Official Protocol Title:	A Phase 3, Randomized Open-label Study of Pembrolizumab (MK-3475) Plus Olaparib Versus Abiraterone Acetate or Enzalutamide in Participants with Metastatic Castration-resistant Prostate Cancer (mCRPC) Who are Unselected for Homologous Recombination Repair Defects and Have Failed Prior Treatment with One Next-generation Hormonal Agent (NHA) and Chemotherapy (KEYLYNK-010)
NCT number:	NCT03834519
Document Date:	02-May-2022

Title Page

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Protocol Title: A Phase 3, Randomized Open-label Study of Pembrolizumab (MK-3475) Plus Olaparib Versus Abiraterone Acetate or Enzalutamide in Participants with Metastatic Castration-resistant Prostate Cancer (mCRPC) Who are Unselected for Homologous Recombination Repair Defects and Have Failed Prior Treatment with One Next-generation Hormonal Agent (NHA) and Chemotherapy (KEYLYNK-010)

Protocol Number: 010-06

Compound Number: MK-7339

Sponsor Name:

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

Legal Registered Address:

126 East Lincoln Avenue

P.O. Box 2000

Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

IND	141,337
EudraCT	2018-004118-16

Approval Date: 02 May 2022

Sponsor Signatory

Typed Name: Date
Title:

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: Date
Title:

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 06	02-MAY-2022	Protocol amended consistent with recommendations of the eDMC after an interim review of the data; specifically, to discontinue the study due to futility. Participants still on treatment may have the option to continue receiving study intervention or SOC if they are deriving clinical benefit, until criteria for discontinuation are met.
Amendment 05	23-AUG-2021	Addition of a contraindication for concurrent administration of abiraterone and radium-223 during abiraterone treatment including a minimum washout period after the last dose of abiraterone. Addition of a consideration for dose reduction of medicinal products that are metabolized by CYP2D6 and have a narrow therapeutic index to potentially prolong the QT interval. Minor administrative changes to ensure consistency and clarity throughout the protocol.
Amendment 04	02-APR-2021	Administrative updates to incorporate recently authored protocol template language for VOP related to rPFS endpoint with BICR and to update IMP/NIMP classification of active comparators based on guidance issued by European Commission. Minor administrative changes identified after Protocol Amendment 03 was finalized to ensure consistency and clarity throughout the protocol. Amendment 04 supersedes Amendment 03; Amendment 03 was not released to any regulatory agencies or to IRB/ERCs.
Amendment 03	26-FEB-2021	Administrative updates to incorporate recently authored protocol template language for VOP related to rPFS endpoint with BICR and to update IMP/NIMP classification of active comparators based on guidance issued by European Commission. Minor administrative changes identified after Protocol Amendment 02 to ensure consistency and clarity throughout the protocol.

Document	Date of Issue	Overall Rationale
Amendment 02	06-NOV-2019	Administrative updates to add missing standard safety causality/intensity language in Appendix 3 that was inadvertently truncated during publishing of the original protocol, and to correct the duplicate numbering of exclusion criterion #12 during publishing of the PA01. Minor administrative changes identified after Protocol Amendment 01 to ensure consistency and clarity throughout the protocol.
Amendment 01	05-JUL-2019	Administrative updates to address HA requests. Minor administrative changes throughout the protocol to ensure consistency and clarity.
Original Protocol	18-JAN-2019	N/A

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 06

Overall Rationale for the Amendments:

Protocol amended consistent with recommendations of the eDMC after an interim review of the data; specifically, to discontinue the study due to futility. Participants still on treatment may have the option to continue receiving study intervention or SOC if they are deriving clinical benefit, until criteria for discontinuation are met.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis, Hypotheses, Objectives, and Endpoints Section 3 Hypotheses, Objectives, and Endpoints	Statement added: NOTE: As of Amendment 06, participants who are still on study treatment and deriving clinical benefit will no longer have tumor response assessments by BICR. However, local tumor imaging assessments should continue per SOC schedule. In addition, ePRO assessments will no longer be performed and biomarker samples will no longer be collected. Updated analyses are described in Section 9.	As the result of the efficacy IA indicated futility, further tumor scans and response assessments by BICR, and ePRO assessments, and collection of additional samples for biomarker evaluation are considered unnecessary.
1.1 Synopsis, Estimated Duration of Study 9.7.1 Efficacy Interim Analyses and Table 15 9.9 Sample Size and Power Calculations	The estimated duration of the study has been changed from approximately 29 months to approximately 40 months.	The actual duration of the study is 40 months.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis, Study Governance Committees	Statement added that as of Amendment 06, the Executive Oversight Committee and eDMC are no longer applicable.	These committees will no longer review the study data.
1.3.1 Initial Treatment Phase (Pembrolizumab Plus Olaparib Versus Abiraterone Acetate or Enzalutamide)	Added statement: NOTE: As of Amendment 06, participants who are still on study treatment and deriving clinical benefit will no longer have tumor response assessments by BICR. However, local tumor imaging assessments should continue per SOC schedule. In addition, ePRO assessments (FACT-P, EQ-5D-5L, BPI-SF, Analgesic Log) will no longer be performed and biomarker samples (blood for: CTC count, genetic analysis, RNA analysis, plasma biomarker analysis, serum biomarker analysis, and ctDNA analysis) will no longer be collected. Updated analyses are described in Section 9.	As of Amendment 06, these assessments and sample collections are considered unnecessary.
1.3.2 Second Course Phase 4.1 Overall Design, Second Course Treatment 6.6.7 Second Course 8.2.1.4 Second Course (Retreatment) Tumor Imaging	Statement added: NOTE: As of Amendment 06, the study will be stopped due to futility and second course treatment is not an option for participants. There are currently no participants in the Second Course Phase.	To update the status of the Second Course Phase of the study.

Section # and Name	Description of Change	Brief Rationale
2.3 Benefit/Risk Assessment	Added paragraph describing the safety and efficacy results of the IA leading to the determination of futility. Added statement: Selected analyses of safety endpoints will be performed at the end of the study. There will be no further analyses of efficacy and PRO endpoints.	To inform of the decision to stop this clinical study.
4.1 Overall Design	Statement regarding Amendment 06 added to beginning of the section.	To provide the rationale for closing MK-7339-010.
5.2 Exclusion Criteria	Added clarification to criterion #49 that the duration of contraception required is listed in inclusion criterion #12.	To correct an inconsistency in eligibility criteria for male contraception.
6.1 Study Intervention(s) Administered	Added statement: As of Amendment 06, the study is being stopped for futility. However, participants currently still on study treatment may have the option of continuing with study intervention or SOC treatment, as appropriate, if they are deriving clinical benefit.	To clarify that participants may continue to receive study intervention or SOC if deriving clinical benefit.

Section # and Name	Description of Change	Brief Rationale
7.1 Discontinuation of Study Intervention	Added the subbullet: o As of Amendment 06, central tumor response assessments will no longer be performed. However, participants still on study treatment and deriving clinical benefit and are continuing to receive study intervention or SOC, will be assessed locally by the investigator for disease progression per SOC schedule.	To clarify that participants still on-treatment with study intervention or SOC at the time of Amendment 06, because they are deriving clinical benefit, will be assessed locally for disease progression. Imaging scans will no longer be collected by vendor for central review for efficacy endpoints, as there will be no further efficacy analyses. Imaging will be performed per local SOC at the treating physician's discretion for patient management.
8.2.1 Tumor Imaging and Assessment of Disease	Added statements: As of Amendment 06: Central tumor response assessments will be discontinued. Imaging scans will no longer be submitted to iCRO nor read by BICR. The subsections below are retained for reference. However, for participants who are still onstudy treatment and deriving clinical benefit and will continue on-study intervention or SOC treatment until criteria for discontinuation are met, local tumor imaging should continue per SOC schedule.	As of Amendment 06, further efficacy assessments are considered unnecessary. To clarify that participants still receiving study intervention or SOC at the time of this amendment because they are deriving clinical benefit will continue with local tumor imaging per SOC schedule.

Section # and Name	Description of Change	Brief Rationale
8.2.4 PROs and Quality of Life Assessments	Added statement: As of Amendment 06: PROs and Quality of Life assessments will be discontinued. The subsections below are retained for reference.	As of Amendment 06, ePRO and Quality of Life assessments are considered unnecessary.
8.10 Biomarkers	Added statement: As of Amendment 06: Biomarker sample collections will be discontinued. The subsection below is retained for reference.	As of Amendment 06, collection of these samples is considered unnecessary.
8.11 Medical Resource Utilization and Health Economics	Added statement: As of Amendment 06: Medical Resource Utilization and Health Economics data collection will be discontinued. The section below is retained for reference.	As of Amendment 06, assessment of these data is considered unnecessary.
8.12.5.2 Efficacy Follow-up Visits	As of Amendment 06: Efficacy Follow-up Visits will be discontinued.	As of Amendment 06, these assessments are considered unnecessary.

Section # and Name	Description of Change	Brief Rationale
8.12.5.3 Survival Follow-up Contacts	Added statement: As of Amendment 06: Survival Follow-up visits will be discontinued. Those participants remaining on study treatment at the time of Amendment 06 should continue to be monitored in the study through the AE reporting period (Section 8.4). The section below is retained for reference.	As of Amendment 06, this 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.
9 Statistical Analysis Plan 9.1 Statistical Analysis Plan Summary 9.6 Statistical Methods 9.7 Interim Analyses 9.7.2 Safety Interim Analyses 9.8 Multiplicity 9.9 Sample Size and Power Calculations	Added statement: As of Amendment 06: The Statistical Analysis Plan is amended as follows: Added note describing the results of the safety and efficacy IAs that led to the determination to stop the study due to futility. In Sections 9, 9.1, and 9.6, added statement: Selected analyses of safety endpoints will be performed at the end of the study; there will be no further analyses of efficacy and PRO endpoints. In Sections 9, 9.1, 9.6, 9.7, 9.8, and 9.9, a statement was added that the prespecified final analysis of the study described in the SAP will not be performed.	To describe the results of the IAs and to specify which analyses will be conducted as of Amendment 06.

Section # and Name	Description of Change	Brief Rationale
Title Page Section 10.1.1 Code of Conduct for Clinical Trials	Sponsor entity name and address change.	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.
Throughout Document	Minor administrative, formatting, grammatical, and/or 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 Open-label Study of Pembrolizumab (MK-3475) Plus Olaparib Versus Abiraterone Acetate or Enzalutamide in Participants with Metastatic Castration-resistant Prostate Cancer (mCRPC) Who are Unselected for Homologous Recombination Repair Defects and Have Failed Prior Treatment with One Next-generation Hormonal Agent (NHA) and Chemotherapy (KEYLYNK-010)

Short Title: Phase 3 Study of Pembrolizumab Plus Olaparib Versus Abiraterone Acetate or Enzalutamide in mCRPC

Acronym: KEYLYNK-010

Hypotheses, Objectives, and Endpoints:

In men with mCRPC, unselected for homologous recombination repair (HRR) gene mutations, whose disease has progressed during prior NHA treatment and chemotherapy:

NOTE: As of Amendment 06, participants who are still on study treatment and deriving clinical benefit will no longer have tumor response assessments by BICR. However, local tumor imaging assessments should continue per SOC schedule. In addition, ePRO assessments will no longer be performed and biomarker samples will no longer be collected. Updated analyses are described in Section 9.

Primary Objectives	Primary Endpoints
To compare pembrolizumab plus olaparib to abiraterone acetate or enzalutamide with respect to overall survival (OS) Hypothesis 1: The combination of pembrolizumab plus olaparib is superior to abiraterone acetate or enzalutamide with respect to OS.	OS: the time from randomization to death due to any cause
To compare pembrolizumab plus olaparib to abiraterone acetate or 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) Hypothesis 2: The combination of pembrolizumab plus olaparib is superior to abiraterone acetate or 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

Secondary Objectives	Secondary Endpoints
To compare pembrolizumab plus olaparib to abiraterone acetate or enzalutamide with respect to time to initiation of the first subsequent anticancer therapy (TFST) Hypothesis 3: The combination of pembrolizumab plus olaparib is superior to abiraterone acetate or enzalutamide with respect to TFST.	TFST: the time from randomization to initiation of the first subsequent anticancer therapy or death, whichever occurs first
To evaluate pembrolizumab plus olaparib versus abiraterone acetate or enzalutamide with respect to the objective response rate (ORR) and duration of response (DOR) per PCWG-modified RECIST 1.1 as assessed by BICR	Objective response (OR): complete response (CR) or partial response (PR) DOR: the time from the earliest date of first documented evidence of confirmed CR or PR until the earliest date of disease progression or death from any cause, whichever comes first
To compare pembrolizumab plus olaparib to abiraterone acetate or enzalutamide with respect to: Time to prostate-specific antigen (PSA) progression Time to first symptomatic skeletal-related event (SSRE) 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)	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 first SSRE: the time from randomization to the first symptomatic skeletal-related event, 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

	Time to radiographic soft tissue progression: the time from randomization to radiographic soft tissue progression TTPP: the time from randomization to pain progression as determined by Item 3 of the Brief Pain Inventory-Short Form (BPI-SF) and by the Analgesic Quantification Algorithm (AQA) score
To evaluate the safety and tolerability of pembrolizumab plus olaparib versus abiraterone acetate or enzalutamide	Adverse events (AEs) Study intervention discontinuations due to AEs

Overall Design:

Study Phase	Phase 3
Primary Purpose	Treatment
Indication	The treatment of participants with mCRPC
Population	Participants with mCRPC unselected for HRR whose disease has progressed on NHA and chemotherapy
Study Type	Interventional
Intervention Model	Parallel This is a multi-site study.
Type of Control	Active
Study Blinding	Unblinded Open-label
Masking	No Masking
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 40 months from the time the first participant signs the informed consent until the last participant's last study-related telephone call or visit.

Number of Participants:

Approximately 780 participants will be randomized in this study.

Intervention Groups and Duration:

Intervention Groups

Intervention Group Name	Drug	Dose Strength	Dose Frequency	Route of Admin.	Regimen/ Treatment Period	Use
Arm 1	Pembrolizumab	200 mg	Q3W	IV	Day 1 of each 21-day cycle for up to 35 cycles	Experimental
	Olaparib	300 mg	BID	PO	Two 150 mg tablets BID	Experimental
Arm 2	Abiraterone acetate[a] + prednisone or prednisolone or Enzalutamide[b]	1000 mg 5 mg 160 mg	QD BID QD	PO PO PO	Two 500 mg or four 250 mg tablets 5 mg BID Four 40 mg capsules/tablets or two 80 mg tablets	SOC

Abbreviations: BID=twice daily; IV=intravenous; QD=once daily; PO=oral; Q3W=every 3 weeks; SOC=standard of care.
[a] Participants previously treated with enzalutamide.
[b] Participants previously treated with abiraterone acetate.

Total Number

2 arms

Duration of Participation

Each participant will be receiving assigned intervention for approximately 2 years. After the end of treatment, each participant will be followed for at least 30 days.

Each participant will participate in the study from the time the participant signs the Informed Consent Form (ICF) through the final protocol-specified contact.

Each participant will be assigned to receive study intervention until disease progression is radiographically documented and verified by BICR per PCWG-modified RECIST 1.1 guidelines, unacceptable adverse event(s) (AEs), intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue the participant, noncompliance with study intervention or procedure requirements or administrative reasons requiring cessation of treatment, or until the participant has received 35 cycles of pembrolizumab (approximately 2 years). Participants who stop study intervention after receiving 35 cycles of pembrolizumab for reasons other than disease progression or intolerability, or participants who attain a complete response (CR) and stop study intervention may be eligible for up to 17 additional cycles of pembrolizumab (approximately 1 year) upon experiencing disease progression (Section 6.6.7) if they meet the criteria for retreatment (Second Course phase) and the study is ongoing (Section 6.6.7).

	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 8.4.5. 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, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. All participants will be followed for overall survival until death, withdrawal of consent, or the end of the study. Once the participant has achieved the study objective or the study has ended, the participant is discontinued from this study.

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 06, the Executive Oversight Committee and Data Monitoring Committee are no longer applicable.	

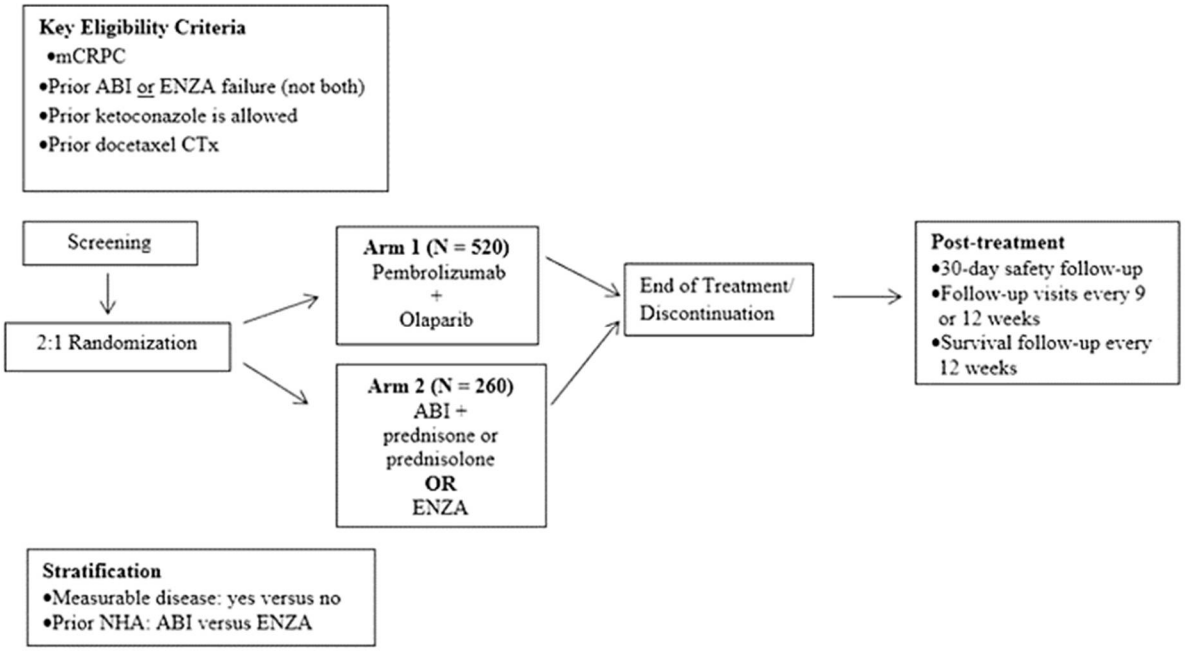
Study Accepts Healthy Volunteers: No

A list of abbreviations used in this document is in Appendix 10.

1.2 Schema

The study design is shown in Figure 1.

Figure 1 Study Diagram



Abbreviations: ABI=abiraterone acetate; BID=twice daily; CTx=chemotherapy; ENZA=enzalutamide; IV=intravenously; mCRPC=metastatic castration-resistant prostate cancer; NHA=next-generation hormonal agent; PO=orally; Q3W=every 3 weeks; QD=once daily.

Participants randomized to pembrolizumab (200 mg IV Q3W) + olaparib (300 mg PO BID) will receive pembrolizumab on Day 1 of each 3-week dosing cycle. Dosing with olaparib will begin on pembrolizumab Cycle 1 Day 1 and continue on a daily dosing schedule. Treatment with pembrolizumab will continue for up to 35 cycles (approximately 2 years) unless a discontinuation criterion (Section 7.1) is met.

If pembrolizumab is stopped due to toxicity, participants may continue to receive olaparib until a discontinuation criterion (Section 7.1) are met. If olaparib is stopped due to toxicity, participants may continue to receive pembrolizumab for up to 35 cycles or until a discontinuation criterion (Section 7.1) is met.

For participants randomized to ABI (1000 mg PO QD) + prednisone or prednisolone (5 mg PO BID) (if previously treated with ENZA) or to ENZA (160 mg PO QD) (if previously treated with ABI + prednisone or prednisolone), dosing will begin on Day 1 and continue on a daily dosing schedule until a discontinuation criterion (Section 7.1) is met.

1.3 Schedule of Activities (SoA)

1.3.1 Initial Treatment Phase (Pembrolizumab Plus Olaparib Versus Abiraterone Acetate or Enzalutamide)

NOTE: As of Amendment 06, participants who are still on study treatment and deriving clinical benefit will no longer have tumor response assessments by BICR. However, local tumor imaging assessments should continue per SOC schedule. In addition, ePRO assessments (FACT-P, EQ-5D-5L, BPI-SF, Analgesic Log) will no longer be performed and biomarker samples (blood for: CTC count, genetic analysis, RNA analysis, plasma biomarker analysis, serum biomarker analysis, and ctDNA analysis) will no longer be collected. Updated analyses are described in Section 9.

