PARKER INSTITUTE
for CANCER IMMUNOTHERAPY

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

Protocol Number: PICI0033

Amendment Number: 2

Compound Number: Not applicable

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

Sponsor Name and Legal Registered Address:

Parker Institute for Cancer Immunotherapy
1 Letterman Drive
Suite D3500
San Francisco, CA 94129

Tel: 415-985-7311

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Approval Date: Final Protocol: 07 December 2018

Amendment 1: 24 January 2019

Amendment 2: 30 April 2019

SPONSOR APPROVAL PAGE

Date: 09 MAY 2019

Ramy Ibrahim, MD
Chief Medical Officer

INVESTIGATOR PROTOCOL AGREEMENT PAGE

I agree:

- To assume responsibility for the proper conduct of the study at this site.
- To conduct the study in compliance with this protocol, any future amendments, and with any other study conduct procedures provided by Parker Institute for Cancer Immunotherapy.
- Not to implement any changes to the protocol without written agreement from Parker Institute for Cancer Immunotherapy and prior review and written approval from the Institutional Review Board or Independent Ethics Committee except where necessary to eliminate an immediate hazard to participants.
- That I am thoroughly familiar with the appropriate use of the study drug(s), as described in the protocol cohort appendices and any other information provided by Parker Institute for Cancer Immunotherapy including, but not limited to, the current Investigator's Brochure(s).
- That I am aware of, and will comply with, the International Conference on Harmonisation for Good Clinical Practice (GCP) and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the study drugs, the Parker Institute for Cancer Immunotherapy study protocol, and of their study-related duties and functions as described in the protocol.
- That I agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on studies for the Parker Institute for Cancer Immunotherapy or for a partnership in which the Parker Institute for Cancer Immunotherapy is involved, and that I will immediately disclose in writing to the Parker Institute for Cancer Immunotherapy if any person who is involved in the study is debarred, or if any proceeding for debarment is pending.

Signature: _____ Date: _____

Name (print): _____

Principal Investigator

Site Number: _____

Amendment(s) to the Protocol

Text revisions resulting from the amendment(s) are incorporated in the synopsis and body of the Protocol Amendment. Major changes to the protocol are summarized below.

Key Revisions in Amendment 1 (24 January 2019)

Section # and Name	Description of Change
Statistical Considerations	
9.5.2 Cohort Expansion Rules	Added safety criteria that would inform the decision to proceed to Stage 2 of each immunotherapy combination.
Clarification of Document	
General Revisions	Document updated to address minor typographical errors and editorial changes for clarity.
Appendix B-1	Reordered the management algorithms to match the order on the appendix cover page.

Key Revisions in Amendment 2 (30 April 2019)

Section # and Name	Description of Change
Study Design	
3 Objectives and Endpoints	Updated primary and secondary endpoints to align with statistical analyses for the study cohorts.
4.1 Overall Design	Added clarification that all cohorts may be enrolling simultaneously.
Study Interventions	
6.5.2 Prohibited Therapy	Provided clarification regarding herbal and natural remedies allowing for use of marijuana and derivatives for treatments of cancer or cancer treatment-related symptoms.
Statistical Considerations	
9.2 Sample Size Determination	Added language and table defining confidence intervals for adverse event rates in determining ORR.
9.3.1.2 Secondary Efficacy Endpoints	Updated language for PSA response endpoint to better define who will not be evaluable in the study population.
9.5.1 Cohort Stopping Criteria	Added language detailing conditions under which an ad hoc Safety Assessment Committee meeting will be held and what stopping criteria will be used for cohorts in the event of serious adverse events.
Clarification of Document	
General Revisions	Document updated to address minor typographical errors and editorial changes for clarity.

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

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: ○ 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 and at least 2 post-baseline PSA assessments will not be evaluated for this criterion. ○ 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.

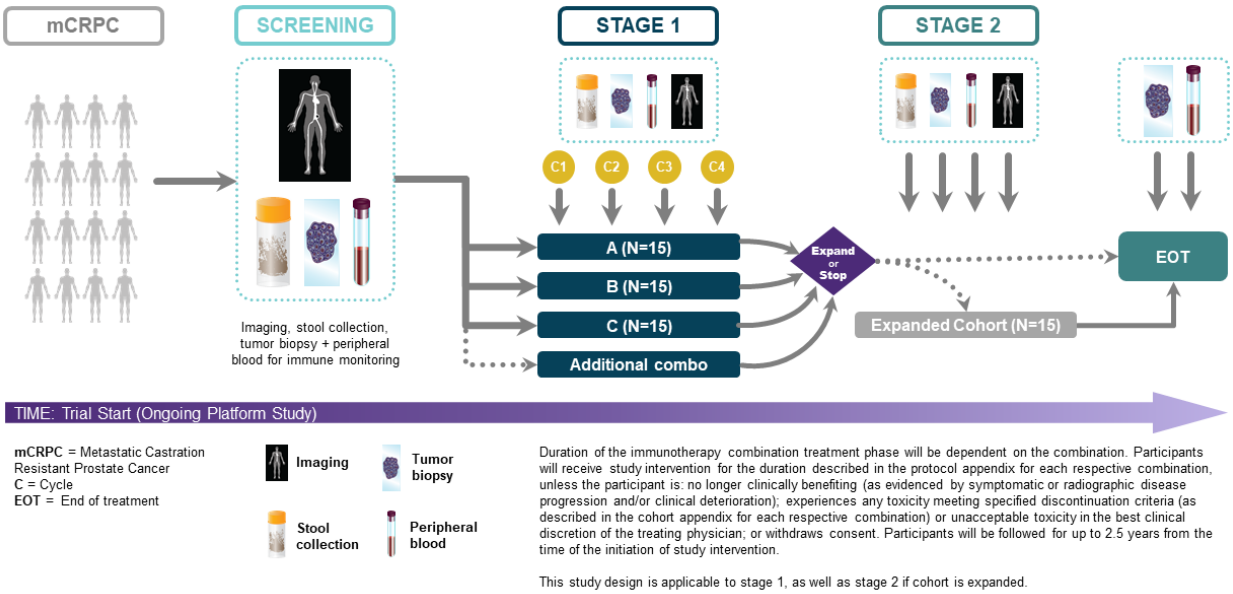
A participant will be considered lost to follow-up if he repeatedly fails to return for scheduled visits and is unable to be contacted by the study site (see Section 7.3).

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 (see Section 9.5.1).

1.2 SCHEMA

The study schema is depicted in Figure 1.

Figure 1: Study Schema



1.3 SCHEDULE OF ACTIVITIES

The Schedule of Activities (SOA) shown in Table 1 provides a general overview of the types and timing of the tests and procedures that will be performed in this study. The combination-specific tests and procedures, as well as the timing, will be described in the cohort appendix for each respective combination and will supersede the general overview provided here.

Table 1: Schedule of Activities

Tests & Procedures	Screening/ Enrollment[a]	On-Treatment: Immunotherapy Combination Treatment					End of Treatment[b]	Follow up	
		Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5 Onward			
Day		To be determined based on immunotherapy combination Refer to the cohort appendix for each respective combination for details on combination-specific timing					14 - 28 days after last dose	110 days after last dose	Q3M[c]
Window (days)	-28		± 3	± 3	± 3	± 3	± 7	± 10	± 14
Informed consent[d]	X								
Review of I/E criteria	X								
Medical and cancer history	X								
Physical examination	X	X	X	X	X	X	X		
ECOG performance status	X	X	X	X	X	X	X	X	
Vital signs (see Section 8.2.3)	X	X	X	X	X	X	X		
Body weight[e]	X			X		X (every 3 cycles)	X		
Hematology (see Table 4)	X	X[f]	X[f]	X[f]	X[f]	X[f]	X	X	
Clinical chemistry (see Table 4)	X	X[f]	X[f]	X[f]	X[f]	X[f]	X	X	
Urinalysis	X						X		
Prostate-specific antigen	X	X	X	X	X	X	X	X	
Testosterone level	X								
12-lead ECG[g]	X		X		X				
Circulating tumor cells[h]		X[f]	X[f]	X[f]	X[f]	X[f]	X		
cfDNA (blood)[i]	X		X[f]		X[f]		X		
Circulating soluble analytes/PK/ADA[j]	X	X[f]	X[f]	X[f]	X[f,]		X		
Blood immune biomarkers[j]	X	X[f]	X[f]	X[f]	X[f]		X		
Archival tumor tissue	X								

Tests & Procedures	Screening/ Enrollment[a]	On-Treatment: Immunotherapy Combination Treatment					End of Treatment[b]	Follow up	
		Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5 Onward			
Day		To be determined based on immunotherapy combination Refer to the cohort appendix for each respective combination for details on combination-specific timing					14 - 28 days after last dose	110 days after last dose	Q3M[c]
Window (days)	-28		± 3	± 3	± 3	± 3	± 7	± 10	± 14
Tumor biopsy[k]	X		X				X (at PD [optional])[k]		
Stool collection[l]	X		X						
Concomitant medications	X	X	X	X	X	X	X	X	
Adverse events	All AEs/AESIs/SAEs will be collected for at least 100 days after the last dose of study intervention[m]								
Immunotherapy combination administration[n]		Refer to the cohort appendix for each respective combination for details on study intervention administration							
Radiographic disease assessment	X	Per PCWG3 guidelines: Every 8 to 9 weeks (± 1 week) for first 24 weeks, and every 12 weeks (± 1 week) thereafter until radiographic PD or start of subsequent therapy. Refer to the cohort appendix for each respective combination for cohort-specific details							
Review of alternate anticancer therapy[o]								X	X
Follow-up for overall survival								X	X

ADA = anti-drug antibodies; AE(s) = adverse event(s); AESI(s) = adverse event(s) of special interest; cfDNA = cell-free deoxyribonucleic acid; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; I/E = inclusion/exclusion; PCWG3 = Prostate Cancer Clinical Trials Working Group 3; PD = progressive disease; PD-1 = programmed cell death 1; PK = pharmacokinetics; Q3M = every 3 months; SAE(s) = serious adverse event(s)

[a] Tests/procedures performed as standard of care prior to obtaining informed consent and within 28 days prior to the first day of study intervention administration do not have to be repeated at screening.

[b] The End of Treatment Visit will be completed following the last dose of study intervention, either at completion of the on-treatment phase or at early discontinuation.

[c] For up to 2.5 years from the initiation of study intervention, participants in the follow up phase will be contacted by the site to collect alternate anticancer therapy information and determine survival status.

[d] Informed consent must be obtained prior to any study-specific procedures and may be obtained prior to the 28-day screening window.

[e] Body weight may be required more frequently for study interventions using weight-based dosing. Combination-specific frequency will be provided in the cohort appendix for each respective combination.

[f] Blood samples should be collected prior to administration of any study intervention.

[g] 12-Lead ECG will be collected at screening, Cycle 2 and Cycle 4.

[h] Circulating tumor cells will be collected at baseline (ie, Day 1 of Cycle 1 prior to study intervention administration), Day 1 of each cycle (prior to study intervention administration), and EOT.

[i] cfDNA (blood) will be collected at baseline (ie, screening visit prior to study intervention administration), Day 1 of Cycle 2 and Cycle 4, and EOT.

[j] Circulating soluble analytes, PK and ADA blood sample, and/or blood immune biomarkers will be collected at baseline (ie, screening and/or Day 1 of Cycle 1 prior to study intervention administration), prior to study intervention administration on Day 1 of Cycles 2-4, and EOT.

[k] Participants will undergo 2-3 tumor biopsies: prior to beginning study intervention (ie, baseline biopsy, mandatory for all participants, including those with bone only disease if medically feasible), and during treatment (ie, on-treatment biopsy during Cycle 2, if medically feasible). On-treatment biopsy should occur as early as possible after the second dose (Day 2 – Day 10 of Cycle 2); however, any on treatment biopsy after Day 1 of Cycle 2 will be accepted. An optional biopsy may be obtained at the time of disease progression, including from participants who respond and subsequently progress. Every attempt should be made for the on-treatment biopsies to be taken from the same lesion as the pre-treatment biopsy when feasible.

[l] Stool will be collected at screening and during Cycle 2, if possible. Otherwise, any on-treatment stool sample will be acceptable. The stool sample may be collected at the clinic or at the participant's home.

[m] All SAEs will be collected from the time the participant signs informed consent. Prior to initiation of study intervention, only SAEs that are related to a protocol-mandated intervention, including those that occur prior to the assignment of study procedures should be reported. All AEs, including AESIs (as applicable and as defined in the cohort appendix for each respective combination), will be collected from the start of study intervention. All AEs/AESIs/SAEs will be collected for at least 100 days after the last dose of study intervention. Refer to Section 8.3 for details regarding safety reporting for this study.

[n] The duration of the immunotherapy combination 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 (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; reaches the maximum duration of study intervention; or withdraws consent.

[o] Collection of information related to any post-study intervention alternate anticancer therapy.

