoints, will be captured as an appendix in this SAP.

Analysis of safety and efficacy endpoints will be performed prior to the time of primary analysis. These analyses will help inform adaptations of the trial, such as expanding, modifying, or terminating a cohort. More information about these interim analyses is presented in Section 5.7. These results may be presented and/or published prior to the primary analysis.

A cohort will formally end once all participants have been followed for survival status for a maximum of 2.5 years or until death, withdrawal of consent, or loss to follow-up. The Sponsor may choose to discontinue survival follow-up of a cohort at any time. A survival analysis of long-term follow-up may be performed after the primary analysis has been completed.

4 STUDY CONDUCT

4.1 Randomization Details

This is a non-randomized study. Assignment to one of the immunotherapy combinations will be made by the Investigator using his/her best clinical discretion based on the participant's medical history and disease status and knowledge of the available immunotherapy combination cohorts open for enrollment.

4.2 Blinding

This is an open-label study with no blinding.

4.3 Data Monitoring

To ensure careful review of the accumulating safety data for the PICI0033 platform study, a Safety Assessment Committee (SAC) will be established.

Ongoing safety data review will be conducted by the SAC for all cohorts. The PICI0033 SAC will have a core membership made up of genitourinary (GU) oncologists and immuno-oncologists and subject matter expert(s) as appropriate for a specific cohort (eg, vaccine expertise). Select Sponsor personnel, including the Medical Monitor and representatives from other functions including, but not limited to, Biostatistics, Clinical Science, and Pharmacovigilance, will be responsible for producing output for review and informing the SAC of any major safety signals in a timely manner.

To ensure participants' safety during the study, the SAC will meet approximately every 3 months to assess the totality of safety information in the clinical study across all cohorts. In addition, the SAC or the Sponsor may request ad hoc reviews at any time to address potential safety concerns.

Safety monitoring by the SAC will include unblinded evaluation of all AEs, SAEs, and laboratory data. If the SAC deems a benefit-risk assessment necessary, the SAC may also

review efficacy data. The SAC may recommend terminating a cohort or suspending enrollment for safety reasons. Roles and responsibilities of the SAC are detailed in a separate charter.

5 STATISTICAL ANALYSES

The data from each cohort will be analyzed independently of the other cohorts. Study conduct of one or more cohorts may be ongoing at the time of final analysis for a given cohort.

Summary statistics will be presented by cohort. Categorical variables will be summarized using frequencies and percentages. Continuous variables will be summarized using means, standard deviations, medians, interquartile ranges, minimums, and maximums.

5.1 Populations for Analysis

5.1.1 Evaluable Population

The evaluable population will serve as the primary population for the analysis of safety and efficacy data in this study. The evaluable population consists of all participants in a cohort who received at least 1 dose of any component of the combination study intervention. Participants will be grouped according to the cohort into which they were enrolled and dosed.

Efficacy analyses may be performed on a subset of the evaluable population, such as participants with measurable disease at baseline or participants with a baseline CTC value ≥ 5 cells/7.5 mL of blood. The specific analysis population used for each efficacy analysis is further detailed in Section 5.4.

5.2 Analysis of Study Conduct

The number of participants who were enrolled and treated, enrolled and not treated, and completed the treatment period will be presented in summary tables by cohort. The reason for treatment discontinuation and study discontinuation will be listed by participant and summarized in a table.

5.3 Analysis of Baseline Characteristics

Demographic and baseline characteristics of the study population will be summarized for each cohort. Variables to be summarized include, but are not limited to, age, sex, race, ethnicity, Eastern Cooperative Oncology Group (ECOG) performance status, cancer stage at initial diagnosis and enrollment, Gleason score, and PSA.

The baseline value of any variable will be defined as the last available value recorded prior to the first administration of study intervention.

5.4 Efficacy Analysis

The analyses for clinical activity will be performed on the evaluable population, consisting of all participants in a cohort who received at least 1 dose of any component of the combination study intervention. Some efficacy endpoints may be analyzed on a subset of the evaluable population, as summarized in Table 3.

This study is not intended or powered for hypothesis testing or comparison between cohorts. Due to the exploratory nature of this study, no control of type I error will be applied for any of the endpoints.