Study Period	**Screening Phase**	**Treatment Cycles (21-day cycles)**								**End of Treatment**	**Posttreatment Visits**			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	Efficacy Follow-up	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 Week 54, then Q12W (±7 days)	Q12W (±7 days)	**Before discontinuing participants from therapy (Section 7.1), submit the Treatment Termination & Disease Assessment Termination Form.** **The Safety Follow-up is not needed if the Discontinuation Visit occurs ≥30 days after the last dose.**
Administrative Procedures														
Informed consent	X													Obtain written consent before performing any protocol-specific procedures. Additional consent may be required after initial disease progression.
Informed consent for future biomedical research (optional)	X													Participants can still participate in the study if they decline to sign the Future Biomedical Research ICF.
Inclusion/exclusion criteria	X													

Study Period	**Screening Phase**	**Treatment Cycles (21-day cycles)**								**End of Treatment**	**Posttreatment Visits**			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	Efficacy Follow-up	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 Week 54, then Q12W (±7 days)	Q12W (±7 days)	**Before discontinuing participants from therapy (Section 7.1), submit the Treatment Termination & Disease Assessment Termination Form.** **The Safety Follow-up is not needed if the Discontinuation Visit occurs ≥30 days after the last dose.**
Participant identification card	X													Update at randomization.
Demographics and medical history	X													
History of blood transfusions	X													Include history of blood transfusion within previous 120 days from start of study intervention and the reasons, eg, bleeding or myelosuppression.
Prior and concomitant medication review	X	X	X	X	X	X	X	X	X	X	X			Report all concomitant medications received within 28 days before the date of randomization and up to 30 days after the last dose of study intervention. Include blood transfusions during concomitant medication review and reasons for transfusions.
SSRE Evaluation	X	X	X	X	X	X`	X	X	X	X	X	X		
HIV and hepatitis B and C status	X													Not required unless mandated by local health authority. Refer to Appendix 7 for country-specific requirements.

Study Period	**Screening Phase**	**Treatment Cycles (21-day cycles)**								**End of Treatment**	**Posttreatment Visits**			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	Efficacy Follow-up	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 Week 54, then Q12W (±7 days)	Q12W (±7 days)	**Before discontinuing participants from therapy (Section 7.1), submit the Treatment Termination & Disease Assessment Termination Form.** **The Safety Follow-up is not needed if the Discontinuation Visit occurs ≥30 days after the last dose.**
Randomization		X												
Telephone contact or visit		X												Telephone contact or visit on Cycle 1 Day 8 (±3 days) will assess for development of early toxicity. An unscheduled visit can occur at any time if deemed necessary by the investigator.
Clinical Procedures/Assessments														
AE monitoring	X	X	X	X	X	X	X	X	X	X	X	X		AEs must be recorded up to 30 days after the last dose of study intervention. SAEs must be recorded up to 90 days after the last dose of study intervention, or 30 days after cessation of study intervention if the participant initiates new anticancer treatment, whichever comes first. Treatment-related SAEs must be reported regardless of the time point when they occur. New diagnosis of MDS or AML should be reported throughout the study including the follow-up phase.

Study Period	**Screening Phase**	**Treatment Cycles (21-day cycles)**								**End of Treatment**	**Posttreatment Visits**			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	Efficacy Follow-up	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 Week 54, then Q12W (±7 days)	Q12W (±7 days)	**Before discontinuing participants from therapy (Section 7.1), submit the Treatment Termination & Disease Assessment Termination Form. The Safety Follow-up is not needed if the Discontinuation Visit occurs ≥30 days after the last dose.**
Full physical examination	X									X				
Directed physical examination		X	X	X	X	X	X	X	X		X			Perform as clinically indicated.
Vital signs, height, and weight	X	X	X	X	X	X	X	X	X	X				Height at screening only Measure vital signs (temperature, blood pressure, heart rate, and respiratory rate) after 5 min rest, before study intervention administration.
12-lead ECG	X													
ECOG performance status	X	X	X	X	X	X	X	X	X	X				Obtain within 7 days of randomization. Obtain before dosing. After Cycle 8, obtain at every other cycle (Cycle 10, 12, 14, etc.)
Subsequent anticancer therapy status											X	X	X	Safety Follow-up Visit must take place before the start of new therapy.
Survival status		◄	———	———	———	———	———	———	———	———	———	———	X	Updated survival status may be requested by the Sponsor at any time during the study.

Study Period	**Screening Phase**	**Treatment Cycles (21-day cycles)**								**End of Treatment**	**Posttreatment Visits**			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	Efficacy Follow-up	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 Week 54, then Q12W (±7 days)	Q12W (±7 days)	**Before discontinuing participants from therapy (Section 7.1), submit the Treatment Termination & Disease Assessment Termination Form. The Safety Follow-up is not needed if the Discontinuation Visit occurs ≥30 days after the last dose.**
Study Intervention Administration														**Begin within 3 days of randomization**
Olaparib dispensed (only participants randomized to pembrolizumab + olaparib)		X	X	X	X	X	X	X	X					Continuous dose of 300 mg BID.
Olaparib container returned (only participants randomized to pembrolizumab + olaparib)			X	X	X	X	X	X	X	X				
Pembrolizumab (only participants randomized to pembrolizumab + olaparib)		X	X	X	X	X	X	X	X					200 mg IV Q3W on Day 1 of each cycle, up to a maximum of 35 cycles
Abiraterone acetate + prednisone or prednisolone dispensed (only participants receiving abiraterone acetate + prednisone or prednisolone)		X	X	X	X	X	X	X	X					Continuous dose of 1000 mg abiraterone acetate QD + 5 mg prednisone or prednisolone BID.

Study Period	**Screening Phase**	**Treatment Cycles (21-day cycles)**								**End of Treatment**	**Posttreatment Visits**			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	Efficacy Follow-up	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 Week 54, then Q12W (±7 days)	Q12W (±7 days)	**Before discontinuing participants from therapy (Section 7.1), submit the Treatment Termination & Disease Assessment Termination Form. The Safety Follow-up is not needed if the Discontinuation Visit occurs ≥30 days after the last dose.**
Abiraterone acetate and prednisone or prednisolone containers returned (only participants receiving abiraterone acetate + prednisone or prednisolone)			X	X	X	X	X	X	X	X				
Enzalutamide dispensed (only participants receiving enzalutamide)		X	X	X	X	X	X	X	X					Continuous dose of 160 mg QD.
Enzalutamide container returned (only participants receiving enzalutamide)			X	X	X	X	X	X	X	X				

Study Period	**Screening Phase**	**Treatment Cycles (21-day cycles)**								**End of Treatment**	**Posttreatment Visits**			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	Efficacy Follow-up	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 Week 54, then Q12W (±7 days)	Q12W (±7 days)	**Before discontinuing participants from therapy (Section 7.1), submit the Treatment Termination & Disease Assessment Termination Form.** **The Safety Follow-up is not needed if the Discontinuation Visit occurs ≥30 days after the last dose.**
Laboratory Procedures/Assessments (CENTRAL laboratory)														**Screening laboratory tests are to be performed within 10 days of the first dose of study intervention.** **After Cycle 1, predose laboratory tests may be performed up to 72 hours predose. Unresolved abnormal 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 anticoagulants during treatment and the Safety Follow-up period.
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			Urinalysis and thyroid function tests every other cycle (Cycle 8, 10, 12, etc.)
T3 or FT3, FT4, and TSH	X		X		X		X	X	X	X	X			

Study Period	**Screening Phase**	**Treatment Cycles (21-day cycles)**								**End of Treatment**	**Posttreatment Visits**			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	Efficacy Follow-up	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 Week 54, then Q12W (±7 days)	Q12W (±7 days)	**Before discontinuing participants from therapy (Section 7.1), submit the Treatment Termination & Disease Assessment Termination Form.** **The Safety Follow-up is not needed if the Discontinuation Visit occurs ≥30 days after the last dose.**
Testosterone	X				X			X	X	X				Testosterone is determined every 4 cycles.
Procedures/Assessments: analysis performed CENTRALLY														**The schedules of scans, PSA determinations, and CTC counts are calculated from the date of randomization and should not be adjusted for dose delays or cycle starts.** **PD-L1, PSA, and CTC results are not reported to sites, to prevent early withdrawal of participants from study intervention.**
Efficacy Measurements														
PSA (central laboratory)	X		Q3W (± 7 days) from randomization							X	X	X		Screening PSA is determined within 10 days before randomization. The window for other PSA sample collections is ±7 days. Only during screening, if the central laboratory PSA result is not expected before randomization, the investigator may perform this test locally and use the result to determine eligibility. The local laboratory may not be used in lieu of the central laboratory.

Study Period	**Screening Phase**	**Treatment Cycles (21-day cycles)**								**End of Treatment**	**Posttreatment Visits**			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	Efficacy Follow-up	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 Week 54, then Q12W (±7 days)	Q12W (±7 days)	**Before discontinuing participants from therapy (Section 7.1), submit the Treatment Termination & Disease Assessment Termination Form.** **The Safety Follow-up is not needed if the Discontinuation Visit occurs ≥30 days after the last dose.**
Tumor imaging (CT/MRI) and bone scan	X	Q9W (± 7 days) through Week 54, then Q12W (± 7 days) thereafter								X		X		Baseline CT/MRI (chest/abdomen/pelvis) and whole-body bone scan must be performed within 28 days before randomization. Participants who discontinue study intervention without BICR-verified radiographic 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, verified disease progression, death, or the end of the study, whichever occurs first. If a scan was obtained within 4 weeks before discontinuation, another scan at discontinuation is not mandatory.
Blood for CTC count (central laboratory)		X	W9 (± 7 days) and W18 (± 7 days) from randomization							X				Collect predose on Cycle 1 Day 1.

Study Period	**Screening Phase**	**Treatment Cycles (21-day cycles)**								**End of Treatment**	**Posttreatment Visits**			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	Efficacy Follow-up	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 Week 54, then Q12W (±7 days)	Q12W (±7 days)	**Before discontinuing participants from therapy (Section 7.1), submit the Treatment Termination & Disease Assessment Termination Form. The Safety Follow-up is not needed if the Discontinuation Visit occurs ≥30 days after the last dose.**
Tumor Tissue Collection/Correlative and Biomarker Studies (CENTRAL laboratory)														**Samples should be collected based on the date of randomization, and the timing of assessments should not be adjusted for dose delays or cycle starts.**
Tumor tissue collection (recent biopsy)	X													Obtained within ≤1 year of screening. Site required to submit an SCF for archived tissue >1 year.
Blood for genetic analyses		X												Collect predose.
Blood for RNA analyses		X	W3 (±7 days) and W12 (±7 days) from randomization							X				Collect predose on days when study intervention is given.
Blood for plasma biomarker analyses		X								X				
Blood for serum biomarker analyses		X								X				
Blood for ctDNA analysis		X	W9 (± 7 days) and W18 (± 7 days) from randomization							X				Collect predose on days when study intervention is given.

Study Period	**Screening Phase**	**Treatment Cycles (21-day cycles)**								**End of Treatment**	**Posttreatment Visits**			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	Efficacy Follow-up	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 Week 54, then Q12W (±7 days)	Q12W (±7 days)	**Before discontinuing participants from therapy (Section 7.1), submit the Treatment Termination & Disease Assessment Termination Form.** **The Safety Follow-up is not needed if the Discontinuation Visit occurs ≥30 days after the last dose.**
Participant-reported Outcomes														
FACT-P EQ-5D-5L		X	X	X	X	X	X	X	X	X	X			Every effort should be made to administer PRO questionnaires before dosing and before other assessments and procedures. To be completed at site before study intervention on Day 1 of every cycle through Cycle 8, then at every 2 cycles through Cycle 24, then at every 4 cycles thereafter until discontinuation, and at Safety Follow-up Visit.
BPI-SF Analgesic Log	X	← Q3W until W24, then Q6W until W72, and thereafter Q12W →								X	X			To be completed at home daily for any 7 consecutive days beginning within 10 days before randomization. At each time point after randomization, to be completed for 7 consecutive days (eg, Days 15 to 21). A 3-day window will be permitted to begin completion of the BPI-SF and Analgesic Log before the 7 expected days.

Study Period	**Screening Phase**	**Treatment Cycles (21-day cycles)**								**End of Treatment**	**Posttreatment Visits**			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	Efficacy Follow-up	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 Week 54, then Q12W (±7 days)	Q12W (±7 days)	**Before discontinuing participants from therapy (Section 7.1), submit the Treatment Termination & Disease Assessment Termination Form.** **The Safety Follow-up is not needed if the Discontinuation Visit occurs ≥30 days after the last dose.**

Abbreviations: AE=adverse event; aPTT=activated partial thromboplastin time; BICR=blinded independent central review; BID=twice daily; BPI-SF=Brief Pain Inventory-Short Form; CT=computed tomography; CTC=circulating tumor cell; ctDNA=circulating tumor deoxyribonucleic acid; discon.=discontinuation; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EQ-5D-5L=EuroQoL 5-Dimension 5-Level Health State Utility Index; FACT-P=Functional Assessment of Cancer Therapy-Prostate; FT3=free triiodothyronine; FT4=free thyroxine; HIV=human immunodeficiency virus; ICF=informed consent form; INR=international normalized ratio; IV=intravenous; MRI=magnetic resonance imaging; PD-L1=programmed cell death ligand 1; PRO=patient-reported outcome; PSA=prostate-specific antigen; PT=prothrombin time; PTT=partial thromboplastin time; Q3W=every 3 weeks; Q6W=every 6 weeks; Q9W=every 9 weeks; Q12W=every 12 weeks; QD=once daily; RNA=ribonucleic acid; SAE=serious adverse event; SCF=Sponsor Communication Form; SSRE=symptomatic skeletal-related event; T3=total triiodothyronine; TSH=thyroid-stimulating hormone; W=week.

1.3.2 Second Course Phase

NOTE: As of Amendment 06, the study will be stopped due to futility and second course treatment is not an option for participants. There are currently no participants in the Second Course Phase.

Study Period	Treatment Cycles (21-day cycles)					End of Treatment	Posttreatment Visits			Notes
Treatment Cycle/Title	1	2	3	4	5 and beyond	Discon.	Safety Follow-up	Efficacy Follow-up	Survival Follow-up	
Scheduling Window (Days)		±3	±3	±3	±3	At time of discon.	30 days from last dose (+7 days)	Q12W (±7 days)	Q12W (±7 days)	**The Safety Follow-up Visit is not needed if the Discontinuation Visit occurs ≥30 days after the last dose.**
Administrative Procedures										
Eligibility criteria	X									
Concomitant medication review	X	X	X	X	X	X	X			Report new medications started 28 days before 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 the last dose of study intervention. SAEs must be recorded up to 90 days after the last dose of study intervention or 30 days after cessation of study intervention if the participant initiates new anticancer treatment, whichever comes first. Treatment-related SAEs must be reported regardless of the time point when they occur. New diagnosis of MDS or AML should be reported throughout the study including the follow-up phase.
Full physical examination	X					X				
Directed physical examination		X	X	X	X		X			Perform as clinically indicated.

Study Period	**Treatment Cycles (21-day cycles)**					**End of Treatment**	**Posttreatment Visits**			**Notes**
Treatment Cycle/Title	1	2	3	4	5 and beyond	Discon.	Safety Follow-up	Efficacy Follow-up	Survival Follow-up	
Scheduling Window (Days)		±3	±3	±3	±3	At time of discon.	30 days from last dose (+7 days)	Q12W (±7 days)	Q12W (±7 days)	**The Safety Follow-up Visit is not needed if the Discontinuation Visit occurs ≥30 days after the last dose.**
Vital signs and weight	X	X	X	X	X	X				Measure vital signs (temperature, blood pressure, heart rate, and respiratory rate) after 5 min rest, before study intervention administration.
ECOG performance status	X	X	X	X	X	X				After Cycle 8, obtain at every other cycle.
Subsequent anticancer therapy status							X	X	X	The Safety Follow-up Visit must take place before the start of new therapy.
Survival status	◄	—	—	—	—	—	—	—	X	Updated survival status may be requested by the Sponsor at any time during the study.
Study Intervention Administration										
Pembrolizumab	X	X	X	X	X					200 mg IV Q3W
Olaparib dispensed	X	X	X	X	X					Treatment with olaparib may be continued at the investigator's discretion.
Olaparib container returned		X	X	X	X	X				
Laboratory Procedures/Assessments (CENTRAL laboratory)										**Perform within 10 days before the participant's receiving the first retreatment infusion.** **After Cycle 1, predose laboratory tests may be performed up to 72 hours predose. Unresolved abnormal 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 anticoagulants during study intervention and the 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			

Study Period	**Treatment Cycles (21-day cycles)**					**End of Treatment**	**Posttreatment Visits**			**Notes**
Treatment Cycle/Title	1	2	3	4	5 and beyond	Discon.	Safety Follow-up	Efficacy Follow-up	Survival Follow-up	
Scheduling Window (Days)		±3	±3	±3	±3	At time of discon.	30 days from last dose (+7 days)	Q12W (±7 days)	Q12W (±7 days)	**The Safety Follow-up Visit is not needed if the Discontinuation Visit occurs ≥30 days after the last dose.**
Urinalysis	X		X		X	X	X			Urinalysis and thyroid function tests are performed every other cycle (Cycle 1, 3, 5, 7, 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										**The schedules of scans and PSA determinations are calculated from the date of the first retreatment infusion. The timing of assessments should not be adjusted for dose delays or cycle starts.**
Efficacy Measurements										
PSA (central laboratory)	X	← Q3W (±7 days) from first retreatment infusion →				X	X	X		Collect samples predose on days when study intervention is given.
Tumor imaging (CT/MRI and bone scan) (evaluated locally)	X	← Week 9 (±7 days) after restart of study intervention, then Q12W (±7 days) thereafter →				X		X		CT/MRI (chest/abdomen/pelvis) and whole-body bone scans must be performed within 28 days before the participant's receiving the first retreatment infusion. If a scan was obtained within 4 weeks before study intervention discontinuation, 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 iCRO.

Study Period	**Treatment Cycles (21-day cycles)**					**End of Treatment**	**Posttreatment Visits**			**Notes**
Treatment Cycle/Title	1	2	3	4	5 and beyond	Discon.	Safety Follow-up	Efficacy Follow-up	Survival Follow-up	
Scheduling Window (Days)		±3	±3	±3	±3	At time of discon.	30 days from last dose (+7 days)	Q12W (±7 days)	Q12W (±7 days)	**The Safety Follow-up Visit is not needed if the Discontinuation Visit occurs ≥30 days after the last dose.**

Abbreviations: AE=adverse event; AML=acute myeloid leukemia; aPTT=activated partial thromboplastin time; CT=computed tomography; discon.=discontinuation; ECI=event of clinical interest; ECOG=Eastern Cooperative Oncology Group; FT3=free triiodothyronine; FT4=free thyroxine; iCRO=imaging contract research organization; INR=international normalized ratio; IV=intravenous; MDS=myelodysplastic syndrome; MRI=magnetic resonance imaging; PSA=prostate-specific antigen; PT=prothrombin time; PTT=partial thromboplastin time; Q3W=every 3 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 incidence of over 1,000,000 cases and >300,000 deaths annually [Ferlay, J., et al 2015]. In the 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, those 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, often for many years. When prostate cancer progresses despite ADT alone, it is called castration-resistant. The disease at this point is known as mCRPC, and systemic therapies must be added to re-establish control of disease. A number of important systemic therapies for mCRPC now compose the current therapeutic landscape. These include the next-generation hormonal agents (NHAs), abiraterone acetate and enzalutamide, and the taxanes, docetaxel and cabazitaxel.

Abiraterone acetate is an androgen biosynthesis inhibitor that inhibits 17α 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 2 Phase 3 randomized, placebo-controlled clinical studies [Ryan, C. J., et al 2013] [Fizazi, K., et al 2012] [Ryan, C. J., et al 2015].

Enzalutamide is an endocrine agent currently used for treatment of mCRPC. Enzalutamide treatment was studied in randomized clinical trials in participants with mCRPC before chemotherapy and found to result in superior OS versus control therapy (placebo and prednisone, respectively) [Beer, T. M., et al 2014].

Docetaxel became the first systemic therapy to improve survival for men with mCRPC. A randomized study demonstrated superior survival of median 18.9 months versus 16.5 for mitoxantrone [Tannock, I, et al 2004]. Cabazitaxel, a second taxane, was studied versus mitoxantrone in participants who had received docetaxel, and it too was found to be associated with superior survival (median 15.1 months versus 12.7 months for mitoxantrone) [de Bono, J. S., et al 2010]. However, cabazitaxel can be a toxic therapy, and 4.9% of participants died of various treatment-related causes, such as treatment-related neutropenia and treatment-related diarrhea. The cabazitaxel label contains a black box warning regarding risks from neutropenia, severe hypersensitivity, and other label warnings and precautions pertaining to diarrhea, renal failure, hepatic impairment, and prohibitive risk in patients ≥65 years of age. Thus, an unmet need remains for patients after treatment in the mCRPC setting with targeted endocrine therapy and docetaxel.

2.1 Study Rationale

Interim results from Cohort A in KEYNOTE-365 (data cutoff 27-JUL-2018), which evaluated the population intended for the current study, suggested promising clinical efficacy and potential synergistic effects in participants with mCRPC, as evidenced by a confirmed biochemical response (≥50% reduction in PSA from baseline) in 12.8% (95% confidence interval [CI] 4.3%, 27.4%) of the 39 participants with elevated PSA at baseline. In addition, over 50% of participants had a reduction in PSA from baseline. An OR (CR or PR) per RECIST 1.1 was observed in 7.1% (95% CI 0.9%, 23.5%) of the 28 participants with measurable disease at baseline, including 2 participants with PR and none with CR. Disease control rate (DCR) for all participants in this cohort was 56.1% (95% CI 39.7%, 71.5%). Notably, none of these participants had a known or suspected deleterious mutation in genes associated with HRR.