2 INTRODUCTION

Immunotherapy is an attractive strategy for patients with advanced prostate cancer because it has the potential to lead to durable responses and is generally better tolerated. However, the only United States (US) Food and Drug Administration (FDA) approved immunotherapy for prostate cancer to date is sipuleucel-T, an autologous cellular vaccine designed to stimulate an immune response targeting prostatic acid phosphatase (PAP) (Kantoff et al., 2010). The only phase 3 randomized controlled trial of immune checkpoint blockade, with ipilimumab in metastatic castration-resistant prostate cancer (mCRPC) patients after docetaxel, failed to meet its primary endpoint of overall survival (OS; Kwon et al., 2014). Early phase studies of programmed cell death 1 (PD-1) blockade in advanced malignancies have not demonstrated clinical activity in advanced prostate cancer (Topalian et al., 2012). More recently, anti-PD-1 therapy has been shown to have limited activity as a single agent in patients with mCRPC who have programmed cell death ligand 1 (PD-L1) expression and tumor-infiltrating leukocytes, including one patient with microsatellite instability (MSI) and mismatch repair (MMR) deficiency (Graff et al., 2016). Thus, there is a critical need to develop new approaches to make immunotherapy available to patients with mCRPC. Using an approach similar to the multi-arm, multi-stage platform trial (STAMPEDE), which has provided an innovative trial design for testing new treatment approaches against the standard of care for prostate cancer, including mCRPC (Sydes et al, 2018; Parmar et al., 2017), a platform study of immunotherapy combinations is proposed. A recently-opened, ongoing study at the National Cancer Institute is investigating a similar platform design for immunotherapy combinations to treat mCRPC (QuEST1; Redman et al., 2018). With the development of new immuno-oncology therapies demonstrating enhanced effects within the immune system, opportunities for combination clinical trials in the area of antitumor immune response in mCRPC have increased. Given the lack of clinical benefit of immunotherapy in mCRPC and the multiple hypotheses around the immune evasion and resistance mechanisms, an adaptive platform clinical study is well suited to advance the understanding to inform treatment of this underserved patient population.

2.1 STUDY RATIONALE

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

2.2 BACKGROUND

Prostate cancer remains the most commonly diagnosed malignancy, accounting for 19% of newly-diagnosed cancer in men in the US. Despite recent decreases, it is estimated that

approximately 164,690 new cases will be diagnosed in 2018, and 29,430 men are estimated to die of prostate cancer in 2018. Prostate cancer is the second leading cause of cancer death among men in the US (Siegel et al., 2018). The 5-year survival for early stage (stage I, II, III) prostate cancer is almost 100%, however, almost one-third of the early stage patients will recur with metastatic disease (stage IV). For patients with metastatic disease, 5-year survival rates decrease to about 30% (Siegel et al., 2018; McNeel et al., 2016). Androgen deprivation therapy (ADT) is the mainstay of initial therapy for metastatic disease. Although prostate cancer usually initially responds to ADT, resistance frequently develops and progresses to mCRPC. Despite the approval of several mCPRC therapies in the past few years, including androgen signaling inhibitors, chemotherapy, radiopharmaceutical, and cancer vaccine, currently available treatments remain inadequate to manage mCPRC.

Immunotherapy has changed the landscape of cancer treatments for a number of malignancies, resulting in marked clinical benefit in patients with cancers, including metastatic melanoma, non-small cell lung cancer and renal cell carcinoma. In 2010, the first cancer vaccine, sipuleucel-T (Provenge®) was approved for prostate cancer; however, subsequent efforts to demonstrate effectiveness of immunotherapies in prostate cancer have been disappointing. While the immune responsiveness of prostate tumors has been contested for nearly 30 years, more recent evidence suggests prostate cancer is an immunologically recognized disease (Drake, 2010). Intratumoral natural killer (NK) cells and macrophages have been observed, and both CD4+ and CD8+ T cells that recognize prostate-cancer-specific antigens have been found in tumor sites, as well as in peripheral immune cells (Lee and Gujar, 2018). Furthermore, the detection of prostate-specific autoantibodies in patients with prostate cancer has strengthened the argument for the immunogenicity of prostate cancer (Di Lorenzo et al., 2011). Thus, there is preclinical and clinical evidence that prostate could be susceptible to immune-based therapy approaches.

Notwithstanding, there have been several notable immunotherapy failures in prostate cancer, including in clinical trials with novel vaccine-based approaches and immune checkpoint inhibitors, including anti-PD-1, anti-PD-L1, and anti- cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) (Kwon et al., 2014; Beer et al., 2017; Brahmer et al., 2010; Topalian et al., 2012). Thus, prostate cancer has been characterized as an immunologically unresponsive, or "cold," tumor with PD-L1 expression in a minority of tumors (Martin et al., 2015). As a "cold" tumor, the immunosuppressive microenvironment may contribute to the low responses to immunotherapy in prostate cancer (Patel and Fong, 2018), including low mutational burden (Alexandrov et al., 2013), low abundance of intratumoral T cells (Flammiger et al. 2012), and low cytolytic activity of NK cells (Pasero et al., 2016), as well as a high accumulation of regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) in the tumor (Miller et al., 2006; Lopez-Bujanda and Drake, 2017). Comprehensive correlative studies of prostate cancer in a window of opportunity study also demonstrated that elevated expression of PD-L1

and VISTA (V-domain Ig suppressor of T cell activation) on macrophages may contribute to the resistance to checkpoint inhibitors (Gao et al., 2017). Therefore, treatment-based approaches that address these mechanisms of immune evasion through novel combination therapies using novel vaccine strategies, alleviating immunosuppression in the tumor microenvironment and new immune agents, or identifying immune-responsive patient subsets may enable effective immunotherapy treatment approaches for mCRPC with high unmet medical need.

2.3 BENEFIT/RISK ASSESSMENT

The benefit/risk assessment is dependent on the combination administered and will be described in the cohort appendix for each respective combination (eg, Appendix Cohort A, Appendix Cohort B, etc.).

3 OBJECTIVES AND ENDPOINTS

The study objectives and endpoints are listed in Table 2.

Table 2: 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 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: ○ 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 and at least 2 post-baseline PSA assessments will not be evaluated for this criterion. ○ 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.
Exploratory	
• To evaluate tumor and immune biomarkers and their association with treatment outcome (antitumor activity and/or safety). • To evaluate the PK of the components of the immunotherapy combination. • To evaluate the immunogenicity (ADA) 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 ≥ 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. • Sparse PK analysis. • Presence of ADA against biologic components of each immunotherapy combination.

ADA = anti-drug antibodies; AE(s) = adverse event(s); CR = complete response; CTC = circulating tumor cells; CTC0 = a measure of zero CTC; 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; PK = pharmacokinetics; PR = partial response; PSA = prostate-specific antigen; RECIST = Response Evaluation Criteria in Solid Tumors; rPFS = radiographic progression-free survival; SD = stable disease

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is an open-label, non-randomized, exploratory platform study 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 the 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 study will be conducted in participants with histologically-confirmed mCRPC that is measurable or non-measurable by Prostate Cancer Clinical Trials Working Group 3 (PCWG3)-modified Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Participants with brain metastases are excluded unless treated and stable by imaging for at least 4 weeks prior to the first dose of study intervention. Participants must have received prior secondary androgen receptor signaling inhibitor therapy (eg, abiraterone, enzalutamide, apalutamide) and may have received prior chemotherapy for mCRPC. Participants must consent to baseline and on-treatment biopsies, if medically feasible. A minimum of 7 participants in each cohort must have a non-bone metastatic lesion that can be biopsied. Participants must have adequate organ and hematologic function and acceptable performance status.

After consenting to participate in this clinical trial, participants will be screened for enrollment. If they meet all inclusion criteria and do not meet exclusion criteria, they will be referred for a pre-treatment biopsy of a metastatic lesion. Participants must also provide consent for archival tissue from a prior biopsy or surgery for prostate cancer. Each participant will be assigned per the Investigator's discretion to receive one of the enrolling combination study interventions.

Participants will be monitored for safety and efficacy. An on-treatment biopsy is required when medically feasible, ideally after the second dose of the immunotherapy combination. An optional biopsy may be obtained at the time of disease progression, including from participants who respond and subsequently progress. The on-treatment biopsies should be taken from the same lesion as the pre-treatment biopsy when feasible.

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. Enrollment of participants in each cohort may occur simultaneously. 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 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 (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; reaches the maximum duration of study intervention; or withdraws consent. Participants will be followed for a up to 2.5 years from the time of the initiation 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.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The scientific rationale for this study is provided in Section 2. The scientific rationale for the individual cohorts will be provided in the cohort appendix for each respective combination.

4.3 JUSTIFICATION FOR DOSE

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.

4.4 TREATMENT BEYOND DISEASE PROGRESSION

Accumulating evidence indicates that a minority of patients treated with immunotherapy may derive clinical benefit from continued treatment despite initial evidence of disease progression (Wolchok et al., 2009). The PCWG3 introduced the concept of treatment beyond progression (where clinical benefit by one or more disease manifestations is being observed) as clinical measure for outcome in prostate cancer (Scher et al., 2016). The PCWG3 recommendation included a reporting metric of no longer clinically benefiting (NLCB), defined as the date and specific reason(s) therapy was ultimately discontinued, to allow individualized provider-patient decisions to discontinue or continue treatment.

Therefore, participants receiving immunotherapy combinations in this study will be permitted to continue study intervention beyond initial Investigator-assessed disease progression (according to PCWG3-modified RECIST 1.1) provided all of the following criteria are met:

- Absence of symptoms and signs indicating rapid disease progression, including decline in performance status, and confirmation of disease status required

- Absence of progressive tumor at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention
- Participant is adequately consented regarding the potential risks of continuation of ineffective therapy/failure to initiate effective alternative therapy, if any
- Written agreement from the Medical Monitor.

The assessment of clinical benefit should consider whether the participant is clinically deteriorating and unlikely to receive further benefit from continued treatment.

All decisions to continue treatment beyond initial progression must be discussed with the Medical Monitor and written agreement from the Medical Monitor should be documented in the study records.

Participants should discontinue study intervention upon evidence of further progression, defined as an additional ≥ 10% increase in tumor burden from the time of initial progression (including all target lesions and new measurable lesions, or unequivocal progression of non-target lesions).

New lesions are considered measurable at the time of initial progression if the diameters are ≥ 10 mm (except for pathological lymph nodes, which must have a short axis of ≥ 15 mm). Any new lesion considered non-measurable at the time of initial progression may become measurable and therefore included in the tumor burden measurement if the diameter increases to ≥ 10 mm (except for pathological lymph nodes, which must have an increase in short axis to ≥ 15 mm).

4.5 END OF STUDY DEFINITION

The end of this study is defined as the date when the last visit of the last participant occurs or the date at which the last data point required for statistical analysis or safety follow-up is received from the last participant, whichever occurs later.

The total length of each study cohort, from screening of the first participant to the end of the cohort, will depend on the study intervention administered and will be described in the cohort appendix for each respective combination.

5 STUDY POPULATION

This study will enroll participants with mCRPC. Eligibility criteria are provided in the cohort appendix for each respective combination (eg, Appendix Cohort A, Appendix Cohort B, etc.).

5.1 INCLUSION CRITERIA

Inclusion criteria are provided in the cohort appendix for each respective combination.

5.2 EXCLUSION CRITERIA

Exclusion criteria are provided in the cohort appendix for each respective combination.

5.3 LIFESTYLE CONSIDERATIONS

Lifestyle considerations or restrictions, if required, will be provided in the cohort appendix for each respective combination (eg, Appendix Cohort A, Appendix Cohort B, etc.).

5.4 SCREEN FAILURES

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s) or placebo intended to be administered to a study participant according to the study protocol.

6.1 STUDY INTERVENTION(S) ADMINISTERED

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.

Administration of study intervention will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

The Investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention and only authorized site staff may dispense and/or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance

with the labeled storage conditions with access limited to the Investigator and authorized site staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manuals.

6.3 RANDOMIZATION AND BLINDING

6.3.1 Intervention Assignment

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.

6.3.2 Blinding

This is an open-label trial; therefore, the Sponsor, Investigator, and participant will know the study intervention administered.

6.4 STUDY INTERVENTION COMPLIANCE

Study intervention compliance will be described in the cohort appendix for each respective combination as compliance measures will be dependent on how the immunotherapy combination is administered.

6.5 CONCOMITANT THERAPY

Any medication or vaccine (including over-the-counter [OTC] or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates (or indicated as ongoing, as applicable)
- Dosage information including dose, route of administration, and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1 Permitted Therapy

Concomitant medications or treatments (eg, acetaminophen/paracetamol, diphenhydramine) may be prescribed if considered necessary for adequate prophylactic or supportive care except for those medications identified as "excluded" in Section 6.5.2 or in the cohort appendix for each respective combination (for combination-specific excluded medications).

All concomitant medication will be recorded on the electronic case report form (eCRF), including all prescription, OTC and intravenous (IV) medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date should also be included on the eCRF.

All concomitant medications received within 28 days prior to the first dose of study intervention and 100 days after the last dose of study intervention should be recorded. Concomitant medications administered after 100 days after the last dose of study intervention should be recorded for SAEs and adverse events of special interest (AESIs) (as applicable and as defined in the cohort appendix for each respective combination).