Table 3: Populations for Efficacy Analysis

Endpoint	Analysis Population
CRR	Evaluable population
CTC response (component of CRR)	Participants with a baseline CTC value ≥ 5 cells/7.5 mL of blood
PSA response (component of CRR)	Participants with a PSA value at baseline
ORR (component of CRR)	Participants with measurable disease at baseline per PCWG3-modified RECIST v1.1
DCR	Evaluable population
rPFS	Evaluable population
OS	Evaluable population
Change in CTC from baseline	Participants with a CTC value at baseline
CTC0	Participants with a baseline CTC value ≥ 1 cell/7.5 mL of blood
Percent change in PSA from baseline	Participants with a PSA value at baseline
Time to PSA progression	Participants with a PSA value at baseline
DOR	Participants with measurable disease at baseline per PCWG3-modified RECIST v1.1 and a best overall response of CR or PR

CR = complete response; CRR = composite response rate; CTC = circulating tumor cells; CTC0 = a measure of zero CTC; DCR = disease control rate; DOR = duration of response; ORR = objective response rate; OS = overall survival; PCWG3 = Prostate Cancer Clinical Trials Working Group 3; PR = partial response; PSA = prostate-specific antigen; RECIST = Response Evaluation Criteria in Solid Tumors; rPFS = radiographic progression-free survival

5.4.1 Primary Efficacy Endpoint

There are no primary efficacy objectives or endpoints for this study.

5.4.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints include CRR, ORR, DCR, rPFS, and OS.

5.4.2.1 Composite Response Rate

CRR is a composite endpoint where response is defined as a participant meeting at least one of the following:

- CTC response: Change from unfavorable ($\geq$ 5 cells/7.5 mL of blood) to favorable ($\leq$ 4 cells/7.5 mL of blood). Participants with a missing baseline CTC value or baseline CTC value < 5 cells/7.5 mL of blood will not be evaluated for this criterion. The baseline CTC value is defined as the last available value recorded prior to the first administration of study intervention.
- PSA response: Confirmed PSA response is defined as $\geq$ 50% reduction in PSA from baseline, with a repeat assessment confirming the result at least 3 weeks later. Participants without a PSA value at baseline will not be evaluable for this criterion. The baseline PSA value is defined as the last available value recorded prior to the first administration of study intervention.
- Objective radiographic response (ORR): Best overall response of CR or PR by objective radiographic disease assessment of soft-tissue, non-bone lesions, as determined by PCWG3-modified RECIST version 1.1. Per RECIST, to be assigned a best overall response of CR or PR, changes in tumor measurements must be confirmed by a repeat radiographic assessment performed no less than 4 weeks after the criteria for initial radiographic response were first met. In addition, responders must not have bone lesions that have progressed, as determined by PCWG3 criteria. Participants with measurable disease at baseline who received at least 1 dose of any component of the combination study intervention but do not have evaluable RECIST assessments for any reason will be counted as not responding. Participants without measurable, soft-tissue disease at baseline will not be evaluable for this criterion.

Response rates will be estimated within each cohort and 95% CIs will be estimated using the Clopper-Pearson method. Response rates and 95% CIs will also be presented for each individual criterion of CRR (CTC response, PSA response, and ORR).

5.4.2.2 Disease Control Rate

DCR is defined as the proportion of participants with a best overall response of (1) CR, (2) PR, or (3) stable disease (SD) lasting at least 6 months. Per RECIST, to be assigned a best overall response of CR or PR, changes in tumor measurements must be confirmed by a repeat radiographic assessment performed no less than 4 weeks after the criteria for initial radiographic response were first met. In addition, DCR responders must not have bone lesions that have progressed, as determined by PCWG3 criteria. The duration of SD (or non-CR/non-PD for participants without measurable, soft-tissue disease) is defined as the time from

treatment initiation until the date of radiographic disease progression (per RECIST or PCWG3). If no radiographic progression has occurred and the most recent tumor assessment with overall response of SD occurred within 6 months of treatment initiation, the participant will not have met the SD duration criterion and will not be considered a DCR responder.

Response rates for DCR will be estimated within each cohort and 95% CIs will be estimated using the Clopper-Pearson method.