These results provide support for further evaluation of the combination of pembrolizumab and olaparib in patients with mCRPC unselected for HRR gene mutation.

Human cancers show genomic instability and an increased mutation rate due to underlying defects in DNA repair. These deficiencies render cancer cells more dependent on the remaining DNA repair pathways, and targeting these pathways is expected to have much greater impact on the survival of tumor cells than on normal cells. This study will evaluate the antitumor effect of olaparib, a potent polyadenosine 5' diphosphoribose (polyADP ribose) polymerization (PARP) inhibitor, in combination with pembrolizumab for the treatment of mCRPC regardless of deficiencies in the HRR pathway.

Limited data are available for patients with mCRPC who have not responded to an NHA and at least 1 taxane-based chemotherapy. In general, responses to treatment decrease with more lines of prior therapy, while differences in baseline prognostic factors still confer heterogeneity in response as measured by rPFS and OS. In 260 patients with mCRPC treated with abiraterone acetate, enzalutamide, or cabazitaxel, median OS was 10 to 15 months (average 11 months) for third-line treatment and 4 to 7 months (average 5 months) for fourth-line treatment [Caffo, O., et al 2015].

Accordingly, there remains a high unmet medical need for an efficacious, well tolerated therapy for patients with mCRPC, including those who have not responded to an NHA and chemotherapy.

This clinical study will study the combination of the PARP inhibitor olaparib and pembrolizumab in the treatment of participants with mCRPC who have failed to respond to either abiraterone acetate or enzalutamide (but not both) and to chemotherapy. Participants will be randomly assigned in a 2:1 ratio to treatment with either pembrolizumab and olaparib or with abiraterone acetate (if previously treated with enzalutamide) or enzalutamide (if previously treated with abiraterone acetate).

2.2 Background

Pembrolizumab

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (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).

Olaparib

Olaparib (AZD2281; KU-0059436) is a potent PARP inhibitor (PARP1, 2, and 3) that is being developed as an oral anticancer therapy, both as monotherapy (including maintenance) and for combination with chemotherapy and other anticancer agents.

PARP inhibition is a novel approach to targeting tumors with deficient DNA repair mechanisms. PARP enzymes are essential for repairing DNA single strand breaks (SSBs). Inhibiting PARPs leads to the persistence of SSBs, which are then converted to the more serious DNA double strand breaks (DSBs) during DNA replication. During cell division, DSBs can be efficiently repaired in normal cells by HRR. Tumors with homologous repair deficiency (HRD), such as ovarian cancers in patients with breast cancer susceptibility gene 1/2 (*BRCA1/2*) mutations (BRCAm), cannot accurately repair the DNA damage, which may become lethal to cells as it accumulates. In such tumor types, olaparib may offer a potentially efficacious and less toxic cancer treatment compared with currently available chemotherapy regimens.

Olaparib traps the inactive form of PARP on DNA at sites of SSBs, thereby preventing their repair [Helleday, T. 2011] [Murai, J., et al 2012]. Olaparib has demonstrated efficacy in ovarian, prostate, and pancreatic tumors with *BRCA1* and *BRCA2* mutations and has shown proof of concept in tumors with ataxia-telangiectasia mutated (*ATM*) and other indicators of HRD. The specificity of olaparib for binding PARP at the replication fork during DNA replication is believed to have applicability to tumors associated with HRR mutations.

Refer to the IB and approved labeling for detailed background information on olaparib.

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 cluster of differentiation (CD)8+ 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 CD28 and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling on 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 binding 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. After 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 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 Inhibition of PARP as a Target for Cancer Therapy

PARP1 and PARP2 are zinc-finger DNA-binding enzymes that play a critical role in DNA repair [Ame, J. C., et al 2004] by sensing DNA damage and converting it to intracellular signals that activate the base excision repair and SSB repair pathways. When a break in DNA occurs, PARP enzymes are recruited to and bind at the end of the broken DNA strands, initiating their enzymatic activity. PARP subsequently catalyzes the addition of long ADP-ribose polymers to several other proteins associated with chromatin (eg, PARP, histones, DNA repair proteins), resulting in chromatin relaxation, rapid recruitment of DNA repair proteins, and efficient repair of the break.

Under normal conditions, HRR is the preferred pathway for repairing DNA damage, as it is associated with a lower rate of errors compared with other forms of DNA repair [Prakash, R., et al 2015]. During DNA replication (S phase), pre-existing or chemotherapy-induced SSBs

are converted to DSBs if not adequately repaired by intracellular mechanisms [Fong, Peter C., et al 2009], such as HRR. Cells unable to perform HRR (eg, due to inactivation of genes required for homologous recombination, such as *BRCA1* or *BRCA2*) are more likely to use the error-prone nonhomologous end-joining (NHEJ) or alternative (alt)-NHEJ pathways to repair these DSBs, and risk accumulating multiple lesions or loss of heterozygosity (LOH) due to an increase in deletions and accompanying genomic instability. Over time, accumulation of excessive DNA errors in combination with inability to complete S phase (ie, because of stalled replication forks due to presence of a PARP inhibitor), leads to cell death, showing that PARP inhibition is synthetic lethal in the context of BRCA mutations [Farmer, H., et al 2005] [Bryant, H. E., et al 2005]. Cells without SSBs or with intact HRR, such as those in somatic tissue, replicate normally in the presence of a PARP inhibitor, thereby minimizing toxicity.

2.2.1.3 Homologous Recombination Repair in Solid Tumors

Defects in DNA repair drive the genesis of several solid tumors, most notably ovarian and pancreatic. DNA strand breaks occur both as part of the recombination and replication process and after intercalating chemotherapy or DNA-damaging radiotherapy. HRR defective tumors are intrinsically sensitive to PARP inhibitors, both in tumor models in vivo [Rottenberg, S., et al 2008] [Hay, T., et al 2009] and in the clinic [Fong, Peter C., et al 2009] [Tutt, A., et al 2010] [Mateo, J., et al 2015] [Kaufman, B., et al 2015]. The main mechanism of action of olaparib results from trapping of inactive PARP on SSBs preventing their repair [Helleday, T. 2011] [Murai, J., et al 2012] and excessive conversion of SSBs to the more serious DSBs, which are lethal or results in incomplete/inaccurate repair of the damaged strands, leading to LOH with subsequent aberrant protein translation and function.

Normally, the process of HRR corrects DSBs using proteins such as BRCA1 and BRCA2. However, the HRR armamentarium includes proteins coded by at least 13 other genes, including *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L*. For example, the protein coded by the *ATM* gene also is involved in the repair of DSB. ATM is activated by DSB and phosphorylates diverse cellular proteins (eg, mediator of DNA damage checkpoint 1, checkpoint kinase 2) leading to cell cycle arrest, activates the tumor suppressor p53, contributes to chromatin relaxation and remodeling, and activates nuclear factor kappa light chain enhancer of activated B-cells (NF-κB). Defective ATM increases the risk of breast, gastrointestinal, lung, and lymphoid cancers. Moreover, defective ATM appears to correlate with a poor prognosis; however, the resulting risk has not been quantified.

A small percentage of tumors have loss of function mutations in HRR genes, with *BRCA1*, *BRCA2*, and *ATM* the best characterized and most frequently mutated [Watkins, J. A., et al 2014] [Marquard, A. M., et al 2015] [Choi, M., et al 2016] [Lord, C. J. 2016]. Approximately half the HRRm detected are germline mutations [Mateo, J., et al 2015]. While an adverse prognostic impact of germline *BRCA2* mutations has been described in prostate cancer [Castro, E., et al 2015], it is less clear if other germline or somatic HRR gene mutations are associated with similar adverse clinical outcomes. To date, HRRm has not been associated with specific patient or tumor characteristics.

2.2.1.4 Overview of Prostate Cancer

Prostate cancer represents one of the most frequently diagnosed malignancies and is the fifth leading cause of cancer-related deaths and the second most frequently diagnosed cancer in men worldwide [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 suggest the great socioeconomic burden prostate cancer imposes worldwide. In the US, analysts estimated that there would be 164,690 new cases of prostate cancer (19% of all new cancer cases in males) and 29,430 deaths caused by prostate cancer (9% of all new cancer deaths in males) in 2018 [Siegel, R. L., et al 2018]. Since the advent of PSA screening about 3 decades ago, the prostate cancer death rate had been falling until it stabilized between 2013 and 2015 [Negoita, S., et al 2018]. However, following the US. Preventive Services Task Force's recommendation in 2012 against routine PSA-based screening regardless of age, the incidence of late-stage disease has increased [Negoita, S., et al 2018]. Furthermore, it is estimated that 1 in 9 men in the US will be diagnosed with prostate cancer in his lifetime [Siegel, R. L., et al 2018]. Although identifying causes and effects 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.

2.2.1.5 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 harm (eg, incontinence and impotence) associated with overtreatment [Loeb, S., et al 2015] [Resnick, M. J., et al 2013]. Additionally, metastatic prostate cancer evolves molecularly during disease progression and/or therapy through 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 androgen receptors is a critical factor for promotion and growth of prostate cancer [Knudsen, K. E. 2010]. Therefore, until 2015 the SOC for initial first-line therapy for metastatic prostate cancer (either recurrent or de novo metastatic tumors, heretofore called castration-sensitive prostate cancer [CSPC]) was ADT (eg, GnRH agonists or antagonists). However, a great stride in treatment of CSPC was made over the last few years. Two randomized, controlled studies, Chemohormonal Therapy Versus Androgen Ablation Randomized Study for Extensive Disease in Prostate Cancer (CHAARTED [Sweeney, C. J., et al 2015]) and Systemic Therapy in Advancing or Metastatic Prostate Cancer (STAMPEDE [James, N. D., et al 2017]) demonstrated significant survival benefit with the addition of docetaxel to ADT.

In a 2018 follow-up CHAARTED 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 with high-volume disease (51.2 versus 34.4 months; hazard ratio [HR] 0.72; 95% CI 0.59, 0.89; p=0.0018). In the similar comparison in the STAMPEDE study, researchers recommended that docetaxel become part of the SOC after a 43-month follow-up found superior results with it against ADT in median OS (81 versus 71 months; HR 0.78; 95% CI 0.66, 0.93; p=0.006).

As part of the STAMPEDE study, participants were randomized to receive ADT and abiraterone acetate plus prednisolone or ADT alone. Participants in the former arm had a significantly higher rate of OS at 3 years (83% versus 76%; HR for death 0.63%; 95% CI 0.52, 0.76; p<0.001) and significantly fewer treatment failure events (248 versus 535; HR 0.29; 95% CI 0.25, 0.34; p<0.001). Findings were similar in the LATITUDE study [Fizazi, K., et al 2017]. At a planned IA in the LATITUDE study at 30.4 months, there was significantly longer OS in the group receiving ADT and abiraterone than in the group receiving ADT and placebo (not reached versus 34.7 months; HR for death 0.62; 95% CI 0.51, 0.76; p <0.001) [Fizazi, K., et al 2017] [Sartor, O. 2018].

While these therapies are initially effective, patients with metastatic prostate cancer invariably develop a lethal disease stage known as mCRPC and succumb to their disease. Though a number of important therapies have been approved since 2004 to treat mCRPC, no available guidance recommends appropriate sequencing or combining of these therapies, and none is curative.

Despite these recent advances, treatment options for men with mCRPC progressing after next-generation (second-generation) hormonal therapy and docetaxel are limited and provide only a modest 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] versus 12.7 months [95% CI 11.6, 13.7]; HR 0.70 [95% CI 0.59, 0.83]; p<0.0001). Also, cabazitaxel maintained its antitumor activity after treatment with docetaxel and abiraterone or docetaxel and enzalutamide [Pezaro, C. J., et al 2014]. However, cabazitaxel can be a toxic therapy, and consequently it is not widely used. Retrospective studies suggest that either abiraterone or enzalutamide may be an option; however, previous therapies [Handy, C. E. 2016], potential for development of cross-resistance [Zhang, T., et al 2015], and potential for emergence of a more aggressive form of prostate cancer after 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 with mCRPC and disease progression after treatment with a next-generation hormonal therapy and/or docetaxel-based chemotherapy.

2.2.1.6 Preclinical and Clinical Studies

Refer to the pembrolizumab and olaparib IBs for summaries of preclinical and clinical experience with pembrolizumab and olaparib, respectively.

2.2.1.7 Pembrolizumab in mCRPC

Participants with PD-L1 positive mCRPC were treated with pembrolizumab monotherapy in the Phase 1b study, KEYNOTE-028 (Cohort E3: advanced [unresectable and/or metastatic] prostate adenocarcinoma). The primary endpoint was objective response rate (ORR) according to RECIST 1.1, determined by investigator review. Twenty-three participants with PD-L1 positive mCRPC (defined by PD-L1 expression in >1% of tumor or stromal cells) were enrolled and treated with pembrolizumab monotherapy. All received at least 1 prior antineoplastic therapy, and 17 (73.9%) and 7 (30.4%) received 2 or more or 5 or more lines of therapy, respectively. Of the 23 participants, only 1 remained on treatment at the time of the last published analysis [Hansen, A. R., et al 2018]. Twenty-one participants (91.3%) had 1 or more postbaseline PSA determinations; 5 of these participants (23.8%) had a PSA decline of ≥50%. There were 4 confirmed PRs according to RECIST 1.1 guidelines, for an ORR at the time of 17.4% (95% CI 5.0%, 38.8%). Responses were durable (median duration of response [DOR] 13.5 months) and treatment was well tolerated.

2.2.1.8 Ongoing Clinical Studies in mCRPC

2.2.1.8.1 Pembrolizumab

KEYNOTE-199 was designed to further evaluate the positive signal of activity seen in KEYNOTE-028, with pembrolizumab monotherapy in participants with mCRPC who had previously received docetaxel-based chemotherapy and undergone abiraterone acetate or enzalutamide treatment. The ORR was 4.5% in participants with measurable disease by RECIST 1.1 and previous chemotherapy (Cohorts 1 and 2) at the IA2 with a data cutoff date of 13-OCT-2017. However, the DCR suggested durable responses, regardless of PD-L1 status, that warranted further evaluation. Additionally, early unpublished results 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 and 2016 with mCRPC and evidence of progression on enzalutamide, and subsequently enrolled a total of 28. Because of failure of immunotherapies (nivolumab and ipilimumab) to produce objective responses in mCRPC in previous studies [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 undertook the Phase 2 study, adding pembrolizumab to enzalutamide in men with mCRPC, and reported a decline in PSA (primary endpoint) of ≥50% in 5 of 28 participants (17.9%) and an ORR (secondary endpoint) in 3 of 12 participants (25.0%) with measurable disease at baseline. At the last report, 3 of the 5 responders continued to respond (range 21.9 to 33.8 months), and median OS was 22.2 months (95% CI 14.7, 28.4 months).

2.2.1.8.2 Olaparib

Olaparib received an FDA breakthrough therapy designation in January 2016 as a treatment for patients with BRCA1/2 or ATM mCRPC who have received prior taxane-based chemotherapy and at least 1 targeted hormonal agent (enzalutamide or abiraterone acetate). This designation was based on data from the Phase 2 Trial of PARP Inhibition in Prostate Cancer (TOPARP-A) that demonstrated an ORR of nearly 90% for olaparib monotherapy in a biomarker-defined subgroup of participants with DNA repair defects [Mateo, J., et al 2015]. Participants were considered biomarker-positive if homozygous deletions or deleterious mutations were identified in a gene reported to be involved either in DNA damage repair or sensitivity to PARP inhibition. Next-generation sequencing identified homozygous deletions, deleterious mutations, or both in DNA repair genes in 16 of 49 participants (33%). Of these 16 participants, 14 (88%) had a response to olaparib, using a composite endpoint of RECIST 1.1 response, a decline in PSA ≥50% from baseline, or a reduction of circulating tumor cells (CTCs) from ≥5 cells per 7.5 mL of blood to ≤5 cells per 7.5 mL of blood. This included all 7 participants with *BRCA2* loss and 4 of 5 with *ATM* aberrations. Defects in DNA repair genes were noted in 33% of the 49 evaluable participants. The overall prevalence of *BRCA2* genomic aberrations was 6% in this cohort of unselected participants, and 10% of participants were found to have aberrations in the *ATM* gene. Whereas only 3% of participants without tumor genomic DNA repair alterations had a PSA response to olaparib, 63% of participants with tumor genomic DNA repair alterations did. In TOPARP-A, Grade 3 or 4 AEs were primarily anemia (20%), fatigue (12%), leukopenia (6%), thrombocytopenia (4%), and neutropenia (4%). Thirteen of the 50 treated participants (26%) required a twice daily dose reduction to 300 mg from the initial dose of 400 mg, and 3 of these required a second dose reduction to 200 mg. Six percent of participants permanently discontinued olaparib because of AEs. The average delivered dose intensity was 87%.

The impressive response rate of 88% in biomarker-positive mCRPC is being further evaluated in the PROfound study (NCT02987543), a randomized Phase 3 study evaluating olaparib in participants with mCRPC and a deleterious homologous recombination DNA repair (HRR) aberration. The study is evaluating olaparib versus abiraterone acetate or enzalutamide (physician's choice) in participants whose disease progressed when they were treated with a new hormonal agent. Participants are to be randomized 2:1 to olaparib or to enzalutamide or abiraterone, stratified based on tumor aberration (Cohort A with mutations in BRCA1, BRCA2, or ATM versus Cohort B with 1 or more of 12 other genes with aberrations). The primary endpoint of the study is rPFS in Cohort A, using RECIST 1.1 (soft tissue) and PCWG3 (bone) criteria. Key secondary efficacy endpoints include confirmed ORR, TTPP, OS (all Cohort A), and rPFS (both cohorts).

Additionally, olaparib as a treatment of mCRPC has been evaluated in combination with abiraterone in a randomized, double-blind, placebo-controlled Phase 2 study [Clarke, N., et al 2018]. Investigators randomized 142 participants to olaparib and abiraterone (N=71) or placebo and abiraterone (N=71). They found a difference of 5.6 months in the median rPFS (olaparib group: rPFS 13.8 months; 95% CI 10.8 to 20.4 months; placebo group: rPFS, 8.2 months; 95% CI 5.5 to 9.7 months) and observed an HR of 0.65 (95% CI 0.44 to 0.97; p=0.034), regardless of HRR mutation status. AEs of Grade 3 or higher were more frequent

in the olaparib group, affecting almost twice as many participants as in the placebo group (38 [54%] versus 20 [28%]), and included anemia (15 [21%] versus 0), pneumonia (4 [6%] versus 3 [4%]), and myocardial infarction (4 [6%] versus 0). Serious adverse events (SAEs) were reported by 24 participants (34%) receiving olaparib (7 events were related to treatment) and 13 participants (18%) receiving placebo (1 was related to treatment). One treatment-related death (attributed to pneumonitis) occurred in the olaparib group. A confirmatory Phase 3 study is under way.

For a summary of ongoing clinical study data for olaparib, refer to the IB.

2.2.2 Information on Other Study-related Therapy

The targeted endocrine therapies, abiraterone acetate and enzalutamide, are potent, orally available treatment options with a favorable tolerability profile that have replaced docetaxel as preferred first-line therapy for mCRPC [Sartor, O. 2018]. Abiraterone acetate and enzalutamide were investigated in randomized clinical studies in participants with mCRPC before chemotherapy and were found to result in superior OS versus control therapies (placebo and prednisone, respectively) and prolonged time to chemotherapy initiation [Ryan, C. J., et al 2013] [Beer, T. M., et al 2014]. Median OS was approximately 3 years with early initiation of abiraterone acetate or enzalutamide treatment [Ryan, C. J., et al 2013] [Beer, T. M., et al 2014], but this is still a greatly reduced life expectancy compared with approximately 15 years for age-matched men (approximately 70 years of age) in the general US population (https://www.socialsecurity.gov/OACT/population/longevity.html). Once patients with mCRPC have failed to respond to abiraterone acetate or enzalutamide, the benefit from approved therapeutic options appears to be substantially diminished, and no currently approved agent has been developed for treatment of mCRPC after an NHA and 1 or more subsequent lines of therapy.

2.3 Benefit/Risk Assessment

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 to a large number of cancer patients with a well characterized safety profile and has received regulatory approval for multiple malignancies. Overall, pembrolizumab is well tolerated at doses up to 10 mg/kg every 2 weeks. Pembrolizumab has also demonstrated anticancer clinical activity and efficacy in a broad range of cancer indications (refer to the current pembrolizumab IB).

Single-agent olaparib has been registered in the US for treatment of deleterious or suspected deleterious germline BRCA-mutated advanced ovarian cancer in patients who have received 3 or more prior lines of chemotherapy for maintenance treatment of recurrent ovarian cancer and for deleterious or suspected deleterious germline BRCA-mutated, HER-2 negative metastatic breast cancer after prior chemotherapy.

Preliminary results from Cohort A of KEYNOTE-365 (Section 2.1), in which participants have received a combination of pembrolizumab and olaparib show a DCR of 56.1%. In this cohort, >50% of participants had a reduction in PSA from baseline. Twenty-eight of 41 participants (68.3%) experienced a Grade 3 to 5 AE, and 23 of 41 (56.1%) experienced SAEs.