6.5.2 Prohibited Therapy

The medications listed below are prohibited during the study. The Sponsor must be notified if a participant receives any of these during the study.

- Any concurrent systemic chemotherapy, immunotherapy, biologic, hormonal treatment or radiotherapy (except palliative radiotherapy) not specified in this protocol or subsequent amendments. Concurrent use of hormones for noncancer-related conditions are permitted.
    - Exception: Androgen deprivation therapy. Participants are required to maintain castrate-level testosterone (< 50 ng/dL) with a gonadotropin-releasing hormone (GnRH) agonist or antagonist ± antiandrogen. Participants without history of bilateral orchiectomy are required to remain on ADT.
- Any concurrent investigational anticancer therapy not specified in this protocol or subsequent amendments.
- Anti-CTLA-4, anti-PD-L1, or anti-PD-1 agents through 100 days after the last dose of study intervention, except for agents that are not part of the immunotherapy combinations.
- Immunosuppressive medications at chronic systemic doses > 10 mg/day prednisone (or equivalent) within 28 days before the first dose (note: hormone replacement therapy (HRT), such as thyroxine, insulin, or physiologic corticosteroid replacement therapy ≤ 10 mg of prednisone/day for adrenal or pituitary insufficiency, etc. is not considered a form of systemic treatment). A temporary course of steroids (ie, contrast allergy, chronic

obstructive pulmonary disease) may be permitted, depending on the duration and dose, after discussion and agreement with the Medical Monitor.

- Live attenuated vaccines within 30 days prior to the first dose of study intervention and through 180 days after the last dose of study intervention. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, bacille Calmette-Guerin (BCG), and typhoid vaccine.
- Any botanical preparation (eg herbal supplements or traditional Chinese medicines) intended to treat the disease under study. Use of marijuana and its derivatives for treatment of symptoms related to cancer or to cancer treatment are permitted.

6.6 DOSE MODIFICATIONS (ESCALATION/TITRATION/ OTHER)

Specific anticipated or potential toxicities associated with the administration of the study intervention, as well as the measures taken intended to avoid or minimize such toxicity in this trial, are described in the cohort appendix for each respective combination.

Refer to the Investigator's Brochure (IB) for the individual components of each combination for complete summaries of safety information.

6.7 INTERVENTION AFTER THE END OF THE STUDY

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.

7 DISCONTINUATIONS OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Participants must discontinue study intervention if they experience any of the following:

- Intolerable toxicity related to study intervention, including the development of an adverse event (AE) determined by the Investigator to be unacceptable even with the participant's potential response to intervention due to the severity of the event
- Any medical condition that may jeopardize participant safety if he continues to receive the study intervention
- Use of another anticancer therapy (see Section 6.5.2 and as described in the cohort appendix for each respective combination, as applicable)
- Symptomatic deterioration attributed to disease progression

- Progression of disease: Either unequivocal symptomatic progression necessitating a change in therapy in the opinion of the treating physician or confirmed radiographic progression as defined by cross-sectional imaging per PCWG3-modified RECIST 1.1 (see Appendix 3) in the absence of clinical benefit (refer to Section 4.4).

Participants have the right to voluntarily withdraw from study intervention at any time for any reason. In addition, the Investigator has the right to withdraw a participant from study intervention at any time. Reasons for withdrawal from the study intervention may include, but are not limited to, the following:

- Investigator or Sponsor determines it is in the best interest of the participant
- Participant noncompliance

The primary reason for study intervention discontinuation should be documented on the appropriate eCRF page.

The visit at which disease assessment shows progressive disease (PD) may be used as the treatment discontinuation visit if it occurs within 28 (± 7) days after the last dose of study intervention. Participants who discontinue study intervention for any reason other than PD or loss of clinical benefit should have an end of treatment discontinuation assessment as outlined in the SOA (see Section 1.3). All participants should continue follow-up as outlined in the SOA.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM STUDY

The total length of study participation, from participant screening to the end of study, is expected to be approximately 31 months.

When study intervention is discontinued, participants should have an end of treatment discontinuation assessment followed up by an assessment 14-28 days after the last dose of study intervention as outlined in the SOA (see Section 1.3). Information on survival follow-up and new anticancer therapy will be collected every 3 months for up to 2.5 years from the initiation of study intervention until any of the following occurs:

- Death
- Loss to follow-up
- Study termination by the Sponsor
- Participant requests to be withdrawn from follow-up

A participant may withdraw consent at any time and discontinue study intervention and further participation in the study. This request must be documented in the source documents and signed by the Investigator. The Sponsor may retain and continue to use any data collected before such withdrawal of consent. Participants who withdraw consent will not be followed for any reason after consent has been withdrawn. However, the study staff may use a public information source (eg, county records) to obtain information about survival status only.

Other reasons for discontinuation of study intervention and/or participation in a follow-up phase of the study may include death, AEs, physician decision, protocol deviation, eligibility not met, progressive disease. A participant is considered to have completed all phases of the study as defined in the cohort appendix for each respective combination, including the lead-in phase, as applicable, the treatment phase, and the safety and survival follow-up after last dose of study intervention.

The primary reason for withdrawal from study should be documented on the appropriate eCRF page.

7.3 LOST TO FOLLOW-UP

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.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he will be considered to have withdrawn from the study.

8 STUDY ASSESSMENTS AND PROCEDURES

Please see Section 1.3 for the schedule of activities and procedures to be performed during the study. All activities should be performed and documented for each participant in the order of the SOA. Participants will be closely monitored for safety and tolerability throughout the study.

Participants should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable as deemed by the Principal Investigator (PI).

If the timing of a protocol-mandated study visit coincides with a holiday, weekend, or other administrative disruption that precludes the visit, the visit should be scheduled on the nearest feasible date. The time between doses must not be less than described in the cohort appendix for each respective combination.

Collection of any non-safety-related data or participant samples may be terminated by the Sponsor at any time if further collection of such data or samples is also not related to the study's primary or secondary objectives. The decision to discontinue any data collection will be communicated to the sites and Institutional Review Board/Independent Ethics Committee (IRB/IEC) by means of a memorandum and will not require a protocol amendment.

8.1 EFFICACY ASSESSMENTS

Participants will undergo tumor assessments as designated in the SOA (see Section 1.3) regardless of dose delays, until loss of clinical benefit as determined by the Investigator (unless the participant withdraws consent, or the Sponsor terminates the study). All participants who discontinue study intervention for reasons other than disease progression (eg, AEs) will continue tumor assessments for up to 2.5 years from initiation of study intervention or until study completion, death, disease progression, loss to follow-up, withdrawal of consent, or study termination, whichever occurs first. At the Investigator's discretion, tumor assessments may be repeated at any time if PD is suspected.

Measurable and evaluable lesions should be assessed and documented at screening. Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to the first dose of study intervention do not have to be repeated at screening.

Screening assessments must include computerized tomography (CT) scans (with IV contrast unless contraindicated and oral contrast as appropriate per institutional standards) of the chest, abdomen, and pelvis. A spiral CT scan of the chest may be obtained but is not a requirement. If a CT scan with contrast is contraindicated (ie, in participants with contrast allergy or impaired renal clearance), a non-contrast CT scan of the chest maybe performed and magnetic resonance imaging (MRI) scans of the abdomen and pelvis should be performed. If the participant has a known history of brain metastases or is symptomatic in the opinion of the Investigator, scans of the head should be obtained.

If a CT scan for a tumor assessment is performed in a positron emission tomography (PET)/CT scanner, the CT acquisition must be consistent with the standards for a full contrast diagnostic CT scan.

Bone scans (technetium-99m [TC-99m]) should be performed at screening if clinically indicated. If bone metastases are present at screening and cannot be seen on CT or MRI scans, or if clinically indicated, TC-99m bone scans should be repeated when complete response (CR) is identified in target disease or when progression in bone is suspected.

CT scans of the neck or extremities should also be performed if clinically indicated and repeated throughout the study if there is evidence of disease at screening.

All measurable and evaluable lesions should be reassessed at each subsequent tumor evaluation. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (eg, same contrast protocol for CT scans).

Response will be assessed by the Investigator using PCWG3-modified RECIST 1.1 (see Appendix 3). Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits. Results must be reviewed by the Investigator before dosing at the next cycle.

Radiographic confirmation of disease progression is required by repeat scans 4 – 6 weeks following any scan suggesting disease progression. Participants will remain on study and continue to receive study intervention during this time.

8.1.1 Laboratory Assessments of Clinical Activity

Samples for the following laboratory assessments of clinical activity and hormone levels will be sent to the study site local laboratory for analysis:

Table 3: Laboratory Tests Sent to the Study Site Local Laboratory for Analysis of Disease-related Endpoints

Profile	Laboratory Test
Clinical activity	PSA
Hormone levels	testosterone

PSA = prostate-specific antigen

8.2 SAFETY ASSESSMENTS

Safety assessments will consist of monitoring and recording AEs, including SAEs and AESIs, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study. Planned timing for all safety assessments is provided in the SOA (Section 1.3).

Certain types of events require immediate reporting to the Sponsor, as described in Section 8.3.1.1.

8.2.1 Medical History and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including stage, date of diagnoses, and prior cancer therapies and procedures), reproductive status, smoking history, use of alcohol, and drugs of abuse, will be recorded at baseline. In addition, all medications (eg, prescription drugs, OTC drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the participant within 28 days prior to the first dose of study intervention will be recorded. Demographic data may include age, sex, and race/ethnicity.

8.2.2 Physical Examinations

A complete physical examination should be performed at screening and should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Any abnormality identified at baseline should be recorded on the Medical History eCRF page.

Eastern Cooperative Oncology Group (ECOG) performance status (see Appendix 2) should be assessed per the SOA in Section 1.3.

At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be recorded in participant notes. New or worsened clinically significant abnormalities should be recorded as AEs on the Adverse Event eCRF page.

8.2.3 Vital Signs

Vital signs should include measurements of respiratory rate, pulse rate, systolic and diastolic blood pressure, pulse oximetry (required only at screening), and temperature as outlined in the SOA (Section 1.3). Vital signs collected at the screening visit should be recorded on the eCRF. For each visit thereafter, only vital signs obtained prior to the study intervention administration as outlined in the SOA or during an AE (eg, temperature or event of fever) should be recorded on the eCRF. All vital signs collected per protocol should be documented in the participant's medical record.

Vital signs should be measured within 15 minutes prior to and after the administration of study intervention. Vital signs may be measured, if medically indicated, at other time points.

8.2.4 Electrocardiograms

A single electrocardiogram (ECG) recording will be obtained at baseline, as outlined in the SOA (Section 1.3) and may be obtained at unscheduled time points as indicated.

All ECG recordings must be performed using an institutionally-approved ECG. Lead placement should be as consistent as possible. ECG recordings should be performed after the participant has been resting in a supine position for at least 10 minutes.

For safety monitoring purposes, the Investigator must review, sign, and date all ECG tracings. ECG tracings will be kept as part of the participant's medical record. The Investigator's assessment (ie, normal, abnormal [not clinically significant], or abnormal [clinically significant]) should be recorded on the appropriate eCRF page. Any morphologic waveform changes or other ECG abnormalities should be documented on the eCRF page.

8.2.5 Clinical Safety Laboratory Assessments

Clinical laboratory tests will be performed at the local institution as described in the SOA (Section 1.3).

The Investigator must review the laboratory report, document this review, and designate results as being not clinically significant of clinically significant. Clinically significant abnormal findings are those for which an action was taken (ie, providing fluid, transfusion, medication, and/or holding, delaying, or discontinuing study intervention) or those that are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition. Clinically significant changes occurring during the study should be documented on the appropriate eCRF. The laboratory reports much be filed with the source documents.

In the event of a Grade 3 or Grade 4 laboratory toxicity, the test for the abnormal laboratory value should be repeated until the event is resolved to ≤ Grade 1 or baseline.

8.2.5.1 Local Laboratory Assessments

Samples for the laboratory tests in Table 4 will be sent to the study site's local laboratory for analysis:

Table 4: Laboratory Tests Sent to the Study Site's Local Laboratory for Analysis of Safety

Profile	Laboratory Test
Hematology	RBC count hemoglobin hematocrit WBC count with automated differential (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells) platelet count manual differential, if clinically indicated
Clinical Chemistry (Serum or Plasma)	sodium potassium chloride bicarbonate glucose BUN or urea creatinine total protein albumin calcium total bilirubin alkaline phosphatase ALT AST LDH TSH (T3 and FT4 should be checked if TSH is outside the normal range) coagulation assessments (PT, PTT, INR)[a]
Urinalysis	

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; INR = international normalized ratio; LDH = lactate dehydrogenase; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell; TSH = thyroid stimulating hormone; WBC = white blood cell

[a] Coagulation assessment not required during treatment phase unless indicated

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The definitions of an AE or SAE can be found in Appendix 5.