5.4.2.3 Radiographic Progression-Free Survival

rPFS is defined as the time from initiation of study intervention to the first objective evidence of radiographic progression or death due to any cause (whichever occurs first). Radiographic disease progression is defined as soft tissue (non-bone) disease progression per RECIST v1.1 or confirmed progression of bone disease per PCWG3 criteria. Participants who continue treatment beyond initial disease progression will be considered to have progression of disease (PD) at the time of the initial progression event.

Participants who do not have radiographic PD at the time of analysis will be censored as follows:

- Participants who do not have radiographic PD and are still on study at the time of analysis will be censored at the date of the last tumor assessment documenting absence of progressive disease
- Participants who have discontinued study treatment and have started subsequent anti-cancer therapy or had subsequent cancer surgery or radiation prior to documentation of radiographic PD will be censored at the date of the last evaluable tumor assessment prior to the initiation of subsequent treatment.
- Participants who discontinued the study prior to documentation of radiographic PD will be censored at the date of the last tumor assessment documenting absence of progressive disease.
- Participants who do not have radiographic PD and who die more than 16 weeks from their last evaluable tumor assessment will be censored at the date of the last tumor assessment documenting absence of progressive disease. Participants who within 16 weeks of their last evaluable tumor assessment will be considered as having an event at the date of death.

rPFS will be estimated using Kaplan-Meier techniques, and the median survival time and 95% CIs will be estimated within each cohort. If median survival is not reached, survival times and 95% CIs will be reported at deciles that are estimable given the observed events.

5.4.2.4 Overall Survival

OS is defined as the time from initiation of study invention until death due to any cause. Participants who are not reported as having died at the time of analysis will be censored at the most recent contact date they were known to be alive. See Section 5.6.2 for handling of missing or partial death dates.

OS will be estimated using Kaplan-Meier techniques, and the median survival time and 95% CIs will be estimated within each cohort. If median survival is not reached, survival times and 95% CIs will be reported at deciles that are estimable given the observed events. In addition, the 12-month OS rate will be estimated within each cohort and 95% CIs will be estimated using the Clopper-Pearson method.

5.4.3 **Exploratory Efficacy Endpoints**

The exploratory efficacy endpoints are listed in Table 1.

5.4.3.1 Biomarker Analysis

Descriptive statistics will be used to evaluate the exploratory biomarkers. Biomarker exploratory analyses will be determined based on study outcomes and further described in a Translational Analysis Plan.

5.4.3.2 Circulating Tumor Cell Analysis

Descriptive statistics will be used to evaluate CTC count at each timepoint. CTC changes from baseline will be plotted and summarized at each timepoint.

The number and proportion of participants who have a baseline CTC value $\geq$ 1 cell/7.5 mL and who subsequently have at least one post-baseline CTC value equal to zero (i.e. CTC0) will be presented within each cohort. 95% CIs for the proportion of CTC0 participants will be estimated using the Clopper-Pearson method. Participants with a missing baseline CTC value or baseline CTC value < 1 cell/7.5 mL will be excluded from the CTC0 analysis.

5.4.3.3 Prostate-specific Antigen Analysis

Descriptive statistics will be used to evaluate PSA at each timepoint. The percent change from baseline will be plotted and summarized at each timepoint. The maximum percent change (decrease) in PSA at any point after initiation of study invention will be summarized and displayed in a waterfall plot. The analysis of percent change in PSA from baseline at 12 weeks will use the first PSA value that is collected at least 12 weeks ($\pm$ visit windows specified in the cohort-specific protocol appendix) after the initiation of study intervention.

Time to PSA progression is defined as the time from initiation of study invention to the date that a $\geq$ 25% increase and absolute increase of $\geq$ 2 ng/mL above the nadir (or baseline value

for participants who did not have a decrease) in PSA. The increase must be confirmed by a second consecutive PSA assessment conducted at least 3 weeks later. If confirmed, the date that the PSA criteria were first met will be considered the date of PSA progression. Participants who do not progress will be censored at the last available PSA measurement prior to the initiation of subsequent anti-cancer therapy. Time to PSA progression will be estimated using Kaplan-Meier techniques, and the median progression time and 95% CIs will be estimated within each cohort. If median progression time is not reached, progression times and 95% CIs will be reported at deciles that are estimable given the observed events.