Abiraterone acetate and enzalutamide have been approved by regulatory agencies globally for treatment of mCRPC and have been recommended for treatment of mCRPC in the guidelines of the NCCN and the European Society for Medical Oncology (ESMO) [Parker, C., et al 2015].

NOTE: Based on the data from an IA of safety and efficacy for KEYLYNK-010 (data cutoff 18-JAN-2022), the eDMC recommended stopping the study for futility because it was extremely unlikely that the efficacy boundary for study success would be reached at the next (final) analysis. In addition, the eDMC indicated that continuing the trial raised the risk of undue toxicities (Grade 3 to 5 AEs and drug-related SAEs) to participants receiving investigational therapy which were greater in the investigational arm compared with control. Based on these data and the recommendation of the eDMC, the study was unblinded (as of 11-MAR-2022). The prespecified final analysis of the study described in the statistical analysis plan (SAP) will not be performed.

Selected analyses of safety endpoints will be performed at the end of the study. There will be no further analyses of efficacy and PRO endpoints.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

In men with mCRPC, unselected for homologous recombination repair (HRR) gene mutations, whose disease has progressed during prior NHA treatment and chemotherapy:

NOTE: As of Amendment 06, participants who are still on study treatment and deriving clinical benefit will no longer have tumor response assessments by BICR. However, local tumor imaging assessments should continue per SOC schedule. In addition, ePRO assessments will no longer be performed and biomarker samples will no longer be collected. Updated analyses are described in Section 9.

Primary Objectives	Primary Endpoints
• To compare pembrolizumab plus olaparib to abiraterone acetate or enzalutamide with respect to **overall survival (OS).** • Hypothesis 1: The combination of pembrolizumab plus olaparib is superior to abiraterone acetate or enzalutamide with respect to OS.	• **OS**: the time from randomization to death due to any cause.
• To compare pembrolizumab plus olaparib to abiraterone acetate or 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). • Hypothesis 2: The combination of pembrolizumab plus olaparib is superior to abiraterone acetate or 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.
Secondary Objectives	Secondary Endpoints
• To compare pembrolizumab plus olaparib to abiraterone acetate or enzalutamide with respect to time to initiation of the first subsequent anticancer therapy (**TFST).** • Hypothesis 3: The combination of pembrolizumab plus olaparib is superior to abiraterone acetate or enzalutamide with respect to **TFST**.	• **TFST:** the time from randomization to initiation of the first subsequent anticancer therapy or death, whichever occurs first.
• To evaluate pembrolizumab plus olaparib versus abiraterone acetate or enzalutamide with respect to the **objective response rate (ORR) and duration of response (DOR)** per PCWG-modified RECIST 1.1 as assessed by BICR	• **Objective response (OR)**: complete response (CR) or partial response (PR) • **DOR**: the time from the earliest date of first documented evidence of confirmed CR or PR until the earliest date of disease progression or death from any cause, whichever comes first

• To compare pembrolizumab plus olaparib to abiraterone acetate or enzalutamide with respect to: • **Time to prostate-specific antigen (PSA) progression** **Time to first symptomatic skeletal-related event (SSRE)** **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)**	• **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 first SSRE**: the time from randomization to the first symptomatic skeletal-related event, defined as: 1) first use of external-beam radiation therapy (EBRT) to prevent or relieve skeletal symptoms; 2) 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**: the time from randomization to radiographic soft tissue progression • **TTPP**: the time from randomization to pain progression as determined by Item 3 of the Brief Pain Inventory-Short Form (BPI−SF) and by the Analgesic Quantification Algorithm (AQA) score
• To evaluate the safety and tolerability of pembrolizumab plus olaparib versus abiraterone acetate or enzalutamide	• **Adverse events (AEs)** • **Study intervention discontinuations** due to AEs

Tertiary/Exploratory Objectives	Tertiary/Exploratory Endpoints
• To evaluate efficacy with respect to **OS**, **rPFS**, **ORR**, and **DOR** in participants with positive PD-L1 (combined positive score [CPS]>1%) versus all-comers	• **OS**, **rPFS**, **OR**, and **DOR**
• To compare pembrolizumab plus olaparib to abiraterone acetate or enzalutamide with respect to the **time to radiographic bone progression (TTBP)** per PCWG-modified RECIST 1.1 as assessed by BICR	• **TTBP**: the time from randomization to radiographic bone progression
• To compare pembrolizumab plus olaparib to abiraterone acetate or enzalutamide with respect to the change from baseline in disease-related symptoms and health-related quality of life (HRQoL) using the **BPI-SF, Functional Assessment of Cancer Therapy-Prostate Cancer (FACT-P), and EuroQoL Five-Dimension Five-Level Health State Utility Index (EQ-5D-5L)** questionnaires	• **BPI-SF**: progression in pain severity domain, change in pain interference domain, and pain palliation • **FACT-P**: FACT-P total score, Functional Assessment of Cancer Therapy-General (FACT-G) total score, trial outcome index, functional well-being, physical well-being, prostate cancer subscale, and FACT Advanced Prostate Symptom Index-6 (FAPSI-6) • **EQ-5D-5L**: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression health states, and EQ-5D-5L visual analog scale
• To characterize health utilities following the administration of pembrolizumab plus olaparib versus abiraterone acetate or enzalutamide	• **EQ-5D-5L**
• To identify molecular (genomic, metabolic, and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, and/or the mechanism of action of pembrolizumab and other interventions	• Molecular (genomic, metabolic and/or proteomic) determinants of response or resistance to treatments, using blood and/or tumor tissue

4 STUDY DESIGN

4.1 Overall Design

NOTE: Based on the data from an IA of safety and efficacy for KEYLYNK-010 (data cutoff 18-JAN-2022), the eDMC recommended stopping the study for futility because it was extremely unlikely that the efficacy boundary for study success would be reached at the next (final) analysis. In addition, the eDMC indicated that continuing the trial raised the risk of undue toxicities (Grade 3 to 5 AEs and drug-related SAEs) to participants receiving investigational therapy which were greater in the investigational arm compared to control.

This is a randomized, active-controlled, parallel-group, multi-site, open-label study of pembrolizumab plus olaparib versus abiraterone acetate or enzalutamide in participants with mCRPC.

After a screening phase of up to 42 days, approximately 780 eligible participants will be randomly assigned in a 2:1 ratio to 1 of the following 2 study intervention arms:

Arm 1: pembrolizumab 200 mg IV Q3W plus olaparib (as tablets) 300 mg BID

Arm 2: abiraterone acetate 1000 mg once daily (QD) plus prednisone or prednisolone 5 mg BID (in participants previously treated with enzalutamide) OR enzalutamide 160 mg QD (in participants previously treated with abiraterone acetate)

There will be no crossover between treatment arms.

Before randomization, participants will be stratified by prior NHA treatment (abiraterone acetate versus enzalutamide) and presence of measurable disease (yes versus no). Of participants randomized to the comparator arm (Arm 2), those previously treated with abiraterone acetate will receive enzalutamide, and those previously treated with enzalutamide will receive abiraterone acetate.

Participants must have had progressive disease (PD) during or after treatment with abiraterone acetate or enzalutamide (but not both) and 1 previous chemotherapy (docetaxel) regimen. Prior treatment with enzalutamide or apalutamide in the hormone-sensitive setting is not allowed. Prior treatment with apalutamide or darolutamide is also not allowed. Participants must provide 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 at 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 sample is not feasible, 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 before randomization. For complete details of the eligibility criteria, refer to Section 5.

Treatment with pembrolizumab may continue for up to 35 cycles (approximately 2 years starting with the first infusion of Cycle 1) or until a criterion for discontinuation of study intervention (Section 7.1) is met. Treatment with olaparib or with abiraterone acetate or enzalutamide will proceed continuously from Day 1 of Cycle 1, unless a criterion for discontinuation of study intervention (Section 7.1) is met.

In this study, an independent eDMC will monitor safety and efficacy (Section 10.1.4.2). Response to study intervention will be evaluated with radiologic imaging (whole-body bone scans and computed tomography [CT]/magnetic resonance imaging [MRI] scans of the chest, abdomen, and pelvis) every 9 weeks for approximately 1 year (through Week 54) and every 12 weeks thereafter. Radiographic progression will be determined according to PCWG-modified RECIST 1.1 (Section 8.2.1).

This study will use a group-sequential design. There will be 2 planned IAs. The final OS analysis will take place when at least 482 OS events (target number of OS events) have been observed. To maintain sufficient minimal follow-up duration, the final analysis should be conducted at least 12 months after the last participant is randomized. There will be only 1 progression-free survival (PFS) analysis, at the time of IA1 when at least 360 rPFS events and 241 OS events (target number of OS events) have been observed. The results of the IAs will be reviewed by the eDMC, which will provide recommendations for the study in accordance with the eDMC Charter and the SAP (Section 9).

Participants who attain an investigator-determined confirmed CR may receive up to 35 cycles of pembrolizumab. If a participant with radiographic progression is clinically stable or clinically improved, an exception to continue study intervention may be considered, on consultation with the Sponsor. Participants showing clinical benefit in the study will be allowed to continue study intervention 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 National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (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 in the study and continue study-related disease assessments until radiographic disease progression, initiating a non-study cancer treatment, participant discontinuation from the study, or becoming lost to follow-up. All participants will be followed for survival. This will be performed in a variety of ways, including by telephone, e-mail, chart review, or review of public records, in compliance to local practices or regulations.

Second Course Treatment:

NOTE: As of Amendment 06, the study will be stopped due to futility and second course treatment is not an option for participants. There are currently no participants in the Second Course Phase.

Participants receiving pembrolizumab in combination with olaparib who stop study intervention with stable disease (SD) or better may be eligible for up to17 additional cycles (approximately 1 year) of pembrolizumab (Second Course phase) if they have BICR-verified PD after stopping study intervention and the study is ongoing (Section 6.6.7). 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, the participant still meets the safety parameters listed in the inclusion/exclusion criteria, and the study remains open. Olaparib may be continued at the investigator's discretion.

The risks of solid organ transplant after 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.

4.2 Scientific Rationale for Study Design

This trial is a randomized open-label study. Based on interim data from Cohort A of KEYNOTE-365 (Section 2.1), the present study was developed to evaluate the efficacy of the combination of pembrolizumab and olaparib in participants who have not responded to abiraterone acetate or enzalutamide and to chemotherapy.

The effect of a PARP inhibitor as monotherapy is sensitive to biomarker positivity in prostate cancer. A case in point is the ORR of nearly 90% in a biomarker-defined subgroup of participants with DNA repair defects in the TOPARP-A study [Mateo, J., et al 2015]. Of 16 participants in this subgroup, 14 (88%) had a response to olaparib, using a composite endpoint of OR, PSA response, or a reduction of CTCs. However, only 2 of 33(6.1%) had a response to olaparib in the biomarker-negative subgroup, and the median survival time in this subgroup was only 7.5 months. For pembrolizumab monotherapy, in KEYNOTE-199, although ORR was 4.5% in participants with measurable disease (Cohorts 1 and 2), survival data were encouraging in the first 3 cohorts whose disease progressed on 1 NHA and 1 taxane-based chemotherapy (median OS 9.6 months). In KEYNOTE-365 Cohort A, which evaluated the population intended for study MK-7339-010 (none with DNA repair defects), DCR was 56.1% at the median follow-up of 11.4 months. The median survival time was approximately 13.5 months. Therefore, clinical benefit from the combination of pembrolizumab and olaparib is far beyond that which would be expected from either drug as

a single agent, especially for olaparib in patients with mCRPC unselected for DNA repair defects.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

The dual primary endpoints of the study will be OS and rPFS. Overall survival has been recognized as the gold standard for 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. Radiographic PFS will be assessed by BICR according to PCWG-modified RECIST 1.1 (Section 8.2).

Time to initiation of the first subsequent anticancer therapy (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 patients 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 frequently 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

Symptomatic improvement is considered a clinical benefit and accepted by health authorities as additional evidence of the risk-benefit profile of any new study intervention. In this study, health-related quality of life (HRQoL) and disease-related symptoms will be investigated via the following assessment tools: the FACT-P and BPI-SF questionnaires. Health utilities will be evaluated using the EQ-5D-5L PRO instrument. PRO instruments will be administered by trained site personnel and completed electronically by participants in the following order: FACT-P and EQ-5D-5L (both completed at the site), and BPI-SF (completed at home). These measures are not pure efficacy or safety endpoints because they are affected by both disease progression and treatment tolerability. The FACT-P is a disease-specific 39-item questionnaire included to assess HRQoL and prostate cancer-specific symptoms. It is a well-established measure of HRQoL/health status frequently used in prostate cancer clinical studies. The FACT-P was developed specifically for patients with advanced prostate cancer and has been found to be reliable and valid in this population [Esper, P., et al 1997].

The EQ-5D-5L is a standardized instrument for use as a measure of health outcome and will provide data to develop health utilities for use in health economic analyses [Rabin, R. 2001]. This instrument has been used extensively in cancer studies and published results from these studies support its validity and reliability [Pickard, A. S., et al 2007].

The BPI-SF is a validated 15-item domain-specific instrument designed to assess the severity of pain and the impact/interference of pain on daily function [Cleeland, C. S. and Ryan, K. M. 1994].

The Analgesic Log will be used to capture all analgesic medication dosages and dose times. Both the BPI-SF and the Analgesic Log will be completed over 7 consecutive days (eg, Days 15 to 21) at each scheduled timepoint after randomization.

4.2.1.4 Planned Exploratory Biomarker Research

PARP inhibitors and cancer immunotherapies represent important classes 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 drugs in treating patients. Thus, to aid future patients, it is important to investigate the determinants of response or resistance to cancer therapy and other treatments administered, as well as determinants of AEs in the course of our clinical studies. These efforts may identify novel predictive/pharmacodynamic biomarkers and generate information that may better guide single-agent and combination therapy. To identify novel biomarkers, biospecimens (ie, blood components, tumor material, tissue material) will be collected to support analyses of cellular components (eg, protein, DNA, RNA, metabolites) and other circulating molecules. Investigations of biomarkers that correlate with response or resistance to treatment 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. In addition to studying variation across the human genome, mutations in DNA damage repair genes including, but not limited to *BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L* as well as genome scars including LOH may be investigated. Based on data from participants in several olaparib studies in multiple cancer types, known or suspected deleterious mutations in these genes and LOH may be predictive of a response to the combination of olaparib and pembrolizumab. 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 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. 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, tissue, 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 olaparib and 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 olaparib (MK-7339) and pembrolizumab (MK-3475) therapy.

Other biomarkers

In addition to expression on the tumor tissue, other tumor derived cells, proteins and DNA/RNA can be shed from tumor and released into the blood. Assays such as enzyme-linked immunoassay (ELISA) that measure proteins and assays that measure cell-free DNA/RNA (cfDNA/cfRNA) may also be evaluated from blood samples. Correlation of these biomarkers with response to treatments 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.

4.2.1.5 Future Biomedical Research

The Sponsor will conduct FBR on specimens for which consent was provided during this study. This research may include genetic analyses (DNA), gene expression profiling (ribonucleic acid [RNA]), proteomics, metabolomics (serum, plasma), and/or the measurement of other analytes, depending on which specimens are consented for FBR.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main study) and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for FBR is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that participants receive the correct dose of the correct drug/vaccine at the correct time. The details of this FBR are presented in Appendix 6.

4.2.2 Rationale for the Use of Comparators

There is no SOC therapy for patients with mCRPC whose disease progressed through both NHA and taxane-based chemotherapy. Cabazitaxel, a second taxane, can be a toxic therapy. Also, patients progressing during docetaxel treatment or becoming intolerant to docetaxel-related toxicities are unlikely to receive cabazitaxel and require a different treatment modality. Most patients with mCRPC have bone metastases, and specifically directed radium-223 dichloride is not applicable for patients with visceral metastatic disease.

Although efficacy of a second NHA after failure of the first is limited based on retrospective studies, it is a reasonable therapy choice.

The effect of olaparib monotherapy is sensitive to biomarker positivity (*BRCA1/2* or *ATM* mutated) in prostate cancer. In the TOPARP-A study [Mateo, J., et al 2015], the response rate was 88% in the biomarker-positive subgroup of participants with DNA repair defects, but only 6.1% in the biomarker-negative subgroup. The median rPFS and OS for olaparib were 9.8 months and 13.8 months, respectively, in the biomarker-positive subgroup. In contrast, the median rPFS and OS for olaparib were only 2.7 and 7.5 months, respectively, in the biomarker-negative subgroup. Given the current clinical evidence for efficacy of olaparib monotherapy in biomarker-positive mCRPC patients and the lack thereof in the biomarker-negative population, testing olaparib monotherapy in an unselected HRR wild-type mCRPC population would not be ethical.

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 and regardless of tumor type. As outlined below, this dose is justified by the following:

- Clinical data from 8 randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W).
- Clinical data showing meaningful improvement in benefit-risk relationship, 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 physiologically based PK [PBPK] analysis) at 200 mg Q3W.

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and NSCLC, covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q3W (KEYNOTE-001 Cohort B2, KEYNOTE-001 Cohort D, KEYNOTE-002, KEYNOTE-010, and KEYNOTE-021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2, and KEYNOTE-006). All these studies demonstrated flat dose- and exposure-response relationships across the doses studied, representing an approximate 5- to 7.5- fold difference in exposure. A dose of 2 mg/kg (or 200 mg fixed dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose- and exposure-response relationships were observed in other tumor types, including head and neck cancer, bladder cancer, gastric cancer, and classical Hodgkin lymphoma, confirming 200 mg Q3W as the appropriate dose independent of tumor type. These findings are consistent with

the mechanism of action of pembrolizumab, which acts by interaction with immune cells and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KEYNOTE-001 evaluating target-mediated drug disposition conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other participant covariates on exposure, has shown that fixed dosing provides similar control of PK variability to weight-based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and the 2 mg/kg Q3W dose. Supported by these PK characteristics, and given that fixed dosing has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed dose was selected for evaluation across all pembrolizumab protocols.

4.3.2 Olaparib

The dose of olaparib used in this study is 300 mg BID (tablet formulation), which is the currently approved dose. Refer to Section 6.6.2 and the approved labeling for detailed information regarding dose regimen/modification.

4.3.3 Abiraterone Acetate

The recommended dose of abiraterone acetate is 1000 mg (four 250 mg tablets or two 500 mg tablets) administered orally QD. Participants receiving abiraterone acetate will also take one 5 mg prednisone or prednisolone tablet BID. Refer to Section 6.6.5 and the approved labeling for detailed information regarding dose regimen/modification.

4.3.4 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 6.6.6 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).

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.

5 STUDY POPULATION

The study population consists of male participants with mCRPC, unselected for HRR gene mutations, whose disease has progressed during prior NHA treatment and docetaxel chemotherapy. Participants must have had PD through or after prior treatment with abiraterone acetate or enzalutamide, but not both, and must have received and had PD during or after no more than 1 previous docetaxel chemotherapy treatment.

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

5.1 Inclusion Criteria

To be eligible for inclusion in this study, the participant must:

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

2. Have prostate cancer progression while receiving ADT (or post bilateral orchiectomy) within 6 months before Screening, as determined by the investigator through 1 of the following:

    - PSA progression shown by local laboratory values, as defined by a minimum of 2 consecutive rising PSA levels with an interval of ≥1 week between each assessment, where PSA at screening should be ≥1 ng/mL. Refer to Section 8.2.2 for further details.

      Note: A PSA level obtained during the screening period can count as the confirmatory second rising PSA.

    - Radiographic disease progression in soft tissue based on RECIST 1.1, with or without PSA progression.

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

3. Have disease progression under the following conditions if the participant received anti-androgen therapy before screening:

    - Evidence of progression >4 weeks since the last flutamide treatment.

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

4. Have current evidence of metastatic disease documented by bone lesions on bone scan and/or soft tissue disease shown by CT/MRI.

5. Have received prior treatment with abiraterone acetate OR enzalutamide, but not both.

    - Have disease that progressed during or after treatment with abiraterone acetate for either mHSPC or mCRPC or enzalutamide for mCRPC for at least 8 weeks (at least 14 weeks for participants with bone progression).

    - Patients that received abiraterone acetate for mHSPC may not have received abiraterone acetate or enzalutamide for mCRPC.

6. Have received docetaxel chemotherapy regimen for mCRPC and have had PD during or after treatment with docetaxel. If docetaxel chemotherapy has been used more than once (eg, once for metastatic hormone-sensitive prostate cancer and once for mCRPC), it will be considered as 1 therapy. Prior docetaxel for mCRPC is allowed if ≥4 weeks have elapsed from the last dose of docetaxel before Day 1 of Cycle 1.

7. 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 (LHRH) agonists or antagonists (in participants who have not undergone orchiectomy), this therapy must have been initiated at least 4 weeks before the date of randomization, and treatment must be continued throughout the study.

8. If receiving bone resorptive therapy, including but not limited to bisphosphonates or denosumab, have been receiving stable doses for ≥4 weeks before the date of randomization.