Investigators will seek information on AEs at each participant contact until at least 100 days after the last dose of study intervention. AEs reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative) or noted by study personnel, will be recorded in the participant's medical record and on the Adverse Event eCRF page. If the AE is determined to meet seriousness criteria, the event will be reported as an SAE on the study-specific SAE Report Form (SAERF) within 24 hours of awareness. Seriousness criteria is defined in Appendix 5.

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE, AESI (as applicable), or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention (see Appendix 5).

8.3.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information

All SAEs will be collected from the time the participant signs informed consent until at least 100 days after the last dose of study intervention. Prior to initiation of study intervention, only SAEs that are-related to a protocol-mandated intervention, including those that occur prior to the assignment of study procedures (eg, screening invasive procedures, such as biopsies) should be reported. After obtaining informed consent, but prior to initiation of study intervention, other medical occurrences will be recorded as medical history.

All AEs, including AESIs (as applicable), will be collected from the start of study intervention until at least 100 days after the last dose of study intervention.

If the Investigator learns of any SAE, including a death, at any time after the end of the AE reporting period, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor or its designee. The Investigator should report these events directly to the Sponsor or its designee, either by faxing or emailing the SAERF.

The method of recording and reporting AEs, AESIs (as applicable), and SAEs are provided in Appendix 5. The procedure for submitting SAE reports is provided in Section 8.3.8.2.

The method of reporting all deaths is provided in Appendix 5.

8.3.1.1 Events Requiring Expedited Reporting to the Sponsor

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The Investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the Investigator becomes aware of the event. The following is a list of events that the Investigator must report to the Sponsor within 24 hours of becoming aware of the event, regardless of relationship to study intervention:

- All SAEs (defined in Appendix 5)
- Protocol-specified AEs, including AESI as applicable, as defined in the cohort appendix for each respective combination

- Pregnancy (female partners of participants; see Section 8.3.5 for details on reporting requirements)
- Occurrence of overdose (see Section 8.4 for details on reporting requirements)

All reported safety data will be evaluated on a regular basis as described in Section 9.5.1.

8.3.2 Follow-up Event Reporting

The Investigator must report new significant follow-up information for the events requiring expedited reported (see Section 8.3.1.1) to the Sponsor immediately (ie, within 24 hours of awareness). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event
- Hospital notes, diagnostic results, and/or discharge summary
- Death certificate/Autopsy report

After the initial AE/AESI/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and AESIs (as applicable and as defined in the cohort appendix for each respective combination), will be followed through the follow-up phase of the study. Events will be followed until event resolution or death, the participant is lost to follow-up (as defined in Section 7.3), or the participant withdraws consent. Further information on follow-up procedures is provided in Appendix 5.

For SAEs, and AESIs, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (eg, from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case. If follow up information is obtained during a monitoring visit, follow up documentation must be reported to the Parker Institute for Cancer Immunotherapy Pharmacovigilance Group.

8.3.3 Method of Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting AE information at all participant evaluation time points. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences. Examples

of non-directive questions include: “How have you felt since your last clinic visit?”, “Have you had any new or changed health problems since you were last here?”

8.3.4 Regulatory Reporting Requirements for SAEs

Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met (see Section 8.3.1.1). Investigators must also comply with local requirements for reporting SAEs to the IRB/IEC or other local health authorities.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators. The Parker Institute for Cancer Immunotherapy Pharmacovigilance Group will report SAEs to regulatory authorities, the overall PI, partner companies, and the IRB, as appropriate. The process for such reporting, including contact information and specific instructions for reporting to each of these organizations, is described in the Safety Monitoring Plan (a separate document).

Expectedness will be assessed using the IB(s) as reference documents. Reporting requirements will also be based on the Investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives specific safety-related information (eg, SUSAR notification; summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5 Pregnancy

Details of all pregnancies in female partners of participants will be collected after the start of study intervention and until at least 7 terminal half-lives after the last dose. Female partners of childbearing potential will be instructed to immediately inform the Investigator if they become pregnant during the study or within 7-half-lives after the last dose of each component of study intervention. If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of becoming aware of the pregnancy and should follow the procedures outlined in Appendix 6. Abnormal pregnancy outcomes that meet serious criteria (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

A clinical trial-specific Pregnancy Reporting Form should be completed and submitted immediately to the Parker Institute for Cancer Immunotherapy Pharmacovigilance Group, either by faxing or by scanning and emailing the form using the fax number or email address provided to Investigators (see Section 8.3.8.2). Pregnancy should not be recorded on the Adverse Event eCRF page. The Investigator should counsel the participant's partner, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the participant's partner should continue until conclusion of the pregnancy. Any SAEs associated with the pregnancy (eg, an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the SAERF. In addition, the Investigator will submit a clinical trial-specific Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

8.3.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

Progression of the cancer under study, as judged by the Investigator, is not considered a reportable event. If, upon further review by the Investigator, the event is determined as not being associated with underlying progression of disease, it must be reported as an SAE within 24 hours to the Parker Institute for Cancer Immunotherapy Pharmacovigilance Group as described in Section 8.3.8.2.

8.3.7 Adverse Events of Special Interest

Selected non-serious and serious AEs known as AESIs are those of scientific and medical concern specific to the study intervention or program for which ongoing monitoring and rapid communication by the Investigator to the Sponsor is appropriate. These events will be identified in the cohort appendix for each respective combination.

8.3.8 Sponsor Contact Information

8.3.8.1 Emergency Medical Contacts

Parker Institute for Cancer Immunotherapy Medical Monitor:

Medical Monitor: Joyson Karakunnel, MD, MSc, FACP

Parker Institute for Cancer Immunotherapy
1 Letterman Drive, Ste. D3500
San Francisco, CA 94080
jkarakunnel@parkerici.org

Telephone No.: (415) 539-3165 (Office; United States)

8.3.8.2 Safety Reporting Contacts

The following contact information should be used when submitting safety-related paper forms (SAERF and Pregnancy Report Form) as described in Appendix 5 for SAEs and other reportable safety events. These forms should be completed and submitted to the Sponsor immediately (ie, no more than 24 hours after becoming aware of the event), by faxing to the Parker Institute for Cancer Immunotherapy Pharmacovigilance Group at: 415-610-5471 within 24 hours of event awareness. If technical issues arise, please contact Parker Institute for Cancer Immunotherapy Pharmacovigilance Group immediately at 415-930-4414, and the form may be scanned and emailed to safety@parkerici.org.

Parker Institute for Cancer Immunotherapy Pharmacovigilance Group:

- Pharmacovigilance Fax Number: 415-610-5471
- Pharmacovigilance Email: safety@parkerici.org
- Pharmacovigilance Telephone Number: 415-930-4414

8.4 TREATMENT OF OVERDOSE

Overdose is defined as any dose higher than the dose specified to be administered in accordance with the protocol, whether accidental or intentional.

The Investigator must immediately notify the Parker Institute for Cancer Immunotherapy Pharmacovigilance Group of any occurrence of overdose with study intervention.

All overdoses should be reported as an SAE with the safety criteria of "**other important medical event**." Details of signs and symptoms, clinical management, and outcome should be reported, if applicable. Overdoses should also be captured as protocol deviations.

The PI has the obligation to report the deviations to the IRB/IEC.

8.5 PHARMACOKINETICS

Sparse pharmacokinetic (PK) blood sampling may be collected as described in the cohort appendix for each respective combination, as applicable.

8.6 ANTI-DRUG ANTIBODIES

Anti-drug antibodies (ADA) to specific biologic components of study intervention may be evaluated as described in the cohort appendix for each respective combination, as applicable.

8.7 BIOMARKERS

The exploratory biomarker objective of this study is to assess tumor tissue and circulating soluble factors, including, but not limited to, deoxyribonucleic acid (DNA), ribonucleic acid

(RNA), enzymes, growth factors, cytokines, antibodies, and immune and tumor cells in tissue and blood, and their association with treatment outcome. Additionally, microbiome profiles may be evaluated from stool samples. Evaluation of baseline levels and/or post-treatment changes from baseline may be performed to determine association with clinical outcomes, including clinical response or lack of response, as well as study intervention tolerability.

- Collection of samples for biomarker research is part of this study. The following samples for biomarker research are required and will be collected from all participants in this study as specified in the SOA (Table 1) and process in accordance with the laboratory manual:
    - Blood
    - Peripheral blood mononuclear cells (PBMCs)
    - Circulating tumor cells (CTC)
    - DNA
    - RNA
    - Tumor tissue biopsy (archival tumor tissue and fresh biopsies at intervals specified in Section 4.1)
    - Stool
- Samples may be tested for genetic analysis on tumor, stool, and blood samples, including, but not limited to, assays on circulating free DNA, DNA from tumor, stool, blood, and/or immune cells and T cell receptor sequencing may be performed. This research may evaluate whether genetic variations correspond with outcomes of treatment. If genetic variation is found to predict efficacy or AEs, the data might inform optimal use of therapies in cancer patients. Circulating soluble analytes may be assessed that may include but are not limited to immune cytokines, growth factors, antibodies, and/or markers associated with immune characteristics and activation or cancer. Additionally, tumor and blood samples will be collected before and on study intervention for immune and/or tumor cell profiling that may include immune cell phenotyping, enumerations, and/or activation state. Both genome-wide and targeted messenger RNA expression profiling and sequencing in tumor, stool, and/or blood may be performed to define gene signatures that correlate with treatment outcomes. Epigenetic analyses may also be performed as these are important biomarkers for some cancers. Stool samples at baseline and on treatment may be evaluated for microbiome profiling to determine if there is any association with treatment outcome.
- Other samples may be used for research, including future research, to develop methods, assays, prognostics, and/or companion diagnostics related to immuno-oncology treatment, disease process, pathways associated with disease state, and/or mechanisms of action of checkpoint inhibitor treatment.

8.7.1 Genetics

Sample collection, storage, and shipment instructions for planned genetic analysis samples will be provided in the Laboratory Manual. Samples should be collected for planned analysis of associations between genetic variants in germline/tumor DNA and clinical outcomes to study interventions(s). Blood and stool for planned genetic analysis will be collected for DNA as described in the SOA (Section 1.3). If a documented law or regulation prohibits (or local IRB/IEC does not approve) sample collection for these purposes, then such samples should not be collected at the corresponding sites. Additional DNA extracted from planned genetic analysis samples will be stored for future biomedical research only if the participant signs the Future Biomedical Research consent.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

See Appendix 7 for Information regarding genetic research.

8.7.2 Exploratory Biomarkers

Archival tumor tissue and a fresh tumor biopsy are required if medically feasible at screening for exploratory analysis. Additional on-treatment tumor biopsies are required when medically feasible: 1) after 2 treatments with study intervention and 2) an optional biopsy at the time of disease progression, including from participants who respond and subsequently progress. Core needle or incisional tumor biopsy samples are required. Furthermore, every attempt should be made for the on-treatment biopsies to be taken from the same lesion site. Fine needle aspiration is not allowed.

Blood will be collected for exploratory biomarkers. Blood may be used for whole blood, PBMCs, CTC, plasma, and/or serum preparation, and nucleic acid extraction. Additionally, blood samples may be used for profiling of circulating soluble analytes, PK analysis, and assessment of ADA for the biologic study intervention components. These blood samples will be collected as described in the SOA in Section 1.3.

Stool samples will be collected for microbiome analysis, which may include microbiome whole metagenomic sequencing and/or metabolites as outlined in the SOA in Section 1.3.

Tissue, blood, and stool sample collection, storage, and shipment instructions are provided in the Laboratory Manual.

8.7.3 Sample Collection for Long-term Future Biomedical Research

8.7.3.1 Overview of Long-term Future Biomedical Research

Participants in this clinical trial will be asked to consent to provide biological samples for long-term future biomedical research. The objective of collecting/retaining specimens for future biomedical research is to explore and identify biomarkers that inform the scientific understanding of disease and/or their therapeutic treatments. The overarching goal is to use such information to understand disease, safety and potential treatments for future participants. Such research is for biomarker testing and hypothesis testing to address emergent questions not described elsewhere in the protocol (as part of the main trial).

This research may include genetic and genomic analyses (DNA), gene expression profiling (RNA), proteomics, microbiome, metabolomics (serum, plasma, stool) and/or the measurement of other analytes, depending on which specimens are consented for future biomedical research.

The collection and submission of biological samples to be stored for long-term future biomedical research must be detailed in the IRB/IEC-approved informed consent form (ICF). Participants who do not wish to participate in the future biomedical research may still participate in the study.

8.7.3.2 Sample Collection

The following samples will be collected and stored in accordance with applicable law for long-term research purposes, including but not limited to, research on biomarkers related to immunotherapies, such as anti-PD-1, and diseases such as cancer or inflammatory disorders:

- Blood, including but not limited to, PBMCs, CTC, and plasma and/or serum
- DNA
- RNA
- Tumor tissue
- Stool samples

These samples may be sent to one or more laboratories for analysis and/or storage.

For sampling procedures, storage conditions, and shipment instructions, see the Laboratory Manual.