5.4.3.4 Duration of Response

For participants who have measurable disease at baseline and who experienced an objective response (confirmed CR or PR) during the study, DOR is defined as the time from the first tumor assessment that documents response (CR or PR, whichever is recorded first) to the first documentation of radiographic PD per PCWG3-modified RECIST v1.1 or death due to any cause (whichever occurs first).

Participants who have not progressed at the time of analysis will be censored as follows:

- Participants who do not have radiographic PD and are still on study at the time of analysis will be censored at the date of the last tumor assessment documenting response
- Participants who have discontinued study treatment and have started subsequent anti-cancer therapy or had subsequent cancer surgery or radiation prior to documentation of radiographic PD will be censored at the date of the last tumor assessment documenting response that occurred prior to the initiation of subsequent systemic treatment.
- Participants who discontinued the study prior to documentation of radiographic PD will be censored at the date of the last tumor assessment documenting response.

DOR will be estimated using Kaplan-Meier techniques, and the median DOR and 95% CIs will be estimated within each cohort. If median DOR is not reached, duration times and 95% CIs will be reported at deciles that are estimable given the observed events.

5.4.3.5 Pharmacokinetic Analysis

Sparse PK analysis may be performed evaluating trough levels for all biologic study intervention and maximum observed drug concentration (Cmax) for exploratory biologic study intervention (non-PD-1 agents). The decision to perform PK analysis will be made on a cohort-by-cohort and compound-by-compound basis.

5.4.3.6 Anti-Drug Antibody Analysis

The number of participants who develop ADA to biologic study intervention and ADA titer may be summarized. The decision to perform ADA analysis will be made on a cohort-by-cohort and compound-by-compound basis.

5.5 Safety Analysis

All safety analyses will be performed on the evaluable population, consisting of all participants who receive at least 1 dose of any component of the combination study intervention. Because this is a non-randomized and open-label study, it is highly unlikely that a participant will receive an incorrect study intervention. Therefore, participants will be grouped according to the cohort into which they were enrolled. If any participants receive incorrect study intervention, it will be recorded as a protocol deviation and described in the Clinical Study Report.

Safety will be assessed through summaries of AEs, laboratory test results (hematology, serum chemistry, and thyroid function testing), vital signs, and ECGs.

5.5.1 Exposure to Study Medication

The number of participants exposed to each study intervention and the extent of exposure (as number of doses and cumulative dose received, as applicable) will be summarized by cohort using descriptive statistics.

5.5.2 Adverse Events

All reported AEs will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) and graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

A treatment-emergent adverse event (TEAE) is defined as any event that either occurs after the initiation of study intervention, having been absent at baseline, or, if present at baseline, appears to have worsened in severity or frequency, whether or not the event is considered related to study intervention. AEs assessed by the Investigator to be "Possibly", "Probably", or "Definitely" related to any study intervention, as well as AEs with missing relationship, will be considered treatment related.

Handling of missing and partial missing AE dates is described in Section 5.6.1.

The incidence of TEAEs will be summarized (overall, by system organ class and preferred term and by severity) by cohort. In addition, separate summaries will be generated for SAEs, deaths, treatment-related AEs, AEs leading to treatment discontinuation, and AEs leading to temporary interruption and/or dose reduction. Participant deaths and the primary cause of death will be listed.

5.5.3 Laboratory Data

Clinical laboratory findings will be summarized using descriptive statistics for each cohort. Changes from baseline to each visit may be presented for select laboratory tests.

5.5.4 Vital Signs

Vital sign measurements will be summarized using descriptive statistics for each cohort. Changes from baseline to each visit may be presented for each cohort.

5.5.5 Physical Examinations

Physical examination data will not be summarized because any significant finding will be captured and summarized as an AE.

5.6 Missing Data

5.6.1 Missing and Partial Missing Adverse Event Dates

If the AE start date is not a complete date, the following rules will be applied to determine whether the event is treatment emergent.

- If the start date is completely missing: The AE will be considered treatment emergent unless the AE stop date is earlier than the date of first dose of study intervention.
- If the day of the AE start date is missing:
    - If the month and year of the start date are later than the month and year of the date of first dose of study intervention, then the AE will be considered treatment emergent.
    - If the month and year of the start date are equal to the month and year of the date of first dose of study intervention and the stop date is unknown or later than the date of first dose of study intervention, then the AE will be considered treatment emergent.
- If the day and month of the start date are missing:
    - If the year of the start date is later than the year of the date of first dose of study intervention, then the AE will be considered treatment emergent.
    - If the year of the start date is equal to the year of the date of first dose of study intervention and the stop date is unknown or later than the date of first dose of study intervention, then the AE will be considered treatment emergent.

