Official Protocol Title:	A Phase 3, Randomized, Double-blind Trial of Pembrolizumab (MK-3475) Plus Enzalutamide Versus Placebo Plus Enzalutamide in Participants With Metastatic Castration-Resistant Prostate Cancer (mCRPC)
NCT number:	NCT03834493
Document Date:	22-May-2023

Title Page

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Protocol Title: A Phase 3, Randomized, Double-blind Trial of Pembrolizumab (MK-3475) Plus Enzalutamide Versus Placebo Plus Enzalutamide in Participants With Metastatic Castration-Resistant Prostate Cancer (mCRPC) (KEYNOTE-641)

Protocol Number: 641-09

Compound Number: MK-3475

Sponsor Name:

Merck Sharp & Dohme LLC
(hereafter referred to as the Sponsor or MSD)

Legal Registered Address:

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Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

IND	122753
EudraCT	2018-004117-40
EU CT	2022-500785-10-00

Approval Date: 22 May 2023

Sponsor Signatory

Typed Name:
Title:

Date

Protocol-specific Sponsor contact information can be found in the Investigator Study File Binder (or equivalent).

Investigator Signatory

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol.

Typed Name:
Title:

Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 09	22-MAY-2023	Protocol amended consistent with recommendations of the eDMC after an interim review of the data; CCI [redacted]
Amendment 08	02-NOV-2022	To update the Statistical Analysis Plan by adding minimum follow-up time for the interim analyses.
Amendment 07	02-JUN-2022	CCI [redacted]
Amendment 06	12-OCT-2021	CCI [redacted]
Amendment 05	14-MAY-2021	To update the dose modification and toxicity management guidelines for immune-related adverse events (irAEs).
Amendment 04	11-DEC-2020	To revise eligibility criteria to align with the latest standard of care (NHAs given prior to mCRPC) and to clarify the verification of progression language.
Amendment 03	03-APR-2020	CCI [redacted]
Amendment 02	05-SEP-2019	Corrections to the Schedule of Activities, Objectives, and Appendices, and minor edits throughout.

Document	Date of Issue	Overall Rationale
Amendment 01	03-JUL-2019	Adding country-specific requirements for the United Kingdom.
Original Protocol	18-JAN-2019	N/A

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 09

Overall Rationale for the Amendments:

Protocol amended consistent with recommendations of the eDMC after an interim review of the data; specifically, to stop the study for futility per the criteria prespecified in the sSAP.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis, Hypotheses, Objectives, and Endpoints 2.3 Benefit/Risk Assessment 3 Hypotheses, Objectives, and Endpoints 4.1 Overall Design 4.4.1 Clinical Criteria for Early Study Termination 9 Statistical Analysis Plan	Added that based on the safety and efficacy results of IA1, the eDMC recommended stopping the study for futility per the futility criteria prespecified in the sSAP.	To inform of the decision to stop this clinical study.
1.1 Synopsis, Hypotheses, Objectives, and Endpoints 3 Hypotheses, Objectives, and Endpoints 4.1 Overall Design 9 Statistical Analysis Plan 9.1 Statistical Analysis Plan Summary	Added that prespecified IA2 and final analysis of the study described in the SAP will not be performed, safety analysis will be performed at the end of the study, and there will be no further analyses for efficacy and PRO endpoints.	To inform of plans for further analyses.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis, Hypotheses, Objectives, and Endpoints 2.3 Benefit/Risk Assessment 3 Hypotheses, Objectives, and Endpoints 4.1 Overall Design 6.3.3 Blinding 8.1.10 Participant Blinding/Unblinding 9 Statistical Analysis Plan	Added that the study has been unblinded.	To clarify status of study blind.
1.1 Synopsis, Hypotheses, Objectives, and Endpoints 1.3.1 Initial Treatment Phase (Pembrolizumab/Placebo Plus Enzalutamide) 3 Hypotheses, Objectives, and Endpoints 4.1 Overall Design 6.1 Study Intervention(s) Administered 9 Statistical Analysis Plan Summary	Added that all participants should be discontinued from study intervention; however, participants deriving clinical benefit may have the option to continue receiving the combination of enzalutamide and pembrolizumab or transition to SOC. In Sections 1.1, 3, 4.1, and 6.1 only, added that if enzalutamide as SOC is not accessible off-study to the participant, central sourcing may continue.	To clarify how participants may continue to receive study intervention.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis, Hypotheses, Objectives, and Endpoints 1.3.1 Initial Treatment Phase (Pembrolizumab/Placebo Plus Enzalutamide) 3 Hypotheses, Objectives, and Endpoints 4.1 Overall Design	Added that participants still on study intervention will have local tumor imaging assessments per SOC schedule, but will no longer have central PSA blood samples collected, SSRE, CCI [redacted] or tumor response assessments by BICR, and Efficacy Follow-up and Survival Follow-up visits will no longer be conducted.	Given that the efficacy IA1 indicated futility, further tumor scans and response assessments by BICR, SSRE and PRO assessments, and collection of additional samples for PSA CCI [redacted] are considered unnecessary.
1.1 Synopsis, Estimated Duration of Study	Changed the estimated duration of the study from approximately CCI [redacted] to approximately CCI [redacted].	To reflect new timelines based on updates made in Amendment 09.
1.1 Synopsis, Study Governance Committees	Added statement that the Executive Oversight Committee and DMC are no longer applicable.	These committees will no longer review the study data.
1.3.2 Second Course Phase (Pembrolizumab Retreatment ONLY) 4.1 Overall Design 6.6.4 Second Course 7.1 Discontinuation of Study Intervention 8.2.1.4 Second Course (Retreatment) Tumor Imaging	Added that as of Amendment 09, Second Course treatment is not an option. In Section 1.3.2 only, added statement indicating the study will be stopped due to futility.	To update the status of the Second Course Phase of the study.

Section # and Name	Description of Change	Brief Rationale
CCI [redacted]		
7.1 Discontinuation of Study Intervention	Added note to the BICR-verified radiographic disease progression criterion indicating that central tumor response assessments will be discontinued and tumor response assessments will be performed locally in participants who are continuing to receive study intervention.	To clarify that participants still on treatment with study intervention at the time of Amendment 09 will be assessed locally for disease progression.
8.2.1 Tumor Imaging and Assessment of Disease 8.2.2 PCWG Modified RECIST 1.1 Assessment of Disease	Added statements indicating that central tumor response assessments will be discontinued, and local tumor imaging should continue per SOC schedule for participants still on study treatment.	To clarify that participants still receiving study intervention will continue with local tumor imaging per SOC schedule.
8.2.3 Prostate-specific Antigen Assessments	Added statement indicating that PSA assessments will be discontinued.	PSA assessments are considered unnecessary given that the efficacy IA1 indicated futility.

Section # and Name	Description of Change	Brief Rationale
8.4 Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Reportable Safety Events	CCI	
CCI		
CCI		
8.12.5.2 Efficacy Follow-up Visits	Added statement indicating that Efficacy Follow-up Visits will be discontinued.	These visits are considered unnecessary given that the efficacy IA1 indicated futility.
8.12.5.3 Survival Follow-up	Added statement that Survival Follow-up visits will be discontinued. Participants remaining on study intervention should continue to be monitored in the study through the AE reporting period.	Survival follow-up is only for participants remaining on study at the time of this amendment, and participants will be followed for the duration of the AE reporting period.

Section # and Name	Description of Change	Brief Rationale
9.1 Statistical Analysis Plan Summary 9.7 Interim Analyses 9.8 Multiplicity 9.9 Sample Size and Power Calculations	Added statements describing the results of the efficacy IA that led to the determination to stop the study due to futility and clarified what analyses will be performed.	To specify which analyses will be conducted and which will no longer be performed given that the efficacy IA1 indicated futility.
9.1 Statistical Analysis Plan Summary 9.7 Interim Analyses	Added that a non-binding futility analysis of OS was added prior to IA1 and described in the sSAP.	Clarification regarding update to sSAP prior to IA1.
Throughout Document	Minor administrative, formatting, grammatical, and typographical changes were made throughout the document.	To ensure clarity and accurate interpretation of the intent of the protocol.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3, Randomized, Double-blind Trial of Pembrolizumab (MK-3475) Plus Enzalutamide Versus Placebo Plus Enzalutamide in Participants With Metastatic Castration-Resistant Prostate Cancer (mCRPC) (KEYNOTE-641)

Short Title: Phase 3 Study of Pembrolizumab/Placebo plus Enzalutamide in mCRPC

Acronym: KEYNOTE-641

Hypotheses, Objectives, and Endpoints:

In participants with mCRPC who are abiraterone-naïve or are intolerant to/progressed on abiraterone acetate:

NOTE: Based on the data from an interim safety and efficacy analysis for KEYNOTE-641 (data cutoff 12-DEC-2022), the eDMC recommended stopping the study for futility per the futility criteria prespecified in the sSAP. Based upon these data and the recommendation of the eDMC, the study has been unblinded (as of 22-FEB-2023). Prespecified IA2 and final analysis of the study described in the SAP will not be performed. Safety analysis will be performed at the end of the study; there will be no further analyses for efficacy[CCI] endpoints collected from participants beyond the IA1 cutoff date.

NOTE: In alignment with the study update memo sent to investigators on 28-FEB-2023, all study participants should stop ongoing treatment with pembrolizumab/placebo. Exceptions may be requested for study participants who, in the assessment of their study physician, are benefitting from the combination of enzalutamide and pembrolizumab, after consulting with the Sponsor. All other study participants should be discontinued from the study and be offered SOC treatment as deemed necessary by the investigator. If enzalutamide as SOC is not accessible off study to the participant, central sourcing may continue. As of Amendment 09, participants who are still on study intervention will no longer have central PSA blood samples collected, SSRE assessments, [CCI] or tumor response assessments by BICR. However, local tumor imaging assessments should continue per SOC schedule. The last required study visit will be the Safety Follow-up Visit; Efficacy Follow-up and Survival Follow-up visits will no longer be conducted. Updated analyses are described in Section 9.

Primary Objectives	Primary Endpoints
To compare pembrolizumab plus enzalutamide versus placebo plus enzalutamide with respect to **overall survival (OS)**	**OS:** the time from randomization to death due to any cause
Hypothesis (H1): The combination of pembrolizumab plus enzalutamide is superior to placebo plus enzalutamide with respect to OS	
To compare pembrolizumab plus enzalutamide versus placebo plus enzalutamide with respect to **radiographic progression-free survival (rPFS)** per Prostate Cancer Working Group (PCWG)-modified Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as assessed by blinded independent central review (BICR) where soft tissue will be assessed per RECIST 1.1 modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, and bone disease will be assessed per PCWG criteria	**rPFS:** the time from randomization to radiographic progression, or death due to any cause, whichever occurs first
Hypothesis (H2): The combination of pembrolizumab plus enzalutamide is superior to placebo plus enzalutamide with respect to rPFS per PCWG-modified RECIST 1.1 as assessed by BICR	
Secondary Objectives	Secondary Endpoints
To compare pembrolizumab plus enzalutamide versus placebo plus enzalutamide with respect to the **time to initiation of the first subsequent anticancer therapy or death (TFST)** Hypothesis (H3): The combination of pembrolizumab plus enzalutamide is superior to placebo plus enzalutamide with respect to TFST	**TFST:** the time from randomization to initiation of the first subsequent anticancer therapy or death, whichever occurs first

To compare pembrolizumab plus enzalutamide versus placebo plus enzalutamide with respect to the: – **Prostate-specific antigen (PSA) response rate** – **PSA undetectable rate** – **Objective response rate (ORR) and duration of response (DOR) per PCWG-modified RECIST 1.1 as assessed by BICR**	**PSA response:** a PSA decline of ≥50% from baseline measured twice at least 3 weeks apart **PSA undetectable**: PSA <0.2 ng/mL during study intervention **Objective response (OR)**: complete response (CR) or partial response (PR) **DOR**: the time from the earliest date of the first documented evidence of CR or PR until earliest date of disease progression or death due to any cause, whichever occurs first
To compare pembrolizumab plus enzalutamide versus placebo plus enzalutamide with respect to the: – **Time to PSA progression** – **Time to radiographic soft-tissue progression** per soft-tissue rules of PCWG-modified RECIST 1.1, as assessed by BICR – **Time to pain progression (TTPP)** based on Brief Pain Inventory-Short Form (BPI-SF) Item 3 "worst pain in 24 hours" and opiate analgesic use Analgesic Quantification Algorithm (AQA) score – **Time to Symptomatic Skeletal-Related Event (SSRE)**	**Time to PSA progression**: the time from randomization to PSA progression. The PSA progression date is defined as the date of 1) ≥25% increase and ≥2 ng/mL above the nadir, confirmed by a second value ≥3 weeks later if there is PSA decline from baseline, or 2) ≥25% increase and ≥2 ng/mL increase from baseline beyond 12 weeks if there is no PSA decline from baseline. **Time to radiographic soft-tissue progression:** the time from randomization to radiographic soft-tissue progression **TTPP** based on BPI-SF Item 3 "worst pain in 24 hours" and opiate analgesic use (AQA score) **Time to Symptomatic Skeletal-Related Event (SSRE)**: the time from randomization to the first SSRE, defined as • first use of external-beam radiation therapy (EBRT) to prevent or relieve skeletal symptoms • occurrence of new symptomatic pathologic bone fracture (vertebral or nonvertebral)

	• occurrence of spinal cord compression • or tumor-related orthopedic surgical intervention, whichever occurs first
To evaluate the **safety and tolerability** of pembrolizumab plus enzalutamide versus placebo plus enzalutamide	**Adverse events (AEs)** Study intervention **discontinuation due to AEs**

Overall Design:

Study Phase	Phase 3
Primary Purpose	Treatment
Indication	Treatment of mCRPC
Population	Participants with mCRPC
Study Type	Interventional
Intervention Model	Parallel This is a multi-site study.
Type of Control	Placebo Control
Study Blinding	Double-blind under in-house blinding procedures
Masking	Investigator Participant Sponsor
Estimated Duration of Study	The Sponsor estimates that the study will require approximately CCI [redacted] from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Approximately 1240 participants will be randomized in this trial.

Intervention Groups and Duration:

Intervention Groups

Intervention Group Name	Drug	Dose Strength	Dose Frequency	Route of Admin.	Regimen/ Treatment Period/ Vaccination Regimen	Use
Arm 1: Pembro + Enzalutamide	Pembrolizumab	200 mg	Q3W	IV	D1 of each 21-day cycle for up to 35 cycles	Test product
	Enzalutamide	160 mg	QD	PO	Four 40-mg capsules/tablets orally QD or two 80-mg tablets orally QD	SOC
Arm 2: Placebo + Enzalutamide	Placebo	NA	Q3W	IV	D1 of each 21-day cycle for up to 35 cycles	Placebo
	Enzalutamide	160 mg	QD	PO	Four 40-mg capsules/tablets orally QD or two 80-mg tablets orally QD	SOC

D=Day; IV=intravenous; NA=not applicable; PO=oral; Q3W=every 3 weeks; QD=once daily; SOC=standard of care.

Total Number	2 arms
Duration of Participation	Each participant will participate in the study from the time the participant provides documented informed consent through the final protocol-specified contact. Each participant will be assigned to receive study intervention (enzalutamide combination with either pembrolizumab or placebo) until one of the conditions for discontinuation of study intervention is met. Treatment with pembrolizumab/placebo may continue for up to 35 cycles (approximately 2 years starting with the first infusion in Cycle 1) or until meeting criteria for discontinuation of study intervention. Treatment with enzalutamide will proceed continuously from Day 1 of Cycle 1 in both arms, unless criteria for discontinuation of study intervention are met. Participants who stop pembrolizumab as a result of obtaining an investigator-determined confirmed CR or those subjects who stop after receiving 35 cycles may be eligible for an additional 17 cycles of

	pembrolizumab (approximately 1 year) after progressive disease if they meet the criteria for re-treatment (Second Course Phase) and the study is ongoing (Section 6.6.4). Participants randomized to placebo will not be permitted to cross over to pembrolizumab following progression. After the end of treatment, each participant will be followed for the occurrence of AEs and spontaneously reported pregnancy of female partner as described under Section 8.4. Participants who discontinue for reasons other than radiographic disease progression will have post-treatment follow-up imaging for disease status until disease progression is documented radiographically per PCWG-modified RECIST 1.1 and verified by BICR, start of new anticancer treatment, or withdrawal of consent, whichever occurs first. All participants will be followed up for OS until death, withdrawal of consent, or the end of the study. The overall study ends when the last participant completes the last study-related contact or visit, withdraws from the study, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

Study Governance Committees:

Steering Committee	No
Executive Oversight Committee	Yes
Data Monitoring Committee	Yes
Clinical Adjudication Committee	No
Study governance considerations are outlined in Appendix 1. As of Amendment 09, the Executive Oversight Committee and Data Monitoring Committee are no longer applicable.	

Study Accepts Healthy Volunteers: No

A list of abbreviations used in this document can be found in Appendix 10.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Schema

1.3 Schedule of Activities (SoA)

1.3.1 Initial Treatment Phase (Pembrolizumab/Placebo Plus Enzalutamide)

Note: As of Amendment 09, study participants should stop ongoing treatment with pembrolizumab/placebo except as described in Section 6.1. The study participants continuing to receive enzalutamide and pembrolizumab (Arm 1) or enzalutamide alone (Arm 2) will follow the therapy regimen described under "Study Intervention Administration" (without placebo) until criteria for discontinuation are met.

As of Amendment 09, participants who are still on study intervention will no longer have central PSA blood samples collected, SSRE assessments, CCI [redacted] or tumor response assessments by BICR. However, local tumor imaging assessments should continue per SOC schedule. The last required study visit will be the Safety Follow-up visit; Efficacy Follow-up and Survival Follow-up visits will no longer be conducted. The full SoA table below is retained for reference.

Trial Period	Screening Phase	Treatment Cycles (21-day cycles)								End of Treatment	Post-Treatment			CCI [redacted]
Treatment Cycle/Title	Screening (Visit 1)	1	2	3	4	5	6	7 to 10	11 and beyond	End of Treatment Visit	Safety Follow-up	Follow-up Visits	Survival Follow-up	
Scheduling Window (Days)	-42 to -1	+ 3	± 3	± 3	± 3	± 3	± 3	± 3	±3	At time of Discon	30 days from last dose (+ 7 days)	Q9W to W54 then Q12W (± 7 days)	Q12W (± 7 days)	
Administrative Procedures														
Informed consent	X													
Inclusion/exclusion criteria	X													

Trial Period	**Screening Phase**	**Treatment Cycles (21-day cycles)**								**End of Treatment**	**Post-Treatment**			CCI [redacted]
Treatment Cycle/Title	Screening (Visit 1)	1	2	3	4	5	6	7 to 10	11 and beyond	End of Treatment Visit	Safety Follow-up	Follow-up Visits	Survival Follow-up	
Scheduling Window (Days)	-42 to -1	+ 3	± 3	± 3	± 3	± 3	± 3	± 3	±3	At time of Discon	30 days from last dose (+ 7 days)	Q9W to W54 then Q12W (± 7 days)	Q12W (± 7 days)	
Participant identification card	X													
Demographics and medical history	X													
Prior and concomitant medication review	X	X	X	X	X	X	X	X	X	X	X			
SSRE Evaluation	X	X	X	X	X	X	X	X	X	X	X	X		
HIV, Hep B, and Hep C status	X													
Randomization		X												
Telephone contact or visit		X												

Trial Period	**Screening Phase**	**Treatment Cycles (21-day cycles)**								**End of Treatment**	**Post-Treatment**			CCI
Treatment Cycle/Title	Screening (Visit 1)	1	2	3	4	5	6	7 to 10	11 and beyond	End of Treatment Visit	Safety Follow-up	Follow-up Visits	Survival Follow-up	
Scheduling Window (Days)	-42 to -1	+ 3	± 3	± 3	± 3	± 3	± 3	± 3	±3	At time of Discon	30 days from last dose (+ 7 days)	Q9W to W54 then Q12W (± 7 days)	Q12W (± 7 days)	
Clinical Procedures/Assessments														
AE monitoring	X	X	X	X	X	X	X	X	X	X	X	X		
Full physical examination	X									X				
Directed physical examination		X	X	X	X	X	X	X	X		X			
Vital signs, height, and weight	X	X	X	X	X	X	X	X	X	X				
12-lead ECG	X													

Trial Period	**Screening Phase**	**Treatment Cycles (21-day cycles)**								**End of Treatment**	**Post-Treatment**			CCI
Treatment Cycle/Title	Screening (Visit 1)	1	2	3	4	5	6	7 to 10	11 and beyond	End of Treatment Visit	Safety Follow-up	Follow-up Visits	Survival Follow-up	
Scheduling Window (Days)	-42 to -1	+ 3	± 3	± 3	± 3	± 3	± 3	± 3	±3	At time of Discon	30 days from last dose (+ 7 days)	Q9W to W54 then Q12W (± 7 days)	Q12W (± 7 days)	
ECOG performance status	X	X	X	X	X	X	X	X	X	X				
Subsequent anticancer therapy status											X	X	X	
Vital status		←----------								----------→			X	
Study Intervention Administration														
Pembrolizumab/ placebo		X	X	X	X	X	X	X	X					
Enzalutamide		X	X	X	X	X	X	X	X					
Enzalutamide container returned			X	X	X	X	X	X	X	X				