8.7.3.3 Withdrawal from Long-term Sample Storage

Participants have the right to withdraw their consent for the future biomedical research of his specimens at any time for any reason and request that their specimens be destroyed. If the participant wishes to withdraw consent for this testing, the Investigator must inform the Sponsor in writing. Any analyses in progress at the time of request for withdrawal or already performed

prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received. In the event that the medical records for the main trial are no longer available (eg, if the Investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely de-identified, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for specimen withdrawal cannot be processed.

8.7.3.4 Protection of Data Privacy and Data Generation

Participant specimens and associated data will be labeled with a unique participant identification number. Participant medical information associated with the long-term storage of specimens is confidential and may be disclosed to third parties only as permitted by the ICF signed by the participant or as permitted or required by law.

Given the complexity and research nature of the exploratory analyses, data derived from long-term stored specimens will generally not be provided to study Investigators or participants unless required by law.

Data generated from specimens that are stored long term must be available for inspection upon request by representatives of national or local health authorities and Sponsor monitors, representatives, and collaborators as appropriate and as described in Section 10.1.11.

8.8 MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

This section is not applicable.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESIS

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

9.2 SAMPLE SIZE DETERMINATION

The study is not intended or powered for hypothesis testing. 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 5 provides 95% exact confidence intervals for the proportion of participants experiencing a specific AE for sample sizes of 15 and 30 participants per immunotherapy combination cohort. These confidence intervals, along with the ORR rate (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 5: 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. An ORR of at least 25% would provide sufficient evidence of clinical activity to warrant further investigation, while an ORR of 10% would not be of interest. In Stage 1, 15 participants will be enrolled. If there are 2 or more responses in these 15 participants, 15 additional participants will 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 ORR is 10% and the alternative hypothesis assumes the ORR is 25%. Under the null hypothesis, the probability of terminating the cohort after Stage 1 is 55%.

9.3 STATISTICAL ANALYSES

Each immunotherapy combination cohort will be assessed independently of the other cohorts, and the data from each cohort will be analyzed separately to preserve confidentiality of data between companies.

The statistical analysis plan (SAP) will be developed and finalized before database lock and will provide further details regarding the definition of analysis variables, analysis methodology, and handling of missing data. Any combination-specific modifications to the statistical methods, including any additional combination-specific endpoints, will be captured in the SAP. The SAP will serve as a compliment to the protocol and supersedes it in case of differences.

9.3.1 Efficacy Analyses

The analyses for clinical activity will be performed on the evaluable population, consisting of all participants who receive at least 1 dose of the combination study intervention or any component of the combination.

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

9.3.1.1 Primary Efficacy Endpoint

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

9.3.1.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints include:

- ORR: A composite endpoint where response is defined as a participant meeting at least one of the following:
    - 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.
    - Prostate-specific antigen (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 PSA value at baseline and at least two post-baseline assessments will not be evaluable for this criterion.
    - Confirmed response of CR or partial response (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.
- Disease control rate (DCR) at 9 months: Defined as CR, PR, or stable disease (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.

- Radiographic progression-free survival (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). Radiographic disease progression includes soft tissue disease progression per PCWG3-modified RECIST 1.1 and confirmed progression of bone disease per PCWG3 criteria. Participants who continue treatment beyond initial disease progression will be considered to have PD at the time of the initial progression event. Participants who do not have radiographic progression will be censored at initiation of subsequent anti-cancer therapy.
- OS: Defined as the time from initiation of study invention until death due to any cause.
- OS rate at 12 months.

Response rates for ORR, DCR, and OS will be estimated within each immunotherapy combination cohort and 95% CIs will be estimated using the Clopper-Pearson method. rPFS and OS will be estimated using Kaplan-Meier techniques, and the median survival time and 95% CIs will be estimated within each immunotherapy combination cohort. If median survival is not reached, survival times and 95% CIs will be reported at deciles that are estimable given the observed events.

9.3.1.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints include but are not limited to:

- 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 a measure of zero CTC (CTC0) on treatment.
- Percent change in PSA from baseline at 12 weeks.
- Maximum change in PSA at any point after study treatment initiation.
- 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.
- Sparse PK analysis.

- Presence of ADA against biologic components of each immunotherapy combination.

9.3.2 Safety Analyses

All safety analyses will be performed on the evaluable population, consisting of all participants who receive at least 1 dose of the combination study intervention or any component of the combination.

Safety will be assessed through summaries of AEs, laboratory test results (hematology and serum chemistry), vital signs, and ECGs. Verbatim descriptions of treatment-emergent AEs (defined in Section 10.5.1.4) will be coded, and their incidence will be summarized by immunotherapy combination cohort. In addition, separate summaries will be generated for SAEs, deaths, AEs leading to study discontinuation, AEs leading to treatment discontinuation, and AEs leading to temporary interruption and/or dose reduction.

9.3.3 Other Analyses

The number of participants who were screened, enrolled and treated, enrolled and not treated, and completed the study will be presented in summary tables. The reason for discontinuation from the study will be listed by participant and summarized in a table. The number of participants in each immunotherapy combination cohort and analysis population will be summarized.

Demographic and baseline characteristics of the study population will be summarized overall and for each immunotherapy combination cohort. Categorical measures will be summarized using frequencies and percentages. Continuous variables will be summarized using means, standard deviations, medians, minimums, and maximums.

9.3.3.1 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) when possible.

9.3.3.2 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 Biomarker Analysis Plan.

9.3.3.3 Anti-Drug Antibody Analysis

The number of participants who develop ADA to biologic study intervention and ADA titer may be summarized.

9.4 POPULATIONS FOR ANALYSIS

For purposes of analysis, the following populations are defined as shown in Table 6.

Table 6: Populations for Analysis

Population	Description
Evaluable Population	All participants who receive at least 1 dose of the combination study intervention or any component of the combination

9.5 INTERIM ANALYSES

Safety and efficacy will be monitored on a regular basis. 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 patients (Stage 2) based on acceptable safety data in addition to preliminary signals in clinical activity and/or biomarker results

Other possible adaptation 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. However, it is not anticipated that findings from safety and efficacy monitoring of this study will influence these decisions. 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.

9.5.1 Interim Safety 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. 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 (ie, vaccine expertise). Select Sponsor personnel, including the Medical Monitor and representatives from other functions including, but not limited to, Biostatistics, Clinical Science, and Drug Safety, 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. In addition, the SAC or the Sponsor may request ad hoc reviews at any time to address potential safety concerns. In the event there are a total of 4 or more of the first 15 participants, or 8 or more of 30 participants if a cohort is expanded, in a single cohort that meet cohort-specific toxicity criteria, an ad hoc SAC meeting will be held. If 1 death in any cohort occurs that is possibly related to the study drugs, the specific cohort will be placed in temporary suspension of enrollment until the information can be assessed by the Sponsor and in consultation with the SAC.

Safety monitoring will include unblinded evaluation of all AEs, SAEs, relevant protocol deviations, 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 combination cohort or suspending enrollment for safety reasons.

Roles and responsibilities of the SAC will be detailed in a separate charter.

9.5.2 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 will be enrolled in Stage 2 for a total of 30 participants in the cohort. For the purposes of cohort expansion, ORR will be used to determine response (ie, CTC response, PSA response, or confirmed response of CR or PR).

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.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 APPENDIX 1: REGULATORY, ETHICAL AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 Compliance with Laws and Regulations

This study will be conducted in accordance with the protocol and with the following:

- Applicable International Council for Harmonisation (ICH) guidelines, including E6(R2) for Good Clinical Practice (GCP) and E2A for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting
- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable laws and regulations.

Studies conducted in the US or under a US Investigational New Drug (IND) application will comply with US FDA regulations and applicable local, state, and federal laws.

10.1.2 Institutional Review Board or Independent Ethics Committee

The protocol, protocol amendments, ICF(s), IB, any information to be given to the participant, and relevant supporting information must be submitted to the IRB/IEC and reviewed and approved by the IRB/IEC before the study is initiated. In addition, any participant recruitment materials (eg, advertisements) must be approved by the IRB/IEC.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants or changes that involve logistical or administrative aspects only (eg, change in Medical Monitor or contact information).

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Promptly documenting and reporting any deviations that might have an impact on participant safety and data integrity to the Sponsor and to the IRB/IEC in accordance with established requirements, policies and procedures

- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.3 Financial Disclosure

Investigators and Sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 4.5).

10.1.4 Informed Consent

The Investigator or his/her representative will explain the nature of the study to the participant or his legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

If applicable, the ICF will contain separate sections for any optional procedures. The Investigator or authorized designee will explain to each participant the objectives, methods, and potential risks associated with each optional procedure. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a participant's agreement to participate in optional procedures. Participants who decline to participate will not provide a separate signature.

Participants must be re-consented to the most current version of the ICF(s) (or to a significant new information/findings addendum in accordance with applicable laws and IRB/IEC policy) during their participation in the study. The medical record should document the re-consent process and that written informed consent was obtained using the updated/revised ICF for continued participation in the study.

A copy of the signed and dated ICF(s) must be provided to the participant or to the participant's legally authorized representative. All signed and dated ICFs must remain in the participant's

study file or in the site study file and must be available for verification by study monitors at any time.

The final revised IRB/IEC-approved ICFs must be provided to the Sponsor for the purpose of health authority submission.

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 30 days from the previous ICF signature date and provided the ICF has not been updated during that time.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The Investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate signature.

10.1.5 Data Protection

The Sponsor maintains confidentiality standards by assigning a unique participant identification number to each participant enrolled in the study. This means that participant names are not included in data sets that are transmitted to any Sponsor location.

Participant medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the ICF (or separate authorization for use and disclosure of personal health information) signed by the participant or as permitted or required by law.

Medical information may be given to a participant’s personal physician or other appropriate medical personnel responsible for the participant’s welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives and collaborators, and the IRB/IEC for each study site, as appropriate.

10.1.6 Dissemination of Clinical Study Data

The results of this study may be reported to the public, in the form of a publication or presentation at scientific congresses, before completion of the study.

10.1.7 Administrative Structure

This trial will be sponsored and managed by the Parker Institute for Cancer Immunotherapy. The Sponsor will provide clinical operations management, data management, medical monitoring, and safety oversight.

Central facilities will be used for certain study assessments throughout the study (eg, specified laboratory tests, PK analyses, biomarker analyses), as specified in Section 8.2.5, Section 8.5, and Section 8.7, respectively. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

10.1.8 Data Quality Assurance

All participant data relating to the study will be collected via the electronic data collection (EDC) on an eCRF unless transmitted to the Sponsor or designee electronically (eg, central laboratory data, biomarker and other biological sample data). Sites will be responsible for data entry into the EDC system and will receive training for appropriate eCRF completion. The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing and dating the eCRF.

The Investigator must maintain accurate documentation (source data, see Section 10.1.9) that supports the information entered on the eCRF. The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The Sponsor is responsible for the data management of this study, including quality checking of the data. Study monitors will perform ongoing source data verification to confirm that data entered on the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

At the end of the study, the Investigator will receive participant data for his/her site in a readable format on a compact disc (or other readable digital format) that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

10.1.9 Source Documentation

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site. Data entered on the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Source documents (paper or electronic) are those in which participant data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, clinical outcomes assessment (COA)/patient-reported outcomes (PRO), evaluation checklists, pharmacy dispensing records, recorded data

from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, participant files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

When clinical observations are entered directly into a study site's computerized medical record system (ie, in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

Source documents that are required to verify the validity and completeness of data entered on the eCRFs must not be obliterated or destroyed and must be retained as described in Section 10.1.12.

10.1.10 Study and Site Closure

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Reasons for terminating the study may include, but are not limited to, the following:

- Discontinuation of further study intervention development
- The incidence or severity of AEs in this or other studies indicate the potential hazard to participants
- Participant enrollment is unsatisfactory

The Sponsor will notify the Investigator if the Sponsor decides to discontinue the study.

Reasons for the early closure of a study site by the Sponsor or Investigator may include, but are not limited to, the following:

- Poor protocol adherence
- Inaccurate or incomplete data recording
- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- No study activity (ie, all participants have completed the study and all obligations have been fulfilled)

10.1.11 Site Inspections

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, participants' medical records, and eCRFs. The Investigator will permit national and local health authorities; Sponsor monitors, representatives and collaborators; and the IRBs/IECs to inspect facilities and records relevant to this study.

10.1.12 Retention of Records

Records and documents pertaining to the conduct of this study and distribution of the investigational medicinal product, including signed eCRFs, electronic or paper COA/PRO data (if applicable), signed ICFs, laboratory test results, and medication inventory records, must be retained by the Investigator for the maximum period required by applicable regulations of relevant national or local health authorities. No records may be disposed of without the written approval of the Sponsor. The Sponsor will notify the Investigator when the records are no longer needed. Following notification from the Sponsor, the documents may be destroyed, subject to local regulations.

Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

10.1.13 Publication Policy and Protection of Trade Secrets

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results.

The Investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the Investigator.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a Coordinating Investigator will be designated in accordance with the Parker Institute for Cancer Immunotherapy publication policy. Authorship will be based on overall scientific contribution and participant enrollment.