5.6.2 Missing and Partial Missing Death Dates

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

- If the date of death is completely or partially missing, but there is an AE with the outcome as 'Fatal', the date of death will be replaced by the end date of the AE.
- If only the day of the month is missing and there is no AE with outcome as 'Fatal', the 1st of the month will be used to replace the missing day. The imputed date will be compared to the last known date alive plus 1 day, 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 plus 1 day.
- 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 plus 1 day.

5.7 Interim Analyses

Safety and efficacy will be monitored on a regular basis by the Sponsor and the SAC. Possible adaptations resulting from these data reviews include:

- Modifying or stopping a cohort early based on a safety signal
- Expanding a cohort to include an additional approximately 15 participants (Stage 2) based on acceptable safety data in addition to preliminary signals in clinical activity and/or biomarker results

Other possible adaptations to the study design, including the addition of new combination cohorts, may be based on a variety of factors, such as emerging biological knowledge of mCRPC biomarkers and/or immunotherapy mechanisms, as well as availability of investigational therapies. Findings will not be used to re-estimate the sample size.

Due to the exploratory nature of this study, effect sizes and CIs will not be adjusted to account for ongoing review of data.

5.7.1 Cohort Expansion Rules

A Simon two-stage minimax design (Simon, 1989) will be implemented for each cohort. In Stage 1, 15 participants will be enrolled. If there are 2 or more responses in these 15 participants, 15 additional participants may be enrolled in Stage 2 for a total of 30 participants in the cohort. For the purposes of cohort expansion, CRR will be used to determine response (ie, CTC response, PSA response, or objective radiographic response).

In addition to efficacy criteria stated above, safety data will also be assessed when determining whether to expand a cohort. If there are ≥ 6 participants meeting cohort-specific toxicity criteria requiring permanent treatment discontinuation, an ad hoc SAC meeting will be held to further review all safety data and provide input on assessing the benefit-risk profile. The SAC will

provide a recommendation in regard to expansion to Stage 2, continuation or discontinuation of the cohort. This ad hoc review will be in addition to the ongoing safety monitoring performed by the SAC, who may recommend terminating a combination cohort at any time for safety reasons. The threshold of 6 participants was chosen because this translates to a posterior probability of 0.69 that the true toxicity rate is > 30%, assuming 15 participants are enrolled per cohort and a minimally informative beta (0.5, 2.5) prior.

If the cohort has an acceptable safety profile but has not demonstrated at least 2 responses, no additional participants will be enrolled into the cohort. However, this decision may be revisited if follow-up translational analysis or emerging external data identifies a subset of participants most likely to derive benefit from the combination therapy that was underrepresented in the cohort. Under this scenario, any modifications to the study design of the combination, including justification for participant selection or enrichment, will be detailed in an amendment to the appropriate cohort appendix.

6 DIFFERENCES COMPARED TO PROTOCOL

The following list provides a high-level overview of the differences between the SAP and the Core Protocol and cohort-specific appendices. The Core Protocol will be amended to address differences related to study endpoints.

- Section 3.2 (Study Objectives and Endpoints):
    - The SAP renames the Secondary composite endpoint from ORR to Composite Response Rate (CRR).
    - The SAP removes the requirement that at least 2 post-baseline PSA measurements must be available for a participant to be evaluable for the PSA response criterion of CRR.
    - The CRR criterion of confirmed response of CR or PR by objective radiographic disease assessment has been named ORR (objective response rate).
    - The SAP clarifies that participants without measurable disease at baseline will not be evaluable for ORR analysis.
    - The SAP modifies the minimum duration of SD required for a participant to be considered a DCR responder from 9 months to 6 months.
    - The SAP adds duration of response (DOR) as an exploratory endpoint.
- Section 3.3 (Determination of Sample Size): The SAP renames the Secondary composite endpoint from ORR to CRR.
- Section 5.1.1 (Evaluable Population): The SAP clarifies that some efficacy analyses may be performed on a subset of the evaluable population, as appropriate and detailed in other sections of the SAP.