9. Have adequate organ function per central laboratory as defined in Table 1; all screening laboratory tests should be performed by the central laboratory within 10 days of the first dose of study intervention.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematologic	
ANC[a]	>1500/µL
Platelets	≥100,000/µL
Hemoglobin[a]	≥10 g/dL or ≥6.2 mmol/L
Renal	
Estimated creatinine clearance using the Cockcroft-Gault equation[b]	≥51 mL/min
Hepatic	
Serum total bilirubin	Total bilirubin ≤1.5 × ULN or direct bilirubin ≤ULN for participants with total bilirubin >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)
Coagulation	
INR or PT PTT or aPTT	≤1.5 × ULN unless participant is receiving anticoagulant therapy, as long as PT or PTT is within the therapeutic range for intended anticoagulant use

Abbreviations: ALT=alanine aminotransferase; ANC=absolute neutrophil count; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; G-CSF=granulocyte colony-stimulating factor; INR=international normalized ratio; PT=prothrombin time; PTT=partial thromboplastin time; SGOT=serum glutamic oxaloacetic transaminase; SGPT=serum glutamic pyruvic transaminase; ULN=upper limit of normal.

[a] This criterion must be met without erythropoietin dependency, and without packed red blood cell transfusion or G-CSF administration within the last 28 days.

[b] Estimated creatinine clearance using the Cockcroft-Gault equation:

$$\frac{(140\text{-age [years]} \times \text{weight [kg]})}{\text{serum creatinine (mg/dL)} \times 72}$$

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

Demographics

10. Be male.

11. Be ≥18 years of age on the day of signing the informed consent.

Male Participants

12. Participants are eligible to participate if they agree to the following during the intervention period and for at least the time needed to eliminate each study intervention after the last dose of study intervention. The length of time required to continue contraception after the last dose of study intervention for each study intervention is as follows:

    - Olaparib: 95 days
    - Abiraterone acetate: 7 days
    - Enzalutamide: 30 days

- 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 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.

Informed Consent

13. The participant (or legally acceptable representative if applicable) provides written informed consent/assent for the study. The participant may also provide consent/assent for FBR. However, the participant may participate in the main study without participating in FBR.

Additional Categories

14. Have provided 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 at 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, participants may provide an archival tumor tissue sample after Sponsor consultation (Sponsor Communication Form [SCF] submission). Formalin-fixed, paraffin embedded tissue blocks are preferred to slides. Newly obtained biopsies are preferred to archived tissue.

    Note: Details pertaining to tumor tissue submission are 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:

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 who have undergone potentially curative therapy are not excluded.

2. Has myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) or features suggestive of MDS/AML.

3. Has persistent toxicities (CTCAE Grade ≥2) caused by previous cancer therapy, excluding alopecia and neuropathy.

4. Has received colony-stimulating factors (eg, granulocyte colony-stimulating factor [G-CSF], granulocyte-macrophage colony-stimulating factor [GM-CSF], or recombinant erythropoietin) within 28 days before the date of randomization.

5. Is considered a high medical risk due to a serious uncontrolled medical disorder, nonmalignant systemic disease, or active uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, extensive interstitial bilateral lung disease on high-resolution CT scan, or any psychiatric disorder that prohibits obtaining informed consent.

6. Has a known psychiatric or substance abuse disorder that would interfere with cooperation with the requirements of the study.

7. Has an active autoimmune disease that has required systemic treatment in the 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.

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

   Note: Participants with rare hereditary problems of galactose intolerance, the lapp lactase deficiency, or glucose-galactose malabsorption are also excluded.

9. Is unable to swallow capsules/tablets.

10. Has a history of (noninfectious) pneumonitis requiring steroids, or has current pneumonitis.

11. Has an active infection, including tuberculosis, requiring systemic therapy.

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

13. Has known active human immunodeficiency virus (HIV), hepatitis B virus (eg, hepatitis B surface antigen reactive) or hepatitis C virus (HCV) infection (eg, HCV RNA [qualitative] is detected). Testing is not required unless mandated by the local health authority. Refer to Appendix 7 for country-specific testing requirements.

14. 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 before the date of randomization) and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and do not use steroids for at least 7 days before the date of randomization. This exception does not include carcinomatous meningitis, which is excluded regardless of clinical stability.

15. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (at doses exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days before the date of randomization.

16. Has (Grade ≥3) hypersensitivity to pembrolizumab and/or any of its excipients.

17. Has known hypersensitivity to the components or excipients in olaparib, abiraterone acetate, prednisone or prednisolone, or enzalutamide.

18. Has CTCAE Grade ≥2 peripheral neuropathy, except when due to trauma.

19. Has ascites or clinically significant pleural effusion.

20. Has had a seizure or seizures within 6 months of signing the informed consent or has any condition that may predispose to seizures, including but not limited to prior cerebrovascular accident, transient ischemic attack, or brain arteriovenous malformation, or intracranial mass such as a schwannoma or meningioma that is causing edema or mass effect.

21. Has a history of loss of consciousness within 12 months of the screening visit.

22. Has symptomatic congestive heart failure (New York Heart Association Class III or IV heart disease).

23. Has had a myocardial infarction or uncontrolled angina within 6 months before the date of randomization.

    Note: Participants with a recent history of revascularization for acute coronary syndrome within 3 months before the date of randomization will be included.

24. Has a history of clinically significant ventricular arrhythmias (eg, ventricular tachycardia, ventricular fibrillation, or torsade de pointes).

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

26. Has hypotension as indicated by systolic blood pressure (BP) <86 mm Hg at the screening visit.

27. Has bradycardia as indicated by heart rate <50 beats/minute on the screening electrocardiogram (ECG).

28. Has uncontrolled hypertension as indicated by systolic BP >170 mm Hg or diastolic BP >105 mm Hg at the screening visit.

Prior/Concomitant Therapy

29. Has received an anticancer mAb within 4 weeks before the date of randomization, or has not recovered (ie, Grade ≤1 or baseline) from AEs due to mAbs administered more than 4 weeks before the date of randomization.

    Note: Treatment with denosumab as SOC for bone metastases is permitted.

30. Has received prior treatment with olaparib or any other PARP inhibitor.

31. Has received prior treatment with apalutamide or darolutamide.

32. Has received prior treatment with enzalutamide or apalutamide for metastatic hormone-sensitive prostate cancer.

33. Has undergone major surgery, including local prostate intervention (except prostate biopsy), within 28 days before the date of randomization, and has not recovered from the toxicities and/or complications.

34. Has used herbal products that may have hormonal antiprostate cancer activity and/or are known to decrease PSA (eg, saw palmetto) within 4 weeks before the date of randomization.

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

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

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

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

39. Is currently receiving either strong (eg, itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, or telaprevir) or moderate (eg, ciprofloxacin, erythromycin, diltiazem, fluconazole, or verapamil) inhibitors of CYP3A4 that cannot be discontinued for the duration of the study. The required washout period before starting olaparib is 2 weeks.

40. Is currently receiving either strong (phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine, or St John's wort) or moderate (eg, bosentan, efavirenz, or modafinil) inducers of CYP3A4 that cannot be discontinued for the duration of the study. The required washout period before starting olaparib is 5 weeks for phenobarbital and 3 weeks for other agents.

    Note: A current list of strong/moderate inhibitors and inducers of CYP3A4 can be found at the following website:

    https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

41. Is currently being treated with CYP450-inducing antiepileptic drugs for seizures. Use of antiepileptic drugs for pain control is allowed in participants without seizures, unless these drugs are excluded due to CYP450 induction (eg, phenytoin, carbamazepine, and phenobarbital).

42. Has received 5α reductase inhibitors (eg, finasteride or dutasteride), estrogens, or cyproterone within 4 weeks before the date of randomization.

43. Has received a previous allogenic bone marrow transplant or double umbilical cord transplantation (dUCBT) or a solid organ transplant.

44. Has received a whole blood transfusion in the last 120 days before the date of randomization. Packed red blood cells and platelet transfusions are acceptable if not given within 28 days of the date of randomization.

45. Has received a live vaccine within 30 days before the date of randomization. Examples of live vaccines include, but are not limited to, measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, *Bacillus* Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

Prior/Concurrent Clinical Study Experience

46. Is currently participating in or has participated in a study of an investigational agent, or has used an investigational device, within 4 weeks before the date of randomization.

    Note: Participants who have entered the 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

47. Has a resting ECG indicating uncontrolled, potentially reversible cardiac conditions as judged by the investigator (eg, unstable ischemia, uncontrolled symptomatic arrhythmia, congestive heart failure, Fridericia-corrected QC interval [QTcF] prolongation >500 msec, electrolyte disturbances, etc.), or has congenital long QT syndrome.

48. Has a bone "superscan," defined as intense symmetric activity in bones and diminished renal parenchymal activity on the baseline bone scan, such that the presence of additional metastases in the future cannot be evaluated.

Other Exclusions

49. Is expecting to father children within the projected duration of the study, starting with the screening visit through the duration (days) after the last dose of study intervention listed in inclusion criterion #12.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Participants receiving pembrolizumab in combination with olaparib should avoid grapefruit, grapefruit juice, Seville oranges, Seville orange juice, and St John's wort (tablet or tea) while receiving study intervention. Otherwise, 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

As of Amendment 06, the study is being stopped for futility. However, participants currently still on study treatment may have the option of continuing with study intervention or SOC treatment, as appropriate, if they are deriving clinical benefit.

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 Administration	Regimen	Use	IMP/ NIMP	Sourcing
Arm 1	Experimental	Olaparib	Drug	Tablet	150 mg 100 mg	600 mg	Oral	Two 150 mg tablets BID	Experimental	IMP	Central
Arm 1	Experimental	Pembrolizumab	Biological/ Vaccine	Solution for Infusion	25 mg/mL	200 mg	IV Infusion	Day 1 of each 21-day cycle	Experimental	IMP	Central
Arm 2	Active Comparator	Abiraterone acetate (a)	Drug	Tablet	500 mg 250 mg	1000 mg	Oral	Two 500 mg tablets QD or Four 250 mg tablets QD	SOC	IMP	Central/ Local(e)
Arm 2	Active Comparator	Prednisone or prednisolone (a) (b)	Drug	Tablet	5 mg	10 mg	Oral	One 5 mg tablet BID	SOC	NIMP	Local
Arm 2	Active Comparator	Enzalutamide (c) (d)	Drug	Capsule/Tablet	40 mg/80 mg	160 mg	Oral	Four 40 mg capsules/tablets QD or Two 80 mg tablets QD	SOC	IMP	Central

Definition of Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product (NIMP) is based on guidance issued by the European Commission. Regional and/or country differences of the definition of IMP/NIMP may exist. In these circumstances, local legislation is followed.

Abbreviations: BID=twice daily; IV=intravenous; QD=once daily; SOC=standard of care.

[a] Participants previously treated with enzalutamide

[b] Prednisone is the preferred steroid for use in the study. Prednisolone should only be used when prednisone is unavailable and requires Sponsor consultation.

[c] Participants previously treated with abiraterone acetate

[d] Participants will take either enzalutamide capsules or enzalutamide tablets.

[e] The 250 mg dosage strength will be sourced locally where available. The 500 mg dosage strength will be sourced centrally depending on local regulations.

All supplies indicated in Table 2 will be provided per the "Sourcing" column depending upon local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number.

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

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.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

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

Olaparib, abiraterone acetate, prednisone or prednisolone, and enzalutamide do not require preparation.

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 take place centrally using an interactive response technology (IRT) system. There are 2 study intervention arms. Participants will be randomly assigned in a 2:1 ratio to pembrolizumab in combination with olaparib or to abiraterone acetate **or** enzalutamide, respectively.

6.3.2 Stratification

Participants will be stratified according to the following factors:

- Prior NHA treatment: abiraterone acetate versus enzalutamide
- Measurable disease at baseline: yes versus no

6.3.3 Blinding

This is an open-label study; therefore, the Sponsor, investigator, and participant will know the treatment administered. Imaging data for the primary analysis will be centrally reviewed by an independent radiologist(s) without knowledge of participants' treatment assignment.

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

6.4 Study Intervention Compliance

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 study interventions taken at home, the site will validate compliance with study intervention at each site visit according to its SOP.

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 OR during time periods specified by this protocol for that medication or vaccination. If there is a clinical indication for any medication or vaccination specifically prohibited, discontinuation from [study intervention or vaccination] may be required. The investigator is to discuss prohibited medication/vaccination 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.

- Based on in vitro data, olaparib may increase exposure to substrates of CYP3A4, organic anion-transporting polypeptide 1B1, organic cation transporter 1/2/3, and multidrug and toxic compound extrusion 1/2, and reduce exposure to substrates of CYP2B6. Caution should be observed if substrates of these isoenzymes or transporter proteins are co-administered, including statins (eg, lovastatin, simvastatin, etc.). A current list of substrates can be found at the following website:

  https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

- Listed below are specific concomitant therapies or vaccinations prohibited during the study:

  - Anticancer hormonal therapy (eg, anti-estrogens).

    Note: Hormonal replacement therapy and ADT with LHRH agonists (eg, leuprolide) and LHRH antagonists (eg, degarelix) are allowed.

  - Strong and moderate inhibitors or inducers of CYP3A4.

    Note: A current list of strong and moderate inhibitors/inducers of CYP3A4 can be found at the following website:

    https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

    Refer to Section 6.6.2.5 for exceptions.

  - Enzalutamide is a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer. Concomitant use of enzalutamide with narrow therapeutic index drugs metabolized by CYP3A4 (eg, alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus), CYP2C9 (eg, phenytoin and warfarin), and CYP2C19 (eg, [S]-mephenytoin and clopidogrel)

should be avoided if possible, as enzalutamide may decrease their exposure. If coadministration with warfarin cannot be avoided, perform additional INR monitoring.

- Abiraterone is an inhibitor of CYP2D6. Dose reduction should be considered for medicinal products that are metabolized by CYP2D6 and have a narrow therapeutic index to prolong the QT interval (ie, pimozide, sertindole, droperidol, haloperidol, thioridazine).

- Strong inhibitors of CYP2C8.

- Antineoplastic systemic chemotherapy or biologic therapy, except denosumab and bisphosphonates for bone metastases as SOC (the participant must have been receiving stable doses for ≥4 weeks before randomization).

- Immunotherapy not specified in this protocol.

- Chemotherapy not specified in this protocol.

- Targeted therapy not specified in this protocol.

- Administration of radium-223 while on study and for at least 5 days after the last administration of abiraterone in combination with prednisone/prednisolone.

  The clinical efficacy and safety of concurrent therapy of abiraterone acetate plus prednisone/prednisolone and radium-223 were evaluated in a Phase 3, randomized, placebo-controlled, multicenter study in patients with asymptomatic or mildly symptomatic castration-resistant prostate cancer with bone metastases. Increased incidences of fractures (28.6% vs 11.4%) and deaths (38.5% vs 35.5%) were observed in patients who received abiraterone plus prednisone/prednisolone in combination with radium-223 compared to patients who received placebo in combination with abiraterone acetate plus prednisone/prednisolone [Smith, M., et al 2019]. Therefore, the combination of abiraterone and prednisone/prednisolone with radium-223 is contraindicated. Additionally, subsequent treatment with radium-223 should not be initiated for at least 5 days after the last administration of abiraterone in combination with prednisone/prednisolone.

- Initiation of bone resorptive therapy including, but not limited to, bisphosphonates or denosumab (unless approved by Sponsor consultation).

- Any second-generation androgen receptor inhibitor, except enzalutamide in participants randomized to abiraterone acetate or enzalutamide arm.

- Investigational agents other than pembrolizumab or olaparib.

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

- Radiation therapy.

- **Note**: Palliative localized radiation therapy to a site of pre-existing disease may be permitted during the study after consultation with the Sponsor. The radiation treatment field may not include a target or measurable lesion per RECIST 1.1.

- Live vaccines within 30 days before the date of randomization and while participating in the study. Examples of live vaccines include, but are not limited to, measles, mumps, rubella, chicken pox, yellow fever, intranasal seasonal influenza, rabies, BCG, and oral typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed.

  Note: If precluded by local regulations, live vaccines should not be given for 90 days after the last dose of study intervention. (See Appendix 7 for country-specific requirements).

- Systemic glucocorticoids for any purpose other than for administration to participants receiving abiraterone acetate, or to modulate symptoms from an AE that is suspected to have an immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

  Note: The following uses of corticosteroids are permitted without Sponsor consultation:

  - Inhaled steroids for management of asthma.

  - Prophylactic corticosteroids to avoid allergic reactions (eg, reactions to IV contrast material).

  - Palliative prednisone or prednisolone up to 10 mg daily or corticosteroid equivalent as used to treat men with prostate cancer.

  - Physiologic doses of corticosteroids for adrenal insufficiency.

  - Intranasal steroids for management of allergies.

- Disease-modifying agents or immunosuppressive drugs.

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

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

The exclusion criteria (Section 5.2) describe other medications 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 date of randomization and up to 30 days after the last dose of study intervention should be recorded. Concomitant medications administered 30 days after the last dose of study intervention should be recorded for SAEs and events of clinical interest (ECIs) 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 6.6.3.1, Table 7. 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 7 in Section 6.6.3.1 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 the Sponsor before the use of radiotherapy or surgical intervention while a participant is in the 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 a participant is in the 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 soft tissue, that meets the criteria for disease progression according to PCWG [Scher, H. I., et al 2016], study intervention 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 is interrupted for >12 weeks for an immune-related AE (irAE) or for administrative reasons, or olaparib is interrupted for 28 consecutive days, the site must gain approval via an SCF to continue the other study intervention. Participants who must discontinue 1 of the 2 interventions due to drug-related AEs may continue with the other intervention after consultation with the Sponsor until a criterion for study intervention discontinuation (e.g., disease progression) is met.

6.6.2 Dose Modification for Olaparib

The dose of olaparib can be reduced to 250 mg BID initially and then to 200 mg BID as needed. If the 200 mg BID dose is not tolerable, no further dose reduction is allowed, and olaparib should be discontinued. Once the dose has been reduced, escalation is not permitted, except after concomitant treatment with CYP3A4 inhibitors (Table 6).

The reason for the dose interruption or reduction should be captured on the appropriate electronic case report form (eCRF).

6.6.2.1 Management of Hematologic Toxicities

Any hematologic toxicity observed during the study could be managed by a brief interruption of olaparib dosing or a reduction of the olaparib dose (Table 3 and Table 4). Repeated interruptions, not exceeding 4 weeks (28 days), are allowed as required. If the interruption is any longer, the Sponsor must be informed.

Table 3 Management of Anemia

Toxicity	NCI CTCAE Grade	Action Taken
Hemoglobin (Hb)	Grade 2 (<10 but ≥8 g/dL)	**First Occurrence:** Give appropriate supportive treatment and investigate causality. • Investigator judgment to either continue olaparib with supportive treatment (eg, transfusion) or interrupt olaparib dosing for a maximum of 4 weeks (28 days). Treatment can be restarted if Hb has recovered to >9 g/dL. **Subsequent Recurrence:** • **Hb <10 but ≥9 g/dL**: Investigator judgment to either continue olaparib with supportive treatment (eg, transfusion) or interrupt olaparib dosing for a maximum of 4 weeks (28 days). On recovery, a dose reduction to 250 mg BID as a first step or 200 mg BID as a second step may be considered. • **Hb <9 but ≥8 g/dL**: Interrupt olaparib for a maximum of 4 weeks (28 days) until Hb improves to >9 g/dL. On recovery, reduce the dose of olaparib to 250 mg BID. A second dose reduction to 200 mg BID may be considered if additional decreases in Hb occur.
	Grade 3 (<8 g/dL)	Give appropriate supportive treatment (eg, transfusion) and investigate causality. • Interrupt olaparib for a maximum of 4 weeks (28 days), until Hb improves to ≥9 g/dL. • On recovery, reduce the dose of olaparib to 250 mg BID. A second dose reduction to 200 mg BID may be considered if additional decreases in Hb occur.
Abbreviations: BID=twice daily; CTCAE=Common Terminology Criteria for Adverse Events; Hb=hemoglobin; NCI=National Cancer Institute. **Note**: Common treatable causes of anemia (eg, iron, vitamin B12 or folate deficiencies, and hypothyroidism) should be investigated and appropriately managed. In some cases, management of anemia may require blood transfusions. Management of prolonged hematologic toxicities is detailed in Section 6.6.2.2.		

Table 4 Management of Neutropenia, Leukopenia, and Thrombocytopenia

Toxicity	NCI CTCAE Grade	Action Taken
Neutropenia, leukopenia, or thrombocytopenia	Grade 1 or 2	Investigator judgment to either continue olaparib or interrupt dosing for a maximum of 4 weeks (28 days). Give appropriate supportive treatment and investigate causality.
	Grade 3 or 4	• Interrupt olaparib for a maximum of 4 weeks (28 days), until event recovers to ≤Grade 1. • Repeated incidence: reduce the dose of olaparib to 250 mg BID. A second dose reduction to 200 mg BID may be considered if additional Grade 3 or 4 events occur.
Abbreviations: AEs=adverse events; BID=twice daily; CTCAE=Common Terminology Criteria for Adverse Events; G-CSF=granulocyte colony-stimulating factor; NCI=National Cancer Institute. • AEs of neutropenia and leukopenia should be managed as deemed appropriate by the investigator with close follow-up and interruption of study intervention if CTCAE Grade 3 or worse neutropenia occurs. • Primary prophylaxis with G-CSF is not recommended; however, if a participant develops febrile neutropenia, study intervention should be stopped and appropriate management including G-CSF should be given according to local hospital guidelines. Please note that G-CSF should not be used within at least 24 hours (7 days for pegylated G-CSF) of the last dose of study intervention unless absolutely necessary. • Platelet transfusions, if indicated, should be performed according to local hospital guidelines. • Management of prolonged hematologic toxicities is detailed in Section 6.6.2.2.		