Trial Period	**Screening Phase**	**Treatment Cycles (21-day cycles)**								**End of Treatment**	**Post-Treatment**			CCI
Treatment Cycle/Title	Screening (Visit 1)	1	2	3	4	5	6	7 to 10	11 and beyond	End of Treatment Visit	Safety Follow-up	Follow-up Visits	Survival Follow-up	
Scheduling Window (Days)	-42 to -1	+ 3	± 3	± 3	± 3	± 3	± 3	± 3	±3	At time of Discon	30 days from last dose (+ 7 days)	Q9W to W54 then Q12W (± 7 days)	Q12W (± 7 days)	
Laboratory Procedures/Assessments: analysis performed by central laboratory														
PT or INR and PTT/aPTT	X													
Complete blood count with differential	X		X	X	X	X	X	X	X	X	X			
Comprehensive chemistry panel	X		X	X	X	X	X	X	X	X	X			
Urinalysis	X		X		X		X	X	X	X	X			
T3 or FT3, FT4, and TSH	X		X		X		X	X	X	X	X			
Testosterone	X				X			X	X	X				

Trial Period	Screening Phase	Treatment Cycles (21-day cycles)								End of Treatment	Post-Treatment			CCI
Treatment Cycle/Title	Screening (Visit 1)	1	2	3	4	5	6	7 to 10	11 and beyond	End of Treatment Visit	Safety Follow-up	Follow-up Visits	Survival Follow-up	
Scheduling Window (Days)	-42 to -1	+ 3	± 3	± 3	± 3	± 3	± 3	± 3	±3	At time of Discon	30 days from last dose (+ 7 days)	Q9W to W54 then Q12W (± 7 days)	Q12W (± 7 days)	
Procedures/Assessments: analysis performed CENTRALLY														
Efficacy Measurements														
PSA by central laboratory	X		← Q3W (± 7 days) from randomization →							X	X	X		

Trial Period	**Screening Phase**	**Treatment Cycles (21-day cycles)**								**End of Treatment**	**Post-Treatment**			CCI
Treatment Cycle/Title	Screening (Visit 1)	1	2	3	4	5	6	7 to 10	11 and beyond	End of Treatment Visit	Safety Follow-up	Follow-up Visits	Survival Follow-up	
Scheduling Window (Days)	-42 to -1	+ 3	± 3	± 3	± 3	± 3	± 3	± 3	±3	At time of Discon	30 days from last dose (+ 7 days)	Q9W to W54 then Q12W (± 7 days)	Q12W (± 7 days)	
Tumor imaging (CT/MRI) and bone scan	X		← Q9W (± 7 days) through Week 54, then Q12W (± 7 days) thereafter →							X		X		
CCI														
CCI														

Trial Period	**Screening Phase**	**Treatment Cycles (21-day cycles)**								**End of Treatment**	**Post-Treatment**			**Notes**
Treatment Cycle/Title	Screening (Visit 1)	1	2	3	4	5	6	7 to 10	11 and beyond	End of Treatment Visit	Safety Follow-up	Follow-up Visits	Survival Follow-up	CCI [redacted]
Scheduling Window (Days)	-42 to -1	+ 3	± 3	± 3	± 3	± 3	± 3	± 3	±3	At time of Discon	30 days from last dose (+ 7 days)	Q9W to W54 then Q12W (± 7 days)	Q12W (± 7 days)	
CCI [redacted]														

Trial Period	Screening Phase	Treatment Cycles (21-day cycles)								End of Treatment	Post-Treatment			Notes
Treatment Cycle/Title	Screening (Visit 1)	1	2	3	4	5	6	7 to 10	11 and beyond	End of Treatment Visit	Safety Follow-up	Follow-up Visits	Survival Follow-up	CCI [redacted]
Scheduling Window (Days)	-42 to -1	+ 3	± 3	± 3	± 3	± 3	± 3	± 3	±3	At time of Discon	30 days from last dose (+ 7 days)	Q9W to W54 then Q12W (± 7 days)	Q12W (± 7 days)	
CCI [redacted]														

Abbreviations: AE=adverse event; aPTT=activated partial thromboplastin time; CCI [redacted]; BICR=blinded independent central review; CCI [redacted] CT=computed tomography; CCI [redacted]; DC=discontinuation; CCI [redacted]; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; CCI [redacted]; FT3=free triiodothyronine; FT4=free thyroxine; Hep=hepatitis; HIV=human immunodeficiency virus; ICF=informed consent form; INR=international normalized ratio; IRB=Institutional Review Board; IV=intravenous; MRI=magnetic resonance imaging; PD=progressive disease; PD-L1=programmed cell death ligand 1; PRO=patient-reported outcome; PSA=prostate-specific antigen; PT=prothrombin time; PTT=partial thromboplastin time; Q9W=every 9 weeks; Q12W=every 12 weeks; CCI [redacted]; SAE=serious adverse event; SCF=Sponsor Communication Form; T3=total triiodothyronine; TSH=thyroid-stimulating hormone; W=week.

1.3.2 Second Course Phase (Pembrolizumab Retreatment ONLY)

NOTE: As of Amendment 09, the study will be stopped due to futility. Second Course treatment is not an option for participants.

Trial Period	**Treatment Cycles (21-day cycles)**					**End of Treatment**	**Post-Treatment**			**Notes**
Treatment Cycle/Title	1	2	3	4	Cycle 5 to 17	End of Treatment Visit	Safety Follow-up	Follow-up Visits	Survival Follow-up	**The safety follow-up is not needed if the Discontinuation Visit occurs >30 days after the last dose**
Scheduling Window (Days)		± 3	± 3	± 3	± 3	At time of Discon	30 days from last dose (+ 7 days)	Q12W (± 7 days)	Q12W (± 7 days)	
Administrative Procedures										
Eligibility criteria	X									
Concomitant medication review	X	X	X	X	X	X	X			Report new medications started 28 days prior to the first retreatment dose and up to 30 days after last dose of study intervention. All medications related to reportable SAEs and ECIs should be recorded
Clinical Procedures/Assessments										
AE monitoring	X	X	X	X	X	X	X	X		AEs must be recorded up to 30 days after last dose of study intervention. SAEs must be recorded up to 90 days after the last dose of study intervention or 30 days following cessation of treatment if the participant initiates new anticancer treatment, whichever comes first. Treatment-related SAEs must be reported regardless of the time point when they occur.
Full physical examination	X					X				
Directed physical examination		X	X	X	X		X			

Trial Period	**Treatment Cycles (21-day cycles)**					**End of Treatment**	**Post-Treatment**			**Notes**
Treatment Cycle/Title	1	2	3	4	Cycle 5 to 17	End of Treatment Visit	Safety Follow-up	Follow-up Visits	Survival Follow-up	**The safety follow-up is not needed if the Discontinuation Visit occurs >30 days after the last dose**
Scheduling Window (Days)		± 3	± 3	± 3	± 3	At time of Discon	30 days from last dose (+ 7 days)	Q12W (± 7 days)	Q12W (± 7 days)	
Vital signs and weight	X	X	X	X	X	X				
ECOG performance status	X	X	X	X	X	X				After Cycle 8, perform every other cycle.
Subsequent anticancer therapy status							X	X	X	Safety Follow-up visit must occur before the start of the new therapy.
Survival status	←----------								→| X	Updated survival status may be requested by the Sponsor at any time during the course of the study.
Study Intervention Administration										
Pembrolizumab	X	X	X	X	X					200 mg IV Q3W
Laboratory Procedures/Assessments: analysis performed by CENTRAL laboratory										**Perform within 10 days prior to participant receiving first retreatment infusion. After Cycle 1, predose laboratory procedures may be conducted up to 72 hours predose. Unresolved abnormal lab results associated with drug-related AEs should be followed until resolution.**
PT or INR and PTT/aPTT	X									PT or INR and aPTT/PTT should be monitored more closely in participants receiving anticoagulant therapy during treatment and safety follow-up period
Complete blood count with differential	X	X	X	X	X	X	X			
Comprehensive chemistry panel	X	X	X	X	X	X	X			

Trial Period	**Treatment Cycles (21-day cycles)**					**End of Treatment**	**Post-Treatment**			**Notes**
Treatment Cycle/Title	1	2	3	4	Cycle 5 to 17	End of Treatment Visit	Safety Follow-up	Follow-up Visits	Survival Follow-up	**The safety follow-up is not needed if the Discontinuation Visit occurs >30 days after the last dose**
Scheduling Window (Days)		± 3	± 3	± 3	± 3	At time of Discon	30 days from last dose (+ 7 days)	Q12W (± 7 days)	Q12W (± 7 days)	
Urinalysis	X		X		X	X	X			Urinalysis and thyroid function tests are performed every other cycle (ie, Cycle 5, 7, 9, etc).
T3 or FT3, FT4, and TSH	X		X		X	X	X			
Testosterone	X			X	X	X				Testosterone is determined every 4 cycles.
Procedures/Assessments:										**Schedule of scans and PSA are calculated from the first retreatment infusion. The timing of assessments should not be adjusted for dose delays or cycle starts.**
Efficacy Measurements										
PSA by central laboratory	X	←---------→ Q3W (±7 days) from first retreatment infusion				X	X	X		Collect predose on days pembrolizumab is given.

Trial Period	**Treatment Cycles (21-day cycles)**					**End of Treatment**	**Post-Treatment**			**Notes**
Treatment Cycle/Title	1	2	3	4	Cycle 5 to 17	End of Treatment Visit	Safety Follow-up	Follow-up Visits	Survival Follow-up	**The safety follow-up is not needed if the Discontinuation Visit occurs >30 days after the last dose**
Scheduling Window (Days)		± 3	± 3	± 3	± 3	At time of Discon	30 days from last dose (+ 7 days)	Q12W (± 7 days)	Q12W (± 7 days)	
Tumor imaging (CT/MRI) and bone scan (evaluated locally)	X	←----------→ W9 (± 7 days) after restart of treatment, then Q12W (± 7 days) thereafter.				X		X		CT/MRI chest/abdomen/pelvis and whole-body bone scans must be performed within 28 days prior to the participant receiving first retreatment infusion. If a scan was obtained within 4 weeks prior to treatment discontinuation, then another scan at discontinuation is not mandatory. Participants who discontinue treatment without documented disease progression should continue to be monitored for disease status by radiologic imaging (CT/MRI and bone scans) until the start of new anticancer treatment, documented disease progression, death or the end of the study, whichever occurs first: Images will be submitted to the imaging Contract Research Organization (iCRO).

Abbreviations: AE=adverse event; aPTT=activated partial thromboplastin time; CT=computed tomography; DC=discontinuation; ECI=events of clinical interest; ECOG=Eastern Cooperative Oncology Group; FT3=free triiodothyronine; FT4=free thyroxine; INR=international normalized ratio; MRI=magnetic resonance imaging; PSA=prostate-specific antigen; PT=prothrombin time; PTT=partial thromboplastin time; Q9W=every 9 weeks; Q12W=every 12 weeks; SAE=serious adverse event; T3=total triiodothyronine; TSH=thyroid-stimulating hormone.

2 INTRODUCTION

Prostate cancer represents the second most common malignancy diagnosed in men worldwide, with an estimated annual incidence of over 1 million and an expected 300,000 plus deaths annually [Ferlay, J., et al 2015]. In the United States (US), approximately 1 in every 9 men will be diagnosed with prostate cancer in his lifetime [Siegel, R. L., et al 2018].

While many men diagnosed with locally confined disease may be treated definitively with radiation or surgery, men who go on to develop or are diagnosed with metastatic prostate cancer, an incurable entity, are typically treated first with androgen deprivation therapy (ADT), usually with a gonadotropin-releasing hormone (GnRH) agonist or antagonist that results in suppression of testosterone production in the testes. This alone often succeeds in controlling disease for some time, years in many cases. However, prostate cancer progresses invariably and requires additional systemic therapies to re-establish control of disease. The point at which metastatic prostate cancer progresses in spite of ADT alone is referred to as castration resistance, and the disease at this point is known as mCRPC.

A number of important systemic therapies have been developed to treat mCRPC, have received regulatory approval, and now comprise the current therapeutic landscape. This includes the next generation hormonal agents (NHA) abiraterone acetate and enzalutamide, and the taxanes docetaxel and cabazitaxel.

Abiraterone acetate is an androgen biosynthesis inhibitor that inhibits 17 α-hydroxylase/ C17,20-lyase (cytochrome P450 [CYP]17). This enzyme is expressed in testicular, adrenal, and prostatic tumor tissues and is required for androgen biosynthesis. The efficacy and safety of abiraterone acetate with prednisone was established in two Phase 3 randomized placebo-controlled clinical studies [Fizazi, K., et al 2012] [Ryan, C. J., et al 2015].

Enzalutamide is an endocrine therapy currently used for the treatment of mCRPC. Enzalutamide was examined in randomized clinical studies in participants with mCRPC before treatment with chemotherapy and found to have superior OS versus control therapy (placebo and prednisone, respectively) [Ryan, C. J., et al 2013] [Beer, T. M., et al 2014].

2.1 Study Rationale

The NHAs enzalutamide and abiraterone acetate were examined in randomized clinical studies in participants with mCRPC before treatment with chemotherapy and found to have superior OS versus control therapy (placebo and prednisone, respectively) [Ryan, C. J., et al 2013] [Beer, T. M., et al 2014].

The efficacy and safety of enzalutamide in participants with mCRPC were demonstrated in 2 randomized, placebo-controlled, multicenter Phase 3 clinical trials. In one study, a total of 1199 participants who had received prior docetaxel-based chemotherapy were randomized 2:1 to receive either enzalutamide orally at a dose of 160 mg once daily (N = 800) or placebo orally once daily (N = 399) [Scher, H. I., et al 2012]. A statistically significant improvement in OS was demonstrated at the prespecified IA at the time of 520 deaths in participants in the enzalutamide arm compared to participants in the placebo arm. Median survival was 18.4

months (95% CI, 17.3 months to "not reached") versus 13.6 months (95% CI, 11.3 to 15.8 months) in the enzalutamide and placebo arms, respectively [Scher, H. I., et al 2012]. In the other study, 1717 chemotherapy-naïve participants were randomized 1:1 to receive either enzalutamide orally at a dose of 160 mg once daily (N = 872) or placebo orally once daily (N = 845). A statistically significant improvement in OS was demonstrated at the prespecified IA, conducted after 540 deaths in participants in the enzalutamide arm compared to participants in the placebo arm. Median survival was 32.4 months (95% CI, 30.1 months to "not reached") versus 30.2 months (95% CI, 28.0 months to "not reached") in the enzalutamide and placebo arms, respectively. Forty percent of enzalutamide-treated participants and 70% of placebo-treated participants received subsequent therapies for mCRPC that may prolong OS [Beer, T. M., et al 2014]. An updated survival analysis was conducted when 784 deaths were observed, and results from this analysis were consistent with those from the prespecified IA. Median survival was 35.3 months (95% CI, 32.2 months to "not reached") versus 31.3 months (95% CI, 28.8 to 34.2 months) in the enzalutamide and placebo arms, respectively [Beer, T. M., et al 2017].

Bishop et al. demonstrated in a mouse xenograft model that enzalutamide-resistant tumors express significantly increased levels of tumor intrinsic programmed cell death ligand 1 (PD-L1) compared to non-enzalutamide resistant tumors [Bishop, J. L., et al 2015]. Additionally, in a small cohort of participants, it was noted that those who progressed while on enzalutamide had a significantly increased number of PD-L1/programmed cell death ligand 2 (PD-L2)-positive dendritic cells in their blood compared to treatment-naïve participants or participants who were responding to enzalutamide. Thus, by blocking the programmed cell death 1 (PD-1) receptor, pembrolizumab treatment may increase the immune response to enzalutamide-resistant cells that emerge in response to treatment with enzalutamide.

The PSA response rate of participants treated with enzalutamide after abiraterone acetate may be modest, as judged by a retrospective study of mCRPC in participants who received various prior sequences of abiraterone acetate, docetaxel, and enzalutamide. The study found that the group that received enzalutamide after abiraterone acetate (N = 79) demonstrated a 50% or greater PSA decline in 18% of participants. The median OS was reached only for participants in the prior abiraterone acetate + docetaxel group and was 12.2 months [Cheng, H. H., et al 2015]. However, in another retrospective study evaluating the PSA response of enzalutamide or docetaxel treatment after abiraterone acetate, the enzalutamide arm (N = 30) demonstrated a 50% or greater PSA decline in 34% of participants. The median PSA progression-free survival (PFS) was 4.1 months and the median PFS was 4.7 months. OS was not described [Suzman, D. L., et al 2014]. It is hoped that the present study of the pembrolizumab + enzalutamide combination will provide data to evaluate the efficacy of this combination in this setting where there is a need for data from prospectively designed studies to demonstrate improved response.

KEYNOTE-365, a Phase 2 umbrella study evaluating pembrolizumab combination therapies in mCRPC participants, included a Cohort C for the evaluation of pembrolizumab in combination with enzalutamide in participants who have received prior abiraterone acetate in the prechemotherapy mCRPC state. Interim results from Cohort C in KN365 (data cutoff 03-APR-2018), which evaluated the population intended for the current study, showed a

response (at least 50% reduction in PSA from baseline) in 23.9% (95% CI: 14.3%, 35.9%) of participants with a baseline PSA value available (n = 67), and 29.6% (95% CI: 18.0%, 43.6%) in those with an elevated PSA at baseline (n = 54). While an OR (CR + PR) was observed in 20.0% (95% CI: 6.8%, 40.7%) of participants with RECIST-measurable disease at baseline (n = 25), the DCR for the cohort was 50.7% (95% CI: 38.4%, 63.0%) driven primarily by the proportion of participants who had SD for at least 24 weeks (43.5%) prior to disease progression. Half of the participants had a reduction in tumor size, of which nearly a third had a reduction of more than 30%. These results provide support for further evaluation of the combination of pembrolizumab and enzalutamide in patients with mCRPC.

The present trial, KEYNOTE-641, will be a randomized, multicenter, double-blind, placebo-controlled, Phase 3 trial in participants with mCRPC in the prechemotherapy mCRPC state. Participants will be randomly assigned 1:1 to treatment with either pembrolizumab + enzalutamide or placebo + enzalutamide.

2.2 Background

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and PD-L2. Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the Investigator's Brochure (IB).

2.2.1 Pharmaceutical and Therapeutic Background

2.2.1.1 Inhibition of PD-1 as a Target for Cancer Therapy

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [Disis, M. L. 2010]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [Dudley, M. E., et al 2005] [Hunder, N. N., et al 2008].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene *Pdcd1*) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively

regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [Greenwald, R. J., et al 2005] [Okazaki, T., et al 2001].

The structure of murine PD-1 has been resolved [Zhang, X., et al 2004]. PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type (IgV-type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade [Okazaki, T., et al 2001] [Chemnitz, J. M., et al 2004] [Sheppard, K-A, et al 2004] [Riley, J. L. 2009]. The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [Parry, R. V., et al 2005] [Francisco, L. M., et al 2010]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in mCRPC.

2.2.1.2 Overview of Prostate Cancer

Prostate cancer represents one of the most commonly diagnosed cancer malignancies and the second leading cause of cancer-related deaths in men worldwide [Center, M. M., et al 2012] [Torre, L. A., et al 2015]. According to the Global Burden of Disease Study [Fitzmaurice, C., et al 2018], there were 1.4 million new prostate cancer cases and 381,000 deaths from the disease globally in 2016. These statistics highlight the socioeconomic burden prostate cancer poses worldwide. In the US, analysts estimated that there will be 164,690 new cases of prostate cancer (19% of all new cases in males) and 29,430 deaths caused by prostate cancer (9% of all new deaths of males) in 2018 [Siegel, R. L., et al 2018]. Since the advent of PSA screening about three decades ago, the prostate cancer death rate had been falling until it stabilized between 2013 and 2015 [Negoita, S., et al 2018]. Additionally, following the US Preventive Services Task Force's recommendation against routine PSA-based screening regardless of age in 2012, incidence of late-stage disease has increased [Negoita, S., et al 2018]. Although identifying cause and effect is difficult, this change in the national trend in late-stage prostate cancer incidence may portend future increases in the number of men requiring treatment for advanced disease. Therefore, there is an urgent need to develop new therapeutic strategies, including combination therapies for prostate cancer.

2.2.1.3 Unmet Medical Need in Prostate Cancer

Patients with mCRPC have a high unmet medical need. The prognosis for men diagnosed with locally confined disease is favorable, and such cases may be treated definitively with radiation therapy or surgery [Gray, P. J., et al 2017]. In fact, prostate cancer has been a prime example of an indolent cancer, with the majority of men found to have localized disease at diagnosis [Loeb, S., et al 2015]. For that reason, in the last decade physicians have increasingly adopted active surveillance as a management option for low-risk prostate cancer, reflecting the low rate of disease progression and enthusiasm for avoiding harms associated

with overtreatment (eg, incontinence and impotence) [Loeb, S., et al 2015] [Resnick, M. J., et al 2013]. Additionally, metastatic prostate cancer evolves molecularly during disease progression and/or therapy through an adaptive response, which may result in emergence of histologic variants that are biologically more aggressive and resistant to therapy [Vlachostergios, P. J., et al 2017].

Androgen signaling mediated through the androgen receptor is a critical factor for promotion and growth of prostate cancer [Knudsen, K. E. and Penning, T. M. 2010]. Therefore, until 2015 the standard of care for initial first-line therapy for metastatic prostate cancer (either recurrent or de novo metastatic tumors, heretofore called CSPC) consisted of ADT (eg, GnRH agonist or antagonist). However, a great stride in treatment of CSPC was made over the last few years. The Chemohormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer (CHAARTED [Sweeney, C. J., et al 2015] [James, N. D., et al 2016]) study demonstrated significant survival benefit with the addition of docetaxel to ADT. In a 2018 follow-up analysis [Kyriakopoulos, C. E., et al 2018], investigators extended the original median duration of follow-up from 28.9 months to 53.7 months and confirmed the median OS advantage in the ADT plus docetaxel group (57.6 vs. 47.2 months; HR, 0.72; 95% CI, 0.50-0.79; $p<0.001$). In a similar comparison from the STAMPEDE study [James, N. D., et al 2017], researchers recommended docetaxel become part of the standard of care after a 43-month follow-up found superior results with it against ADT in median OS (81 vs 71 months; 0.78; 95% CI, 0.66-0.93; p=.006) [James, N. D., et al 2016].