10.2 APPENDIX 2: EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS

Grade	ECOG Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

Source: Oken et al., 1982

10.3 APPENDIX 3: RECIST CRITERIA (VERSION 1.1) WITH MODIFICATIONS AS RECOMMENDED BY PCWG3

Tumor response will be assessed according to RECIST v1.1 (Eisenhauer et al., 2009; Section 10.3.1 and Section 10.3.2), with modifications as recommended by PCWG3 (Scher et al., 2016; Section 10.3.3), as described below.

10.3.1 Measurability of Tumor at Baseline

At baseline, tumor lesions/lymph nodes will be categorized as measurable or nonmeasurable as follows:

- **Measurable**

  Tumor lesions: Must be accurately measured in ≥ 1 dimension (longest diameter in the plane of measurement to be recorded) with a minimum size of:

  - 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
  - 10 mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as nonmeasurable)
  - 20 mm by chest X-ray

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

- **Nonmeasurable**

  - All other lesions (or disease sites), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis)
  - Lesions considered truly nonmeasurable include the following: leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, and abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques

10.3.2 Tumor Response Evaluation

10.3.2.1 Baseline Documentation of Target and Nontarget Lesions

- **Target lesions**
  - When > 1 measurable lesion is present at baseline, all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions
  - It may be the case that, on occasion, the largest lesion that can be measured reproducibly should be selected
- **Nontarget lesions**
  - All other lesions (or disease sites), including pathological lymph nodes, should be identified as nontarget lesions
  - It is possible to record multiple nontarget lesions involving the same organ as a single item (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases')

10.3.2.2 Evaluation of Target Lesions

Target lesions will be evaluated and response recorded as defined in Appendix Table 1.

Appendix Table 1: Response Based on Evaluation of Target Lesions at Each Assessment

Complete response	Disappearance of all target lesions; if a pathologic lymph node, reduction in the shortest axis to < 10 mm[a]
Partial response[b]	≥ 30% decrease in the sum of the diameters of target lesions relative to the baseline sum diameters[c]
Stable disease[b,d]	Neither a sufficient reduction to qualify as a partial response nor a sufficient increase to qualify as progression[c]
Progressive disease[b]	≥ 20% increase in the sum diameters relative to the smallest sum diameters recorded (including the baseline sum diameters) in conjunction with an increase of at least 5 mm in that smallest sum diameters, or the appearance of 1 or more new lesions[c,e]

[a] For each pathologic lymph node considered a target lesion, the node must have a short axis measuring < 10 mm to be considered as a complete response. In such cases, the sum diameters may not be zero (as a normal lymph node can have a short axis of < 10 mm).

[b] For each pathologic lymph node considered a target lesion, the measurement of the short axis of the node is to be included in the sum diameters when determining partial response, stable disease, and progression.

[c] In this study, the "baseline sum diameters" is calculated based on the lesion measurements obtained at screening.

[d] Duration of stable disease is measured from the date of the first dose of Study treatment until criteria for progressive disease are met based on the smallest sum diameters recorded (including the baseline sum diameters).

[e] The finding of a new lesion should be unequivocal and not possibly attributable to a difference in imaging modality or scanning technique. Post-baseline, fluorodeoxyglucose positron emission tomography (FDG-PET) may be useful in assessing new lesions apparent on CT scan.

10.3.2.3 Evaluation of Nontarget Lesions

Nontarget lesions will be evaluated and response recorded as defined in Appendix Table 2.

Appendix Table 2: Response Based on Evaluation of Nontarget Lesions at Each Assessment

Complete response	Disappearance of all non-target lesions; all lymph nodes must be nonpathologic in size (ie, < 10 mm on the short axis)
Not complete response nor progressive disease	Persistence of 1 or more non-target lesions
Progressive disease	Unequivocal progression[a] of any existing non-target lesion or the appearance of 1 or more new lesions[b]

[a] The participant should stop study intervention, even in the presence of a partial response or stable disease, based on assessment of target lesions.

[b] The finding of a new lesion should be unequivocal and not possibly attributable to a difference in imaging modality or scanning technique. Post-baseline, fluorodeoxyglucose positron emission tomography (FDG-PET) may be useful in assessing new lesions apparent on CT scan.

10.3.2.4 New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (eg, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the participant's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan as report as a 'new' cystic lesion, which it is not.

10.3.2.5 Evaluation of Overall Response

Overall response based on the evaluation of target and nontarget lesions will be determined as shown in Appendix Table 3.

Appendix Table 3: Evaluation of Overall Response at Each Assessment

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
Complete response	Complete response	No	Complete response
No target lesion[a]	Complete response	No	Complete response
Complete response	Not evaluable[b]	No	Partial response
Complete response	Not complete response/ non-progressive disease	No	Partial response

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
Partial response	Non-progressive disease and not evaluable[b]	No	Partial response
Stable disease	Non-progressive disease and not evaluable[b]	No	Stable disease[c]
Not all evaluated	Non-progressive disease	No	Not evaluable
No target lesion[a]	Not all evaluated	No	Not evaluable
No target lesion[a]	Non-complete response/ non-progressive disease	No	Non-complete response/ non-progressive disease
Progressive disease	Any	Yes or no	Progressive disease
Any	Progressive disease	Yes or no	Progressive disease
Any	Any	Yes	Progressive disease
No target lesion[a]	Unequivocal progressive disease	Yes or No	Progressive disease
No target lesion[a]	Any	Yes	Progressive disease

[a] Defined as no target lesions at baseline.

[b] Not evaluable is defined as either when no or only a subset of lesion measurements are made at an assessment.

[c] The minimum duration on-study required for an overall assessment of stable disease is 49 days.

10.3.3 Modifications for mCRPC as Recommended by PCWG3

In 2016, the PCWG3 (Scher et al., 2016) updated the recommendations of the Prostate Cancer Working Group 2 (PCWG2; Scher et al., 2008). The key new recommendations related to disease assessment, including the following, which are described in more detail in Section 10.3.3.1 and Section 10.3.3.2:

- emphasizing the importance of serial biologic profiling of the disease using minimally invasive blood-based assays of tumor material, imaging, or biopsy of a metastatic tumor site to identify and target mechanisms of primary or adaptive resistance and to better enable treatment selection to be based on disease biology;
- including clinically relevant time-to-event end points, such as symptomatic skeletal events (SSEs);
- with increased recognition of disease heterogeneity and emerging resistance, focusing more on determining when a treatment should be discontinued when the patient is NLCB rather than strictly at the first evidence of progression.

10.3.3.1 PCWG3 Recommendations with Regard to Baseline Disease Assessments

A summary of major changes in PCWG3 recommendations compared with PCWG2 with regard to baseline disease assessments follows:

- Expands baseline assessments to include tumor histology; the timing, duration, and response (if available) for all prior systemic treatments; a standardized assessment of blood-based, PRO-based, and imaging-based biomarkers; and the molecular characterization of the tumor (detailed in Appendix Table 4).
- Emphasizes molecular/biologic subtypes of castration-resistant prostate cancer in addition to the 5 clinical subtypes (defined by extent and location of metastases)
- Defines the type of progression at trial entry as PSA-only progression, radiographic progression by site of disease spread, or both; for radiographic progression, records whether progression was caused by growth of existing lesions, appearance of new lesions, or both

Appendix Table 4: Criteria for Progression at Trial Entry by Disease Manifestation

Variable	PCWG3 Recommendation
Blood-based	
PSA	Obtain sequence of rising values at a minimum of 1-week intervals 1.0 ng/mL minimal starting value (1.0 ng/mL is the minimal starting value if confirmed rise is only indication of progression unless pure small-cell carcinoma) Estimate pretherapy PSA doubling time if at least 3 values available ≥ 4 weeks apart
Imaging	
Nodes	Nodal progression sufficient for trial entry independent of PSA Measurable lesions not required for entry Modified RECIST 1.1 criteria, separate pelvic and disease, up to five nodal lesions total recorded Previously normal (< 1.0-cm) lymph nodes must have grown by ≥ 5 mm in the short axis from baseline or nadir and be ≥ 1.0 cm in the short axis to be considered to have progressed If the node progresses to ≥ 1.5 cm in the short axis, it is measurable; nodes that have progressed to 1.0 to less than 1.5 cm are pathologic, subject to clinical discretion, and nonmeasurable For existing pathologic adenopathy, progression is defined per RECIST 1.1 Record presence of nodal and/or visceral disease separately Nodal sites: Locoregional: pelvic only Extrapelvic: retroperitoneal, mediastinal, thoracic, or other

Variable	PCWG3 Recommendation
Viscera	Visceral progression sufficient for trial entry independent of PSA; recorded separately by site of spread (lung, liver, adrenal, CNS); up to 5 lesions per site of spread recorded Measurable lesions not required for entry Use RECIST to record visceral lesions as target or nontarget Visceral sites: lung, liver, adrenal, CNS
Prostate/prostate bed (primary site)	Record prior treatment of primary tumor Perform directed pelvic imaging (CT, MRI, PET/CT, endorectal MRI, transrectal ultrasound) to document presence or absence of disease
Bone	Two new lesions Confirm ambiguous results by other imaging modalities (eg, CT or MRI); only positivity on the bone scan defines metastatic disease to bone
Other sites of disease	Patients with treated epidural lesions and no other epidural progression are eligible
Type of progression at trial entry	
	Report separately: PSA only Bone only ± nodal disease Nodal disease only (no bone disease present) Visceral (lung, liver, adrenal, CNS) disease (± other sites) Record new lesions and site of new lesions vs growth of pre-existing lesions, or both
Other markers	
Patient-reported outcomes	For pain palliation analyses, presence of clinically meaningful pain at baseline (eg, ≥ 4 on a 10-point pain intensity scale) is a prerequisite; for pain progression analyses, patients may have any level of pain at baseline, including no pain

Source: Scher et al., 2016

CNS = central nervous system; CT = computed tomography; MRI = magnetic resonance imaging; PCWG3 = Prostate Cancer Clinical Trials Working Group 3; PET = positron emission tomography; PSA = prostate-specific antigen; RECIST = Response Evaluation Criteria in Solid Tumors; vs = versus

10.3.3.2 PCWG3 Recommendations with Regard to Measuring Outcomes and Reporting

PCWG3 reaffirmed the PCWG2 recommendation for the use of the following endpoints to assess antitumor effects, and suggested the outcome measures described in Appendix Table 5 are differentiated according to these endpoints, where applicable:

- Control/relieve/eliminate endpoints for therapies that are anticipated to kill tumor cells, particularly in early clinical development
- Delay/prevent endpoints for therapies not expected to kill tumor cells

A summary of major changes in PCWG3 recommendations compared with PCWG2 with regard to measuring outcomes and reporting follows:

Blood-based and Molecular Measures

- When there are progressing lesions, recommends rebiopsy of the progressing metastatic site for histology and biomarker assessment
- Suggests that PSA outcomes should be interpreted within the context of a drug's mechanism of action, and the anticipated timing of a potential favorable/unfavorable effect on PSA should be considered
- Includes suggestions on how to define and report outcomes related to CTC enumeration (using CellSearch platform)

Patient-reported Outcomes

- Recognizes the importance of the patient perspective in prostate cancer clinical trials and the need to further optimize the assessment, collection, analysis, and presentation of PRO data
- Recommends measuring disease-related symptoms including pain intensity and interference, and physical functioning, using validated instruments
- Recommends collecting patient-reported AEs using the National Cancer Institute's (NCI's) PRO- Common Terminology Criteria for Adverse Events (CTCAE)

Imaging and Clinical Measures

- Reconsiders the mixed response designation, which may be a manifestation of disease heterogeneity
- Advises recording whether disease progression represents growth of pre-existing lesions, development of new lesions, or both, and separately recording whether progression is occurring in a single organ or disease site versus (vs) multiple sites
- Suggests that the first post-treatment bone scan be used as the baseline scan with which all future bone scans are compared; also emphasizes the notion of response in bone, caused by the advent of novel bone-targeting agents
- Advises recording the location of nodal disease (pelvic vs extrapelvic) and visceral disease (lung/liver/adrenal/central nervous system [CNS]) separately, because these sites have separate prognostic implications
- Also advises monitoring up to 5 individual lesions per site of spread (eg, nodes, lung, liver as separate sites) to address disease heterogeneity

- Proposes new criteria to define the first occurrence of metastatic disease in men with nonmetastatic CRPC (nmCRPC) at enrollment
- Highlights and defines the bone-related outcomes, skeletal-related events (SREs) and SSEs, but suggests focusing on SSEs, which represent a more direct clinical benefit to patients
- Introduces the concept of treatment beyond progression where clinical benefit by one or more disease manifestations is being observed, thus defining an objective of NLCB

Appendix Table 5: Suggested Outcome Measures for Clinical Trials in Metastatic Prostate Cancer: Report by Disease Manifestation