- Section 5.4 (Efficacy Analysis): The SAP clarifies that some efficacy analyses may be performed on a subset of the evaluable population, as detailed in Table 3.
- Section 5.4.2.1 (Composite Response Rate):
    - The SAP renames the Secondary composite endpoint from ORR to Composite Response Rate (CRR).
    - The SAP clarifies that participants with a missing CTC value at baseline will not be evaluable for the CTC response criterion of CRR.
    - The SAP removes the requirement that at least 2 post-baseline PSA measurements must be available for a participant to be evaluable for the PSA response criterion of CRR.
    - The CRR criterion of confirmed response of CR or PR by objective radiographic disease assessment has been named ORR.
    - The SAP clarifies that participants without measurable disease at baseline will not be evaluable for ORR analysis.
    - The SAP clarifies that ORR responders must not have bone lesions that progressed, as determined by PCWG3 criteria.
    - The SAP clarifies that response rates and 95% CIs will be presented for each individual criterion of CRR.
- Section 5.4.2.2 (Disease Control Rate):
    - The SAP modifies the minimum duration of SD required for a participant to be considered a DCR responder from 9 months to 6 months.
    - The SAP clarifies that DCR responders must not have bone lesions that progressed, as determined by PCWG3 criteria.
- Section 5.4.3.2 (Circulating Tumor Cell Analysis): The SAP clarifies that participants with a missing CTC value at baseline will not be evaluable for the CTC0 analysis.
- Section 5.4.3.4 (Duration of Response): The SAP adds DOR as an exploratory endpoint.
- Section 5.7.1 (Cohort Expansion Rules): The SAP renames the Secondary composite endpoint used for expansion decision making from ORR to CRR.

7 REFERENCES

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

4. Simon R. Optimal two-stage designs for phase II clinical trials. Control Clin Trials 1989;10(1):1-10.

8 APPENDICES

8.1 Core Protocol Synopsis (Protocol Amendment 2; 30 April 2019)

Protocol Title:

A Multicenter, Open-Label, Exploratory Platform Study to Evaluate Biomarkers and Immunotherapy Combinations for the Treatment of Patients with Metastatic Castration-resistant Prostate Cancer

Short Title:

Platform Study for Prostate Researching Translational Endpoints Correlated to Response to Inform Use of Novel Combinations (PORTER)

Rationale:

This study is designed to test multiple clinical hypotheses and mechanistically-defined combinations to evaluate the safety and efficacy of immunotherapy combination in participants with metastatic castration-resistant prostate cancer (mCRPC) who have received prior secondary androgen receptor signaling inhibitor therapy (eg, abiraterone, enzalutamide, apalutamide).

Key Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To determine the safety of each immunotherapy combination in participants with mCRPC.	• Incidence and severity of AEs.
Secondary	
• To determine the ORR of each immunotherapy combination in participants with measurable mCRPC. • To determine the DCR ≥ 9 months of each immunotherapy combination in participants with measurable mCRPC. • To evaluate the rPFS of each immunotherapy combination in participants with mCRPC. • To estimate the OS of each immunotherapy combination in participants with mCRPC.	• ORR: A composite endpoint where response is defined as a participant meeting at least one of the following: o CTC response: Change from unfavorable (≥ 5 cells/7.5 mL of blood) to favorable (≤ 4 cells/7.5 mL of blood). Participants with a baseline CTC value < 5 cells/7.5 mL of blood will not be evaluated for this criterion. o PSA response: Confirmed PSA response is defined as ≥ 50% reduction in PSA from baseline, with a repeat assessment confirming the result at least 3 weeks later. Participants without a baseline and at least 2 post-baseline PSA assessments will not be evaluated for this criterion. o Confirmed response of CR or PR by objective radiographic disease assessment using modified RECIST version 1.1 (ie, CR or PR and no progression in bone per the PCWG3; Scher et

	al., 2016). Per RECIST, to be assigned a best overall response of CR or PR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Participants who received at least 1 dose of the combination study intervention or component of the combination but do not have RECIST assessment for any reason will be counted as not responding. • DCR at 9 months: Defined as CR, PR, or SD for 9 months as best response by PCWG3-modified RECIST 1.1. Participants who received at least 1 dose of the study intervention combination or component of the combination but do not have RECIST assessment for any reason will be counted as not responding. • rPFS: Defined as time from initiation of study intervention to the first objective evidence of radiographic progression, or death due to any cause (whichever occurs first). • OS: Defined as the time from initiation of study invention until death due to any cause. • OS rate at 12 months.