As part of the STAMPEDE study, participants were randomly assigned to receive either ADT and abiraterone acetate plus prednisolone or ADT alone. Participants in the former arm had a significantly higher OS rate at 3 years (83% vs 76%; HR for death, 0.63%; 95% CI, 0.52-0.76; $p<0.001$) and significantly fewer treatment failure events (248 vs. 535; HR, 0.29; 95% CI, 0.25-0.34; $p<0.001$). Fizazi and collaborators in the LATITUDE trial [Fizazi, K., et al 2017] had similar findings. At a planned IA at 30.4 months, they reported significantly longer OS in the group receiving abiraterone acetate along with ADT than in the group receiving ADT and placebo (not reached vs 34.7 months; HR for death, 0.62; 95% CI, 0.51-0.76; $p<0.001$). While these therapies are initially effective, patients with metastatic prostate cancer invariably develop a lethal stage of the disease known as mCRPC and succumb to their disease. Though, a number of important therapies have been approved since 2004 to treat mCRPC, including chemotherapy (docetaxel and cabazitaxel), NHAs that target the androgen-receptor axis (abiraterone acetate and enzalutamide), immunotherapy (sipuleucel-T), and a bone-specific radionuclide (radium-223), no available guidance recommends appropriate sequencing or combining of these therapies, and none are curative.

In spite of these recent advances, treatment options for men with mCRPC progressing after NHA therapy and docetaxel are limited and provide limited survival benefit. In the TROPIC Phase 3 study [de Bono, J. S., et al 2010], investigators compared cabazitaxel, a second-generation semisynthetic tubulin-binding taxane, with mitoxantrone, (each in combination with prednisone) for mCRPC progressing during or after docetaxel-based therapy and detected a significant improvement in median OS in the cabazitaxel group (15.1 months [95% CI, 14.1-16.3] vs 12.7 months [95% CI, 11.6-13.7]; HR, 0.70 [95% CI, 0.59–0.83];

p<0.0001). Also, cabazitaxel retained its antitumor activity following treatment with docetaxel and abiraterone or docetaxel and enzalutamide [Pezaro, C. J., et al 2014]. However, cabazitaxel can be a toxic therapy. Deaths have occurred on study after the onset of treatment-related neutropenia or treatment-related diarrhea. Furthermore, the cabazitaxel label contains a black box warning regarding risks from neutropenia and severe hypersensitivity [U.S. Prescribing Information 2018]. Other label warnings and precautions pertain to diarrhea, renal failure, prohibitive risk in elderly patients (patients ≥65 years of age), and hepatic impairment. Consequently, cabazitaxel is not utilized widely. Retrospective studies suggest that either abiraterone or enzalutamide may be an option; however, previous therapies [Handy, C. E. and Antonarakis, E. S. 2016], the potential for developing cross-resistance [Zhang, T., et al 2015], and potential for the emergence of a more aggressive form of prostate cancer following prolonged treatment [Roubaud, G., et al 2017] must be considered and could be limiting factors. Additionally, consensus guidelines, such as those from the National Comprehensive Cancer Network (NCCN) [National Comprehensive Cancer Network 2015], recommend that men with mCRPC be encouraged to participate in clinical studies. Thus, there remains an unmet medical need for patients diagnosed with mCRPC with disease progression following treatment with an NHA therapy and/or docetaxel-based chemotherapy.

2.2.1.4 Preclinical and Clinical Studies

Refer to the pembrolizumab IB for a summary of the preclinical and clinical experience with pembrolizumab.

2.2.1.5 Pembrolizumab in mCRPC

Participants with PD-L1 positive mCRPC have been treated with pembrolizumab monotherapy in the Phase 1b KEYNOTE-028 study (Cohort E3: advanced [unresectable and/or metastatic] prostate adenocarcinoma). The primary endpoint was the ORR, according to the RECIST 1.1, which was determined by investigator review. Participants with PD-L1 positive (defined by PD-L1 expression in >1% tumor or stroma cells) mCRPC were enrolled and treated with pembrolizumab monotherapy. All had treatment with at least 1 prior antineoplastic therapy, and 17 of 23 (73.9%) and 7 of 23 (30%) had been treated with 2 or more or 5 or more lines of therapy, respectively. Of the 23 participants, only one patient remained on treatment at the time of last published analysis [Hansen, A. R., et al 2018]. Twenty-one (91.3%) had one or more post-baseline PSA level determinations; five of these participants (24%) had a ≥PSA level decline of 50%. There were 4 confirmed partial responses, according to RECIST 1.1 guidelines, for an ORR at that time of 17.4% (95% CI, 5.0-38.8%). Responses were durable (median DOR, 13.5 months), and treatment was well tolerated.

2.2.2 Ongoing Clinical Studies

2.2.2.1 Ongoing Clinical Studies in mCRPC

KEYNOTE-199 was designed to further evaluate the positive signal of activity seen in KEYNOTE-028 with pembrolizumab monotherapy in participants with mCRPC who

previously received docetaxel-based chemotherapy and underwent abiraterone acetate or enzalutamide treatment. The ORR was 4.5% (Cohorts 1 and 2) at the second IA (IA2) with a data cutoff date of 13-OCT-2017. However, the DCR suggested a durable response and potential OS benefit, regardless of PD-L1 status, that warranted further evaluation. Additionally, early unpublished results from Graff et al suggest a potential survival benefit in the advanced mCRPC population with pembrolizumab monotherapy [Graff, J. N., et al 2016].

Graff et al [Graff, J. N., et al 2016], initially enrolled 10 men in 2015-2016 who had mCRPC with evidence of progression on enzalutamide, and subsequently enrolled a total of 28. Because previous immunotherapies (nivolumab, ipilimumab) had failed to produce an objective response in mCRPC [Topalian, S. L., et al 2012] [Kwon, E. D., et al 2014], interest in pursuing further studies waned. Nonetheless, after some success, Graff et al [Graff, J. N., et al 2018], undertook the Phase 2 study adding pembrolizumab to enzalutamide for men with mCRPC progressing on enzalutamide and reported a decline in PSA ≥50% (primary endpoint) in 5 of 28 participants (17.9%) and an OR (secondary endpoint) in 3 of 12 participants (25.0%) who had measurable disease at baseline. At last report, 3 of the 5 responders continued to respond (range, 21.9-33.8 months), and median OS was 22.2 months (95% CI, 14.7-28.4 months).

KEYNOTE-365, a Phase 2 umbrella study evaluating pembrolizumab combination therapies in mCRPC participants, included a cohort for the evaluation of pembrolizumab in combination with enzalutamide (Cohort C). Participants in this cohort were required to have had previously received abiraterone acetate. The primary endpoint is the percentage of participants with a decrease in PSA level of ≥50%. In a recent amendment of the protocol, ORR based on RECIST 1.1 by BICR was changed from a secondary endpoint to a (dual) primary endpoint. Additionally, the target enrollment in each of the three cohorts was expanded to 100, and a new cohort for pembrolizumab in combination with abiraterone acetate with target enrollment of 100 mCRPC participants was added. See Section 2.1 for a summary of interim results.

Ongoing clinical trials are being conducted in multiple additional tumor types. For study details, please refer to the pembrolizumab IB.

2.2.3 Information on Other Study-Related Therapy

2.2.3.1 Enzalutamide

Enzalutamide (Xtandi®) is an androgen-receptor inhibitor indicated for the treatment of patients with mCRPC. Enzalutamide acts on different steps in the androgen-receptor signaling pathway. Enzalutamide has been shown to competitively inhibit androgen binding to androgen receptors and inhibit androgen-receptor nuclear translocation and interaction with deoxyribonucleic acid (DNA). A major metabolite, N-desmethyl enzalutamide, exhibited similar in vitro activity to enzalutamide. Enzalutamide decreased proliferation and induced cell death of prostate cancer cells in vitro and decreased tumor volume in a mouse prostate cancer xenograft model. Refer to the approved labeling for detailed background information on enzalutamide.

For additional information on enzalutamide, refer to the approved product label.

2.3 Benefit/Risk Assessment

NOTE: Based on the data from an interim safety and efficacy analysis for KEYNOTE-641 (data cutoff 12-DEC-2022), the eDMC recommended stopping the study for futility per the futility criteria prespecified in the sSAP. Based upon these data and the recommendation of the eDMC, the study has been unblinded (as of 22-FEB-2023).

It cannot be guaranteed that participants in clinical studies will directly benefit from treatment during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine.

Pembrolizumab has been administered in a large number of cancer participants with a well characterized safety profile and has received regulatory approval for advanced melanoma and non-small cell lung cancer (NSCLC). Overall, pembrolizumab is well tolerated at doses up to 10 mg/kg every 2 weeks (Q2W). Pembrolizumab has also demonstrated anticancer clinical activity and efficacy in a broad range of cancer indications (see the pembrolizumab IB).

Enzalutamide has been approved by regulatory agencies globally for the treatment of mCRPC and has been recommended for treatment for mCRPC by NCCN and ESMO guidelines [Torre, L. A., et al 2016].

Preliminary results from Cohort C of KEYNOTE-365 (Section 2.1), in which participants have been treated with a combination of pembrolizumab and enzalutamide, showed a modest OR although the DCR was 50.7%, driven primarily by the proportion of participants who had SD for at least 24 weeks (43.5%) prior to disease progression. Half of the participants had a reduction in tumor size, of which nearly a third had a reduction of more than 30%. The safety profile of the combination of pembrolizumab with other therapies is being characterized in KEYNOTE-365, a Phase 2 umbrella study in mCRPC. Pembrolizumab combination therapies have not been associated with new safety signals. In Cohort C, 37 of 69 (53.6%) participants reported Grade 3 to 5 AEs, and 24 of 69 (34.8%) participants experienced serious adverse events (SAEs).

Additional details regarding specific benefits and risks for participants participating in this clinical study may be found in the accompanying IB and informed consent documents.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

In participants with mCRPC who are abiraterone-naïve or are intolerant to/progressed on abiraterone acetate:

NOTE: Based on the data from an interim safety and efficacy analysis for KEYNOTE-641 (data cutoff 12-DEC-2022), the eDMC recommended stopping the study for futility per the futility criteria prespecified in the sSAP. Based upon these data and the recommendation of the eDMC, the study has been unblinded (as of 22-FEB-2023). Prespecified IA2 and final analysis of the study described in the SAP will not be performed. Safety analysis will be

performed at the end of the study; there will be no further analyses for efficacy CCI endpoints collected from participants beyond the IA1 cutoff date.

NOTE: In alignment with the study update memo sent to investigators on 28-FEB-2023, all study participants should stop ongoing treatment with pembrolizumab/placebo. Exceptions may be requested for study participants who, in the assessment of their study physician, are benefitting from the combination of enzalutamide and pembrolizumab, after consulting with the Sponsor. All other study participants should be discontinued from the study and be offered SOC treatment as deemed necessary by the investigator. If enzalutamide as SOC is not accessible off study to the participant, central sourcing may continue. As of Amendment 09, participants who are still on study intervention will no longer have central PSA blood samples collected, SSRE assessments, CCI , or tumor response assessments by BICR. However, local tumor imaging assessments should continue per SOC schedule. The last required study visit will be the Safety Follow-up Visit; Efficacy Follow-up and Survival Follow-up visits will no longer be conducted. Updated analyses are described in Section 9.

Objectives	Endpoints
Primary	
To compare pembrolizumab plus enzalutamide versus placebo plus enzalutamide with respect to **OS** Hypothesis (H1): The combination of pembrolizumab plus enzalutamide is superior to placebo plus enzalutamide with respect to **OS**	**OS**: the time from randomization to death due to any cause
To compare pembrolizumab plus enzalutamide versus placebo plus enzalutamide with respect to **rPFS** per PCWG-modified RECIST 1.1 as assessed by BICR where soft-tissue will be assessed per RECIST 1.1 modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ and bone disease will be assessed per PCWG criteria Hypothesis (H2): The combination of pembrolizumab plus enzalutamide is superior to placebo plus enzalutamide with respect to **rPFS** per PCWG-modified RECIST 1.1 as assessed by BICR	**rPFS**: the time from randomization to radiographic progression, or death due to any cause, whichever occurs first

Objectives	Endpoints
Secondary	
To compare pembrolizumab plus enzalutamide versus placebo plus enzalutamide with respect to **TFST** Hypothesis 3: The combination of pembrolizumab plus enzalutamide is superior to placebo plus enzalutamide with respect to **TFST**	**TFST:** the time from randomization to initiation of the first subsequent anticancer therapy or death, whichever occurs first
To compare pembrolizumab plus enzalutamide versus placebo plus enzalutamide with respect to the: – **PSA response rate** – **PSA undetectable rate** – **ORR and DOR per PCWG-modified RECIST 1.1 as assessed by BICR**	**PSA response**: a PSA decline of ≥50% from baseline measured twice at least 3 weeks apart **PSA undetectable**: PSA < 0.2 ng/mL during study intervention **OR**: CR or PR **DOR**: the time from the earliest date of the first documented evidence of CR or PR until earliest date of disease progression or death due to any cause, whichever occurs first
– To compare pembrolizumab plus enzalutamide versus placebo plus enzalutamide with respect to the: – **Time to PSA progression** – **Time to radiographic soft-tissue progression** per soft-tissue rules of PCWG-modified RECIST 1.1, as assessed by BICR – **TTPP** based on BPI-SF Item 3 “worst pain in 24 hours” and opiate analgesic use (AQA score) – **Time to SSRE**	**Time to PSA progression**: the time from randomization to PSA progression. The PSA progression date is defined as the date of 1) ≥25% increase and ≥2 ng/mL above the nadir, confirmed by a second value ≥3 weeks later if there is PSA decline from baseline, or 2) ≥25% increase and ≥2 ng/mL increase from baseline beyond 12 weeks if there is no PSA decline from baseline **Time to radiographic soft-tissue progression:** the time from randomization to radiographic soft-tissue progression **TTPP** based on BPI-SF Item 3 “worst pain in 24 hours” and opiate analgesic use (AQA score) **Time to SSRE**: the time from randomization to the first SSRE, defined as

Objectives	Endpoints
	• first use of EBRT to prevent or relieve skeletal symptoms • occurrence of new symptomatic pathologic bone fracture (vertebral or nonvertebral) • occurrence of spinal cord compression • or tumor-related orthopedic surgical intervention, whichever occurs first
To evaluate the **safety and tolerabili**ty of pembrolizumab plus enzalutamide versus placebo plus enzalutamide	**AEs** Study intervention **discontinuation due to AEs**
Tertiary/Exploratory	
CCI [redacted]	

Objectives	Endpoints
CCI [redacted]	

4 STUDY DESIGN

4.1 Overall Design

NOTE: Based on the data from an interim safety and efficacy analysis for KEYNOTE-641 (data cutoff 12-DEC-2022), the eDMC recommended stopping the study for futility per the futility criteria prespecified in the sSAP. Based upon these data and the recommendation of the eDMC, the study has been unblinded (as of 22-FEB-2023). Prespecified IA2 and final analysis of the study described in the SAP will not be performed. Safety analysis will be performed at the end of the study; there will be no further analyses for efficacy CCI [redacted] endpoints collected from participants beyond the IA1 cutoff date.

NOTE: In alignment with the study update memo sent to investigators on 28-FEB-2023, all study participants should stop ongoing treatment with pembrolizumab/placebo. Exceptions may be requested for study participants who, in the assessment of their study physician, are benefitting from the combination of enzalutamide and pembrolizumab, after consulting with the Sponsor. All other study participants should be discontinued from study and be offered SOC treatment as deemed necessary by the investigator. If enzalutamide as SOC is not accessible off study to the participant, central sourcing may continue. As of Amendment 09, participants who are still on study intervention will no longer have central PSA blood samples collected, SSRE assessments, CCI [redacted]), or tumor response assessments by BICR. However, local tumor imaging assessments should continue per SOC schedule. The last required study visit will be the Safety Follow-up Visit; Efficacy Follow-up and Survival Follow-up visits will no longer be conducted. Updated analyses are described in Section 9.

This is a randomized, placebo-controlled, parallel-group, multi-site, double-blind/mask study of pembrolizumab plus enzalutamide versus placebo plus enzalutamide in participants with mCRPC.

Approximately 1240 participants will be randomly assigned in a 1:1 ratio to 1 of 2 treatment arms following a screening period of up to 42 days. There will be no crossover between treatment arms.

Arm 1: pembrolizumab 200 mg every 3 weeks (Q3W) plus enzalutamide 160 mg once daily (QD)

Arm 2: placebo Q3W plus enzalutamide 160 mg QD

CCI [redacted]

Participants are allowed to have previously received and progressed on or become intolerant to abiraterone acetate in the prechemotherapy mHSPC or mCRPC state. Prior docetaxel for mHSPC is allowed if more than 4 weeks have elapsed from the last dose of docetaxel. Prior treatment with second-generation androgen-receptor inhibitor or CYP17 inhibitor other than abiraterone acetate is not allowed. Participants must provide a tumor tissue from a fresh core or excisional biopsy (obtained within 12 months of screening) from soft tissue not previously irradiated (samples from tumors progressing in a prior site of radiation are allowed; other exceptions may be considered after Sponsor consultation). Participants with bone only or bone predominant disease may provide a bone biopsy sample (decalcification not allowed). However, if obtaining a fresh biopsy is not feasible, then participants may provide an archival tumor tissue sample after Sponsor consultation. Adequacy of these specimens for biomarker analysis will be evaluated by a central laboratory prior to randomization. For complete details about eligibility criteria, refer to Section 5.

Treatment with pembrolizumab/placebo may continue for up to 35 cycles (approximately 2 years starting with the first infusion in Cycle 1) or until meeting criteria for discontinuation of study intervention (Section 7.1). Treatment with enzalutamide will proceed continuously from Day 1 of Cycle 1 in both arms, unless criteria for discontinuation of study intervention are met (Section 7.1).

Participants will be evaluated with radiologic imaging to assess response to treatment at regular intervals during the study (Section 8.2.2).

If a participant with radiographic progression is clinically stable or clinically improved, after obtaining documented informed consent addendum and Sponsor communication, the investigator may elect to continue treatment following radiographic disease progression confirmed by central vendor. Participants showing clinical benefit in the study will be allowed to continue treatment regardless of any decision to stop enrollment or suspend the study.

AEs will be monitored throughout the study and graded in severity according to the guidelines outlined in the NCI CTCAE version 4.0. After the end of treatment, each participant will be followed for 30 days for AE monitoring. SAEs will be collected for 90 days after the end of treatment or 30 days after the end of treatment if the participant initiates new anticancer therapy, whichever is earlier. Treatment-related SAEs must be reported regardless of the time point when they occur. Participants who discontinue treatment for reasons other than radiographic disease progression will stay on study and continue study-related disease assessments until radiographic disease progression, initiating a nonstudy cancer treatment, participant discontinuation from the study, or becoming lost to follow-up. All participants will be followed for survival. This will be done in a variety of ways including phone, email, chart review, or review of public records in compliance to local practices or regulations.

Second Course Treatment: As of Amendment 09, Second Course treatment is not an option for participants.

Participants who stop study intervention as a result of obtaining an investigator-determined confirmed CR or those subjects who stop after receiving 35 cycles may be eligible for an additional 17 cycles (approximately 1 year) of pembrolizumab after BICR-verified progressive disease if they meet the criteria for re-treatment (Second Course Phase) and the study is ongoing (Section 6.6.4). Enzalutamide may be continued at the investigator's discretion during the Second Course treatment. The decision to retreat with pembrolizumab will be at the discretion of the investigator only if no anticancer treatment was administered since the last dose of pembrolizumab/placebo, the participant still meets the safety parameters listed in the Inclusion/Exclusion criteria, and the study remains open.

The risks of solid organ transplant following treatment with PD-1 inhibitor therapy have not been extensively studied. The timeframe for safe or appropriate solid organ transplantation after the last dose of pembrolizumab is unknown. Therefore, it is recommended not to perform solid organ transplantation within at least 120 days (5 half-lives) of stopping pembrolizumab. The risks and benefits of transplant should be discussed with the participant by the treating investigator.

Specific procedures to be performed during the study, as well as their prescribed times and associated visit windows, are outlined in the SoA in Section 1.3. Details of each procedure are provided in Section 8.

This study will use a group sequential design, using an independent, external Data Monitoring Committee (eDMC) to monitor safety and efficacy during the course of the study. CCI [redacted] The final OS analysis will be conducted when approximately 784 OS events (target number of OS events) have been observed. CCI [redacted]

4.2 Scientific Rationale for Study Design

This study is a randomized, double-blind, placebo-controlled study, a design selected to eliminate potential bias.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

The dual primary endpoints of the study will be OS and rPFS. OS has been recognized as the gold standard for the demonstration of superiority of a new antineoplastic therapy in randomized clinical studies.

Radiographic PFS is an acceptable measure of clinical benefit for a late-stage study that demonstrates superiority of a new antineoplastic therapy, especially if the magnitude of the effect is large and the therapy has an acceptable risk/benefit profile. The rPFS will be assessed by BICR according to PCWG-modified RECIST 1.1 (Section 8.2). Time-to-progression endpoints, including DOR and rPFS, will be measured until PD per PCWG-modified RECIST 1.1.

TFST or death will be assessed as a key secondary endpoint. A delay in the need to initiate the next anticancer therapy is clinically meaningful for participants and an important goal of any anticancer therapy. TFST is supportive of rPFS as it incorporates reasons to switch therapies in addition to radiographic progression (eg, due to toxicity or clinical progression), thus providing a comprehensive measure of when an agent is considered no longer of clinical benefit.