Variable	PCWG3 Recommendation
Histology	
	Encourage rebiopsy of metastatic sites or local recurrence at progression to evaluate for histologic (ie, neuroendocrine/ small cell) transformation; in the context of clinical trials, encourage rebiopsy for biomarker assessment
Blood-based markers	
PSA	Recognize that a favorable effect on PSA may be delayed for ≥ 2 weeks, even for a cytotoxic drug Monitor PSA by cycle but plan to continue through early rises for a minimum of 8-9 or 12 weeks (depending on trial design) unless other evidence of progression Ignore early rises (before 12 weeks) in determining PSA response For control/relieve/eliminate end points: Record the percent change from baseline (rise or fall) at 12 weeks, and separately, the maximal change (rise or fall) at any time using a waterfall plot Separately report the proportion of patients who have undergone radical prostatectomy and achieved a nadir less than 0.2 ng/mL v primary radiation therapy–treated patients who achieved a nadir less than 0.5 ng/mL Describe absolute changes in PSA over time from baseline to best response For delay/prevent end points (progression): After decline from baseline: record time from start of therapy to first PSA increase that is ≥ 25% and ≥ 2 ng/mL above the nadir, and which is confirmed by a second value ≥ 3 weeks later (ie, a confirmed rising trend); the requirement for an increase of 5 ng/mL was decreased to 2 ng/mL, and the requirement for a 50% increase was reduced to 25% Recording the duration of PSA decline of little value No decline from baseline: PSA progression ≥ 25% increase and ≥ 2 ng/mL increase from baseline beyond 12 weeks; relate to mechanism of drug and anticipated timing of potential favorable/unfavorable effects on PSA, if present
CTC	Enumerate at the start of treatment: Record as favorable (≤ 4 cells/7.5 mL of blood) or unfavorable (≥ 5 cells/7.5 mL) If unfavorable, monitor for changes after treatment For control/relieve/eliminate end points: Report as change from unfavorable (≥ 5 cells/7.5 mL of blood) to favorable (≤ 4 cells/7.5 mL) and separately, the percent change from baseline using a waterfall plot

Variable	PCWG3 Recommendation
	For delay/prevent end points: no validated definition exists (however, rising CTC counts are associated with a poor prognosis)
LDH, total alkaline phosphatase, bone-specific alkaline phosphatase, urine N-telopeptide, hemoglobin, NLR	Descriptively report changes over time, may include the proportion showing normalization of a given biomarker and/or waterfall plots of percent change from baseline in a given biomarker Report institutional normal ranges to determine normalization of a given biomarker
Imaging biomarkers: nodal and visceral For control/relieve/eliminate endpoints	
General	Record up to 5 lesions per site of disease Use RECIST 1.1 with caveats: Record changes in size using waterfall plot Confirm favorable change with second scan Record complete elimination of disease at any site separately
Nodes	Only report changes in lymph nodes that were ≥ 1.5 cm in the short axis Record changes in pelvic (regional) nodes vs extrapelvic (distant/metastatic) nodes separately
Visceral	Use RECIST 1.1 with caveats: Record changes in liver, lung, adrenal, and CNS separately Only report changes in lesions ≥ 1.0 cm in the longest dimension
For delay/prevent endpoints	
Nodal and visceral	Record changes in nodal and visceral (lung, liver, adrenal, and CNS) disease separately Use RECIST 1.1 but clearly record type of progression (growth of existing lesions vs development of new lesions) separately by site The recommendations apply to both nmCRPC and mCRPC Record up to 5 lesions per site of spread Report the proportion who have not progressed at fixed time points (6 or 12 months) Note that for some treatments, a lesion may increase in size before it decreases
Nodal	Previously normal (< 1.0-cm) lymph nodes must have grown by ≥ 5 mm in the short axis from baseline or nadir and be ≥ 1.0 cm in the short axis to be considered to have progressed Nodes that have progressed to 1.0 to less than 1.5 cm are pathologic, subject to clinical discretion, and nonmeasurable For existing pathologic adenopathy (≥ 1.5 cm), progression is defined per RECIST 1.1
Imaging biomarkers: bone	
Metastatic	For control/relieve/eliminate endpoints: Record changes as resolved, improved, or stable (no new lesions) or worse (new lesions) Changes in intensity of uptake alone do not constitute progression or regression No new lesions: continue therapy in absence of other signs of progression New lesions (See Progression below) For delay/prevent endpoints (progression): Progression: Exclude pseudoprogression in the absence of symptoms or other signs of progression At least 2 new lesions on first post-treatment scan, with at least 2 additional lesions on the next scan (2+2 rule)

Variable	PCWG3 Recommendation
	If at least 2 additional new lesions are seen on the next (confirmatory) scan, the date of progression is the date of the first post-treatment scan, when the first 2 new lesions were documented For scans after the first post-treatment scan, at least 2 new lesions relative to the first post-treatment scan confirmed on a subsequent scan Date of progression is the date of the scan that first documents the second lesion Changes in intensity of uptake alone do not constitute either progression or regression Report the proportion of patients who have not progressed at fixed time intervals (6 and 12 months)
nmCRPC	Nonmetastatic to metastatic progression: Any new unequivocal bone lesion, except if that lesion appears in the first post-treatment scan; in that case, document the event, continue treatment until 2 additional new lesions appear, and record both events
Patient-reported outcomes	
	Pain palliation assessment requires a patient population with clinically meaningful pain at baseline (eg, ≥ 4 on a 10-point pain intensity scale) and response defined as a clinically meaningful score improvement at a subsequent time point (eg, a 30% relative or 2-point absolute improvement from baseline at 12 weeks, confirmed at least 2 weeks later, without an overall increase in opiate use) For control/relieve/eliminate endpoints: Document pain and analgesia at entry with a lead-in period and measure repeatedly at 3- to 4-week intervals; serial (eg, daily x 7 days) assessments at each time point can improve the stability of values Perform serial assessments of global changes in HRQoL, urinary or bowel compromise, pain management, additional anticancer therapy; principles may be extended for any PRO for which a clinically meaningful baseline PRO score has been determined together with a responder definition that is based on a sustained clinically meaningful score improvement Ignore early changes (≤ 12 weeks) in pain or HRQoL in absence of compelling evidence of disease progression For delay/prevent endpoints: Confirm response or progression of pain or HRQoL end points ≥ 3 weeks later; patients with any level of baseline pain, including no pain, are eligible to be evaluated for prevent/delay end points; those without pain are followed for development of pain, whereas those with baseline pain are followed for progression (eg, a 2-point increase without an overall decrease in opiate use) Pain assessment should be administered at treatment discontinuation and once again if feasible (eg, 2 to 4 weeks later) Time to deterioration of physical function and/or HRQoL scores should also be included, with a priori thresholds defining clinically meaningful deterioration score changes that are based on prior published data for the selected questionnaire

Source: Scher et al., 2016

CNS = central nervous system; CTC = circulating tumor cell; HRQoL = health-related quality of life; LDH = lactate dehydrogenase; mCRPC = metastatic castration-resistant prostate cancer; NLR = neutrophil/lymphocyte ratio; nmCRPC = nonmetastatic castration-resistant prostate cancer; PCWG3 = Prostate Cancer Clinical Trials Working Group 3; PSA = prostate-specific antigen; RECIST = Response Evaluation Criteria in Solid Tumors; vs = versus

10.4 APPENDIX 4: CLINICAL LABORATORY TESTS

- Protocol-specific requirements for inclusion or exclusion of participants are detailed in the cohort appendix for each respective combination.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.
- Investigators must document their review of each laboratory safety report.

10.5 APPENDIX 5: ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

10.5.1 Definitions

10.5.1.1 Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

Events Meeting the AE Definition
• Any abnormality or deterioration in a laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, or are considered clinically significant in the medical and scientific judgment of the Investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • A new condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. • Serious events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study procedures (eg, screening invasive procedures, such as biopsies, discontinuation of non-study medications that may be required by protocol such as a prohibited medication). • Any new cancer (that is not a condition of the study). • Note: Progression of the cancer under study is not a reportable event. Refer to Section 8.3.6 for additional details.

Events NOT Meeting the AE Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen. • Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.

10.5.1.2 Definition of SAE

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

A SAE is defined as any AE that suggests a significant hazard, contraindication, side effect, or untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. Note: Hospitalizations for the following reasons are not considered SAEs in this study: • a visit to the emergency room or other hospital department for < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event) • elective surgery planned prior to signing consent • admissions as per protocol for a planned medical/surgical procedure • routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)

- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

In offspring of a participant exposed to the study intervention for timing as determined for study intervention based on product half-life. Any spontaneous abortion should be reported in the same fashion (as the Sponsor considers spontaneous abortions to be medically significant).

f. Other important medical events:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.5.1.3 Definition of Unexpected AE

Unexpected AE Definition
• Any AE, the specificity or severity of which is not consistent with the current IB. Expected means that the event has previously been observed with the study intervention and is identified and/or described in the current IB. It does not mean that the event is expected with the underlying disease(s), co-morbidities or concomitant medications.

10.5.1.4 Definition of Treatment-emergent AE

Treatment-emergent AE Definition
• Any unfavorable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding that is considered to be clinically significant), syndrome or disease that either occurs during the study, 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 the study intervention.

10.5.2 Additional Events Reported in the Same Manner as an SAE

Additional Events Reported in the Same Manner as a SAE
• In addition to the SAE criteria in Section 10.5.1.2, AEs meeting any of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by the Sponsor for collection purposes. o A new cancer (not the indicated condition of the study) o An overdose or is an associated event that meets safety criterion with an overdose (as specified in Section 8.4) o Protocol-specified AEs, including AESIs (as applicable and as defined in the cohort appendix for each respective combination) o Pregnancy (as specified in Section 8.3.5)

10.5.3 Recording AEs and SAEs

AE and SAE Recording

- When an AE/AESI/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event. Only a single AE term should be recorded for the event.
- The Investigator will record all relevant AE/AESI/SAE information on the eCRF.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the Adverse Event eCRF/Serious Adverse Event Report Form (SAERF).
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Severity

- The terms 'severe' and 'serious' are not synonymous. An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe. Severity (intensity) and seriousness need to be independently assessed for each AE recorded on the eCRF.
- The Investigator will assess the intensity for each AE, including AESI, and SAE (and other reportable safety events) according to the NCI Common Terminology for Adverse Events (CTCAE), version 5.0, which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.
  The following grading will be used for assessing intensity for AEs not specifically listed in the NCI CTCAE:
    - Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
    - Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
    - Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
    - Grade 4: Life threatening consequences; urgent intervention indicated.

- Grade 5: Death related to AE.

- Any AE that changes CTCAE grade over the course of a given episode (ie, persistent AE) will have each change of grade recorded on the Adverse Event eCRF.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/AESI/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use their clinical judgment, knowledge of the participant, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine the relationship.
- The following guidance will be considered and investigated:
    - Temporal relationship of the event onset to study intervention administration
    - Course of the event, with special consideration of the effects of dose reduction, discontinuation of study intervention, or reintroduction of study intervention (as applicable)
    - Known association of the event with the study intervention or with similar treatments
    - Known association of the event with the disease under study
    - Presence of risk factors in the participant or use of concomitant medications known to increase the occurrence of the event
    - Presence of non-treatment-related factors that are known to be associated with the occurrence of the event
- The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/AESI/SAE, the Investigator must document in the medical notes that he/she has reviewed the AE/AESI/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

- For studies in which multiple agents are administered as part of a combination regimen, the Investigator may attribute each AE causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (ie, to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the Investigator's opinion, there are sufficient data to support full attribution of the AE to the single agent.

Causality for this protocol should be assessed as follows:

- **Unrelated**: This category applies to those AEs that are clearly and incontrovertibly due to extraneous causes (disease, environment, etc.).

  Note: If an AE is assessed as unrelated to the study intervention(s), there must be an alternative etiology in the Investigator's assessment for that event documented in the participant's medical records.

- **Unlikely Related**: This category applies to those AEs that are judged to be unrelated to the study intervention(s), but for which no extraneous cause may be found. An AE may be considered unlikely to be related to study intervention(s) if or when it meets 2 of the following criteria:
  - it does not follow a reasonable temporal sequence from administration of the study intervention(s);
  - it could readily have been produced by the participant's clinical state, environmental or toxic factors, or other modes of therapy administered to the participant;
  - it does not follow a known pattern of response to the study intervention(s); or
  - it does not reappear or worsen when the study intervention(s) is re-administered.

- **Possibly Related**: This category applies to those AEs for which a connection with the study intervention administration appears unlikely but cannot be ruled out with certainty. An AE may be considered possibly related if or when it meets 2 of the following criteria:
  - it follows a reasonable temporal sequence from administration of the study intervention(s);
  - it could not readily have been produced by the participant's clinical state, environmental or toxic factors, or other modes of therapy administered to the participant; or
  - it follows a known pattern of response to the study intervention(s).

- **Probably Related**: This category applies to those AEs that the Investigator feels with a high degree of certainty are related to the study intervention(s). An AE may be considered probably related if or when it meets 3 of the following criteria:
  - it follows a reasonable temporal sequence from administration of the study intervention(s);

- it could not be reasonably explained by the known characteristics of the participant's clinical state, environmental or toxic factors, or other modes of therapy administered to the participant;
- it disappears or decreases on cessation or reduction in dose (note that there are exceptions when an AE does not disappear upon discontinuation of the study intervention, yet study intervention relatedness clearly exists; for example, as in bone marrow depression, fixed study intervention eruptions, or tardive dyskinesia); or
- it follows a known pattern of response to the study intervention(s).