AE(s) = adverse event(s); CR = complete response; CTC = circulating tumor cells; DCR = disease control rate; ECOG = Eastern Cooperative Oncology Group; mCRPC = metastatic castration-resistant prostate cancer; ORR = objective response rate; OS = overall survival; PCWG3 = Prostate Cancer Clinical Trials Working Group 3; PR = partial response; PSA = prostate-specific antigen; RECIST = Response Evaluation Criteria in Solid Tumors; rPFS = radiographic progression-free survival; SD = stable disease

Overall Design:

This is an open-label, non-randomized, exploratory platform protocol designed to assess the safety and antitumor activity of multiple immunotherapy combinations in participants with mCRPC who have received prior therapy. The platform study will consist of 2 stages: Stage 1, an initial stage to evaluate safety, biomarkers, and clinical activity of a combination and Stage 2, an expanded cohort, when warranted, based on the safety, clinical activity, and/or biomarker results from Stage 1. The Sponsor intends to modify and/or add new combinations to the protocol as data emerge from this and other trials.

Participants must provide consent for archival tissue from a prior biopsy or surgery for prostate cancer and must consent to baseline and on-treatment biopsies, if medically feasible. Participants will be assigned to receive one of the enrolling combination study interventions and will be monitored for safety and response.

The duration of immunotherapy combination study intervention will be dependent on the combination administered and will continue for the duration described in the cohort appendix

for each respective combination, unless the participant: is no longer clinically benefiting (NLCB; as evidenced by symptomatic or radiographic disease progression and/or clinical deterioration); experiences any toxicity meeting specified discontinuation criteria (as described in the cohort appendix for each respective combination) or unacceptable toxicity in the best clinical discretion of the treating physician (ie, Investigator discretion); reaches the maximum duration of study intervention; or withdraws consent. Participants will be followed for up to 2.5 years from the time of the initiation of study intervention (see Follow-up). Depending on the combination administered, participants who are clinically benefiting, as defined by the Investigator at the end of the study treatment period, may have post-study access to the immunotherapy combination received during the study after written agreement from the Medical Monitor.

Number of Participants:

The study is not intended or powered for hypothesis testing. The study is intended to provide preliminary estimates of adverse event (AE) rates, response rates, effect sizes, and confidence intervals (CIs) to aid the design of later studies. A sample size of approximately 15 participants per combination intervention will provide these preliminary estimates while limiting exposure. An additional approximately 15 participants will be enrolled in Stage 2, if the cohort is expanded.

Intervention Groups and Duration:

This is not a randomized study. Assignment to one of the immunotherapy combinations will be made by the Investigator using his/her best clinical discretion based on the participant's medical history and disease status and knowledge of the available immunotherapy combinations open for enrollment.

The dose and schedule selected will be described in the cohort appendix for each respective combination (eg, Appendix Cohort A, Appendix Cohort B, etc.). The duration of immunotherapy combination study intervention will be dependent on the combination administered. Depending on the combination administered, participants who are clinically benefiting as defined by the Investigator at the end of the study may have post-study access to the immunotherapy combination after agreement from the Medical Monitor.

Follow-up:

For up to 2.5 years from the initiation of study intervention, participants in the follow up phase will be contacted by telephone by the site personnel every 3 months to collect alternate anticancer therapy information and determine survival status.

Participants will be followed for a up to 2.5 years from the time of the initiation of study intervention unless the consent is withdrawn. All participants will be followed for safety for at least 100 days after discontinuation of study intervention.

Depending on the combination administered, participants who are clinically benefiting, as defined by the Investigator at the end of the study treatment period, may have post-study access to the immunotherapy combination received during the study after agreement from the Medical Monitor.

A participant will be considered lost to follow-up if he repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

Data Monitoring Committee:

This study will use a Safety Assessment Committee (SAC) of genitourinary (GU) oncologists and immuno-oncologists, who will meet regularly with the Sponsor to monitor safety on an ongoing basis.

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