4.2.1.2 Safety Endpoints

Safety parameters commonly used for evaluating investigational systemic anticancer treatments are included as safety endpoints including, but not limited to, the incidence of, causality, and outcome of AEs/SAEs; and changes in vital signs and laboratory values. AEs will be assessed as defined by CTCAE, Version 4.0.

4.2.1.3 Patient-reported Outcomes (PROs)

CCI [redacted]

CCI [redacted]

4.2.1.4 Planned Exploratory Biomarker Research

Cancer immunotherapies represent an important and novel class of antitumor agents. However, the mechanism of action of these exciting new therapies is not completely understood and much remains to be learned regarding how best to leverage these new drugs in treating patients. Thus, to aid future patients, it is important to investigate the determinants of response or resistance to cancer immunotherapy and other treatments administered, as well as determinants of AEs in the course of our clinical studies. These efforts may identify novel predictive/PD biomarkers and generate information that may better guide single-agent and combination therapy with immuno-oncology drugs. To identify novel biomarkers, biospecimens (ie, blood components, tumor material) will be collected to support analyses of cellular components (eg, protein, DNA, RNA, metabolites) and other circulating molecules. Investigations may include but are not limited to:

Germline (blood) genetic analyses (eg, SNP analyses, whole exome sequencing, whole genome sequencing)

This research may evaluate whether genetic variation within a clinical study population correlates with response to the treatment(s) under evaluation. If genetic variation is found to predict efficacy or AEs, the data might inform optimal use of therapies in the patient population. Furthermore, it is important to evaluate germline DNA variation across the genome in order to interpret tumor-specific DNA mutations. Finally, microsatellite instability (MSI) may be evaluated as this is an important biomarker for some cancers (ie, colorectal cancer).

Genetic (DNA) analyses from tumor

The application of new technologies, such as next generation sequencing, has provided scientists the opportunity to identify tumor-specific DNA changes (ie, mutations, methylation status, microsatellite instability). Key molecular changes of interest to immuno-oncology drug development include the mutational burden of tumors and the clonality of T-cells in the tumor microenvironment. Increased mutational burden (sometimes referred to as a 'hyper-mutated' state) may generate neo-antigen presentation in the tumor microenvironment. To conduct this type of research, it is important to identify tumor-specific mutations that occur across all genes in the tumor genome. Thus, genome-wide approaches may be used for this effort. Note that in order to understand tumor-specific mutations, it is necessary to compare the tumor genome with the germline genome. Microsatellite instability may also be evaluated as this is an important biomarker for some cancers (ie, colorectal cancer). Circulating tumor DNA and/or RNA may also be evaluated from blood samples.

Tumor and blood RNA analyses

Both genome-wide and targeted messenger RNA (mRNA) expression profiling and sequencing in tumor tissue and in blood may be performed to define gene signatures that correlate to clinical response to treatment with pembrolizumab or other immunotherapies. Pembrolizumab induces a response in tumors that likely reflects an inflamed/immune phenotype. Specific immune-related gene sets (ie, those capturing interferon-gamma transcriptional pathways) may be evaluated and new signatures may be identified. Individual genes related to the immune system may also be evaluated (eg, IL-10). MicroRNA profiling may also be pursued as well as exosomal profiling.

Proteomics and immunohistochemistry (IHC) using blood or tumor

Tumor and blood samples from this study may undergo proteomic analyses (eg, PD-L1 IHC). PD-L1 protein level in tumor sections, assessed by IHC, has been shown to correlate with response to pembrolizumab in patients with NSCLC, and an in vitro diagnostic (IVD) device has been developed for use with pembrolizumab in NSCLC. Preliminary data indicates that this association may also be true in additional cancer types (ie, triple negative breast cancer, head and neck, and gastric). Additional tumor or blood-derived proteins may also correlate with response to pembrolizumab. Therefore, tumor tissue may be subjected to proteomic analyses using a variety of platforms that could include but are not limited to immunoassays and liquid chromatography/mass spectrometry. This approach could identify novel protein biomarkers that could aid in patient selection for pembrolizumab (MK-3475) therapy.

Other blood-derived biomarkers

In addition to expression on the tumor tissue, PD-L1 and other tumor derived proteins can be shed from tumor and released into the blood. Assays such as enzyme-linked immunoassay (ELISA) measure such proteins in serum. Correlation of expression with response to pembrolizumab therapy may identify new approaches for predictive biomarkers in blood, representing a major advance from today's reliance on assessing tumor biomarkers. This research would serve to develop such assays for future clinical use.

Other molecular changes of interest include the subtype of T-cells in the tumor microenvironment. The T-cell repertoire from tumor tissue and blood components may be evaluated.

4.2.1.4.1 Planned Genetic Analysis

Genetic variation may impact a participant's response to therapy, susceptibility to, severity, and progression of disease. Variable response to therapy may be due to genetic determinants that impact 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 sample will be collected for DNA analysis from consenting participants.

DNA samples may be used for research related to the study intervention(s), the disease under study, or related diseases. They may also be used to develop tests/assays including diagnostic tests related to the disease under study, related diseases, and study intervention(s). Genetic research may consist of the analysis of 1 or more candidate genes, the analysis of genetic markers throughout the genome, or analysis of the entire genome. Analysis may be conducted if it is hypothesized that this may help further understand the clinical data.

The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to understand study disease or related conditions.

4.2.2 Rationale for the Use of Comparator/Placebo

Normal saline or dextrose infusion Q3W will be used as placebo for pembrolizumab. The use of saline or dextrose placebo in combination with enzalutamide will ensure the objectivity of the investigator. Normal saline is the primary diluent/placebo for pembrolizumab; use dextrose only if saline is not available. The use of a placebo will allow for testing the hypotheses that OS for participants treated with pembrolizumab and enzalutamide is superior to the combination of placebo and enzalutamide in participants with mCRPC to be tested.

4.3 Justification for Dose

4.3.1 Pembrolizumab

The planned dose of pembrolizumab for this study is 200 mg Q3W. Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all indications. As outlined below, this dose is justified by the following:

- Clinical data from 8 randomized studies in melanoma and NSCLC indications demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg Q2W representing an approximate 5- to 7.5-fold exposure range (refer to IB)

- Population PK analysis showing that both fixed dosing and weight-based dosing provides similar control of PK variability with considerable overlap in the distributions of exposures, supporting suitability of 200 mg Q3W

- Clinical data showing meaningful improvement in benefit-risk including OS at 200 mg Q3W across multiple indications

- Pharmacology data showing full target saturation in both systemic circulation (inferred from PK data) and tumor (inferred from PBPK analysis) at 200 mg Q3W

4.3.2 Enzalutamide

The recommended dose of enzalutamide is 160 mg (four 40-mg capsules/tablets or two 80-mg tablets) administered orally QD. Refer to Section 6.6 and the approved labeling for detailed information regarding dose regimen/modification.

4.4 Beginning and End of Study Definition

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent.

The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory result or at the time of final contact with the last participant, whichever comes last.

If the study includes countries in the European Economic Area (EEA), the local start of the study in the EEA is defined as First Site Ready (FSR) in any Member State.

4.4.1 Clinical Criteria for Early Study Termination

The clinical study may be terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the study population as a whole is unacceptable. In addition, further recruitment in the study or at (a) particular study site(s) may be stopped due to insufficient compliance with the protocol, Good Clinical Practice (GCP), and/or other applicable regulatory requirements, procedure-related problems or an unacceptably high number of discontinuations or withdrawals due to administrative reasons.

In the event of Sponsor decision to no longer supply study interventions, ample notification will be provided so that appropriate adjustments to participant treatment can be made.

NOTE: Based on the data from an interim safety and efficacy analysis for KEYNOTE-641 (data cutoff 12-DEC-2022), the eDMC recommended stopping the study for futility per the futility criteria prespecified in the sSAP.

5 STUDY POPULATION

Male participants with mCRPC in the prechemotherapy mCRPC state who have not received abiraterone acetate or who were previously treated with abiraterone acetate (without prior enzalutamide) and have progressed on treatment or became intolerant of the drug. Prior docetaxel for mHSPC is allowed if more than 4 weeks have elapsed from the last dose of docetaxel. Prior treatment with abiraterone acetate for mHSPC is allowed if the participant received more than 4 weeks of treatment and as long as there was no progression on this agent.

As stated in the Code of Conduct for Clinical Trials (Section 10.1.1), our studies include people of varying age, race, ethnicity, and sex. The collection and use of these demographic data is to follow all local laws and guidelines in keeping with the needs for participant confidentiality while supporting the study of the disease, its related factors, and the IMP under investigation.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

A participant will be eligible for inclusion in the study if the participant meets the following criteria:

1. Have histologically- or cytologically-confirmed (if acceptable according to local health authority regulations) adenocarcinoma of the prostate without small cell histology. Diagnosis must be stated in a pathology report and confirmed by the investigator.

2. Have prostate cancer progression while on ADT (or post bilateral orchiectomy) within 6 months prior to randomization, as determined by the investigator, by means of one of the following:

    a. PSA progression using local laboratory values as defined by a minimum of 2 consecutive rising PSA levels with an interval of ≥1 week between each assessment where the PSA value at screening should be ≥1 ng/mL. See Section 8.2.3 – Prostate-specific Antigen Assessment for further details.

    b. Radiographic disease progression in soft tissue based on RECIST 1.1 criteria with or without PSA progression.

    c. Radiographic disease progression in bone based on PCWG defined as the appearance of 2 or more new bone lesions on bone scan with or without PSA progression.

3. Have progression under the following conditions if the participant received anti-androgen therapy prior to enrollment:

    a. Evidence of progression >4 weeks since last flutamide treatment.

    b. Evidence of progression >6 weeks since last bicalutamide or nilutamide treatment.

4. Have current evidence of metastatic disease documented by either bone lesions on bone scan and/or soft-tissue disease by CT/MRI. Participants whose disease spread is limited to regional pelvic lymph nodes are not eligible.

5. Have met one of the following criteria with regard to abiraterone acetate exposure:

    a. Not received prior abiraterone acetate (ie, abiraterone-naïve)
    CCI [redacted]

    b. Received prior abiraterone acetate for the treatment of mHSPC or mCRPC, for a minimum of 4 weeks and must not have progressed while on treatment.

    c. Received prior abiraterone acetate for the treatment of mHSPC or mCRPC and progressed on treatment after a minimum of 8 weeks treatment (minimum 14 weeks for those with bone progression).

6. Have ongoing androgen deprivation with serum testosterone <50 ng/dL (<2.0 nM). If the participant is currently being treated with luteinizing hormone-releasing hormone agonists or antagonists (participants who have not undergone an orchiectomy), this therapy must have been initiated at least 4 weeks prior to randomization, and treatment must be continued throughout the study.

7. Participants receiving bone resorptive therapy (including, but not limited to, bisphosphonate or denosumab) must have been on stable doses for ≥4 weeks prior to randomization.

8. Demonstrate adequate organ function as defined in Table 1; all screening labs should be performed in central laboratory within 10 days of the first dose of study intervention.

Table 1 Laboratory Values for Adequate Organ Function

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/μL
Platelets	≥100,000/μL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[a]
Renal	
Creatinine OR Measured or calculated[b] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN OR ≥50 mL/min for participant with creatinine levels >1.5 × ULN
Hepatic	
Total bilirubin	≤1.5 × ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT) or PTT	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants

ALT (SGPT) = alanine aminotransferase (serum glutamic-pyruvic transaminase); AST (SGOT) = aspartate aminotransferase (serum glutamic-oxaloacetic transaminase); GFR = glomerular filtration rate; ULN = upper limit of normal.

[a] Hemoglobin and platelet requirements cannot be met by use of recent transfusion or growth factor support (GCSF or erythropoietin) within 2 weeks prior to randomization.

[b] Creatinine clearance (CrCl) should be calculated per institutional standard.

Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.

Demographics

9. Participant is male.

10. Participant is ≥18 years of age on day of signing the informed consent.

Contraception

11. Participants are eligible to participate if they agree to the following during the intervention period and for at least 90 days after the last dose of enzalutamide:

- Refrain from donating sperm

  Plus Either:

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent

  OR

- Must agree to use contraception, unless confirmed to be azoospermic (vasectomized or secondary to medical cause, documented from the site personnel's review of the participant's medical records, medical examination, or medical history interview) as detailed below:

  - Agree to use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP (see Section 10.5) who is not currently pregnant. Note: 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-vaginal penetration.

  - Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions is more stringent than the requirements above, the local label requirements are to be followed.

12. Removed.

Informed Consent

13. The participant (or legally acceptable representative if applicable) provides documented informed consent for the study.

Additional Categories

14. Have provided newly obtained core or excisional biopsy (obtained within 12 months of screening) from soft tissue not previously irradiated (samples from tumors progressing in a prior site of radiation are allowed; other exceptions may be considered after Sponsor consultation). Participants with bone only or bone predominant disease may provide a bone biopsy sample. However, if obtaining a fresh biopsy is not feasible, then participants may provide an archival tumor tissue sample after Sponsor consultation and completion of an SCF. FFPE tissue blocks are preferred to slides. Newly obtained biopsies are preferred to archive tissue.

    Note: Details pertaining to tumor tissue submission can be found in the Procedures Manual.

15. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 assessed within 7 days of randomization.

5.2 Exclusion Criteria

The participant must be excluded from the study if the participant meets any of the following criteria:

Medical Conditions

1. Has a known additional malignancy that is progressing or has required active treatment in the last 3 years. Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ that have undergone potentially curative therapy are not excluded.

2. Has an active autoimmune disease that has required systemic treatment in past 2 years (ie, with use of disease modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

3. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone or equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study intervention.

4. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study or interfere with the participant's participation for the full duration of the study, such that it is not in the best interest of the participant to participate, in the opinion of the treating investigator.

    Note: Refer to Appendix 7 for additional country-specific conditions that require participant exclusion.

5. Has undergone major surgery, including local prostate intervention (excluding prostate biopsy), within 28 days prior to randomization and not recovered adequately from the toxicities and/or complications.

6. Has a gastrointestinal disorder affecting absorption (eg, gastrectomy, active peptic ulcer disease within last 3 months).

7. Is unable to swallow tablets/capsules.

8. Has an active infection (including tuberculosis) requiring systemic therapy.

9. Has a history of (noninfectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease.

10. Has known active HIV, concurrent active hepatitis B (defined as HBsAg positive reactive and/or detectable HBV DNA) or known active hepatitis C virus (defined as anti-HCV Ab positive and detectable HCV RNA infection).

    Note: Hepatitis B and C screening tests are not required unless:

    - Known history of HBV and HCV infection.

    - As mandated by local health authority.

11. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least 4 weeks prior to randomization and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to randomization. This exception does not include carcinomatous meningitis, which is excluded regardless of clinical stability.

12. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study.

13. Has a history of seizure or any condition that may predispose to seizure (including, but not limited to prior cerebrovascular accident, transient ischemic attack, or brain arteriovenous malformation; or intracranial masses such as a schwannoma or meningioma that is causing edema or mass effect).

14. Has a history of loss of consciousness within 12 months of the Screening Visit.

15. Has had myocardial infarction or uncontrolled angina within 6 months prior to randomization.

    Note: Participants with recent history of revascularization for acute coronary syndrome within 3 months prior to randomization are included.

16. Has a history of clinically significant ventricular arrhythmias (eg, ventricular tachycardia, ventricular fibrillation, torsades de pointes).

17. Has a history of Mobitz II second degree or third-degree heart block without a permanent pacemaker in place.

18. Has hypotension as indicated by systolic blood pressure <86 mmHg at the Screening Visit.

19. Has bradycardia as indicated by a heart rate of <50 beats per minute on the Screening electrocardiogram (ECG).

20. Has uncontrolled hypertension as indicated by systolic blood pressure >170 mmHg or diastolic blood pressure >105 mmHg at the Screening Visit.

21. Has hypersensitivity to pembrolizumab and/or enzalutamide and/or any of their excipients.

Prior/Concomitant Therapy

22. Has history of prostate cancer progression on ketoconazole.

23. Has had prior treatment with second-generation androgen-receptor inhibitor (eg, enzalutamide, apalutamide, darolutamide) or CYP17 inhibitor other than abiraterone acetate.

24. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or coinhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137).

25. Has received prior treatment with radium or other therapeutic radiopharmaceuticals for prostate cancer.

26. Has had prior chemotherapy for mCRPC. Prior docetaxel for mHSPC is allowed if more than 4 weeks have elapsed from the last dose of docetaxel.

27. Has received prior targeted small molecule therapy or abiraterone treatment within 4 weeks prior to randomization or who has not recovered (ie, Grade ≤1 or at baseline), with the exception of Grade ≤2 neuropathy or Grade ≤2 alopecia from AEs due to a previously administered agent.

28. Has received an anticancer mAb within 4 weeks prior to randomization or has not recovered (ie, Grade ≤1 or at baseline) from AEs due to mAbs administered more than 4 weeks prior to randomization.

    Note: Treatment with denosumab as standard of care for bone metastases is permitted.

29. Has used herbal products that may have hormonal antiprostate cancer activity and/or are known to decrease PSA levels (eg, saw palmetto) within 4 weeks prior to randomization.

30. Has received treatment with 5-α reductase inhibitors (eg, finasteride, dutasteride), estrogens, and/or cyproterone within 4 weeks prior to randomization.

31. Has received a live or live attenuated vaccine within 30 days prior to randomization. Administration of killed vaccines is allowed.

    Refer to Section 6.5 for information on COVID-19 vaccines.

32. Has received prior radiotherapy within 2 weeks of randomization. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease.

Prior/Concurrent Clinical Study Experience

33. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to randomization.

    Note: Participants who have entered the nontreatment follow-up phase of an investigational study may participate as long as it has been 4 weeks after the last dose of the previous investigational agent.

Diagnostic Assessments

34. Has a "superscan" bone scan. This is defined as an intense symmetric activity in the bones and diminished renal parenchymal activity on baseline bone scan such that the presence of additional metastases in the future could not be evaluated.

Other Exclusions

35. Is to father children within the projected duration of the study, starting with the screening visit through 90 days after the last dose of study intervention.

36. Has had an allogenic tissue/solid organ transplant.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Participants should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study, but are not subsequently randomized 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 AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines.

5.5 Participant Replacement Strategy

A participant who is discontinued from study intervention OR withdraws from the study will not be replaced.

6 STUDY INTERVENTION

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

Clinical supplies (study interventions provided by the Sponsor) will be packaged to support enrollment. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

NOTE: In alignment with the study update memo sent to investigators on 28-FEB-2023, all study participants should stop ongoing treatment with pembrolizumab/placebo. Exceptions may be requested for study participants who, in the assessment of their study physician, are benefitting from the combination of enzalutamide and pembrolizumab, after consulting with the Sponsor. All other study participants should be discontinued from the study and be offered SOC treatment as deemed necessary by the investigator. If enzalutamide as SOC is not accessible off study to the participant, central sourcing may continue.

The study interventions to be used in this study are outlined in Table 2.

Table 2 Study Interventions

Arm Name	Arm Type	Intervention Name	Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Admin-istration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Arm 1	Experimental	pembrolizumab	Biological/Vaccine	Solution for Infusion	25 mg/mL	200 mg	IV Infusion	Day 1 of each 21-day cycle	Test Product	IMP	Central
Arm 1	Experimental	enzalutamide	Drug	Capsule/Tablet	40 mg/80 mg	160 mg	Oral	Four 40-mg capsules/tablets orally per day/two 80-mg tablets orally per day	Test Product	IMP	Central
Arm 2	Comparator	enzalutamide	Drug	Capsule/Tablet	40 mg/80 mg	160 mg	Oral	Four 40-mg capsules/tablets orally per day/two 80-mg tablets orally per day	Comparator	IMP	Central
Arm 2	Comparator	Normal saline or dextrose	Drug	Solution for infusion	0 mg	0 mg	IV Infusion	Day 1 of each 21-day cycle	Placebo	IMP	Local

IMP=investigational medicinal product; IV=intravenous; NIMP/AxMP=noninvestigational/auxiliary medicinal product.

The classification of IMP and NIMP/AxMP in this table is based on guidance issued by the European Commission and applies to countries in the European Economic Area (EEA). Country differences with respect to the definition/classification of IMP and NIMP/AxMP may exist. In these circumstances, local legislation is followed.

In this protocol, placebo for pembrolizumab is diluent alone (normal saline and/or dextrose); diluent is used for blinding purposes and does not contain active ingredients.

Please see Appendix 7 for country-specific requirements.

All study interventions will be administered on an outpatient basis.

All products indicated in Table 2 will be provided centrally by the Sponsor or locally by the study site, subsidiary or designee, depending on local country operational or regulatory requirements.

For any commercially available product that is provided by the study site, subsidiary, or designee, every attempt will be made to source these supplies from a single lot/batch number. The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

Refer to Section 8.1.8 for details regarding administration of the study intervention.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Details on preparation and administration of pembrolizumab or placebo are provided in the Pharmacy Manual.

Specific calculations or evaluations are not required to administer the proper dose of enzalutamide to each participant. The rationale for selection of doses to be used in this study is provided in Section 4.3.

6.2.2 Handling, Storage, and Accountability

The investigator or designee must confirm 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 supply or administer study intervention. All study interventions 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).

For all study sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product (if applicable) as per local guidelines unless otherwise instructed by the Sponsor.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of study interventions in accordance with the protocol and any applicable laws and regulations.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Intervention randomization will occur centrally using an interactive response technology (IRT) system. There are 2 study intervention arms. Participants will be randomly assigned in a 1:1 ratio to pembrolizumab + enzalutamide or placebo + enzalutamide, respectively.

6.3.2 Stratification

Randomization will be stratified according to the following factors:

6.3.3 Blinding

As of IA1, the study has been unblinded. The subsection below is retained for reference.