- **Definitely Related**: This category applies to those AEs that the Investigator believes are incontrovertibly related to study intervention(s). An AE may be assigned an attribution of definitely related if or when it meets all of the following criteria:
  - it follows a reasonable temporal sequence from administration of the study intervention(s);
  - it could not be reasonably explained by the known characteristics of the participant's clinical state, environmental or toxic factors, or other modes of therapy administered to the participant;
  - it disappears or decreases on cessation or reduction in dose and recurs with re-exposure to study intervention(s) (if rechallenge occurs); and
  - it follows a known pattern of response to the study intervention(s).

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded on the eCRF.
- The Investigator will submit any updated data related to SAEs or AESIs to the Sponsor within 24 hours of receipt of the information.

10.5.4 Reporting of AEs, SAEs, and Other Reportable Safety Events to the Sponsor

Reporting of AEs, SAEs, and Other Reportable Safety Events to the Sponsor via an Electronic Data Collection Tool
• The primary mechanism for reporting AEs to the Sponsor will be via the electronic data collection (EDC) tool. • Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent). • If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE reporting tool (see next section). • Reference Section 8.3.1 – Time Period and Frequency for Collecting AE, AESI, SAE, and Other Reportable Safety Event Information for reporting time requirements • After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data. • The site will report all AESIs, as applicable, on the study-specific SAERF to the Parker Institute for Cancer Immunotherapy Pharmacovigilance Group within 24 hours of site awareness. The AESI should also be reported on the Adverse Event eCRF. • The site will report all SAE data on the study-specific SAERF to the Parker Institute for Cancer Immunotherapy Pharmacovigilance Group within 24 hours of site awareness. • Contacts for reporting SAEs, AESIs, and other reportable safety events can be found in Section 8.3.8.2.

SAE and Other Reportable Safety Event Reporting to the Sponsor
• In the instance where an SAE or AESI occurs, a facsimile transmission of the SAERF and/or Pregnancy Report Form is the preferred method to transmit this information to the Parker Institute for Cancer Immunotherapy Pharmacovigilance Group. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAERF sent via email. • Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAERF within the designated reporting time frames. • Contacts for SAE, AESI, and other reportable safety event reporting can be found in Section 8.3.8.2.

10.5.5 Additional Reporting Considerations

AE and SAE Recording for Special Circumstances

Diagnosis versus Signs and Symptoms

- A diagnosis (if known) or cause of death should be recorded on the Adverse Event eCRF page rather than individual signs and symptoms (eg, record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases).
- If a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded separately on the Adverse Event eCRF page.
- If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be nullified and replaced by one AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

Adverse Events That Are Secondary to Other Events

- In general, AEs that are secondary to other events (eg, cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary AE that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF page. For example:
    - If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
    - If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
    - If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
    - If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
    - If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.
- All AEs should be recorded separately on the Adverse Event eCRF page if it is unclear as to whether the events are associated.

Persistent or Recurrent Adverse Events

- A persistent AE is one that extends continuously, without resolution, between participant evaluation time points. Such events should only be recorded once on the Adverse Event eCRF page. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported.
- If a persistent AE becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF page, and details regarding any increases or decreases in severity will be captured on the Adverse Event eCRF.
- If the event becomes serious, it should be reported to the Sponsor as a SAE, and the Adverse Event eCRF page should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to SAEs.
- A recurrent AE is one that resolves between participant evaluation time points and subsequently recurs. Each recurrence of an AE should be recorded as a separate event on the Adverse Event eCRF page.

Abnormal Laboratory Values

- A clinical laboratory test value must be reported as an AE if it meets any of the following criteria:
    - is accompanied by clinical symptoms
    - results in a change in study intervention (eg, dose modification, treatment interruption, or treatment discontinuation)
    - results in a medical intervention or change in concomitant medication
    - is clinically significant in the Investigator's judgment

Abnormal Vital Sign Values

- Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an AE.
- If a clinically significant vital sign abnormality is a sign of a disease or syndrome (eg, high blood pressure), only the diagnosis (ie, hypertension) should be recorded on the Adverse Event eCRF page.
- Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF page (see above for details on recording persistent AE).

Abnormal Liver Function Tests

- The finding of an elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) (> 3 x baseline value) in combination with either an elevated total bilirubin (> 2 x upper limit of normal [ULN]) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, Investigators must report as an AE the occurrence of either of the following:
    - Treatment-emergent ALT or AST > 3 x baseline value in combination with total bilirubin > 2 x ULN (of which ≥ 35% is direct bilirubin)
    - Treatment-emergent ALT or AST > 3 x baseline value in combination with clinical jaundice
- The most appropriate diagnosis or if a diagnosis cannot be established, the abnormal laboratory values should be recorded on the Adverse Event eCRF page and reported to the Sponsor immediately, either as an SAE or an AESI (as applicable and as defined in the cohort appendix for each respective combination).

Lack of Efficacy or Worsening of Underlying Disease

- Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as AEs. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on the PCWG3-modified RECIST 1.1 used in this study. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an AE.

Deaths

- All deaths that occur during the protocol-specified AE reporting period, regardless of relationship to study intervention, must be recorded on the Death eCRF page and immediately reported to the Sponsor (see Section 8.3.1), unless the death is attributed to progression of disease.
- Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF page. Generally, only one such event should be reported.
- If the cause of death is unknown and cannot be ascertained at the time of reporting, "unexplained death" should be recorded on the Adverse Event eCRF page.
- If the cause of death later becomes available (eg, after autopsy), "unexplained death" should be replaced by the established cause of death.
- The term "sudden death" should not be used unless combined with the presumed cause of death (eg, "sudden cardiac death").

- If the death is attributed to progression of underlying disease, "underlying disease" should be recorded on the appropriate eCRF page; no SAERF is necessary.
- Deaths that occur after the AE reporting period should be reported as described in Section 8.3.2.

Pre-existing Medical Conditions

- A pre-existing medical condition is one that is present at the baseline visit for this study. Such conditions should be recorded on the Medical History eCRF page.
- A pre-existing medical condition should be recorded as an AE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF page, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors (eg, "more frequent headaches").

Adverse Events Associated with Overdose or Error in Drug Administration

- Overdose should be reported as specified in Section 8.4.
- All AEs associated with an overdose or incorrect administration of study intervention should be recorded on the Adverse Event eCRF page.
- If the associated AE fulfills seriousness criteria, the event should be reported to the Sponsor as a separate SAE.

10.6 APPENDIX 6: CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION

It is acknowledged that only men will be enrolled in this study. Although women will not be enrolled, participants in this study may have female partners of childbearing potential. Therefore, sections have been included in this appendix to provide information relevant to women of childbearing potential (WOCBP) who may be partners of study participants.

10.6.1 Definitions

10.6.1.1 Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories **are not considered WOCBP**

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

    Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT while their partner participates in the study.

10.6.2 Contraception Guidance

Male participants with female partners of childbearing potential are eligible to participate if they agree to ONE of the following (during the protocol-defined time frame in the cohort appendix for each respective combination):

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
- Agree to use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in Appendix Table 6 when having penile-vaginal intercourse with a WOCBP who is not currently pregnant. In addition, male participants must refrain from donating sperm for the duration of the study and for 5 half-lives after the last dose of study intervention.

Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the protocol-defined time frame and for 5 half-lives after the last dose of study intervention.

Appendix Table 6: Highly Effective Contraceptive Methods for Partner Use

Highly Effective Contraceptive Methods That Are User Dependent[a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[b] • Oral • Intravaginal • Transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Methods That Are User Independent[a]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion
Vasectomized partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.

Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
NOTES: a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. b) Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. In this case, two highly effective methods of contraception should be utilized during the treatment period and for at least 5 half-lives after the participant's last dose of study intervention

10.6.3 Collection of Pregnancy Information from Male Participants with Partners who Become Pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

10.7 APPENDIX 7: GENETICS

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact immune response, drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood and tumor sample will be collected for DNA analysis from consenting participants.
- DNA samples will be used for research related to study intervention and/or mCRPC and related diseases or evaluation of new assay technologies. They may also be used to develop tests/assays including diagnostic tests related to study intervention and/or therapies of this drug class and/or immuno-oncology therapies and mCRPC. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).
- Stool samples will be collected, and microbiome nucleic acid extracted and analyzed to evaluate a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to bacterial genetic determinants that impact immune response, drug absorption, distribution, metabolism, and excretion; or by the mechanism of action of the drug.
- DNA samples may be analyzed for whole genome sequencing and bacterial DNA may be analyzed by 16s and/or whole metagenomic sequencing and relationship to clinical outcomes in response to study intervention. Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data and/or treatment of mCRPC.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to study intervention or study interventions of this class to understand study disease or related conditions.
- The results of genetic analyses may be reported in the clinical study report (CSR) or in a separate study summary.
- The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on study intervention or study interventions of this class or indication (eg, immunotherapy) continues in accordance with applicable law.

10.8 APPENDIX 8: LISTS OF TERMINOLOGY AND ABBREVIATIONS

10.8.1 List of Terminology

Terminology	Description
Cohort	A group of participants receiving the same immunotherapy combination.
Cohort appendix	A document that guides the treatment of participants in a given cohort. The cohort appendices are identified using a letter designation (eg, Appendix Cohort A, Appendix Cohort B, etc.).
Core protocol	The master document that provides the elements common across the study and among all cohorts, unless otherwise specified.
Immunotherapy combination	Two or more study interventions administered to a cohort of participants.

10.8.2 List of Abbreviations

Abbreviation	Definition
ADA	anti-drug antibody(ies)
ADT	androgen deprivation therapy
AE(s)	adverse event(s)
AESI(s)	AE(s) of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BCG	bacille Calmette-Guerin
BUN	blood urea nitrogen
C	cycle
Cmax	maximum observed drug concentration
cfDNA	cell-free deoxyribonucleic acid
CI(s)	confidence interval(s)
CIOMS	Council for International Organizations of Medical Sciences
CNS	central nervous system
COA	clinical outcomes assessment
CONSORT	Consolidated Standards of Reporting Trials
CR	complete response
CSR	clinical study report
CT	computerized tomography
CTC	circulating tumor cells

Abbreviation	Definition
CTC0	a measure of zero CTC
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
DCR	disease control rate
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data collection
EOT	end of treatment
FDA	Food and Drug Administration
FDG-PET	fluorodeoxyglucose positron emission tomography
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GnRH	gonadotropin-releasing hormone
GU	genitourinary
HIPAA	Health Insurance Portability and Accountability Act
HRQoL	health-related quality of life
HRT	hormone (hormonal) replacement therapy
I/E	inclusion/exclusion
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IND	Investigational New Drug
INR	international normalized ratio
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous(ly)
LDH	lactate dehydrogenase
mCRPC	metastatic castration-resistant prostate cancer
MDSC(s)	myeloid-derived suppressor cell(s)
MMR	mismatch repair
MRI	magnetic resonance imaging
MSI	microsatellite instability
NCI	National Cancer Institute
NK	natural killer
NLCB	no longer clinically benefiting

Abbreviation	Definition
NLR	neutrophil/lymphocyte ratio
nmCRPC	nonmetastatic castration-resistant prostate cancer
ORR	objective response rate
OS	overall survival
OTC	over-the-counter
PAP	prostatic acid phosphatase
PBMC(s)	peripheral blood mononuclear cell(s)
PCWG2	Prostate Cancer Clinical Trials Working Group 2
PCWG3	Prostate Cancer Clinical Trials Working Group 3
PD	progressive disease
PD-1	programmed cell death 1
PD-L1	programed cell death ligand 1
PET	positron emission tomography
PI	Principal Investigator
PK	pharmacokinetic
PORTER	Prostate Researching Translational Endpoints Correlated to Response
PR	partial response
PRO	patient-reported outcome
PSA	prostate-specific antigen
PT	prothrombin time
PTT	partial thromboplastin time
Q3M	every 3 months
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
rPFS	radiographic progression-free survival
SAC	Safety Assessment Committee
SAE(s)	serious adverse event(s)
SAERF	Serious Adverse Event Report Form
SAP	statistical analysis plan
SD	stable disease
SOA	Schedule of Activities
SRE(s)	skeletal-related event(s)
SSE(s)	symptomatic skeletal event(s)
SUSAR	suspected unexpected serious adverse reactions
TC-99m	technetium-99m
Treg(s)	regulatory T cell(s)
TSH	thyroid stimulating hormone

Abbreviation	Definition
ULN	upper limit of normal
US	United States
VISTA	V-domain Ig suppressor of T cell activation
vs	versus
WBC	white blood cell
WOCBP	woman of childbearing potential

10.9 APPENDIX 9: PROTOCOL AMENDMENT HISTORY

DOCUMENT HISTORY	
Documents	**Date of Issue**
Amendment 2	30 April 2019
Amendment 1	24 Jan 2019
Original Protocol	07 Dec 2018

11 REFERENCES

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