6.6.2.2 Management of Prolonged Hematologic Toxicities

If a participant develops prolonged hematologic toxicity, such as:

- ≥2-week interruption/delay of olaparib dosing due to NCI CTCAE Grade 3 or worse anemia and/or development of blood transfusion dependence,
- ≥2-week interruption/delay of olaparib dosing due to NCI CTCAE Grade 3 or worse neutropenia (absolute neutrophil count $<1 \times 10^9$/L), or
- ≥2-week interruption/delay of olaparib dosing due to NCI CTCAE Grade 3 or worse thrombocytopenia and/or development of platelet transfusion dependence (platelets $<50 \times 10^9$/L),

differential blood count, including reticulocytes and peripheral blood smear, should be checked weekly. If any blood parameters remain clinically abnormal after olaparib dosing has been interrupted for ≥4 weeks (≥28 days), the participant should be referred to a hematologist for further investigations. Bone marrow analysis and/or blood cytogenetic analysis should be considered, according to local regulations and/or standard institutional hematologic practice. Olaparib should be discontinued if blood counts do not recover to NCI CTCAE Grade 1 or better within 4 weeks (28 days) of dose interruption.

Development of confirmed MDS or other clonal blood disorder should be reported as an SAE, and full reports must be provided by the investigator to the Sponsor as outlined in Section 8.4.4. Olaparib should be discontinued for confirmed MDS and/or AML (Section 7.1).

6.6.2.3 Management of Nonhematologic Toxicity

Repeated dose interruptions, not exceeding 4 weeks (28 days), are allowed as required. If toxicity recurs after rechallenge with olaparib, and where further dose interruptions are considered inadequate for management of toxicity, either a dose reduction should be considered (Section 6.6.2) or the participant must permanently discontinue olaparib.

Olaparib dosing must be interrupted if any NCI CTCAE Grade 3 or 4 AE occurs that the investigator considers to be related to olaparib administration.

6.6.2.3.1 Management of New or Worsening Pulmonary Symptoms

If new or worsening pulmonary symptoms (eg, dyspnea) or radiologic abnormalities occur in the absence of a clear diagnosis, an interruption of olaparib dosing is recommended, and further diagnostic workup (including a high-resolution CT scan) should be performed to exclude pneumonitis.

After investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, olaparib can be restarted if deemed appropriate by the investigator. If significant pulmonary abnormalities are identified, these need to be discussed with the Sponsor.

6.6.2.3.2 Management of Nausea and Vomiting

Events of nausea and vomiting are known to be associated with olaparib administration. These events are generally mild to moderate in severity (NCI CTCAE Grade 1 or 2), intermittent, and manageable with continued treatment. The first onset generally occurs in the first month of olaparib dosing for nausea and within the first 6 months of olaparib dosing for vomiting. For nausea, the incidence generally plateaus at around 9 months, and for vomiting at around 6 to 7 months.

No routine prophylactic antiemetic treatment is required at the start of olaparib treatment; however, participants should receive appropriate antiemetic treatment at the first onset of nausea or vomiting and as required thereafter, in accordance with local regulations or institutional guidelines. Alternatively, olaparib tablets can be taken with a light meal/snack (ie, 2 pieces of toast or a couple of crackers).

Per international guidance on antiemetic use in cancer patients (ESMO; NCCN), generally a single-agent antiemetic should be considered (eg, a dopamine receptor antagonist, antihistamines, or dexamethasone).

6.6.2.3.3 Management of Renal Impairment

If, after study entry and/or while still receiving olaparib, a participant's estimated creatinine clearance (CrCl) falls below the threshold for study inclusion (≥51 mL/min), retesting should be performed promptly.

A dose reduction is recommended for participants who develop moderate renal impairment (calculated CrCl 31 to 50 mL/min, either as calculated with the Cockcroft-Gault equation or based on a 24-hour urine test) for any reason during the study.

Table 5 Olaparib Dose Reduction to Manage Moderate Renal Impairment

Initial Dose	**Moderate Renal Impairment[a]**
300 mg BID	200 mg BID
Abbreviation: BID=twice daily. [a] Creatinine clearance 31 to 50 mL/min as calculated with the Cockcroft-Gault equation or based on a 24-hour urine test	

Because CrCl determination is only an estimate of renal function, in instances where CrCl falls to 31 to 50 mL/min the investigator should use his or her discretion in determining whether a dose change or discontinuation of olaparib is warranted.

Olaparib has not been studied in participants with severe renal impairment (CrCl ≤30 mL/min) or end-stage renal disease. If participants develop severe renal impairment or end-stage renal disease, it is recommended that olaparib be discontinued.

6.6.2.4 Interruptions for Intercurrent Nontoxicity-related Events

Olaparib dose interruption for conditions other than toxicity resolution should be kept as short as possible. If a participant cannot restart olaparib within 4 weeks (28 days) for resolution of intercurrent conditions not related to disease progression or toxicity, the case should be discussed with the Sponsor and approved via an SCF.

All dose reductions and interruptions (including any missed doses) and the reasons for the reductions/interruptions are to be recorded in the eCRF.

Olaparib should be stopped at least 3 days before planned surgery and can be restarted when the wound has healed. It is not required to stop olaparib for any needle biopsy procedure.

Localized palliative radiation therapy to a site of pre-existing disease may be permitted while a participant is in the study. Olaparib should be discontinued for a minimum of 3 days before radiation therapy and should be restarted within 4 weeks (28 days), as long as any bone marrow toxicity has recovered.

Because AEs related to olaparib may include asthenia, fatigue, and dizziness, participants should be advised to use caution while driving or using machinery if these symptoms occur.

6.6.2.5 Dose Reductions for Concurrent CYP3A4 Inhibitor Use

Strong or moderate CYP3A inhibitors should not be taken with olaparib. If there is no suitable alternative concomitant medication, the dose of olaparib should be reduced for the period of concomitant administration as described in Table 6. After washout of the inhibitor is complete (Section 5.2), the olaparib dose can be re-escalated. The olaparib dose reduction should be recorded in the eCRF, with the reason documented as concomitant CYP3A4 inhibitor use.

Table 6 Olaparib Dose Reduction with a Strong or Moderate CYP3A4 Inhibitor

Initial Dose	Strong CYP3A Inhibitor	Moderate CYP3A Inhibitor
300 mg BID	100 mg BID	150 mg BID
Abbreviation: BID=twice daily.		

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

6.6.3.1 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 7.

Table 7 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) • 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.
	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
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]		
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]		

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

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).

6.6.3.2 Dose Modification and Toxicity Management of Infusion Reactions Associated with 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 for pembrolizumab-associated infusion reactions are provided in Table 8.

Table 8 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) before infusion 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 after 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 Abbreviations: NCI=National Cancer Institute; NSAID=nonsteroidal anti-inflammatory drug; IV=intravenous; po=orally.		

Other Allowed Dose Interruption for Pembrolizumab

Pembrolizumab 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 for Q3W (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 Management of Overlapping Toxicities

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

1. Timing of AE Onset

Since olaparib is dosed daily and continuously due to a relatively short half-life (11.9 hours) and pembrolizumab is dosed Q3W due to a long half-life, olaparib 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 olaparib dose interruption is needed.

- If an AE is identified at the beginning of a treatment cycle, olaparib can be interrupted and pembrolizumab dosing should be held.

If the participant recovers from an AE in response to olaparib interruption (ie, positive dechallenge), the event is more likely to be related to olaparib. Otherwise, after excluding other alternative explanations, an irAE 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 rapidly worsens, action, including interrupting both drugs and initiating treatment with a corticosteroid (with the exception of hypothyroidism and type 1 diabetes mellitus [T1DM]) and other supportive care, should be promptly taken.

6.6.5 Dose Modification for Abiraterone Acetate

Dose modification guidelines for abiraterone acetate are given in Table 9. The dose regimen/modification should be adopted according to the efficacy and safety risk information according to local regulations and guidelines for administration of abiraterone acetate. Once the dose has been reduced, it may not be escalated to a previous dose level.

6.6.5.1 Management of Hepatotoxicity

In participants who develop hepatotoxicity during treatment with abiraterone acetate ALT and/or AST >5 × ULN or total bilirubin >3 × ULN), interrupt treatment. Treatment may be restarted at a reduced dose of 750 mg QD after return of liver function test results to baseline

or to AST and ALT ≤2.5 × ULN and total bilirubin ≤1.5 × ULN. If hepatotoxicity recurs at the dose of 750 mg QD, treatment may be restarted at a reduced dose of 500 mg QD after return of liver function test results to baseline or to AST and ALT ≤2.5 × ULN and total bilirubin ≤1.5 × ULN. If hepatotoxicity recurs at the reduced dose of 500 mg QD, treatment with abiraterone acetate is to be discontinued.

Abiraterone acetate is to be permanently discontinued in participants who develop a concurrent elevation of ALT >3 × ULN and total bilirubin >2 × ULN in the absence of biliary obstruction or other causes responsible for this concurrent elevation.

Participants who develop AST or ALT ≥20 × ULN and/or bilirubin ≥10 × ULN should be discontinued from treatment with abiraterone acetate.

6.6.5.2 Management of Hypokalemia

Correct hypokalemia before and during treatment. For Grade 1 or 2 hypokalemia, initiate oral potassium supplementation, and titrate to maintain serum potassium ≥3.5 mEq/L and ≤5.0 mEq/L (maintenance at ≥4.0mEq/L is recommended). Treatment without dose reduction can continue after hypokalemia is corrected to Grade 0.

If a participant develops Grade 3 hypokalemia (serum potassium <3.0 mEq/L to 2.5 mEq/L [NCI CTCAE Version 4.0]) or life-threatening hypokalemia with serum potassium <2.5 mEq/L (Grade 4 hypokalemia [NCI CTCAE Version 4.0]), abiraterone acetate should be withheld and the participant hospitalized for IV potassium replacement and cardiac monitoring. Re-initiation of abiraterone acetate after normalization (Grade 0) of serum potassium must be discussed with and approved by the Sponsor.

6.6.5.3 Management of Hypertension

For Grade 1 to 2 hypertension, continue abiraterone acetate without dose reduction. Management of hypertension is per the investigator.

For Grade 3 to 4 hypertension, withhold abiraterone acetate. Adjust or add medications to mitigate the toxicity, and/or consider a specific mineralocorticoid receptor blocker such as eplerenone. When hypertension resolves to Grade ≤1, resume abiraterone acetate at the full dose.

If Grade 3 to 4 hypertension recurs, withhold abiraterone acetate and adjust or add medications to mitigate the toxicity. When hypertension is resolved to Grade ≤1, resume abiraterone acetate at 750 mg QD.

If Grade 3 to 4 hypertension recurs again, withhold abiraterone acetate and adjust or add medications to mitigate the toxicity. When hypertension is resolved to Grade ≤1, resume abiraterone acetate at 500 mg QD.

If Grade 3 to 4 hypertension recurs despite optimal medical management and 2 dose reductions, discontinue abiraterone acetate.

6.6.5.4 Management of Edema and Fluid Retention

Supportive management of pedal edema is per the investigator. Dose reduction of abiraterone acetate is not necessary.

If anasarca and/or pulmonary edema requiring supplemental oxygen occurs, withhold abiraterone acetate. Adjust or add medications to mitigate the toxicity, and/or consider a specific mineralocorticoid receptor blocker such as eplerenone. When anasarca and/or pulmonary edema resolves to Grade ≤1, resume abiraterone acetate at the full dose.

If anasarca and/or pulmonary edema recurs, withhold abiraterone acetate and adjust or add medications to mitigate the toxicity. When anasarca and/or pulmonary edema is resolved to Grade ≤1, resume abiraterone acetate at 750 mg QD.

If anasarca and/or pulmonary edema recurs again, withhold abiraterone acetate and adjust or add medications to mitigate the toxicity. When anasarca and/or pulmonary edema is resolved to Grade ≤1, resume abiraterone acetate at 500 mg QD.

If anasarca and/or pulmonary edema recurs despite optimal medical management and 2 dose reductions, discontinue abiraterone acetate.

6.6.5.5 Management of Other AEs Believed to be Related to Abiraterone Acetate

For Grade 1 to 2 toxicities, give supportive care per institutional guidelines. Dose reduction of abiraterone acetate is not necessary.

For Grade 3 to 4 toxicities, withhold abiraterone acetate. Adjust or add medications to mitigate the toxicity, and/or consider a specific mineralocorticoid receptor blocker such as eplerenone. When the toxicity is resolved to Grade ≤1, resume abiraterone acetate at the full dose.

If the toxicity recurs, withhold abiraterone acetate and adjust or add medications to mitigate the toxicity. When the toxicity is resolved to Grade ≤1, resume abiraterone acetate at 750 mg QD.

If the toxicity recurs again, withhold abiraterone acetate and adjust or add medications to mitigate the toxicity. When the toxicity is resolved to Grade ≤1, resume abiraterone acetate at 500 mg QD.

If the toxicity recurs despite optimal medical management and 2 dose level reductions, discontinue abiraterone acetate.

Symptoms and signs of adrenocortical insufficiency may be masked by adverse reactions associated with mineralocorticoid excess seen in participants treated with abiraterone acetate. If clinically indicated, perform appropriate tests to confirm the diagnosis of adrenocortical insufficiency. Increased corticosteroid dosage may be indicated before, during, and after stressful situations. Monitor the participant for symptoms and signs of adrenocortical

insufficiency. If stress doses of corticosteroids are necessary, withhold abiraterone acetate and contact the Sponsor to discuss when to restart abiraterone acetate.

Table 9 Abiraterone Acetate Dose Modification Guidelines for Drug-related Adverse Events

	Dose	Regimen
Initial abiraterone acetate dose	1000 mg	Two 500 mg tablets PO QD
First dose reduction	750 mg	One 500 mg tablet and one 250 mg tablet PO QD
Second dose reduction	500 mg	One 500 mg tablet PO QD
Abbreviations: PO=orally; QD=once daily.		

Note: Table 9 is in accordance with the US FDA drug label. The dose regimen/modification should be adopted according to the efficacy and safety risk information according to local regulations and guidelines for administration of abiraterone acetate.

6.6.6 Dose Modification for Enzalutamide

If a participant experiences any Grade ≥3 toxicity related to enzalutamide, the drug should be withheld until the toxicity decreases to Grade ≤2. Enzalutamide can then be resumed at a reduced dose of 120 mg QD. If Grade ≥3 toxicity recurs, enzalutamide can again be withheld until toxicity decreases to Grade ≤2 and resumed at a reduced dose of 80 mg QD. Dose reduction below 80 mg QD is not permitted.

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

Enzalutamide should be permanently discontinued in participants who experience a seizure during treatment.

Posterior reversible encephalopathy syndrome (PRES) has been observed in participants treated with enzalutamide. This syndrome 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. PRES is diagnosed by brain imaging (preferably MRI). Enzalutamide must be permanently discontinued in participants who develop PRES during treatment.

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

After resolution of toxicity, enzalutamide can be resumed with dose reduction according to Table 10.

Table 10 Enzalutamide Dose Modification Guidelines for Drug-related Adverse Events

	Dose	Regimen
Initial enzalutamide dose	160 mg	Four 40 mg capsules/tablets PO QD or Two 80 mg tablets PO QD
First dose reduction	120 mg	Three 40 mg capsules/tablets PO QD or One 80 mg tablet and one 40 mg tablet PO QD
Second dose reduction	80 mg	Two 40 mg capsules/tablets PO QD or One 80 mg tablet PO QD
Abbreviations: PO=orally; QD=once daily.		

Note: Table 10 is in accordance with the US FDA drug label. The dose regimen/modification should be adopted according to the efficacy and safety risk information according to local regulations and guidelines for administration of enzalutamide.

6.6.7 Second Course

NOTE: As of Amendment 06, the study will be stopped due to futility and second course treatment is not an option for participants. There are currently no participants in the Second Course Phase.

All participants receiving pembrolizumab in combination with olaparib who stop study intervention with SD or better may be eligible for up to 17 additional cycles (approximately 1 year) of pembrolizumab treatment if their disease progresses after stopping study intervention in the initial treatment phase. Olaparib may be continued at the investigator's discretion. This retreatment is termed the Second Course phase of this study, and is only available if the study remains open and the participant meets the following conditions:

Either

- The participant stopped initial study intervention after attaining a BICR-verified CR based on PCWG-modified RECIST 1.1, and
- The participant was treated with at least 8 cycles of study intervention before discontinuing treatment, and
- The participant received at least 2 treatments with pembrolizumab beyond the date when the initial CR was declared.

OR

- The participant had SD, PR, or CR and stopped study intervention after completion of 35 cycles (approximately 2 years) of study intervention for reasons other than disease progression or intolerability.

AND

- The participant experienced BICR-verified radiographic disease progression per PCWG-modified RECIST 1.1 after stopping initial treatment.
- No new anticancer treatment was administered after the last dose of study intervention.
- The participant meets all safety parameters listed in the inclusion criteria and none of the safety parameters listed in the exclusion criteria.
- The study is ongoing.

An OR disease progression occurring during the Second Course phase will not be counted as an event for the primary analysis of either endpoint in this study.

6.7 Intervention After the End of the Study

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

6.8 Clinical Supplies Disclosure

Not applicable

6.9 Standard Policies

Study site personnel will have access to a central electronic IRT system to allocate participants, to assign study intervention to participants, and to manage the distribution of clinical supplies. Each person accessing the IRT system must be assigned an individual unique personal identification number (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 study intervention 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 discontinued 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 intervention 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. Before discontinuing participants from study intervention, submit the Treatment Termination and Disease Assessment Termination Form.

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.
- Bone marrow findings consistent with MDS or AML.
- The participant interrupts pembrolizumab administration for >12 consecutive weeks for an irAE, or >12 weeks for administrative reasons, without Sponsor consultation.
- The participant interrupts olaparib administration for more than 28 consecutive days without Sponsor consultation.
- The participant interrupts abiraterone acetate or enzalutamide administration for more than 28 consecutive days without Sponsor consultation.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, places 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 as outlined in Section 8.2.1 (except if the Sponsor approves study intervention continuation).
    - As of Amendment 06, central tumor response assessments will no longer be performed. However, participants still on study treatment and deriving clinical benefit and are continuing to receive study intervention or SOC, will be assessed locally by the investigator for disease progression per SOC schedule.
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment.
- Recurrent Grade 2 pneumonitis.

- Recurrent Grade 3 colitis/diarrhea.
- Completion of 35 cycles (approximately 2 years) of pembrolizumab treatment.
- Intercurrent illness that prevents further administration of study intervention.
- Noncompliance with study intervention or procedure requirements.
- Administrative reasons requiring cessation of study intervention.
- **Note**: The number of treatments is calculated starting with the first dose. Participants who stop pembrolizumab + olaparib or pembrolizumab after 35 cycles may be eligible for retreatment if their disease progresses after stopping study intervention, provided they meet the requirements detailed in Section 6.6.7. Participants may be retreated in the Second Course phase (retreatment) for up to 17 additional cycles of pembrolizumab (approximately 1 year). Olaparib may be continued at the investigator's discretion.
- Discontinuation of treatment may be considered for participants randomized to pembrolizumab + olaparib who have attained a confirmed CR and been treated for at least 8 cycles (at least 24 weeks), receiving 2 cycles of pembrolizumab and olaparib including 2 doses of pembrolizumab and at least 80% of the planned doses of olaparib, beyond the date when the initial CR was declared. These participants may be eligible for Second Course treatment as described in Section 6.6.7.

  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

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

If a participant withdraws from the study, they will no longer receive study intervention or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from future biomedical research, are outlined in Section 8.1.9.

The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

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 consent from each potential participant or each participant's legally acceptable representative prior to participating in a clinical study or future biomedical research. 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 consent is in place.

8.1.1.1 General Informed Consent

Consent must be documented by the participant's dated signature or by the participant's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the participant before participation in the study.

The initial ICF, any subsequent revised written ICF, and any written information provided to the participant must receive the Institutional Review Board/Independent Ethics Committee's (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 dated signature or by the participant's legally acceptable representative's dated signature.

The participant or his legally acceptable representative will be asked to sign consent at the point of initial radiographic disease progression.

Specifics about a study and the study population will be added to the consent form template at the protocol level.

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

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or medically qualified designee will explain the FBR consent to the participant, answer all of his questions, and obtain written informed consent before

performing any procedure related to the FBR. A copy of the informed consent will be given to the participant.

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 written 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.

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 before the date of 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.

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 reassigned to another participant.

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

8.1.8 Study Intervention Administration

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

Administration of olaparib, abiraterone acetate and prednisone or prednisolone, or enzalutamide will be administered by the investigator and/or study staff according to the specifications within the Pharmacy Manual, at the Cycle 1 Day 1 clinic visit. Participants will then self-administer olaparib, abiraterone acetate and prednisone or prednisolone, or enzalutamide orally on a continuous daily dosing schedule.