A double-blinding technique with in-house blinding will be used. Pembrolizumab and placebo will be prepared and/or dispensed in a blinded fashion by an unblinded pharmacist or qualified site personnel so that the blind is maintained. The participant, the investigator, and Sponsor personnel or delegate(s) who are involved in the study intervention administration or clinical evaluation of the participants are unaware of the intervention assignments.

The treatment identity of enzalutamide will be open-label; the identity of those treatments will be known by the participant, the investigator, the Sponsor, and delegate(s) who are involved in study intervention administration or the clinical evaluation of participants.

See Section 8.1.10 for a description of the method of unblinding a participant during the study should such action be warranted.

PD-L1, PSA, CTC, and AR-V7 results are not reported back to sites to prevent early withdrawal of participants from study intervention.

6.4 Study Intervention Compliance

The total volume of study medication infused will be compared with the total volume prepared to determine compliance with each dose administered.

Interruptions from the protocol-specified treatment plan for more than 12 weeks between pembrolizumab doses for nondrug-related or administrative reasons require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

For enzalutamide, the site will validate compliance with study intervention at each site visit according to their standard operating procedure. If doses are missed or vomited, this must be indicated in the source documents and CRFs.

6.5 Concomitant Therapy

6.5.1 Prohibited Concomitant Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medication or vaccination specifically prohibited, discontinuation from study therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Sponsor's Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

The following medications and vaccinations are prohibited during the study:

- Antineoplastic systemic chemotherapy or biological therapy (except denosumab and bisphosphonate for bone metastases as standard of care if on stable doses ≥4 weeks prior to randomization)
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Targeted therapy not specified in this protocol
- Initiation of bone resorptive therapy including but not limited to bisphosphonate or denosumab (unless approved by Sponsor consultation)
- Second-generation androgen-receptor inhibitor except enzalutamide
- Investigational agents other than pembrolizumab

- Herbal products that may have hormonal antiprostate cancer activity and/or are known to decrease PSA levels (eg, saw palmetto)

- Radiation therapy

  Note: Palliative localized radiation therapy to a site of pre-existing disease may be permitted while on study after consultation with Sponsor. The radiation treatment field may not include a target lesion by RECIST 1.1.

- Live or live attenuated vaccines within 30 days prior to randomization and while participating in the study.

  Note: If precluded by local regulations, live vaccines should not be given for 120 days after the last dose of pembrolizumab is administered.

  Note: Any licensed COVID-19 vaccine (including for Emergency Use) in a particular country is allowed in the study as long as they are mRNA vaccines, replication-incompetent adenoviral vaccines, or inactivated vaccines. These vaccines will be treated just as any other concomitant therapy.

  Investigational vaccines (ie, those not licensed or approved for Emergency Use) are not allowed.

- Systemic glucocorticoids except when used for the following purposes:

  - To modulate symptoms of an AE that is suspected to have an immunologic etiology

  - For the prevention of emesis

  - To premedicate for IV contrast allergies

  - To treat asthma or COPD exacerbations (only short-term oral or IV use in doses >10 mg/day prednisone equivalent)

  - For chronic systemic replacement not to exceed 10 mg/day prednisone equivalent

- Other glucocorticoid use except when used for the following purposes:

  - For topical use or ocular use

  - Intraarticular joint use

  - For inhalation in the management of asthma or chronic obstructive pulmonary disease

- 5-α reductase inhibitors (eg, finasteride, dutasteride), estrogens, and/or cyproterone

- Strong CYP2C8 inhibitors or strong CYP3A4 inducers should be avoided. However, if these medications are necessary and cannot be avoided then enzalutamide dose should be

adjusted as indicated in the approved product label. Enzalutamide is a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer. Concomitant use of enzalutamide with narrow therapeutic index drugs that are metabolized by CYP3A4 (eg, alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus), CYP2C9 (eg, phenytoin, warfarin), and CYP2C19 (eg, S-mephenytoin, clopidogrel) should be avoided if possible as enzalutamide may decrease their exposure. If coadministration with warfarin cannot be avoided, conduct additional INR monitoring.

Note: a list of strong/moderate inducers of CYP3A4 can be found at the following website: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table2-2.

In addition to the medications listed here, site staff should refer to the local approved product label for permitted and prohibited medications, as well as drug-drug interactions for enzalutamide. Caution should be used if participants are receiving concomitant medications that may lower the seizure threshold.

The exclusion criteria describe other medications which are prohibited in this study.

Participants who, in the assessment of the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study.

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the eCRF including all prescription, over-the-counter (OTC) products, herbal supplements, and IV medications and fluids. If changes occur during the study 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 up to 30 days after the last dose of study intervention should be recorded. If participants experience an SAE or ECI, all concomitant medications administered 30 days after the last dose of study intervention are to be recorded as defined in Section 8.4.7.

6.5.2 Rescue Medications and Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 6.6, Table 4. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment

guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the investigator does not need to follow the treatment guidance. Refer to Table 4 in Section 6.6 for guidelines regarding dose modification and supportive care.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

6.5.3 Radiotherapy

Sites must consult with the Sponsor prior to the use of radiotherapy or surgical intervention while a participant is on study, and the intervention must be recorded in the study database.

Localized palliative radiation therapy to a site of pre-existing disease may be permitted while on study. However, if the participant develops a new lesion or a definite increase in the size of existing bone or visceral lesions with or without extension into the soft tissue that meets the criteria for disease progression according to PCWG3 [Scher, H. I., et al 2016], treatment must be discontinued for PD regardless of whether radiation therapy is initiated.

6.6 Dose Modification (Escalation/Titration/Other)

6.6.1 Concomitant Combination Therapy

If either pembrolizumab/placebo is interrupted for >12 weeks (immune-related AE) or >12 consecutive weeks for administrative reasons or enzalutamide is interrupted for 28 consecutive days, the site must gain approval from the Sponsor to continue the other partner drug. Participants who must discontinue 1 of the 2 drugs in the combination due to drug-related AEs may continue with the other combination partner following consultation with the Sponsor until criteria for discontinuation of treatment are met.

In response to AEs that occur in either treatment group refer to the approved labeling for enzalutamide for more detailed information regarding dose regimen/modification and refer to Table 4 for pembrolizumab/placebo dose modification. Additionally, refer to the approved enzalutamide label for additional information about avoidance of concomitant medications or foods that may affect the metabolism of these drugs.

6.6.2 Dose Modification for Enzalutamide

If a participant experiences any Grade ≥3 toxicity related to enzalutamide treatment, the drug should be withheld until the toxicity decreases to Grade ≤2. Enzalutamide can then be resumed at the reduced dose of 120 mg daily. For repeat Grade ≥3 toxicity, it can again be held until toxicity decrease to Grade ≤2 and resumed at the reduced dose of 80 mg daily. Reduction below 80 mg is not allowed.

Once the dose has been reduced, it may not be escalated up to a previous dose level.

Enzalutamide should be permanently discontinued in participants who develop a seizure while on treatment.

PRES has been observed in patients treated with enzalutamide. This may present with rapidly evolving symptoms of seizure, lethargy, headache, confusion, blindness or visual disturbances, or other neurologic symptoms. Hypertension may or may not be present. Posterior reversible encephalopathy syndrome is diagnosed by brain imaging (preferably MRI). Discontinue enzalutamide treatment if the participant develops PRES. Enzalutamide must be permanently discontinued in participants who develop seizures or PRES on treatment. Pembrolizumab/placebo may be resumed in these participants after consultation with the Sponsor.

Participants should be directed to report the development of rash, regardless of severity, promptly to investigators. Participants with rash should be treated promptly with steroids, dose interruption per protocol, and monitored closely for worsening of rash, which may require additional treatment.

After resolution of the toxicity, the participant can resume treatment with enzalutamide with a dose reduction according to Table 3.

Table 3 Enzalutamide Dose Modification Guidelines for Drug-related Adverse Events

Drug	Dose/Potency	Dose Frequency	Regimen
Initial enzalutamide dose	160 mg	QD	Four 40-mg capsules/tablets or two 80-mg tablets
First dose reduction	120 mg	QD	Three 40-mg capsules/tablets[a]
Second dose reduction	80 mg	QD	Two 40-mg capsules/tablets or one 80-mg tablet

QD=every day
[a.] This dose level is not applicable for 80 mg tablets.

6.6.3 Immune-Related Events and Dose Modification (Withhold, Treat, Discontinue)

Dose Modification and Toxicity Management for Immune-related AEs Associated with Pembrolizumab

AEs associated with pembrolizumab exposure may represent an immune-related response. These irAEs may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously.

Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids.

Dose Modification and Toxicity Management Guidelines for irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations are provided in Table 4.

Table 4 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab Monotherapy, Coformulations or IO Combinations

General instructions:

1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Pembrolizumab monotherapy, coformulations or IO combinations must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If pembrolizumab monotherapy, coformulations or IO combinations have been withheld, treatment may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Recurrent Grade 2 or Grade 3 or 4	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus)

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
	Recurrent Grade 3 or Grade 4	Permanently discontinue		• Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
AST / ALT Elevation or Increased Bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5-1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [a]	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [a]		

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or Permanently discontinue [a]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis and renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
All Other irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue [b]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

[a] The decision to withhold or permanently discontinue pembrolizumab monotherapy, coformulations or IO combinations is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab monotherapy, coformulations or IO combinations may be resumed.

[b] Events that require discontinuation include, but are not limited to: Guillain-Barre Syndrome, encephalitis, myelitis, DRESS, SJS, TEN and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

Dose Modification and Toxicity Management of Infusion Reactions Related to Pembrolizumab

Pembrolizumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in [Table 5].

Table 5 Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	Stop Infusion Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug intervention.	Participant may be premedicated 1.5 h (±30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg PO (or equivalent dose of analgesic).

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study drug intervention.	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

Other Allowed Dose Interruption for Pembrolizumab

Pembrolizumab/placebo may be interrupted for situations other than treatment-related AEs such as medical or surgical events and/or unforeseen circumstances not related to study intervention. However, study intervention is to be restarted within 3 weeks (21 days) of the originally scheduled dose and within 42 days of the previously administered dose, unless otherwise discussed with the Sponsor. The reason for study intervention interruption is to be documented in the participant's study record.

6.6.4 Second Course

NOTE: As of Amendment 09, Second Course treatment is not an option for participants.

All participants who have completed the first course of the pembrolizumab plus enzalutamide arm or stopped for confirmed CR may be eligible for up to an additional 17 cycles of pembrolizumab, with or without enzalutamide, at the investigator's discretion, if there is investigator-determined progressive disease by RECIST 1.1 after initial treatment. This retreatment is the Second Course of this study.

Participants may enter the Second Course if all of the following criteria are met:

1. The participant received pembrolizumab, determined on unblinding if applicable
2. No new anticancer treatment was administered after the last dose of study intervention
3. The participant meets all of the inclusion criteria and none of the exclusion criteria
4. The study is ongoing

An objective response or disease progression that occurs during the Second Course Phase for a participant will not be counted as an event for the primary analysis of either endpoint in this study.

6.6.5 Management of Overlapping Toxicities

Based on the known toxicity profiles of pembrolizumab and enzalutamide, certain treatment-related AEs are uniquely associated with one drug versus the other. For example, seizure is a known risk for enzalutamide treatment, while immune-related AEs are risks for pembrolizumab treatment. However, certain AEs, such as diarrhea, may be initially considered attributable to either study intervention. Therefore, evaluation of attribution is important for determining the study intervention most likely related to the AE, or an alternative etiology, and subsequently proper clinical management. The following aspects should be considered:

1. Timing of AE onset:

   Since enzalutamide is dosed daily and continuously due to a relatively short half-life (5.8 days), and pembrolizumab is dosed Q3W due to a long half-life, enzalutamide can be interrupted to assess whether an AE improves/resolves with dechallenge (ie, interruption of treatment) based on the following 2 scenarios:

   - If an AE is identified during a treatment cycle (ie, between 2 pembrolizumab doses), only enzalutamide dose interruption is needed.
   - If an AE is identified at the beginning of a treatment cycle, enzalutamide can be interrupted and dosing of pembrolizumab should be held.

   If the participant recovers from an AE in response to enzalutamide interruption (ie, positive dechallenge), the event is more likely to be related to enzalutamide. Otherwise, after excluding other alternative explanations, an immune-related AE should be considered.

2. Severity of AE:

   If an AE is suspected to be treatment-related and is severe/life-threatening at the time of onset or is rapidly worsened, action including interrupting both drugs and initiating

treatment with a corticosteroid (with exception of hypothyroidism, Type 1 diabetes mellitus) and other supportive care should be taken promptly.

6.7 Intervention After the End of the Study

There is no study-specified intervention following the end of the study.

6.8 Clinical Supplies Disclosure

The emergency unblinding call center will use the intervention/randomization schedule for the study to unblind participants and to unmask study intervention identity. The emergency unblinding call center should only be used in cases of emergency (see Section 8.1.10). In the event that the emergency unblinding call center is not available for a given site in this study, the central electronic IRT should be used to unblind participants and to unmask study intervention identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

6.9 Standard Policies

Trial site personnel will have access to the IRT system to allocate participants, to assign intervention to participants and to manage the distribution of clinical supplies. Each person accessing the IRT system must be assigned an individual unique PIN. They must use only their assigned PIN to access the system, and they must not share their assigned PIN with anyone.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

Discontinuation of study intervention does not represent withdrawal from the study.

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention prior to completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 1.3 and Section 8.12.3.

Participants may discontinue study intervention at any time for any reason or be dropped from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Participants should be placed back on study therapy within 3 weeks of any scheduled interruption, unless otherwise discussed with the Sponsor. Specific details regarding procedures to be performed at study intervention discontinuation are provided in Section 8.1.9.

A participant must be discontinued from study intervention but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- The participant interrupts pembrolizumab or placebo administration for more than 12 consecutive weeks for an irAE or >12 consecutive weeks for administrative reasons without Sponsor consultation.
- The participant has missed 28 consecutive days of enzalutamide without Sponsor consultation.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant has a clinical indication for any medication or vaccination specifically prohibited in this study (Section 6.5.1).
- BICR-verified radiographic disease progression outlined in Section 8.2.2 (exception if the Sponsor approves treatment continuation with enzalutamide)

  Note: As of Amendment 09, central tumor response assessments will no longer be performed. Participants on study treatment will be assessed locally by the investigator for disease progression per SOC schedule. Participants with PD per local investigator assessment should be discontinued (exception if the Sponsor approves treatment continuation with enzalutamide following PD).
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment
- Completion of 35 cycles (approximately 2 years) with pembrolizumab/placebo (does not apply to enzalutamide)

  Note: The number of treatments is calculated starting with the first dose. Participants who stop the combination or pembrolizumab after receiving 35 doses may be eligible for retreatment if they progress after stopping study intervention provided they meet the requirements detailed in Section 6.6.4. Participants may be retreated in the Second Course Phase (Retreatment) for up to an additional 17 cycles (approximately 1 year).

Discontinuation of pembrolizumab/placebo may be considered for participants who have attained a confirmed CR and have been treated for at least 8 cycles (at least 24 weeks), receiving 2 cycles of pembrolizumab or placebo beyond the date when the initial CR was declared. These participants may be eligible for second course treatment described in Section 6.6.4.

Note: As of Amendment 09, second course treatment is not an option for participants.

For participants who are discontinued from study intervention but continue to be monitored in the study, all visits and procedures, as outlined in the SoA, should be completed.

7.2 Participant Withdrawal From the Study

It has been well documented that a higher rate of withdrawal can render a study uninterpretable; therefore, unnecessary withdrawal of participants should be avoided.

As clinical event data are important study endpoints, participants who discontinue study intervention prior to completion of the treatment period should be encouraged to continue all remaining study visits for follow-up and vital status assessment as outlined in the SoA and Section 8.12.3.

If a participant repeatedly fails to return for scheduled visits and/or if the study site is unable to contact the participant after multiple attempts (ie, is lost to follow-up), the procedures to be performed are outlined in Section 7.3.

If a participant decides not to continue receiving study intervention, the participant is to be encouraged to continue visits in the study for follow-up, imaging, and vital status assessment.

Participants who withdraw consent during the study

If the participant or participant's legally acceptable representative withdraws consent, the participant must be withdrawn from the study.

Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

7.3 Lost to Follow-up

If a participant fails to return to the clinic for a required study visit and/or if the site is unable to contact the participant, the following procedures are to be performed:

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.

- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

- Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.

- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).

- All study-related medical decisions must be made by an investigator who is a qualified physician.

- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.

- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, Hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

The maximum amount of blood collected from each participant over the duration of the study is provided in the Procedures Manual.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General Procedures

8.1.1 Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented informed consent from each potential participant (or their legally acceptable representative) prior to participating in this clinical study. If there are changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate documented informed consent is in place.

8.1.1.1 General Informed Consent

Informed consent given by the participant or their legally acceptable representative must be documented on a consent form. The form must include the trial protocol number, trial protocol title, dated signature, and agreement of the participant (or his/her legally acceptable representative) and of the person conducting the consent discussion.

A copy of the signed and dated informed consent form should be given to the participant (or their legally acceptable representative) before participation in the study.

The initial ICF, any subsequent revised ICF, and any written information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's or the participant's legally acceptable representative's dated signature.

If the investigator recommends continuation of study intervention beyond disease progression, the participant or their legally acceptable representative will be asked to provide documented informed consent.

Specifics about the study and the study population are to be included in the study informed consent form.

Informed consent will adhere to IRB/IEC requirements, applicable laws and regulations, and Sponsor requirements.

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator who is a qualified physician to ensure that the participant qualifies for the study.

8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study site contact information (including direct telephone numbers) to be used in the event of an emergency. The investigator or qualified designee will provide the participant with a participant identification card immediately after the participant provides documented informed consent. At the time of intervention allocation/randomization, site personnel will add the treatment/randomization number to the participant identification card.

The participant identification card also contains contact information for the emergency unblinding call center so that a healthcare provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. The medical history will collect all active conditions and any condition diagnosed within the prior 10 years that the investigator considers to be clinically important. In addition, significant and potentially relevant conditions that occurred >10 years previously should be collected. Details regarding the disease for which the participant has enrolled in this study will be recorded separately and not listed as medical history.

If a medical condition is diagnosed at the time of screening due to the physical examination, laboratory tests, radiologic assessment, other assessment, and/or a combination of these evaluations, the medical condition is to be recorded as a baseline condition along with the participant's other medical history unless due to any protocol-specified intervention (eg, procedure, washout, or run-in treatment including placebo run-in).

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 28 days prior to randomization. Treatment for the disease for which the participant has enrolled in this study will be recorded separately and not listed as a prior medication.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study through the Safety Follow-up visit. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 8.4.1. In addition, new medications started during the Second Course Phase through the Second Course Safety Follow-up visit should be recorded.

8.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur prior to randomization. Each participant will be assigned only 1 screening number. Screening numbers must not be re-used for different participants.

Any participant who is screened multiple times will retain the original screening number assigned at the initial screening visit. Specific details on the screening/rescreening visit requirements are provided in Section 8.12.1.

8.1.6.1 Treatment Eligibility Assessment Form

A TEA form is included in this study to document the investigator assessment of participant suitability for potential treatment with enzalutamide, and the rationale. These data may be required to support reimbursement efforts for pembrolizumab plus enzalutamide.

The investigator must complete this form and provide rationale to document the choice of enzalutamide before randomization.

8.1.7 Assignment of Treatment/Randomization Number

All eligible participants will be randomly allocated and will receive a treatment/randomization number. The treatment/randomization number identifies the participant for all procedures occurring after treatment randomization. Once a treatment /randomization number is assigned to a participant, it can never be re-assigned to another participant.

A single participant cannot be assigned more than 1 treatment/randomization number.

8.1.8 Study Intervention Administration

Administration of pembrolizumab/placebo will be monitored by the investigator and/or study staff.

On Day 1 of each cycle, study intervention should be administered after all procedures and assessments have been completed. Study intervention can be administered ±3 days of the targeted Day 1 for each cycle, except Cycle 1 where treatment can only be administered +3 days of the targeted Day 1.

8.1.8.1 Timing of Dose Administration

8.1.8.1.1 Pembrolizumab/Placebo

Pembrolizumab/placebo treatments will begin on Day 1 of each cycle after all predose study procedures and assessments have been completed as detailed in the SoA.

Pembrolizumab will be administered as a fixed-dose of 200 mg using a 30-minute IV infusion Q3W. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (ie, infusion time is 30 minutes -5 min/+10 min).

8.1.8.1.2 Enzalutamide

Enzalutamide will be administered at a dose of 160 mg (four 40-mg capsules/tablets or two 80-mg tablets) orally QD. Enzalutamide treatment should begin on the same day as Cycle 1, Day 1 of pembrolizumab/placebo treatment, with the first dose administered after the end of the pembrolizumab/placebo IV infusion.

Subsequent enzalutamide treatments will be taken PO QD at approximately the same time each day on a continuous daily dosing schedule. Capsules/tablets can be taken with or without food. Capsules/tablets must be swallowed whole and should not be chewed, dissolved, or opened.

Participants must be instructed that if they miss a dose, or vomit at any time after taking a dose, they should take their next dose at its scheduled time. The site will validate compliance with study intervention (including missed or vomited doses) at each site visit according to their standard operating procedure. If doses are missed or vomited, this must be indicated in the source documents and CRFs.

Detailed information regarding dose regimen/modification can be found in the approved labeling for enzalutamide.

8.1.9 Discontinuation and Withdrawal

Participants who discontinue study intervention prior to completion of the treatment period should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA and Section 8.12.3.

When a participant withdraws from participation in the study, all applicable activities scheduled for the final study visit should be performed (at the time of withdrawal). Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.10 Participant Blinding/Unblinding

As of IA1, the study has been unblinded. The subsections below are retained for reference.

STUDY INTERVENTION IDENTIFICATION INFORMATION IS TO BE UNBLINDED ONLY IF NECESSARY FOR THE WELFARE OF THE PARTICIPANT. EVERY EFFORT SHOULD BE MADE NOT TO UNBLIND.

For emergency situations where the investigator or medically qualified designee (consistent with local requirements) needs to identify the intervention used by a participant and/or the

dosage administered, he/ she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or medically qualified designee, the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the Sponsor. Prior to contacting the emergency unblinding call center to request unblinding of a participant's intervention assignment, the investigator who is a qualified physician should make reasonable attempts to enter the toxicity grade of the AEs observed, the relation to study drug, the reason thereof, etc., in the medical chart. If it is not possible to record this assessment in the chart prior to the unblinding, the unblinding should not be delayed.

In the event that unblinding has occurred, the circumstances around the unblinding (eg, date, reason, and person performing the unblinding) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible.

Once an emergency unblinding has taken place, the principal investigator, site personnel, and Sponsor personnel may be unblinded so that the appropriate follow-up medical care can be provided to the participant.

Participants whose treatment assignment has been unblinded by the investigator or medically qualified designee and/or nonstudy treating physician must be discontinued from study intervention, but should continue to be monitored in the study.

8.1.10.1 Nonemergency Unblinding

In the event of PD, there may be a need to unblind the participant's treatment assignment prior to initiating second course treatment (Section 6.6.4). In this circumstance, unblinding to pembrolizumab versus placebo administration may occur on an individual basis and only after consultation with the Sponsor Clinical Director. Every effort should be made not to unblind the participant unless necessary.

8.1.11 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical study that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or maintained to ensure that the data obtained is reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

8.1.12 Tumor Tissue for Biomarker Status

During the screening period, a tissue sample is required for each participant consisting of:

- A newly obtained core or excisional biopsy of a tumor lesion, which was not previously irradiated.

Or

- An archival tumor tissue sample if a new biopsy is unavailable.

FFPE tissue blocks are preferred to slides. Newly obtained biopsies are preferred to archived tissue.

Details pertaining to tumor tissue submission can be found in the Procedures Manual.

8.2 Efficacy Assessments

8.2.1 Tumor Imaging and Assessment of Disease

As of Amendment 09: Central tumor response assessments will be discontinued. Imaging scans will no longer be submitted to iCRO nor read by BICR. Local tumor imaging should continue per SOC schedule for participants still on study treatment. The subsections below are retained for reference.

The process for image collection and transmission to the central imaging vendor can be found in the SIM.

- Chest, abdomen, and pelvis scans are required for all participants at screening and on study. CT with IV and oral contrast is preferred or non-contrast CT of the chest and MRI of the abdomen and pelvis with IV gadolinium for participants in whom iodinated contrast is contraindicated, or when mandated by local practice.

- Bone scans (bone scintigraphy, bone scan, radionuclide bone scan, etc.) are required for all participants at screening and on-study.

- Other modalities (eg, FDG PET, PSMA PET, MRI, SPECT) cannot be a substitute for the bone scan.

- Additional imaging acquired as per standard of care or as clinically indicated, used to support radiographic disease progression or efficacy assessments, should be sent to the iCRO.

  Note: Radiographic disease progression is per PCWG Modified RECIST 1.1.

Note: For the purposes of assessing tumor imaging, the term “investigator” refers to the local investigator at the site and/or the radiological reviewer at the site or at an offsite facility.

Participant eligibility will be determined using local assessment (investigator assessment) based on PCWG-modified RECIST 1.1. All scheduled images for all study participants from the sites will be submitted to the central imaging vendor. In addition, images (including via other modalities) that are obtained at an unscheduled time point to determine disease progression, as well as imaging obtained for other reasons, but which demonstrates radiologic progression, should also be submitted to the central imaging vendor.

When the investigator identifies radiographic progression, the central imaging vendor will perform expedited verification of radiologic PD and communicate the results to the study site and Sponsor. Treatment should continue until PD has been verified. Images should continue to be submitted to the central imaging vendor.

The primary measure used by BICR for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (eg, discontinuation of study intervention) will be PCWG-modified RECIST 1.1.

Assessment of treatment response in the soft tissues will be according to soft-tissue rules of PCWG-modified RECIST 1.1, modified to follow a maximum of 10 target soft-tissue lesions and a maximum of 5 target lesions per organ. Assessment of treatment response in bone will be according to the bone lesion rules of PCWG-modified RECIST 1.1, as described in Appendix 8.

Soft-tissue and bone response assessments will be combined to produce an overall radiographic response, as follows:

Soft-tissue Response	Bone Scan Result	PCWG-modified RECIST 1.1 Time Point Response Entered Into CRF
PD	Any	PD
Any	PD	PD
Any (except PD)	PDu	PDu
NE	Non-PD, NED or NE	NE
NED	NE	NE
NED	Non-PD	Non-CR/Non-PD
NED	NED	NED
SD	Non-PD, NED, or NE*	SD
Non-CR/Non-PD	Non-PD, NED, or NE*	Non-CR/Non-PD
PR	Non-PD, NED or NE*	PR
CR	Non-PD or NE*	PR (if target lesions were present at baseline)
		Non-CR/Non-PD (if no target lesions at baseline)
CR	NED	CR

CR=complete response; CRF=case report form; NE=nonevaluable; NED=no evidence of disease; PCWG=Prostate Cancer Working Group; PD=progressive disease; PDu=progressive disease unconfirmed; PR=partial response; RECIST 1.1=Response Evaluation Criteria in Solid Tumors Version 1.1.

*If the bone scan is entirely missing or was not done, and bone lesions were present at baseline, then the overall response is nonevaluable.

Initial tumor imaging showing site-assessed PD should be submitted immediately for BICR verification of PD. The site will be notified if the BICR verifies PD using PCWG-modified RECIST 1.1.

8.2.1.1 Initial Tumor Imaging

Initial tumor imaging at screening must be performed within 28 days prior to the date of randomization. Tumor imaging by CT (or MRI) and radionuclide bone scan is required at screening.

Scans performed as part of routine clinical management are acceptable for use as the screening scans if they are of diagnostic quality and performed within 28 days prior to the

date of randomization. Scans are required to be sent to the central imaging vendor prior to enrollment; however, central imaging assessment is not required prior to enrollment.

At screening, all soft-tissue lesions seen by CT (or MRI) and all bone lesions seen by radionuclide bone scan will be documented. In determining response to treatment or progression, investigators must evaluate all target and nontarget lesions and search for new lesions at each imaging time point.

8.2.1.2 Tumor Imaging During the Study

In the first year, on-study imaging assessments must be performed every 9 weeks (63 days ± 7 days) from the date of randomization (through Week 54). Participants who remain on treatment beyond Week 54 will have imaging performed every 12 weeks (84 days ± 7 days). All supplemental imaging must be submitted to the central imaging vendor.

Timing of imaging should follow calendar days from date of randomization and should not be adjusted for delays in cycle starts. Response must be confirmed at least 4 weeks later to be considered for best overall response.

Radiographic progression will be determined according to PCWG-modified RECIST 1.1. Disease progression in bone lesions should be confirmed by another bone scan ≥6 weeks after site assessed first radiographic evidence of disease progression.

8.2.1.3 End-of-Treatment and Follow-up Tumor Imaging

For participants who discontinue study intervention, tumor imaging should be performed at the time of treatment discontinuation (±4 week window). If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory.

For participants who discontinue study intervention without documented disease progression, every effort should be made to continue monitoring disease status by tumor imaging using the same imaging schedule used while on treatment (every 9 weeks in Year 1 or 12 weeks after Year 1) until the start of a new anticancer treatment, disease progression, death, withdrawal of consent, or the end of the study, whichever occurs first.

8.2.1.4 Second Course (Retreatment) Tumor Imaging

As of Amendment 09, Second Course treatment is not an option for participants. The section below is retained for reference.

Tumor imaging must be performed within 28 days prior to restarting treatment with pembrolizumab. Local reading (investigator assessment with site radiology reading) will be used to determine eligibility. All second course imaging should be submitted to the central imaging vendor for quality control, storage, and possible retrospective review.

The first on-study imaging assessment should be performed at 9 weeks (63 days ±7 days) after the restart of treatment. Subsequent tumor imaging should be performed every 12 weeks (84 days ±7 days) or more frequently, if clinically indicated.

Imaging should continue to be performed until disease progression, the start of a new anticancer treatment, withdrawal of consent, death, or notification by the Sponsor, whichever occurs first.

For participants who discontinue Second Course study intervention, tumor imaging should be performed at the time of intervention discontinuation (±4 week window). If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at intervention discontinuation is not mandatory. For participants who discontinue study intervention due to documented disease progression, this is the final required tumor imaging.

For participants who discontinue Second Course study intervention without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 12 weeks (84 days ±7 days) until either the start of a new anticancer treatment, disease progression, death, or the end of the study, whichever occurs first.

8.2.2 PCWG Modified RECIST 1.1 Assessment of Disease

As of Amendment 09: Central tumor response assessments will be discontinued. Imaging scans will no longer be submitted to iCRO nor read by BICR. The section below is retained for reference.

Local tumor imaging should continue per SOC schedule for participants still on study treatment.

PCWG Modified RECIST 1.1 will be used by BICR as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (eg, discontinuation of study intervention).

Upon investigator-assessed disease progression, the indicative scans are to be submitted immediately to iCRO for BICR verification of progression. After submission of scans, the iCRO will email the assessment to the site and Sponsor.

If disease progression is not verified, the process continues as follows:

- If participant is clinically stable, continue study intervention per protocol
    - Resume imaging per protocol schedule (≥4 weeks to next scan)
    - Send scans to iCRO
    - Continue local assessment

- Do not change investigator assessment of progression
- If subsequent scan(s) indicate progression, submit scans to iCRO to request verification

- If the participant is not clinically stable, best medical practice is to be applied

Before stopping study intervention or imaging or starting new anticancer therapy in a participant who is clinically stable, communication with the Sponsor is required.

If disease progression is verified, the process continues as follows:

- Investigator judgment will determine action
- If the participant is clinically stable and study intervention is to continue, communication with the Sponsor is required and a reconsent addendum must be signed

  Note: the reconsent addendum may be signed any time after investigator-assessed progression is identified but must be signed prior to starting study intervention after verification of disease progression is provided by the iCRO.

- Obtain scans locally per original protocol schedule
- Do not send scans to iCRO
- For the purpose of this decision process, lack of clinical stability is defined as:
  - Unacceptable toxicity
  - Clinical signs or symptoms indicating clinically significant disease progression
  - Decline in performance status
  - Rapid disease progression or threat to vital organs or critical anatomical sites (eg, CNS metastasis, respiratory failure due to tumor compression, spinal cord compression) requiring urgent alternative medical intervention.

8.2.3 Prostate-specific Antigen Assessments

As of Amendment 09: PSA assessments will be discontinued. The section below is retained for reference.

There are 2 components required for defining trial eligibility by PSA, 1) a rising PSA as determined by local laboratory and 2) a PSA $\geq$1 ng/mL as defined by central laboratory. PSA determination by central laboratory has to be performed within 10 days prior to randomization (refer to Section 1.3.1). If central laboratory result for PSA is not expected to be available to the site prior to randomization, the investigator may also perform the test locally and if >1 ng/mL, use that result to determine eligibility. However, a sample must still

be collected within 10 days prior to randomization for submission to central laboratory. During the remainder of the study, local laboratory may not be used in lieu of central laboratory.

For defining rising PSA, the reference value to use (No. 1) is the last PSA before a sequence of PSA increases (see Figure 2 below from Prostate Cancer Working Group 2).

Figure 2 Change in Prostate-specific Antigen

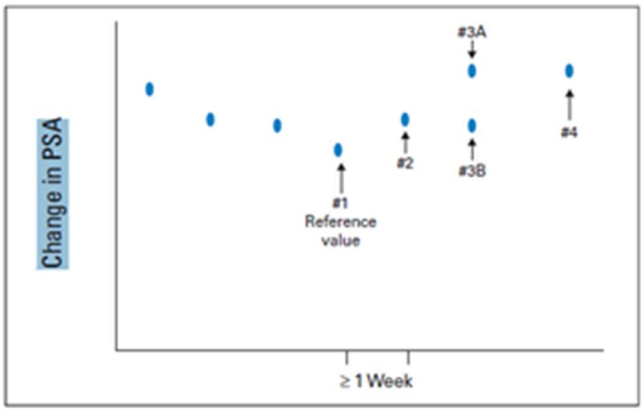

Fig 2. Eligibility based on prostate-specific antigen (PSA) changes. The reference value (#1) is the last PSA measured before increases are documented, with subsequent values obtained a minimum of 1 week apart. If the PSA at time point 3 (value #3A) is greater than that at point 2, then eligibility has been met. If the PSA is not greater than point 2 (value #3B), but value #4 is, the patient is eligible assuming that other criteria are met, if values 3A or #4 are 2 ng/mL or higher, a reduction from the 5 ng/mL specified in the previous guidelines.[1] Reprinted from Bubley et al.[1]

The screening value obtained during the screening period can count as the confirmatory second rising PSA compared to a prior single increased PSA value. If a PSA value obtained during screening is used as the second data point to confirm a rising PSA and it does not confirm the PSA increase, but is still greater than the reference point, the PSA determination should be repeated by the local laboratory in 1 week to prove that there is a sequence of rising PSA.

If there are 2 consecutive rising PSA test results before screening, but the value obtained is less than the previous value (but still above the reference value), the participant is still eligible for the study.

If a local laboratory PSA value obtained during screening is less than the reference point, this constitutes a new PSA nadir and another sequence of 2 rising PSAs are needed to ensure that PSA is rising.

Central laboratory PSA assessment must occur every 3 weeks (±7 days) from the date of randomization while the participant is on study intervention. PSA timing should follow calendar days from the date of randomization and should not be adjusted for delays in cycle starts.

In participants who discontinue study intervention without documented disease progression, every effort should be made to continue monitoring their disease status by PSA assessments until: (1) the start of new anticancer treatment, (2) disease progression, (3) death or (4) the end of the study, whichever occurs first. In these participants, PSA will be measured by a central laboratory at the same time points as imaging.

Sample collection, storage, and shipment instructions will be in the Procedures Manual. The window for PSA collections is ±7 days.

8.2.4 Tumor Tissue Collection

Baseline tumor tissue for biomarker analysis must be sent to the testing laboratory and analyzed for adequacy prior to enrollment.

8.2.5 PROs and Quality of Life Assessments

CCI

[redacted]

8.2.5.1 FACT-P

CCI

[redacted]

8.2.5.2 BPI-SF

CCI

[redacted]

CCI

[redacted]

[redacted]

8.2.5.3 EQ-5D-5L

CCI

[redacted]

8.2.6 Patient Analgesic Log

CCI

[redacted]

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided.

Planned time points for all safety assessments are provided in the SoA.

8.3.1 Physical Examinations

8.3.1.1 Full Physical Examination

The investigator or qualified designee will perform a complete physical exam during the Screening period. Clinically significant abnormal findings should be recorded as medical history. The time points for full physical exams are described in Section 1.3. After the first dose of study intervention, new clinically significant abnormal findings should be recorded as AEs.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.1.2 Directed Physical Examination

For cycles that do not require a full physical exam as defined in Section 1.3, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to study intervention administration. New clinically significant abnormal findings should be recorded as AEs.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.2 Vital Signs

Vital signs will be measured in a sitting, semirecumbent or supine position after 5 minutes rest and will include weight, temperature, systolic and diastolic blood pressure, heart, and respiratory rate. Record vital signs prior to study intervention administration at treatment visits. Height will be measured at screening only.

8.3.3 Electrocardiograms

A standard 12-lead ECG will be performed once at the screening visit using local standard procedures. Clinically significant abnormal findings should be recorded as medical history.

8.3.4 Clinical Safety Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the case report form (CRF). The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

- If laboratory values from nonprotocol specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).

- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

Details regarding specific laboratory procedures/assessments to be performed in this study are provided below. The total amount of blood/tissue to be drawn/collected over the course of the study (from prestudy to poststudy visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant can be found in the Study Procedures Manual. Refer to the Study Flow Chart (Section 1.3) for the timing of laboratory assessments.

8.3.4.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, and urinalysis are specified in Appendix 2.

8.3.5 Performance Assessments

8.3.5.1 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (Appendix 11) at screening and prior to the administration of each dose of study intervention as specified in the SoA (Section 1.3).

8.4 Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Reportable Safety Events

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in Appendix 3.

Adverse events, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3.

The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity and causality. Investigators need to document if an SAE was associated with a medication error, misuse, or abuse.

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

All AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent, but before intervention allocation/randomization, must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event causes the participant to be excluded from the study, or is the result of a protocol-specified intervention, including, but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

- All AEs from the time of intervention allocation/randomization through 30 days following cessation of study intervention must be reported by the investigator.

- All AEs meeting serious criteria, from the time of intervention allocation/randomization through 90 days following cessation of study intervention or 30 days following cessation of study intervention if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator.

- All pregnancies and exposure during breastfeeding, from the time of intervention allocation/randomization through the time required to eliminate systemic exposure after cessation of study intervention as described in Sections 5.1 and 8.4.5, or 30 days after cessation of study intervention if the participant initiates new anticancer therapy must be reported by the investigator.

- Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately to the Sponsor if the event is considered related to study intervention.

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

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in [Table 6].

Table 6 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Time Period: Consent to Randomization/ Allocation**	**Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period**	**Reporting Time Period: After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Sponsor:**
Nonserious Adverse Event (NSAE)	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
Serious Adverse Event (SAE) including Cancer and Overdose	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/ Lactation Exposure	Report if: - due to intervention - causes exclusion	Report all	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event
Event of Clinical Interest (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - potential drug-induced liver injury (DILI) - require regulatory reporting	Not required	Within 24 hours of learning of event
Event of Clinical Interest (ECI) (do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event

8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.4.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events including pregnancy and exposure during breastfeeding, events of clinical interest (ECIs), cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of 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.

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 and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, and investigators.

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

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAE) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a participant's female partner (spontaneously reported to the investigator or their designee), that occurs during the study are reportable to the Sponsor.

All reported pregnancies of participants' female partners must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

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

Efficacy endpoints as outlined in this section will not be reported to the Sponsor as described in Section 8.4.1.

Specifically, the suspected/actual events covered in this exception include any event that is disease progression of the cancer under study.

The Sponsor will monitor unblinded aggregated efficacy endpoint events and safety data to ensure the safety of the participants in the study. Any suspected endpoint that upon review is not progression of the cancer under study will be forwarded to Global Pharmacovigilance as an SAE within 24 hours of determination that the event is not progression of the cancer under study.

8.4.7 Events of Clinical Interest (ECIs)

Selected nonserious and SAEs are also known as ECIs and must be reported to the Sponsor.

Events of clinical interest for this study include:

- An overdose of Sponsor's product, as defined in Section 8.5, that is not associated with clinical symptoms or abnormal laboratory results.

- An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

  *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study site guidance for assessment and follow up of these criteria can be found in the Investigator Study File Binder (or equivalent).

8.5 Treatment of Overdose

For this study, an overdose of pembrolizumab will be defined as any dose of 1000 mg or greater (≥5 times the indicated dose).

No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

An enzalutamide overdose is defined as at least 2 daily doses of study intervention taken the same calendar day. In the event of an overdose, treatment with study drug should be stopped and general supportive measures initiated, taking into consideration the half-life is 5.8 days

for enzalutamide. Participants may be at increased risk of seizures following an overdose of enzalutamide. Neither the effects of overdose of enzalutamide nor an antidote to overdose are known.

The medical monitor must be contacted in the event of a study drug overdose.

8.6 Pharmacokinetics

PK parameters will not be evaluated in this study.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Future Biomedical Research Sample Collection

Not applicable.

8.9 Planned Genetic Analysis Sample Collection

The planned genetic analysis sample should be obtained predose on Day 1 but may be collected at the next scheduled blood draw, if needed. Sample collection, storage, and shipment instructions for planned genetic analysis samples will be provided in the Procedures Manual.

Samples should be collected for planned analysis of associations between genetic variants in germline/tumor DNA and drug response. 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.

8.10 Biomarkers

CCI [redacted]

CCI [redacted]

CCI [redacted]

8.11 Medical Resource Utilization and Health Economics

CCI [redacted]

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

CCI [redacted]

8.12 Visit Requirements

Visit requirements are outlined in Section 1.3. Specific procedure-related details are provided in Section 8.

8.12.1 Screening

Documented informed consent must be provided before performing any protocol-specific procedure. Results of a test performed prior to the participant signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 42 days prior to randomization except for the following:

- Laboratory tests are to be performed within 10 days prior to the first dose of study intervention. An exception is HIV and hepatitis testing which may be done up to 42 days prior to randomization if required by local regulations. Refer to Appendix 7 for country-specific requirements.

- Evaluation of ECOG status is to be performed within 7 days prior to randomization.

- Tumor tissue from a fresh core or excisional biopsy obtained within 12 months of screening. Archival tumor tissue sample (>12 months) can be submitted after Sponsor consultation.

- Initial tumor imaging at screening must be performed within 28 days prior to the date of randomization.

Participants may be rescreened after initially failing to meet the inclusion/exclusion criteria. Results from assessments during the initial screening period are acceptable in lieu of a repeat screening test if performed within the specified time frame and the corresponding inclusion/exclusion criteria met. Participants who are rescreened will retain their original screening number.

8.12.2 Treatment Period Visit

Visit requirements are outlined in the SoA (Section 1.3). Specific procedure-related details are provided in Section 8.1.