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

8.1.8.1 Timing of Dose Administration

8.1.8.1.1 Pembrolizumab

Pembrolizumab 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 at a fixed dose of 200 mg, as a 30-minute IV infusion Q3W. Sites should make every effort to target infusion time 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).

The Pharmacy Manual contains specific instructions for pembrolizumab reconstitution, preparation of the infusion fluid, and administration.

8.1.8.1.2 Olaparib

Olaparib will be administered at a dose of 300 mg (two 150 mg tablets) po BID for a total daily dose of 600 mg.

At the Cycle 1 Day 1 clinic visit, the first dose of olaparib will be administered after all predose assessments and procedures and pembrolizumab infusion have been completed. Participants will be instructed to self-administer olaparib. Olaparib tablets should be taken BID with 1 glass of water at the same time each day, approximately 12 hours between doses. The tablets should be swallowed whole and not chewed, crushed, dissolved or divided. Olaparib tablets can be taken with or without food.

If vomiting occurs shortly after olaparib tablets are swallowed, the dose should only be replaced if all the intact tablets can be seen and counted. Should any participant enrolled in the study miss a scheduled dose for any reason (eg, because of forgetting to take the tablets or vomiting), the participant will be allowed to take the scheduled dose up to a maximum of 2 hours after that scheduled dose time. If it is more than 2 hours after the scheduled dose time, the missed dose is not to be taken, and the participant should take his allotted dose at the next scheduled time.

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 its SOP. If doses are missed or vomited, this must be indicated in the source documents and CRFs.

8.1.8.1.3 Abiraterone Acetate + Prednisone or Prednisolone

Abiraterone acetate will be administered at a dose of 1000 mg (two 500 mg tablets or four 250 mg tablets) PO QD. Participants taking abiraterone acetate must also take prednisone or prednisolone (one 5 mg tablet PO BID).

Abiraterone acetate will be taken at approximately the same time each day on a continuous daily dosing schedule and must be taken on an empty stomach. No food should be consumed for at least 1 hour after the dose of abiraterone acetate. The tablets should be swallowed whole with water and not crushed or chewed.

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 its SOP. If doses are missed or vomited, this must be indicated in the source documents and CRFs.

Detailed information regarding the dose regimen/modification is in the approved labeling for abiraterone acetate.

8.1.8.1.4 Enzalutamide

Enzalutamide will be administered at a dose of 160 mg (four 40 mg capsules/tablets or two 80 mg tablets PO QD).

Enzalutamide will be taken at approximately the same time each day on a continuous daily dosing schedule and 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 its SOP. If doses are missed or vomited, this must be indicated in the source documents and CRFs.

Detailed information regarding the dose regimen/modification is in the approved labeling for enzalutamide.

8.1.9 Discontinuation and Withdrawal

Participants who discontinue study intervention prior to completion of the study intervention 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 end of treatment 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 and Section 8.12.4.

8.1.9.1 Withdrawal From Future Biomedical Research

Participants may withdraw their consent for future biomedical research. Participants may withdraw consent at any time by contacting the principal investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com). Subsequently, the participant's consent for future biomedical research will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the participant of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main study records) or the specimens have been completely anonymized, there will no longer be a link between the participant’s personal information and their specimens. In this situation, the request for specimen withdrawal cannot be processed.

8.1.10 Participant Blinding/Unblinding

Not applicable

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.

8.2 Efficacy Assessments

8.2.1 Tumor Imaging and Assessment of Disease

As of Amendment 06: Central tumor response assessments will be discontinued. Imaging scans will no longer be submitted to iCRO nor read by BICR. The subsections below are retained for reference.

However, for participants who are still on study treatment and deriving clinical benefit and will continue on study intervention or SOC treatment until criteria for discontinuation are met, local tumor imaging should continue per SOC schedule.

The process for image collection and transmission to the central imaging vendor is given in the Site Imaging Manual.

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

- Bone scans (eg, 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, etc) cannot be a substitute for the bone scan.

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

  Note: For the purposes of assessing tumor imaging, the term “investigator” refers to the local investigator at the site and/or the radiologic 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 participants from the

sites will be submitted to the iCRO. In addition, images (including via other modalities) obtained at an unscheduled time point to determine disease progression, as well as imaging obtained for other reasons, but which demonstrates radiologic progression, should be submitted to the iCRO.

On 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 e-mail 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
  - 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 must be signed

  Note: the reconsent may be signed any time after investigator-assessed progression is identified but must be signed before 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.

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 (e.g., discontinuation of study intervention) will be PCWG-modified RECIST 1.1. PCWG PDu is not considered radiographic PD.

Assessment of treatment response in soft tissue will be according to the 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
Abbreviations: 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; SD=stable disease.		

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

8.2.1.1 Initial Tumor Imaging

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

Scans performed as part of routine clinical management are acceptable as screening scans if they are of diagnostic quality and performed within 28 days before the date of randomization. Scans are required to be sent to the iCRO before enrollment; however, central imaging assessment is not required before enrollment.

At screening, all soft tissue lesions seen with CT (or MRI) and all bone lesions seen with radionuclide bone scanning will be documented. In determining response to study intervention 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 continue receiving study intervention beyond Week 54 will have imaging performed every 12 weeks (84 days ± 7 days). All supplemental imaging must be submitted to the iCRO.

Timing of imaging should follow calendar days from the 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 radiologic evidence of progression is initially observed.

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 before the date of discontinuation, 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 with the same schedule used while on treatment (every 9 weeks in Year 1 or every 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.

Scans are to be continued until one of the following conditions are met:

- disease progression as defined by PCWG-modified RECIST 1.1 verified by BICR
- the start of a new anticancer treatment
- death
- withdrawal of consent
- the end of the study

8.2.1.4 Second Course (Retreatment) Tumor Imaging

NOTE: As of Amendment 06, the study will be stopped due to futility and second course treatment is not an option for participants. There are currently no participants in the Second Course Phase.

Tumor imaging must be performed within 28 days before restarting treatment with pembrolizumab. Local reading (investigator assessment with site radiology reading) will be used to determine eligibility.

Response assessments and progressive disease are determined by investigator assessment.

The only Second Course scan to be provided to the iCRO is the baseline scan if it is the final scan for the Initial Treatment or First Course.

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 before the date of discontinuation, 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 the start of a new anticancer treatment, disease progression, death, or the end of the study, whichever occurs first.

8.2.2 Prostate-specific Antigen Assessments

Two components are required for defining trial eligibility in terms of PSA: 1) rising PSA as determined by the local laboratory and 2) PSA ≥1 ng/mL as determined by the central laboratory. PSA determination by the central laboratory must be performed within 10 days before randomization (Section 1.3.1). If this central laboratory result for PSA is not expected to be available to the site before randomization, the investigator may also perform the test locally, and, if PSA is ≥1 ng/mL, may use that result to determine eligibility. However, a sample must still be collected within 10 days before randomization for submission to the central laboratory. During the remainder of the study, the local laboratory may not be used in lieu of central laboratory results.

For defining rising PSA, the reference value to use (#1) is the last PSA value 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 value compared with a prior single increased PSA value. If a PSA value during screening is used as the second data point to confirm rising PSA and does not confirm the PSA rise but is still greater than the reference point, PSA determination should be repeated by the local laboratory in 1 week to prove that there is a sequence of rising PSA values.

If there are 2 consecutive rising PSA values before screening but the local laboratory value 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 PSA values is needed to ensure that PSA is rising.

8.2.3 Tumor Tissue Collection

Baseline tumor tissue for biomarker analysis must be sent to the testing laboratory and analyzed for adequacy before enrollment. Details of tumor tissue submission are in the Procedures Manual.

8.2.4 PROs and Quality of Life Assessments

As of Amendment 06: PROs and Quality of Life assessments will be discontinued. The subsections below are retained for reference.

The FACT-P, EuroQoL EQ-5D-5L, and BPI-SF questionnaires and the Analgesic Log should be administered per the SoA in Section 1.3.1. Both the FACT-P and the EQ-5D-5L will be administered at the site, while the BPI-SF and Analgesic Log will be completed by the participant at home. It is best practice and strongly recommended that electronic patient-reported outcomes (ePROs) are administered to randomized participants before study intervention administration, AE evaluation, and disease status notification. If the participant does not complete the ePROs at a scheduled time point, the MISS_MODE form must be completed to capture the reason that the assessment was not performed. Site staff must not read, administer, or complete the PRO questionnaires for the participant. If the participant is unable to read the questionnaire (eg, is blind or illiterate), that participant may still participate in the study, but is exempted from completing PRO questionnaires, including the Analgesic Log. Participants exempted in this regard should be flagged appropriately by the site staff.

8.2.4.1 Functional Assessment of Cancer Therapy-Prostate (FACT-P)

FACT-P was developed as a disease-specific adjunct to the FACT measurement system, and consists of FACT-G (general), which is a 27-item self-report questionnaire measuring general HRQoL in 4 domains (physical, social, emotional, and functional well-being), and 12 prostate cancer-specific items. FACT-P (version 4) is self–administered and requires approximately 8 to 10 minutes to complete.

8.2.4.2 EQ-5D-5L

The 5 health state dimensions in the EQ-5D-5L include mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is rated on a 5-point scale from 1 (no problem) to 5 (unable to/extreme problems). The EQ-5D-5L also includes a graded (0 to 100) vertical visual analog scale on which the participant rates his general state of health at the time of the assessment.

8.2.4.3 Brief Pain Inventory-Short Form (BPI-SF) and Analgesic Log

BPI-SF

The BPI-SF is provided on an ePRO device and will be completed by the participant daily for 7 consecutive days at the time points specified in the SoA (Section 1.3.1). It does not have to be completed at the site.

The BPI-SF has 15 items that are rated on a 0 to 10 numeric rating scale, with 0=No Pain and 10=Worst Pain Imaginable. This instrument consists of 2 domains, pain severity and pain interference. The pain severity domain includes 4 items (Items 3, 4, 5, and 6), which assess pain at its "worst," "least," "average," and "now" (current pain) respectively on an 11-point scale. In this study, the "worst pain" (Item 3) will be used as a single item in assessing pain progression. A composite pain severity score from all 4 items will also be evaluated as "pain severity progression". A ≥2-point change in the average pain severity or in "worst pain" item is considered clinically meaningful.

The pain interference domain score is a mean of 7 items: general activity (Item 9A), mood (Item 9B), walking ability (Item 9C), normal work (Item 9D), relations with other people (Item 9E), sleep (Item 9F), and enjoyment of life (Item 9G), each scored on an 11-point scale from 0 (does not interfere) to 10 (completely interferes). Based on the BPI-SF scoring manual [Cleeland, C. S. 2009], the following items are not used in scoring pain severity or pain interference domains: Items 1, 2, 7, and 8. Item 7 (a free text field) describing pain medication use is captured separately in more detail, using the Analgesic Log.

Analgesic Log

The Analgesic Log is a paper form that will be completed by the participant daily for 7 consecutive days per the SoA (Section 1.3.1). Participants will record all analgesic medication dosages and dose times. The Analgesic Log is study-specific (not generic). All medications captured in the paper log will be reconciled at every visit with the concomitant medications data to address any discrepancies.

8.3 Safety Assessments

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 examination during the Screening period. Clinically significant abnormal findings should be recorded as medical history. The time points for full physical examinations are given in Section 1.3.1. 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

In cycles that do not required a full physical examination as defined in Section 1.3.1, the investigator or qualified designee will perform a directed physical examination as clinically indicated before study intervention administration. New, clinically significant abnormal findings should be recorded as Aes.

8.3.2 Vital Signs

- Vital signs will be measured with the participant in a sitting, semirecumbent, or supine position after 5 minutes of rest, and will include temperature, systolic and diastolic BP, heart rate, and respiratory rate. Record vital signs before study intervention administration at treatment visits.

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 assessments to be performed in this study are provided below. The total amount of blood to be drawn over the course of the study (from prestudy to poststudy visits), including approximate blood volumes drawn by visit and by sample type per participant, are in the Study Procedures Manual. Refer to 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 Performance Scale

The investigator or qualified designee will assess ECOG performance status (Appendix 11) at screening (within 7 days of randomization) and before dosing during the study intervention period as specified in the SoA (Section 1.3.1).

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.

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 consent form is signed 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 cause 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 120 days following cessation of study intervention, or 30 days following cessation of study intervention if the participant initiates new anticancer therapy must be reported by the investigator.

- For Pharmacovigilance purposes and characterization, any SAE of MDS/AML or new primary malignancy occurring after the 30 day follow up period should be reported to the Sponsor regardless of investigator's assessment of causality or knowledge of the treatment arm. Investigators will be asked during the regular follow up for OS if the participant has developed MDS/AML or a new primary malignancy and prompted to report any such cases.

- 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 11.

Table 11 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 (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, nonleading verbal questioning of the participant is the preferred method of inquiring 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 on 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:

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

2. 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).

3. Any event of MDS/AML, new primary malignancy, or pneumonitis should be reported whether it is considered a non-serious AE (eg non-melanoma skin cancer) or SAE and regardless of investigator's assessment of causality.

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.

Olaparib must only be used in accordance with the dosing recommendations in this protocol. Any dose or frequency of dosing that exceeds the dosing regimen specified in this protocol should be reported as an overdose.

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

Abiraterone acetate must only be used in accordance with the dosing recommendations in this protocol. Any dose or frequency of dosing that exceeds the dosing regimen specified in this protocol should be reported as an overdose.

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

An overdose of enzalutamide 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 intervention should be stopped and general supportive measures initiated, taking into consideration the half-life of 5.8 days for enzalutamide. Participants may be at an increased risk of seizures after 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 intervention overdose.

8.6 Pharmacokinetics

Not applicable

8.7 Pharmacodynamics

Not applicable

8.8 Future Biomedical Research Sample Collection

The following specimens are to be obtained as part of FBR:

- Leftover DNA
- Leftover tumor
- Leftover RNA
- Leftover plasma and serum from biomarker analyses
- Leftover plasma or derivative for ctDNA

8.9 Planned Genetic Analysis Sample Collection

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 the local IRB/IEC does not approve) sample collection for these purposes, then such samples should not be collected at the corresponding sites. Leftover DNA extracted from planned genetic analysis samples will be stored for FBR only if the participant signs the FBR consent.

Sample collection, storage, and shipment instructions for planned genetic analysis samples will be provided in the Procedures Manual.

8.10 Biomarkers

As of Amendment 06: Biomarker sample collections will be discontinued. The section below is retained for reference.

To identify novel biomarkers, the following biospecimens to support exploratory analyses of cellular components (e.g., protein, RNA, DNA, and metabolites) and other circulating molecules will be collected from all participants as specified in the SoA (Section 1.3):

- Newly obtained tumor tissue
- Blood for genetic analysis
- Blood for RNA analyses
- Blood for serum and plasma biomarker analyses
- Blood for ctDNA analysis

Sample collection, storage, and shipment instructions for the exploratory biomarker specimens will be provided in the Procedures Manual.

8.11 Medical Resource Utilization and Health Economics

As of Amendment 06: Medical Resource Utilization and Health Economics data collection will be discontinued. The section below is retained for reference.

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.

The data collected may be used to conduct exploratory economic analyses and will include:

- All-cause hospitalizations and emergency room visits from the time of treatment randomization through 90 days after cessation of study treatment or 30 days after cessation of study treatment, if the participant initiates new anticancer therapy, whichever is earlier.

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

Written consent must be obtained before performing any protocol-specific procedure. Results of a test performed before the participant's 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 before the date of randomization except for the following:

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

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

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

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

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 are met. Participants who are rescreened will retain their original screening number.

8.12.2 Treatment Period

Visit requirements are outlined in the SoA (Section 1.3). Specific procedure-related details are provided in Section 8.

8.12.3 Discontinuation Visit

The Discontinuation Visit should occur at the time when 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 the SoA (Section 1.3). Specific procedure-related details are provided in Section 8. Before discontinuing participants from study intervention submit the Treatment Termination and Disease Assessment Termination Form.

8.12.4 Discontinued Participants Continuing to be Monitored in the Study

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

8.12.5 Posttreatment Visits

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 comes first.

Participants who are eligible for retreatment with pembrolizumab may have up to 2 Safety Follow-up Visits, 1 after the initial treatment period and 1 after Second Course treatment.

8.12.5.2 Efficacy Follow-up Visits

As of Amendment 06: Efficacy Follow-up Visits will be discontinued. The section below is retained for reference.

Participants who complete the protocol-required cycles of study intervention or who discontinue study intervention for a reason other than BICR-verified radiographic PD will move into the Efficacy Follow-up Phase. Follow-up visits will be scheduled every 9 weeks (63 days ± 7 days) through Week 54 and every 12 weeks (84 days ± 7 days) thereafter, from the date of randomization, to coincide with the imaging schedule at the time of discontinuation from study intervention. Participants who discontinue study intervention without documented confirmed disease progression should continue monitoring of disease status by radiologic imaging (CT/MRI and bone scans) and PSA determinations according to the imaging schedule 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, or the end of the study, or if the participant begins retreatment with pembrolizumab as detailed in Section 6.6.7. Information regarding poststudy anticancer treatment will be collected if new treatment is initiated. Participants who completed all efficacy assessments and/or will not have further efficacy assessments must enter the Survival Follow-up Phase.

Participants who are eligible to receive retreatment with pembrolizumab according to the criteria in Section 6.6.7 will move from the Efficacy Follow-up Phase to the Second Course phase when they experience disease progression. Details are provided in the SoA (Section 1.3.2) for retreatment with pembrolizumab.

8.12.5.3 Survival Follow-up Contacts

As of Amendment 06: Survival Follow-up visits will be discontinued. Those participants remaining on study treatment at the time of Amendment 06, should continue to be monitored in the study through the AE reporting period (Section 8.4). The section below is retained for reference.

Participants who experience confirmed disease progression or start a new anticancer therapy, will move into the Survival Follow-up Phase and should be contacted approximately every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the

study, whichever occurs first. Investigators will be asked during the regular follow-up for OS if the participant has developed MDS/AML or a new primary malignancy and prompted to report any such cases.

The first survival follow-up assessment should be scheduled as described below:

- For participants who discontinue treatment intervention and who will not enter the Efficacy Follow-up Phase, the first survival follow-up assessment will be scheduled 12 weeks after the Discontinuation Visit and/or Safety Follow-up Visit (whichever is last).

- For participants who completed assessments in the Efficacy Follow-up Phase, the first survival follow-up assessment will be scheduled 12 weeks after the last efficacy assessment follow-up visit has been performed.

8.12.6 Survival Status

To ensure that current and complete survival data are available at the time of database locks, updated survival status may be requested during the study by the Sponsor. For example, updated survival status may be requested before but not limited to an eDMC review, interim, and/or final analysis. On Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor-defined period will be contacted for their survival status (excluding participants with a previously recorded death event in the collection tool).

9 STATISTICAL ANALYSIS PLAN

As of Amendment 06: The Statistical Analysis Plan is amended as follows.

NOTE: Based on the data from an interim safety and efficacy for KEYLYNK-010 (data cutoff 18-JAN-2022), eDMC recommended stopping the study for futility because it was extremely unlikely that the efficacy boundary for study success would be reached at the next (final) analysis. In addition, the eDMC indicated that continuing the trial raised the risk of undue toxicities (Grade 3 to 5 AEs and drug-related SAEs) to patients receiving investigational therapy which were greater in the investigational arm compared to control. Based upon these data and the recommendation of the eDMC, the study was unblinded (as of 11-MAR-2022). The prespecified final analysis of the study described in the SAP will not be performed. Selected analyses of safety endpoints will be performed at the end of the study; there will be no further analyses of efficacy and PRO endpoints.

This section outlines the statistical analysis strategy and procedures for the study. The study has been unblinded (as of 11-MAR-2022). Changes made to primary and/or key secondary hypotheses or the statistical methods related to those hypotheses that occurred prior to Amendment 06 were documented in previous protocol amendments(s) (consistent with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Guideline [ICH] E9). Changes to exploratory or other nonconfirmatory analyses made after the protocol has been finalized, but before the final database lock, will be

documented in a supplemental Statistical Analysis Plan (sSAP) and referenced in the clinical study report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR. Other planned analyses (ie, those specific to the analysis of PROs and FBR) are beyond the scope of this document or will be documented in separate analysis plans.

9.1 Statistical Analysis Plan Summary

Key elements of the SAP are summarized here. The comprehensive plan is provided in Sections 9.2 through 9.12. As of Amendment 06, the prespecified final analysis of the study described in the SAP will not be performed. Selected analyses of safety endpoints will be performed at the end of the study; there will be no further analyses of efficacy and PRO endpoints. The SAP summary has been updated accordingly.