8.12.3 Discontinuation Visit

The Discontinuation Visit should occur at the time study intervention is discontinued. If the Discontinuation Visit occurs 30 days after the last dose of study intervention, at the time of the mandatory Safety Follow-up Visit, procedures do not need to be repeated. Visit requirements are outlined in Section 1.3 – Schedule of Activities. Specific procedure-related details are provided above in Section 8 – Study Assessments and Procedures. Prior to discontinuing participants from therapy, submit the Treatment Termination & Disease Assessment Termination Form.

8.12.4 Participants Discontinued From Study Intervention but Continuing to be Monitored in the Study

Prior to discontinuing participants from therapy, submit the Treatment Termination & Disease Assessment Termination Form.

8.12.5 Post-treatment Visit

8.12.5.1 Safety Follow-up Visit

The mandatory Safety Follow-up Visit should be conducted approximately 30 days after the last dose of study intervention or before the initiation of a new anticancer treatment, whichever occurs first.

Participants who are eligible for retreatment with pembrolizumab may have up to 2 safety follow-up visits, 1 after the Initial Treatment or First Course and 1 after the Second Course.

8.12.5.2 Efficacy Follow-up Visits

NOTE: As of Amendment 09: Efficacy Follow-up visits will be discontinued. The section below is retained for reference.

Participants who discontinue study intervention for a reason other than BICR-verified radiographic disease progression will move into Follow-up. Follow-up visits will be scheduled every 9 weeks (63 days ± 7 days) through Week 54 and then every 12 weeks (84 days ± 7 days) thereafter, from the date of randomization, to coincide with the imaging schedule the participant was on at the time of discontinuation from treatment. Participants who discontinue study intervention without documented disease progression (including confirmation of bone progression) should continue monitoring disease status by radiologic imaging (CT/MRI and bone scans) and PSA according to the schedule that the participant was on at the time of discontinuation (every 9 or 12 weeks). Every effort should be made to collect information regarding disease status until the start of new anticancer therapy, disease progression, death, end of study (or if the participant begins retreatment with pembrolizumab as detailed in Section 6.6.4). Information regarding poststudy anticancer treatment will be collected if new treatment is initiated.

Participants who are eligible to receive retreatment with pembrolizumab according to the criteria in Section 6.6.4 will move from Follow-up to Second Course when they experience disease progression. Details are provided in the SoA (Section 1.3) for retreatment with pembrolizumab.

8.12.5.3 Survival Follow-up

CCI

8.12.6 Vital Status

To ensure current and complete survival information (vital status) is available at the time of database locks, updated vital status may be requested during the course of the study by the Sponsor. For example, updated survival status may be requested prior to but not limited to an external Data Monitoring Committee (eDMC) review, interim and/or final analysis. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted.

9 STATISTICAL ANALYSIS PLAN

As of Amendment 09: The Statistical Analysis Plan is amended as follows.

NOTE: Based on the data from an interim safety and efficacy analysis for KEYNOTE-641 (data cutoff 12-DEC-2022), the eDMC recommended stopping the study for futility per the futility criteria prespecified in the sSAP. Based upon these data and the recommendation of the eDMC, the study has been unblinded (as of 22-FEB-2023). Prespecified IA2 and final analysis of the study described in the SAP will not be performed. Safety analysis will be performed at the end of the study. There will be no further analyses for efficacy CCI endpoints collected from participants beyond the IA1 cutoff date.

This section outlines the statistical analysis strategy and procedures for the study. The study has been unblinded as of 22-FEB-2023. Changes made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses that occurred prior to Amendment 09 were documented in previous protocol amendments(s) and sSAP (consistent with ICH Guideline E-9). Changes to exploratory or other nonconfirmatory analyses made after the protocol has been finalized, but prior to unblinding/final data base lock, will be documented in a sSAP and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR. CCI

9.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 9.2 through 9.12. As of Amendment 09, prespecified IA2 and final analysis of the study described in the SAP will not be performed. Safety analysis will be performed at the end of the study; there will be no further analyses of efficacy CCI endpoints collected from participants beyond the IA1 cutoff date. The SAP summary has been updated accordingly.

Study Design Overview	A Phase 3, Randomized, Double-blind Study of Pembrolizumab (MK-3475) Plus Enzalutamide versus Placebo Plus Enzalutamide in Metastatic Castration-Resistant Prostate Cancer (mCRPC)
Treatment Assignment	Approximately 1240 eligible participants will be randomized in a 1:1 ratio to one of the following 2 treatment arms: • Arm 1: pembrolizumab plus enzalutamide • Arm 2: placebo plus enzalutamide CCI [redacted] In alignment with the study update memo sent to investigators on 28-FEB-2023, all study participants should stop ongoing treatment with pembrolizumab/placebo.
Analysis Populations	Efficacy: Intent-to-Treat (ITT) Safety: All Participants as Treated (APaT)
Primary Endpoint(s)	1. Overall survival (OS) 2. Radiographic progression-free survival (rPFS)
Key Secondary Endpoints	1. Time to initiation of the first subsequent anticancer therapy (TFST) or death
Statistical Methods for Key Efficacy Analyses	The primary hypotheses will be evaluated by comparing pembrolizumab plus enzalutamide arm to placebo plus enzalutamide arm with respect to OS, rPFS, and TFST using a stratified log-rank test. The hazard ratio will be estimated using a Cox regression model. Event rates over time will be estimated within each treatment group using the Kaplan-Meier method.
Statistical Methods for Key Safety Analyses	The analysis of safety results will follow a tiered approach. The tiers differ with respect to the analyses that will be performed. There are no events of interest that warrant elevation to Tier 1 events in this study. Tier 2 parameters will be assessed via point estimates with 95% confidence interval (CIs) provided for between-group comparison; only point estimates by treatment group are provided for Tier 3 safety parameters. The 95% CIs for the between-treatment differences in percentages will be provided using the Miettinen & Nurminen method.

Interim Analyses	CCI [redacted]
Multiplicity	
Sample Size and Power	

9.2 Responsibility for Analyses/In-house Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the Sponsor.

This study will be conducted as a double-blind study under in-house blinding procedures. The official, final database will not be unblinded until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete.

The Clinical Biostatistics department of the Sponsor will generate the randomized allocation schedule for study intervention assignment for this protocol, and the randomization will be implemented in an IRT by a study vendor.

CCI [redacted]

9.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.

9.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated for within- and between-treatment differences are listed below, followed by the descriptions of the derivations of selected endpoints.

9.4.1 Efficacy Endpoints

9.4.1.1 Primary

Overall Survival

OS is defined as the time from randomization to death due to any cause.

Radiographic Progression-free Survival – PCWG-modified RECIST 1.1 by BICR is defined as the time from randomization to the first documented disease progression or death due to any cause, whichever occurs first.

9.4.1.2 Key Secondary

Time to initiation of the first subsequent anticancer therapy or death (TFST) is defined as the time from randomization to initiation of the first subsequent anticancer therapy or death, whichever occurs first.

9.4.1.3 Secondary

PSA response rate is defined as the proportion of participants in the analysis population with PSA decline of ≥50% from baseline measured twice at least 3 weeks apart.

Objective response rate -- PCWG-modified RECIST 1.1 by BICR is defined as the proportion of participants in the analysis population who have a best overall response of either confirmed CR or PR.

Duration of response - PCWG-modified RECIST 1.1 by BICR is defined as the time from the earliest date of first documented evidence of confirmed CR or PR until earliest date of disease progression or death from any cause, whichever occurs first.

Time to PSA progression is defined as the time from randomization to PSA progression. Participants without PSA progression will be censored at the last PSA assessment date. The PSA progression date is defined as the date that 1) ≥25% increase and ≥2 ng/mL above the nadir, and which is confirmed by a second value ≥3 weeks later if there is PSA decline from baseline 2) or ≥25% increase and ≥2 ng/mL increase from baseline beyond 12 weeks if there is no PSA decline from baseline.

PSA undetectable rate is defined as the proportion of participants in the analysis population with PSA < 0.2 ng/mL during study intervention.

Time to first symptomatic skeletal-related event is defined as the time from randomization to the first symptomatic skeletal-related event, which is defined as to the

1) first use of EBRT to prevent or relieve skeletal symptoms,

2) the occurrence of new symptomatic pathologic bone fracture (vertebral or nonvertebral),

3) occurrence of spinal cord compression

4) or tumor-related orthopedic surgical intervention,

whichever occurs first.

Time to radiographic soft-tissue progression – soft-tissue rule of PCWG-modified RECIST 1.1 by BICR is defined as the time from randomization to radiographic soft-tissue progression.

9.4.1.4 Exploratory

CCI [redacted]

9.4.2 Safety Endpoints

Safety measurements are described in Section 4.2.1.2.

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse events, laboratory values and vital signs.

9.4.3 PRO Endpoints

9.4.3.1 CCI [redacted]

CCI [redacted]

CCI [redacted]

9.5 Analysis Populations

9.5.1 Efficacy Analysis Populations

CCI [redacted]

9.5.2 Safety Analysis Populations

CCI [redacted]

9.5.3 PRO Analysis Population

CCI [redacted]

9.6 Statistical Methods

Statistical testing and inference for safety analyses are described in Section 9.6.2. Efficacy results that will be deemed to be statistically significant after consideration of the Type I error control strategy are described in Section 9.8, Multiplicity. Nominal p-values may be computed for other efficacy analyses, but should be interpreted with caution due to potential issues of multiplicity, sample size, etc. Unless otherwise stated, all statistical tests will be conducted at the $\alpha = 0.05$ (2-sided) level. In the event that there are a small number of responses/events in one or more strata, for the purpose of analysis strata will be combined to ensure sufficient number of responses/events in each stratum. Details regarding the combining of strata will be specified in the sSAP prior to database lock based on a blinded review of response counts by stratum.

9.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary and key secondary objectives. CCI [redacted]

9.6.1.1 Overall Survival

The nonparametric Kaplan-Meier method will be used to estimate the survival curves. The treatment difference in survival will be assessed by the stratified log-rank test (based on the stratification factors defined in Section 6.3.2). A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, the hazard ratio). The HR and its 95% CI from the stratified Cox model with a single treatment covariate will be reported. The stratification factors used for randomization (Section 6.3.2) will be applied to both the stratified log-rank test and the stratified Cox model. Participants without documented death at the time of analysis will be censored at the date of last known contact. CCI [redacted]

CCI [redacted]

9.6.1.2 Radiographic Progression-Free Survival

The nonparametric Kaplan-Meier method will be used to estimate the rPFS curve in each treatment group. The treatment difference in rPFS will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, hazard ratio) between the treatment arms. The hazard ratio and its 95% CI from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate will be reported. The stratification factors used for randomization (see Section 6.3.2) will be applied to both the stratified log-rank test and the stratified Cox model.

CCI [redacted]

[redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

[redacted]

9.6.1.3 TFST

The nonparametric Kaplan-Meier method will be used to estimate the TFST curve in each treatment group. The treatment difference in TFST will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, hazard ratio) between the

treatment arms. The hazard ratio and its 95% confidence interval from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate will be reported. The stratification factors used for randomization (See Section 6.3.2) will be applied to both the stratified log-rank test and the stratified Cox model.

Details of efficacy analyses for other endpoints will be provided in the sSAP.

9.6.1.4 Analysis Strategy for Key Efficacy Endpoints

Table 8 summarizes the primary analysis approach for key efficacy endpoints.

Table 8 Efficacy Analysis Methods for Key Efficacy Endpoints

Endpoint/Variable	Statistical Method[a]	Analysis Population	Missing Data Approach
Primary Analyses:			
OS	Testing: Stratified log-rank Test Estimation: Stratified Cox model with Efron's tie handling method.	ITT	Censored at last known alive date.
rPFS per PCWG-modified RECIST 1.1 as assessed by BICR	Testing: Stratified log-rank Test Estimation: Stratified Cox model with Efron's tie handling method.	ITT	Censored according to rules in Table 7
Key Secondary Analysis:			
TFST	Testing: Stratified Log-rank Test Estimation: Stratified Cox model with Efron's tie handling method.	ITT	Censored at the last known time to have not received subsequent new anticancer therapy

BICR=blinded independent central review; ITT=intention-to-treat; OS=overall survival; PCWG=Prostate Cancer Working Group; RECIST 1.1= Response Evaluation Criteria in Solid Tumors Version 1.1; rPFS=radiographic progression-free survival; TFST=Time to initiation of the first subsequent anticancer therapy or death;

[a] Statistical models are described in further detail in the text. For stratified analyses, the stratification factors used for randomization (Section 6.3.2) will be applied to the analysis. Small strata will be combined in a way specified by a blinded statistician prior to the analysis.

CCI [redacted]

9.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse experiences, laboratory tests, vital signs, and ECG measurements.

The analysis of safety results will follow a tiered approach (Table 9). The tiers differ with respect to the analyses that will be performed. Adverse experiences (specific terms as well as system organ class terms) and events that meet predefined limits of change in laboratory and vital signs, and ECG parameters are either prespecified as Tier-1 endpoints or will be classified as belonging to "Tier 2" or "Tier 3", based on observed proportions of participants with an event.

Tier 1 Events

Safety parameters or AEs of special interest that are identified a priori constitute Tier 1 safety endpoints that will be subject to inferential testing for statistical significance.

AEs that are immune-mediated or potentially immune-mediated are well documented and will be evaluated separately; however, these events have been characterized consistently throughout the pembrolizumab clinical development program and determination of statistical significance is not expected to add value to the safety evaluation. The combination of pembrolizumab and enzalutamide has not been associated with any new safety signals. Finally, there are no known AEs associated with participants with prostate cancer for which determination of a p-value is expected to impact the safety assessment. Therefore, there are no Tier 1 events for this protocol.

Tier 2 Events

Tier 2 parameters will be assessed via point estimates with 95% confidence intervals provided for between-treatment differences in the proportion of participants with events.

Membership in Tier 2 requires that at least CCI of participants in any treatment group exhibit the event; all other AEs and predefined limits of change will belong to Tier 3. The threshold of at least CCI of participants was chosen for Tier 2 events because the population enrolled in this study are in critical conditions and usually experience various AEs of similar types regardless of treatment; events reported less frequently than CCI of participants would obscure the assessment of the overall safety profile and add little to the interpretation of potentially meaningful treatment differences. Because many 95% CIs may be provided without adjustment for multiplicity, the CIs should be regarded as a helpful descriptive measure to be used in safety review, not a formal method for assessing the statistical significance of the between-group differences in AEs and safety parameters that meet predefined limits of change.

In addition, the broad AE categories consisting of the proportion of participants with any AE, a drug-related AE, a Grade 3 to 5 AE, an AE that is both Grade 3 to 5 and drug-related, an SAE, an AE which is both serious and drug-related, a dose modification due to an AE, a discontinuation due to an AE, and death will be considered Tier 2 endpoints.

Tier 3 Events

Safety endpoints that are not Tier 1 or 2 events are considered Tier 3 events. Only point estimates by treatment group are provided for Tier 3 safety parameters.

Continuous Safety Measures

For continuous measures such as changes from baseline in laboratory, vital signs, and ECG parameters, summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in table format.

Table 9 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	Any AE CCI [redacted]	X	X
	Any Grade 3 to 5 AE CCI [redacted]	X	X
	Any serious AE CCI [redacted]	X	X
Tier 3	Any AE		X
	Change from baseline results (laboratory test toxicity grade, vital signs, ECGs)		X

AE=adverse event; CI=confidence interval; ECG=electrocardiogram; X=results will be provided.

9.6.3 Analysis Methods for PRO Endpoints

CCI [redacted]

9.6.4 Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant demographic and baseline characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants screened and randomized and the primary reason for screening failure and discontinuation will be displayed. Demographic variables, baseline characteristics, primary and secondary

diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

9.7 Interim Analyses

CCI

[redacted]

9.7.1 Efficacy Interim Analyses

CCI

[redacted]

CCI [redacted]

9.7.2 Safety Interim Analyses

CCI [redacted]

9.8 Multiplicity

CCI [redacted]

[redacted]

CCI [redacted]

9.8.1 rPFS

CCI [redacted]

CCI

[redacted]

9.8.2 OS

CCI

[redacted]

CCI

[redacted]

9.8.3 TFST

CCI

[redacted]

CCI [redacted]

[redacted]

CCI [redacted]

9.8.4 Safety Analyses

CCI [redacted]

9.9 Sample Size and Power Calculations

NOTE: As of Amendment 09, prespecified IA2 and final analysis of the study described in the SAP will not be performed. This section is retained for reference.

The sample size is estimated based on the dual primary endpoints of rPFS and OS.

A total of approximately 1240 participants will be randomized in a 1:1 ratio to the pembrolizumab plus enzalutamide group and the placebo plus enzalutamide group, (approximately 600 participants per group) respectively. CCI [redacted]

CCI [redacted]

With CCI [redacted], the study has approximately CCI [redacted] power to demonstrate males treated with pembrolizumab + enzalutamide has a longer median CCI [redacted] than males treated with enzalutamide CCI [redacted] if the underlying constant HR is CCI [redacted]. Sample size and power calculations are based on the following assumptions: (1) an HR of CCI [redacted] where the CCI [redacted] follows CCI [redacted] distribution with a median of CCI [redacted] in the pembrolizumab + enzalutamide group and a median of CCI [redacted] in the enzalutamide group CCI [redacted] (2) CCI [redacted] (3) an enrollment duration of CCI [redacted] under an average enrollment rate of CCI [redacted] participants per month CCI [redacted]; and (4) a monthly drop-out rate of CCI [redacted]

CCI [redacted] will be conducted CCI [redacted] when approximately CCI [redacted] events are observed. Approximately CCI [redacted] events are expected to be observed at that time.

With CCI [redacted], the study has approximately CCI [redacted] power to demonstrate that males treated with pembrolizumab + enzalutamide have a longer median CCI [redacted] than males treated with enzalutamide at a one- sided significance level of CCI [redacted] if the underlying constant HR is CCI [redacted]. These calculations are based on the following assumptions: (1) a hazard ratio of CCI [redacted] where CCI [redacted] follows CCI [redacted] distribution with a median of CCI [redacted] in the pembrolizumab + enzalutamide group and a median of CCI [redacted] in the enzalutamide group CCI [redacted] (3) an enrollment duration of CCI [redacted] under an average enrollment rate of CCI [redacted] participants per month CCI [redacted] and (4) an approximately monthly drop-out rate of CCI [redacted]

CCI [redacted] will be conducted CCI [redacted] when approximately CCI [redacted] events are observed. Approximately CCI [redacted] events are expected to be observed at that time. With CCI [redacted], the study has approximately CCI [redacted] power to demonstrate males treated with pembrolizumab + enzalutamide have a longer median CCI [redacted] than males treated with enzalutamide at a one-sided significance level of CCI [redacted] if the underlying constant CCI [redacted]. These calculations are based on the following assumptions: (1) a hazard ratio of CCI [redacted] where CCI [redacted] follows CCI [redacted] distribution with a median of CCI [redacted] in the pembrolizumab + enzalutamide group and a median of CCI [redacted] in the enzalutamide group CCI [redacted] (2) interim analyses for efficacy evaluation as outlined in Section 9.7; (3) an enrollment duration of CCI [redacted] under an average enrollment rate of CCI [redacted]

participants per month [redacted] and (4) an approximately [redacted]

The sample size and power calculations for rPFS, TFST, and OS were performed [redacted]

9.10 Subgroup Analyses

To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the primary endpoints will be estimated and plotted within each category of the following classification variables:

[redacted]

In addition, a Forest plot will be produced, which provides the estimated point estimates and confidence intervals for the treatment effect across the categories of subgroups listed above.

In the event that there are a small number of responses/events in one or more strata, for the purpose of analysis strata will be combined to ensure sufficient number of responses/events in each stratum. Details regarding the combining of strata will be specified in the sSAP prior to database lock based on a blinded review of response counts by stratum.

9.11 Compliance (Medication Adherence)

Drug accountability data for study intervention will be collected during the study. Any deviation from protocol-directed administration will be reported.

9.12 Extent of Exposure

The extent of exposure for enzalutamide will be summarized as duration of treatment in days. The extent of exposure for pembrolizumab/placebo will be summarized as duration of treatment in cycles. Dose interruption for each drug, dose reduction or dose increase for enzalutamide will be summarized. Summary statistics will be provided on Extent of Exposure for the APaT population.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Code of Conduct for Clinical Trials

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD)

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (eg, International Council for Harmonisation Good Clinical Practice [ICH-GCP]) and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD irrespective of the party (parties) employed for their execution (eg, contract research organizations, collaborative research efforts). This Code is not intended to apply to trials that are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials, which are not under the full control of MSD.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy, and/or pharmacokinetic or pharmacodynamic indices of MSD or comparator products. Alternatively, MSD may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine patient preferences, etc.

The design (ie, participant population, duration, statistical power) must be adequate to address the specific purpose of the trial. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if fraud, scientific/research misconduct, or serious GCP-noncompliance is suspected, the issues are investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the prespecified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing, in such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

A. Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All clinical trials will be reviewed and approved by an IRB/IEC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the ethics committee prior to implementation, except changes required urgently to protect participant safety that may be enacted in anticipation of ethics committee approval. For each site, the ethics committee and MSD will approve the participant informed consent form.

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible. Unless required by law, only the investigator, Sponsor (or representative), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

Genomic research will only be conducted in accordance with a protocol and informed consent authorized by an ethics committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is MSD's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of MSD trials. MSD does not pay incentives to enroll participants in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

MSD does not pay for participant referrals. However, MSD may compensate referring physicians for time spent on chart review to identify potentially eligible participants.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by MSD and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local ethics committee may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, all publications resulting from MSD trials will indicate MSD as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (eg, to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices.

V. Investigator Commitment

Investigators will be expected to review MSD's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

10.1.2 Financial Disclosure

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.1.3 Data Protection

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.3.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the IRB, IEC, or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.3.2 Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents to verify worksheet/CRF data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all participant data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations.

10.1.3.3 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.1.4 Committees Structure

10.1.4.1 Executive Oversight Committee

The EOC is comprised of members of Sponsor Senior Management. The EOC will receive and decide upon any recommendations made by the DMC regarding the study.

10.1.4.2 External Data Monitoring Committee

To supplement the routine study monitoring outlined in this protocol, an external DMC will monitor the interim data from this study. The voting members of the committee are external to the Sponsor. The members of the DMC must not be involved with the study in any other way (eg, they cannot be study investigators) and must have no competing interests that could affect their roles with respect to the study.

The DMC will make recommendations to the EOC regarding steps to ensure both participant safety and the continued ethical integrity of the study. Also, the DMC will review interim

study results, consider the overall risk and benefit to study participants (Section 9.7 Interim Analysis) and recommend to the EOC whether the study should continue in accordance with the protocol.

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the Sponsor protocol team; meeting facilitation; the study governance structure; and requirements for and proper documentation of DMC reports, minutes, and recommendations will be described in the DMC charter that is reviewed and approved by all the DMC members.

10.1.5 Publication Policy

The results of this study may be published or presented at scientific meetings. 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 studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

If publication activity is not directed by the Sponsor, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007 and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials directive, or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this study or its results to those registries.

10.1.7 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP

(eg, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use GCP: Consolidated Guideline and other generally accepted standards of GCP); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in this appendix under the Code of Conduct for Clinical Studies.

The investigator agrees not to seek reimbursement from participants, their insurance providers, or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this study.

The investigator agrees to provide the Sponsor with relevant information from inspection observations/findings to allow the Sponsor to assist in responding to any citations resulting from regulatory authority inspection and will provide the Sponsor with a copy of the proposed response for consultation before submission to the regulatory authority.

Persons debarred from conducting or working on clinical studies by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

10.1.8 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the study site upon request for inspection, copying, review, and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are

requested by the Sponsor or any regulatory authorities as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/CRFs.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF 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.

Records and documents, including participants' documented informed consent, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.9 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's participants. Source documents and data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator/institution may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.10 Study and Site Closure

The Sponsor or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor will promptly notify that study site's IRB/IEC.

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 14 will be performed by the central laboratory.
- Results of predose laboratory procedures must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment. During initial treatment, local laboratory results are permitted in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is used, it is important that the sample for central analysis is obtained in parallel. Additionally, if the use of local laboratory test results in a change in study participant management, or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.1 and Section 5.2 of the protocol, respectively.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- PD-L1, PSA, CTC and AR-V7 results are not reported back to sites to prevent early withdrawal of participants from study intervention.

Table 14 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: Neutrophils (ANC) Lymphocytes Monocytes Eosinophils Basophils	
Chemistry	Blood Urea Nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the upper limit of normal)
	Albumin	Bicarbonate	Chloride	Phosphorous
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose (Indicate if fasting, or nonfasting)	Calcium	Alkaline phosphatase	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, (bilirubin, urobilinogen, nitrite, leukocyte esterase) • Microscopic examination (if blood or protein is abnormal)			
Other Tests	• Testosterone • Thyroid function tests • PT or INR and PTT/aPTT			

ALT=alanine aminotransferase; ANC=absolute neutrophil count; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; BUN=blood urea nitrogen; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; PT/INR=prothrombin time/international normalized ratio; PTT=partial thromboplastin time; RBC=red blood cell; SGOT= serum glutamic-oxaloacetic transaminase; SGPT=serum glutamate pyruvate transaminase; WBC=white blood cell.

The investigator (or medically qualified designee) must document their review of each laboratory safety report.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication Error

This is an unintended failure in the drug treatment process that leads to or has the potential to lead to harm to the patient.

Misuse

This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the product information.

Abuse

This corresponds to the persistent or sporadic, intentional excessive use of a medicinal product for a perceived psychological or physiological reward or desired non-therapeutic effect.

10.3.2 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study 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.
- NOTE: For purposes of AE definition, study intervention (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, diagnostic agent, or protocol specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

- Any abnormal 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.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

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.
- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.3 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.

An SAE is defined as any untoward medical occurrence that, at any dose:

Results in death

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.

Requires inpatient hospitalization or prolongation of existing hospitalization

- Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not an SAE.) A pre-existing condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant's medical history.

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) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

Is a congenital anomaly/birth defect

- In offspring of participant taking the product regardless of time to diagnosis.

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 1 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.

10.3.4 Additional Events Reported in the Same Manner as SAE

Additional events that require reporting in the same manner as SAE

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same time frame as SAEs to meet certain local requirements. Therefore, these events are considered serious by the Sponsor for collection purposes.

- Is a new cancer (that is not a condition of the study)
- Is associated with an overdose

10.3.5 Recording AE and SAE

AE and SAE recording

- When an AE/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.
- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.
- 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 AE CRF page.
- 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 blinded 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 intensity/toxicity

- 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.

- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI CTCAE, version 4.0. Any AE that changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.

    - 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 ADL.

    - Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.

    - Grade 4: Life threatening consequences; urgent intervention indicated.

    - Grade 5: Death related to AE.

Assessment of causality

- Did the Sponsor's product cause the AE?

- The determination of the likelihood that the Sponsor's product caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.

- **The following components are to be used to assess the relationship between the Sponsor's product and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the AE:**

    - **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?

    - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with investigational medicinal product)?

    - **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.

- **Dechallenge:** Was the Sponsor's product discontinued or dose/exposure/frequency reduced?
    - If yes, did the AE resolve or improve?
    - If yes, this is a positive dechallenge.
    - If no, this is a negative dechallenge.

  (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the study is a single-dose drug study; or (4) Sponsor's product(s) is/are only used 1 time.)

- **Rechallenge:** Was the participant re-exposed to the Sponsor's product in this study?
    - If yes, did the AE recur or worsen?
    - If yes, this is a positive rechallenge.
    - If no, this is a negative rechallenge.

  (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the study is a single-dose drug study; or (3) Sponsor's product(s) is/are used only 1 time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL, AND IF REQUIRED, THE INIRB/IEC.

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?
- The assessment of relationship will be reported on the case report forms/worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.

- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).
  - Yes, there is a reasonable possibility of Sponsor's product relationship:
    - There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.
  - No, there is not a reasonable possibility of Sponsor's product relationship:
    - Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to 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 1 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 is sufficient data to support full attribution of the AE to the single agent.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by 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 in the CRF.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

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

AE, SAE, and other reportable safety event reporting to Sponsor via electronic data collection tool

- The primary mechanism for reporting to the Sponsor will be 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 form.
        - Reference Section 8.4.1 for reporting time requirements.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- 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.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure e-mail of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

10.4 Appendix 4: Device Events, Adverse Device Events, and Medical Device Incidents: Definitions, Collection, and Documentation

Not applicable.

10.5 Appendix 5: Contraceptive Guidance and Pregnancy Testing

10.5.1 Definitions

Women of Childbearing Potential (WOCBP) Nonparticipant Only

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below):

- Women in the following categories are not considered WOCBP:
  - Premenarchal
  - Premenopausal female with 1 of the following:
    - Hysterectomy
    - Bilateral salpingectomy
    - Bilateral oophorectomy
    - Permanent infertility due to an alternate medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity.
  - Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

10.5.2 Pregnancy Testing

Not applicable.

10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research

Not Applicable.

10.7 Appendix 7: Country-specific Requirements

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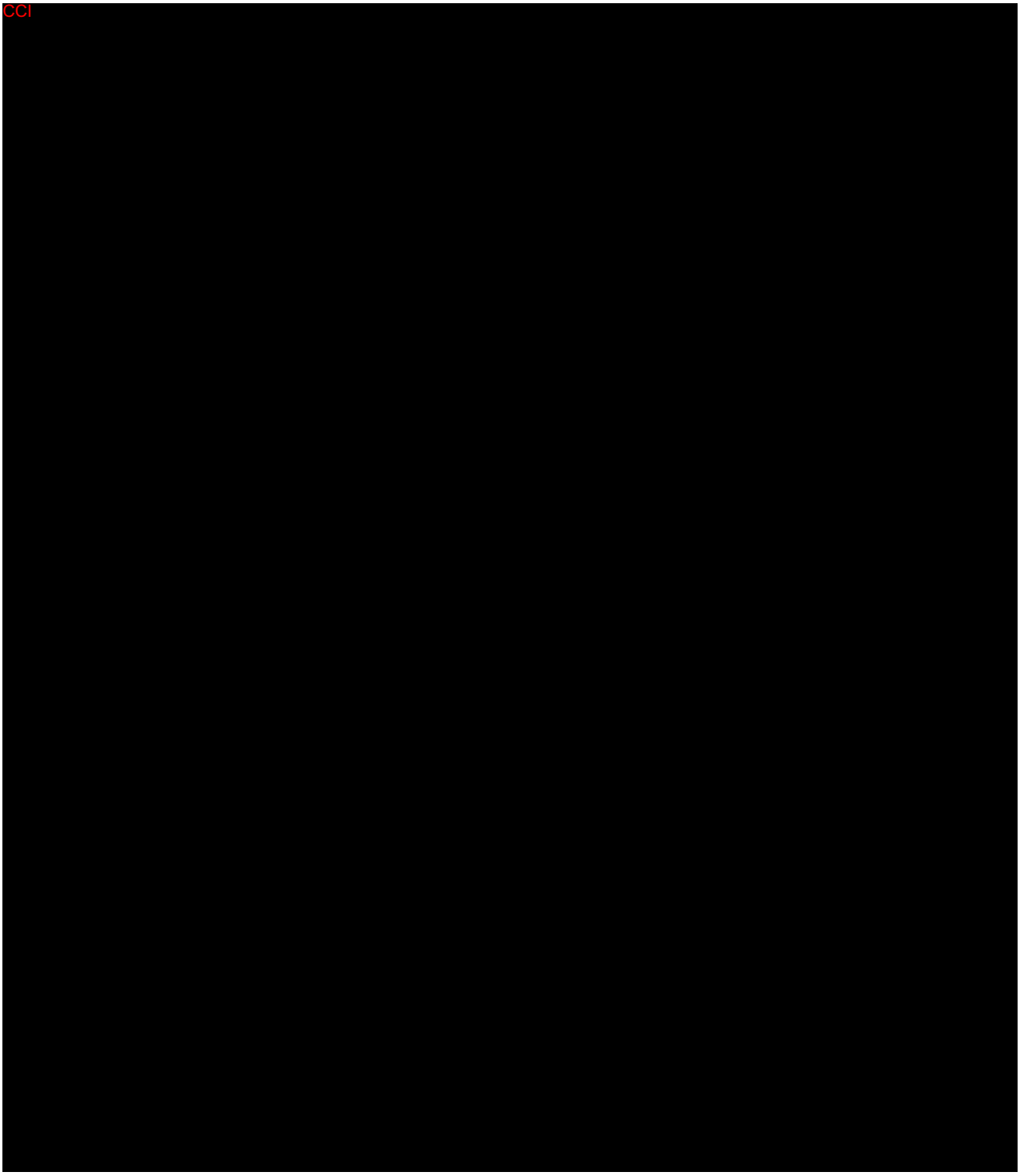

10.8 Appendix 8: Description of the Prostate Cancer Working Group (PCWG) Process for Assessment of Bone Lesions

The rules for evaluation of response and progression based on bone lesions were created by the PCWG and published as part of both PCWG2 and PCWG3 [Scher, H. I., et al 2016]. All bone lesions are evaluated according to these rules, including assessment at screening/baseline and evaluation of response.

10.8.1 Imaging Methods

The PCWG rules were designed based on the radionuclide (Tc-99m) bone scintigraphy. Other modalities, including FDG-PET, sodium fluoride PET, bone MRI, etc. may have individual advantages, but the PCWG rules were not created with the performance characteristics of these methods in mind and should not be used instead of radionuclide bone scan.

Only bone lesions seen by bone scan may be followed for assessment of tumor treatment response. Bone disease seen by CT only (not visible on bone scan) is presumed not to represent active disease and should not be documented as a bone lesion (sclerotic lesions seen on CT may represent healed disease or nonmalignant confounders such as bone infarcts or other benign findings).

10.8.2 Documentation of Bone Lesions at Baseline

At baseline, individual bone lesions may be recorded as nontarget lesions only, and the number of bone lesions should be noted.

10.8.3 Assessment of Bone Response at Subsequent Imaging Time Points

At all follow-up timepoints, bone disease will be classified as PD (progressive disease), PDu (progressive disease unconfirmed), Non-PD (no progressive disease), NED (no evidence of disease), or NE (nonevaluable). The definitions are summarized in the following table and described in more detail below.

Bone Response	Definition
PD	**Progressive disease:** 2 new lesions, not flare, persistent
PDu	**Progressive disease unconfirmed:** Temporary marker of possible PD, to be updated to PD or non-PD once a subsequent scan is available. If this is the final visit, the visit response will remain PDu, but is updated to PD during analysis by MSD.
Non-PD	**Nonprogressive disease:** At least one bone lesion present, but not enough to trigger PD
NE	**Nonevaluable:** Status of bone lesions cannot be determined (scan quality, scan missing, etc.)
NED	**No evidence of disease:** No lesions seen on bone scan

10.8.4 Descriptions of Bone Response Categories

10.8.4.1 No Evidence of Disease

No lesions seen on bone scan at this visit. Either none were seen at baseline, or all completely resolved on subsequent imaging.

10.8.4.2 Nonprogression (Non-PD)

At least one bone lesion is present on the scan at this visit, but the conditions for progression have not been met, because there are not at least two new lesions present.

10.8.4.3 Unconfirmed Progressive Disease (PDu)

At least two new bone lesions are present, but an additional scan is required for confirmation. This response category is meant as a placeholder that reflects temporary uncertainty and is updated to PD or non-PD once a subsequent bone scan is available.

10.8.4.4 Progressive Disease (PD)

At least two new bone lesions are present, which have been confirmed to not represent flare or any other confounder (see below), and which are persistent for at least 6 weeks. The new bone lesions do not all have to appear at the same time. Thus, if one new lesion appears at visit N, and another new lesion at visit N+1, visit N+1 is considered to represent progressive disease.

10.8.4.5 Confirmation of Progression

Radiographic progression of bone lesions is defined as the appearance of ≥2 new bone lesions on radionuclide bone scan. When ≥2 new bone lesions are first observed, this is classified as PDu, which marks the possibility of progression that will be resolved by the next scan.

10.8.4.5.1 For New Lesions Within the Flare Window (<12 weeks)

After a scan classified as PDu within the first 12 weeks of treatment, if the next bone scan outside the flare window shows at least two additional new bone lesions (in addition to the new lesions seen on the prior scan), the initial progression is considered confirmed, and the bone scan response updated to PD. Because this requires at least 2 new lesions, followed by another 2 new lesions, this is known as the "2+2 rule".

If the next bone scan outside the flare window does not show at least two additional new bone lesions, the lesions seen on the prior scan within the flare window are considered to be pre-existing lesions that became more visible because of the tumor flare phenomenon.

- The bone response at the prior visit is updated to non-PD
- The bone lesions seen within the flare window are ignored for the purposes of counting new lesions at later timepoints, since they were not new. This may be referred to as "re-baselining".

10.8.4.5.2 For New Lesions Outside the Flare Window (>12 weeks)

After a scan classified as PDu after the first 12 weeks of treatment, if at least 2 of the new lesions seen on that scan persist on the next bone scan performed at least 6 weeks later, this confirms the initial progression. The prior response is then updated to PD. If the new lesions have disappeared on this later scan, the prior response is updated to non-PD because these lesions are presumed to be nonmalignant in nature. No re-baselining of lesions will occur in this scenario.

10.8.4.6 Superscan

A "superscan" occurs when there is diffuse skeletal involvement by tumor, such that individual bone lesions are not distinguishable. The bone scan may initially appear normal, because the increase bone uptake may be uniform, but can be distinguished by the faint or absent activity in the kidneys and urinary tract.

If there is a true superscan at baseline, identifying individual new bone lesions, and determining progression based on bone lesions, may be impossible.

If a superscan occurs after baseline, the patient's bone response will be recorded as PD. No subsequent imaging will be required for confirmation, because a superscan is extremely unlikely to be caused by benign conditions or tumor flare.

10.8.4.7 Management Following Confirmed PD

If repeat imaging does confirm PD, participants will be discontinued from study intervention.

Note: If a participant has confirmed radiographic progression as defined above, but the participant is achieving a clinically meaningful benefit, an exception to continue study intervention may be considered following consultation with the Sponsor. In this case, if study intervention is continued, tumor imaging should continue (see Section 8.2).

10.9 Appendix 9: Description of the iRECIST Process for Assessment of Disease Progression

Not Applicable.

10.10 Appendix 10: Abbreviations

Abbreviation	Expanded Term
ABI	abiraterone acetate
ADT	androgen deprivation therapy
AE	adverse event
ALT	alanine aminotransferase
APaT	All-Participants-as-Treated
aPTT	activated partial thromboplastin time
AQA	analgesic quantification algorithm
AR	androgen receptor
AR-V7	androgen-receptor splice variant 7
AST	aspartate aminotransferase
BCG	Bacillus Calmette–Guérin
BICR	blinded independent central review
BPI-SF	Brief Pain Inventory-Short Form
CD28	cluster of differentiation 28
CD3 ζ	cluster of differentiation 3 zeta
CHAARTED	Chemohormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease
CI	confidence interval
cLDA	constrained longitudinal data analysis
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COPD	chronic obstructive pulmonary disease
CPS	combined (tumor and immune cells) positive score
CR	complete response
CRF	case report form
CSPC	castration-sensitive prostate cancer
CSR	Clinical Study Report
CT	computed tomography
CTC	circulating tumor cell
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor deoxyribonucleic acid
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
CTx	chemotherapy
DCR	disease control rate
DNA	deoxyribonucleic acid
DOR	duration of response
EBRT	external-beam radiation therapy
ECG	electrocardiogram
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
eDMC	external Data Monitoring Committee

Abbreviation	Expanded Term
EEA	European Economic Area
ELISA	enzyme-linked immunoassay
EOC	Executive Oversight Committee
ePRO	electronic PRO
EQ-5D-5L	EuroQoL 5- dimension, 5-level health state utility
ESMO	European Society for Medical Oncology
EU CTR	European Union Clinical Trials Regulation
EWB	Emotional Well-Being
FACT-P	Functional Assessment of Cancer Therapy-Prostate
FAPSI6	FACT Advanced Prostate Symptom Index 6
FAS	full analysis set
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
FFPE	formalin-fixed, paraffin embedded
FSH	follicle stimulating hormone
FWB	Functional Well-Being
GCP	Good Clinical Practice
GnRH	gonadotropin-releasing hormone
H	hypothesis
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	human immunodeficiency virus
HR	hazard ratio
HRQoL	health-related quality of life
IA	interim analysis
IA1	first interim analysis
IA2	second interim analysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
iCRO	Imaging Contract Research Organization
IEC	Independent Ethics Committee
Ig	immunoglobulin
IHC	immunohistochemistry
IL	interleukin
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
irAE	Immune-related adverse event
IRB	Institutional Review Board
IRT	interactive response technology
ITT	Intent-to-Treat
IV	intravenous

Abbreviation	Expanded Term
IVD	in vitro diagnostic
IVRS	Integrated Voice Response System
IWRS	Integrated Web Response System
mAb	monoclonal antibody
mCRPC	metastatic castration-resistant prostate cancer
mHSPC	metastatic hormone-sensitive prostate cancer
MID	minimum important difference
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MSI	microsatellite instability
N	number
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	nonevaluable
NED	no evidence of disease
NHA	next generation hormonal agents
NIMP	Non-Investigational Medicinal Product
Non-PD	nonprogression
NRS	numeric rating scale
NSCLC	Non-small cell lung cancer
OR	objective response
ORR	objective response rate
OS	overall survival
OTC	over-the-counter
PBPK	physiologically-based pharmacokinetic
PCS	Prostate Cancer Subscale
PCWG	Prostate Cancer Working Group
PD	progressive disease
PDu	unconfirmed progressive disease
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PET	positron emission tomography
PFS	progression-free survival
PIN	personal identification number
PK	pharmacokinetic
PKCθ	protein kinase C-theta
PR	partial response
PRES	posterior reversible encephalopathy syndrome
PRO	patient-reported outcome
PSA	prostate-specific antigen
PSMA	prostate-specific membrane antigen
PT	prothrombin time

Abbreviation	Expanded Term
PTT	partial thromboplastin time
PWB	Physical Well-Being
Q2W	every 2 weeks
Q3W	every 3 weeks
QD	every day
QTc	corrected QT interval
RECIST 1.1	Response Evaluation Criteria in Solid Tumors Version 1.1
RMST	Restricted Mean Survival Time
RNA	ribonucleic acid
rPFS	radiographic progression-free survival
RPSFT	Rank Preserving Structural Failure Time
SAE	serious adverse event
SCF	Sponsor Communication Form
SD	stable disease
SIM	Site Imaging Manual
SLAB	supplemental laboratory
SNP	single nucleotide polymorphism
SoA	schedule of activities
SOC	standard of care
SPECT	single photon emission computerized tomography
sSAP	supplemental Statistical Analysis Plan
SSRE	Symptomatic Skeletal-related Event
SUSAR	suspected unexpected serious adverse reaction
SWB	Social Well-Being
TB	tuberculosis
TEA	treatment eligibility assessment
TFST	time to initiation of the first subsequent anticancer therapy
TMDD	target-mediated drug disposition
TOI	Trial Outcome Index
TTBP	time to bone progression
TTPP	time to pain progression
US	United States
VOP	verification of progression
WOCBP	woman/women of childbearing potential
ZAP70	zeta-chain-associated protein kinase

10.11 Appendix 11: Eastern Cooperative Oncology Group 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 MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-55. http://ecog-acrin.org/resources/ecog-performance-status

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