Study Design Overview	A Phase 3 Randomized Open-label Study of Pembrolizumab (MK-3475) Plus Olaparib versus Abiraterone Acetate or Enzalutamide in Participants with Metastatic Castration-resistant Prostate Cancer (mCRPC) Who are Unselected for Homologous Recombination Repair Defects and Have Failed Prior Treatment with One Next-generation Hormonal Agent (NHA) and Chemotherapy (KEYLYNK-010)
Treatment Assignment	Approximately 780 eligible participants will be randomized in a 2:1 ratio to one of the following 2 study intervention arms: • Arm 1: pembrolizumab plus olaparib • Arm 2: abiraterone acetate or enzalutamide Randomization stratification factors are: • Measurable disease at baseline: yes versus no • Prior NHA treatment: abiraterone acetate versus enzalutamide As of Amendment 06, all ongoing participants may have the option to continue receiving study intervention or SOC, until criteria for discontinuation are met, if they are deriving clinical benefit.
Analysis Populations	Efficacy: Intent to Treat (ITT) Safety: All Participant as Treated (APaT)
Primary Endpoints	1. Overall survival (OS) 2. Radiographic progression-free survival (rPFS)
Key Secondary Endpoint	Time to initiation of the first subsequent anticancer therapy or death (TFST)
Statistical Methods for Key Efficacy Analyses	The primary hypotheses will be evaluated by comparing pembrolizumab plus olaparib to abiraterone acetate or enzalutamide with respect to rPFS, TFST, and OS using a stratified log-rank test. The hazard ratio will be estimated using a stratified Cox regression model. Event rates over time will be estimated within each study intervention 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 in this study. Tier 2 parameters will be assessed via point estimates with 95% CIs provided for between-group comparison; only point estimates by study intervention group are provided for Tier 3 safety parameters. The 95% CIs for the between-treatment differences in percentages will be provided using the Miettinen and Nurminen method.

Interim Analyses	As of Amendment 06, the prespecified final analysis of the study described in the SAP will not be performed. Two IAs will be performed in this study. Results will be reviewed by an eDMC. These IAs are summarized below. Details are provided in Section 9.7. • IA1: o Timing: To be performed when at least 360 rPFS events and at least 241 OS events (target number of OS events) are observed (approximately 17 months after the first participant is randomized). If rPFS event number achieves but OS event number does not achieve, IA1 may be delayed for up to 3 months as long as the enrollment is complete. o Testing: primary analysis for rPFS, primary analysis for TFST, and IA for OS. • IA2: o Timing: To be performed when at least 386 OS events (target number of OS events) are observed (approximately 23 months after the first participant is randomized). IA2 should be conducted at least 6 months after the last participant is randomized. o Testing: IA for OS.
Multiplicity	The Type I error rate over the multiple endpoints tested, as well as for the multiple analyses planned, will be strongly controlled at 2.5% (one-sided) by sequential interim monitoring and the methods of Maurer and Bretz [Maurer, W. 2013]. A total of 2.0% Type I error rate is initially allocated to test OS superiority between 2 arms, and a total of 0.5% Type I error rate is initially allocated to test rPFS superiority between 2 arms.
Sample Size and Power	As of Amendment 06, no final analysis of the study will be performed. The planned sample size is approximately 780 participants, with approximately 520 and 260 in the pembrolizumab and olaparib and abiraterone/enzalutamide arms, respectively. For rPFS, with 432 rPFS events, the study has approximately 95% power to demonstrate that pembrolizumab + olaparib is superior to abiraterone/enzalutamide (HR: 0.65) at an overall 1-sided 0.5% α level. For OS, with 482 OS events, the study has about 90% power to demonstrate that pembrolizumab and olaparib is superior to abiraterone/enzalutamide (HR: 0.725) at an initial overall 1-sided 2.0% α level.

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.

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.

This study will be conducted as an unblinded, open-label study (ie, participants, investigators, and Sponsor personnel will be aware of participant treatment assignments after each participant is enrolled and treatment is assigned). Although the study is open-label,

analyses or summaries generated by randomized treatment assignment or actual treatment received will be limited and documented.

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 (rPFS) (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.

9.4.1.3 Secondary

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 (DOR) (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 to the earliest date of disease progression or death from any cause, whichever comes 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 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 initiation of first skeletal-related event is defined as the time from randomization to the first symptomatic skeletal-related event, defined as:

- 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
- tumor-related orthopedic surgical intervention whichever comes 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

Time to radiographic bone progression (PCWG-modified RECIST 1.1 by BICR) is defined as the time from randomization to radiographic bone progression.

Additional details of the efficacy measurements are described in Section 4.2.1.1.

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 AEs, laboratory values, and vital signs.

9.4.3 PRO Endpoints

9.4.3.1 Time to Pain Progression

TTPP is defined as the time from randomization to pain progression based on the BPI-SF Item 3 “worst pain in 24 hours” and opiate analgesic use (AQA score). Pain progression is defined as follows: 1) for participants who are asymptomatic at baseline, a ≥2-point change from baseline in the average (4-7 days) BPI-SF Item 3 score OR initiation of opioid use for pain; 2) for participants who are symptomatic at baseline (average BPI-SF Item 3 score >0 and/or currently taking opioids), a ≥2-point change from baseline in the average BPI-SF Item 3 score and an average worst pain score ≥4 and no decrease in average opioid use (≥1-point decrease in AQA score from a starting value of 2 or higher) OR any increase in opioid use (eg, 1-point change in AQA score) at 2 consecutive follow-up visits. Any participant who has more than 2 consecutive visits that are not evaluable for pain progression will be censored at the last evaluable assessment.

Details of exploratory PRO endpoints will be included in the sSAP.

9.5 Analysis Populations

9.5.1 Efficacy Analysis Populations

The ITT population will serve as the primary population for the analysis of efficacy data in this study. All randomized participants will be included in this population. Participants will be included in the treatment group to which they were randomized for the analysis of efficacy data using the ITT population.

9.5.2 Safety Analysis Populations

Safety analyses will be conducted in the APaT population, which consists of all randomized participants who received at least 1 dose of study intervention. Participants will be included in the study intervention group corresponding to the study intervention they actually received for the analysis of safety data using the APaT population. This will be the study intervention group to which they were randomized except for participants who take incorrect study intervention for the entire treatment period; such participants will be included in the study intervention group corresponding to the study intervention actually received.

At least 1 laboratory, vital sign, or ECG measurement obtained after at least 1 dose of study intervention is required for inclusion in the analysis of the respective safety parameter. To assess change from baseline, a baseline measurement is also required.

Details of the approach to handling safety analyses are provided in Section 9.6.2.

9.5.3 PRO Analysis Population

The PRO analyses are based on the PRO full analysis set (FAS) population, defined as participants who have at least 1 PRO assessment available and have received at least 1 dose of study intervention.

9.6 Statistical Methods

NOTE: As of Amendment 06, the prespecified final analysis of the study described in the SAP will not be performed. Selected analyses of safety endpoints will be performed at end of study; there will be no further analyses of efficacy and PRO endpoints. The subsections below are retained for reference.

Statistical testing and inference for safety analyses are described in Section 9.6.2. Methods related to exploratory objectives will be described in the sSAP. 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. 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 α=0.05 (2-sided) level. If 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 before 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. Methods related to other objectives will be described in the sSAP.

9.6.1.1 OS

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, HR). 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. The restricted mean survival time (RMST) method proposed by Uno et al [Uno, H., et al 2014] may be used for OS to account for the possible nonproportional hazards effect.

9.6.1.2 rPFS

The nonparametric Kaplan-Meier method will be used to estimate the rPFS curve in each study intervention 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, HR) between the study intervention arms. The HR 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 (Section 6.3.2) will be applied to both the stratified log-rank test and the stratified Cox model.

Since disease progression is assessed periodically, PD can occur any time between the last assessment where PD was not documented and the assessment when PD is documented. The true date of disease progression will be approximated by the date of the first assessment at which PD is objectively documented per PCWG-modified RECIST 1.1 by BICR. Death is always considered as a confirmed PD event. Participants who do not experience an rPFS event will be censored at the last disease assessment. Sensitivity analyses will be performed for comparison of rPFS based on the investigator's assessment.

To evaluate the robustness of the rPFS endpoint, 1 primary and 2 sensitivity analyses with a different set of censoring rules will be performed. For the primary analysis, if the events (PD or death) are immediately after more than 1 missed disease assessment, the data are censored at the last disease assessment before missing visits. In addition, data after new anticancer

therapy are censored at the last disease assessment before the initiation of new anticancer therapy.

The first sensitivity analysis follows the ITT principle; PDs/deaths are counted as events regardless of missed study visits or initiation of new anticancer therapy. The second sensitivity analysis considers discontinuation of study intervention or initiation of an anticancer treatment after discontinuation of study intervention due to reasons other than CR, whichever occurs later, to be a PD event for participants without documented PD or death. If a participant meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied. The censoring rules for primary and sensitivity analyses are summarized in Table 12.

Table 12 Censoring Rules for Primary and Sensitivity Analyses of rPFS

Situation	**Primary Analysis**	**Sensitivity Analysis 1**	**Sensitivity Analysis 2**
PD or death documented after ≤1 missed disease assessment, and before new anticancer therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death	Progressed at date of documented PD or death
Death or progression after ≥ 2 consecutively missed disease assessments without further valid non-PD disease assessments, or after new anticancer therapy	Censored at last disease assessment before the earlier date of ≥2 consecutive missed disease assessment and new anticancer therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death
No PD and no death; and new anticancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment	Progressed at treatment discontinuation due to reasons other than CR; otherwise censored at last disease assessment if still on study treatment or completed study treatment.
No PD and no death; new anticancer treatment is initiated	Censored at last disease assessment before new anticancer treatment	Censored at last disease assessment	Progressed at date of new anticancer treatment
Abbreviations: PD=progressive disease; rPFS=radiographic progression-free survival.			

In case the proportional hazards assumption is not valid, supportive analyses using the RMST method may be conducted for rPFS to account for the possible nonproportional hazards effect.

Further details of sensitivity analyses will be described in the sSAP as needed.

9.6.1.3 TFST

The nonparametric Kaplan-Meier method will be used to estimate the TFST curve in each treatment arm. 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, HR) between the treatment arms. The HR 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 (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 13 summarizes the primary analysis approach for key efficacy endpoints.

Table 13 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 12
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

Abbreviations: BICR=blinded independent central review; ITT=intention to treat; TFST=time to initiation of the first subsequent anticancer therapy or death; OS=overall survival; PCWG=Prostate Cancer Working Group; rPFS=radiographic progression-free survival.

[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 before the analysis.

The strategy to address multiplicity issues regarding multiple efficacy endpoints and IAs is described in Sections 9.7 and 9.8.

9.6.2 Statistical Methods for Safety Analyses

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

The analysis of safety results will follow a tiered approach (Table 14). 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 the 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 participant to inferential testing for statistical significance.

AEs of special interest 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. 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% CIs provided for differences in the proportion of participants with events using the Miettinen and Nurminen method, an unconditional, asymptotic method [Miettinen, O. 1985].

Membership in Tier 2 requires that at least 10% of participants in any study intervention group show the event; all other AEs and predefined limits of change will belong to Tier 3. The threshold of at least 10% of participants was chosen for Tier 2 events because the population enrolled in this study are in critical condition and usually experience various AEs of similar types regardless of treatment; events reported less frequently than 10% of participants would obscure assessment of the overall safety profile and add little to the interpretation of potentially meaningful treatment differences. In addition, Grade 3 to 5 AEs (≥5% of participants in 1 of the treatment groups) and SAEs (≥5% of participants in 1 of the treatment groups) will be considered Tier 2 endpoints. 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.

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 study intervention group in table format.

Table 14 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	Any AE (≥10% of participants in one of the treatment groups)	X	X
	Any Grade 3 to 5 AE (≥5% of participants in one of the treatment groups)	X	X
	Any serious AE (≥5% of participants in one of the treatment groups)	X	X
Tier 3	Any AE		X
	Change from baseline results (laboratory test toxicity grade, vital signs, ECGs)		X
Abbreviations: AE=adverse event; CI=confidence interval; ECG=electrocardiogram; X=results will be provided.			

9.6.3 Analysis Methods for PRO Endpoints

For TTPP, the Kaplan-Meier method will be used to estimate the survival curves for TTPP, separately, in each study intervention arm. In addition, corresponding survival curves will be estimated by study intervention arm. Stratified Cox proportional hazards models with Efron's method of tie handling will be used to assess the magnitude of the treatment difference. Stratification factors used for randomization will be used in the stratified Cox proportional hazards models. The HR, 95% CI, and nominal p-value will be reported.

Details of additional PRO analyses will be included in the sSAP.

9.6.4 Demographic and Baseline Characteristics

The comparability of the study intervention groups for each relevant demographic and baseline characteristic will be assessed using 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 study intervention either by descriptive statistics or categorical tables.

9.7 Interim Analyses

NOTE: As of Amendment 06, the prespecified final analysis of the study described in the SAP will not be performed. This section is retained for reference.

An eDMC will serve as the primary reviewer of the results of the IAs and will make recommendations for discontinuation of the study or protocol modifications to an Executive Oversight Committee (EOC) of the Sponsor. Depending on the recommendation of the eDMC, the Sponsor may prepare a regulatory submission. Additional logistic details, revisions to the above plan, and data monitoring guidance will be provided in the eDMC Charter.

9.7.1 Efficacy Interim Analyses

Two IAs and a final analysis are planned for this study. There is no plan to stop the study before superiority hypotheses for OS have been adequately evaluated. However, earlier positive findings may form the basis for earlier regulatory submission based on the recommendation of the eDMC. The final analysis is to be performed approximately 29 months after the first participant is randomized.

The analyses planned, endpoints evaluated, and drivers of the timing are summarized in Table 15. Type I error control for the efficacy analyses, as well as efficacy bounds, are described in Section 9.8.

Table 15 Summary of Interim and Final Analyses

Analysis	Endpoint(s)	Criteria for Conduct of Analysis	Estimated Time After First Participant Randomized	Primary Purpose of Analysis
IA 1: final rPFS and TFST analyses; interim OS analysis	rPFS, TFST, OS	• Enrollment is complete • At least 360 rPFS events • At least 241 OS events (target number of OS events) • If rPFS event number achieves but OS event number does not achieve, IA1 may be delayed for up to 3 months.	~17 months	• rPFS final analysis • TFST final analysis • OS IA
IA 2: interim OS analysis	OS	• At least 386 OS events (target number of OS events) • At least 6 months after the last participant is randomized.	~23 months	• OS IA
Final analysis: final OS analysis	OS	• At least 482 OS events (target number of OS events) • At least 12 months after the last participant is randomized.	~29 months	• OS final analysis
Abbreviations: IA=interim analysis; OS=overall survival; rPFS=radiographic progression-free survival; TFST=time to initiation of the first subsequent anticancer therapy or death.				

9.7.2 Safety Interim Analyses

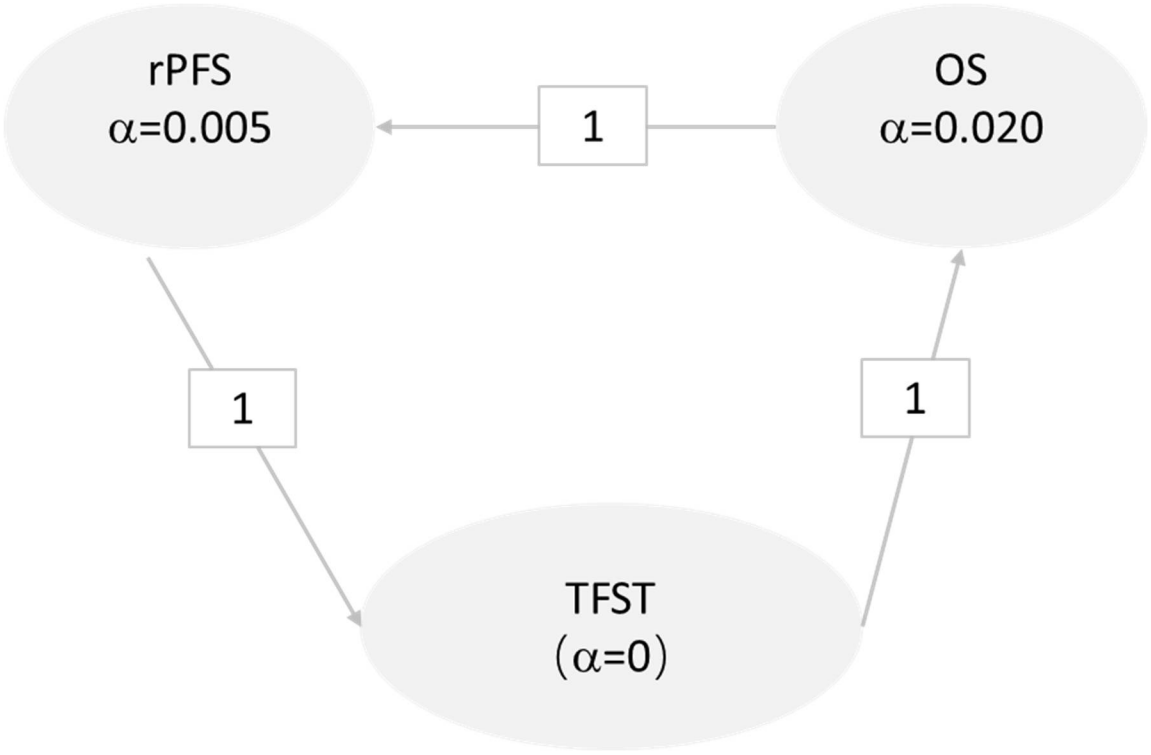
The eDMC conducted regular safety IAs. The timing of these safety IAs was specified in the eDMC charter. No further analysis is warranted.

9.8 Multiplicity

NOTE: As of Amendment 06, the prespecified final analysis of the study described in the SAP will not be performed. This section is retained for reference.

The study uses the graphical method of Maurer and Bretz [Maurer, W. 2013] to strongly control multiplicity for multiple hypotheses as well as IAs. Figure 3 shows the initial one-sided α allocation for each hypothesis in the ellipse representing the hypothesis. The weights for reallocation from each hypothesis to the others are represented in the boxes on the lines connecting the hypotheses.

Figure 3 Multiplicity Graph for One-sided Alpha Reallocation Strategy



9.8.1 rPFS

This study initially allocates 1-sided α=0.005 for superiority testing of rPFS between 2 study intervention arms. If the OS null hypothesis has been rejected, the rPFS hypothesis will be tested at a Type I error level of α=0.025.

Table 16 shows the boundary properties for rPFS. Note that the final row indicates the total power to reject the null hypothesis for rPFS superiority. In addition, if testing of rPFS is not positive at IA1 but testing of OS is positive at IA2 or final analysis, then rPFS at IA1 will be retested.

Table 16 Efficacy Boundaries and Properties for rPFS

Analysis	Value	α=0.005	α=0.025
IA1: N: 780 Events: 432[a] Month: 16.7	Z	2.576	1.96
	p (1-sided)[c]	0.005	0.025
	HR at bound[d]	0.769	0.819
	P(Cross) if HR=1[e]	0.005	0.025
	P(Cross) if HR=0.65[f]	95%	98.8%
IA1: N: 780 Events: 360[b] (Required rPFS events)	Z	2.576	1.96
	p (1-sided)[c]	0.005	0.025
	HR at bound[d]	0.75	0.803
	P(Cross) if HR=1[e]	0.005	0.025
	P(Cross) if HR=0.65[f]	90%	97.1%

Abbreviations: HR=hazard ratio; IA=interim analysis; rPFS=radiographic progression-free survival.
[a]Projected rPFS events
[b]Required rPFS events
[c]p (1-sided) is the nominal α for testing.
[d]HR at bound is the approximate HR required to reach an efficacy bound.
[e]P(Cross if HR=1) is the cumulative probability of crossing a bound under the null hypothesis.
[f]P(Cross if HR=0.725) is the cumulative probability of crossing a bound under the alternative hypothesis.

9.8.2 OS

This study initially allocates 1-sided α=0.020 for superiority testing of OS between the 2 treatment arms. If both the rPFS and TFST null hypotheses have been rejected, then the OS hypothesis will be tested at a Type I error level of α=0.025.

Table 17 shows the boundary properties for the IAs and the final OS analysis, which were derived using a Lan-DeMets O'Brien-Fleming approximation spending function. Note that the final row indicates the total power to reject the null hypothesis for OS superiority. If the actual number of OS events differs from that specified in Table 17, the bounds will be adjusted using the Lan-DeMets O'Brien-Fleming α spending function accordingly. The cumulative α spent in the IA will not exceed the prespecified level based on the projected number of events as shown in Table 17 (ie, if the number of events exceeds the prespecified event number in the IA, the prespecified cumulative α spent in the IA based on the projected number of events will be used). Otherwise, cumulative α based on the observed number of events will be used. The boundary thresholds at final analysis will be updated using the actual observed number of events at previous IAs and final analysis.

Table 17 Efficacy Boundaries and Properties for Overall Survival Analyses

Analysis	Value	α=0.020	α=0.025
IA1: 50% N: 780 Events: 241 Month: 16.7	Z	3.0896	2.9626
	p (1-sided)[a]	0.0010	0.0015
	HR at bound[b]	0.6554	0.6667
	P(Cross) if HR=1[c]	0.0010	0.0015
	P(Cross) if HR=0.725[d]	0.2393	0.2804
IA2: 80% N: 780 Events: 386 Month: 22.7	Z	2.3668	2.2662
	p (1-sided)[a]	0.0090	0.0117
	HR at bound[b]	0.7743	0.7826
	P(Cross) if HR=1[c]	0.0093	0.0122
	P(Cross) if HR=0.725[d]	0.7423	0.7740
Final analysis N: 780 Events: 482 Month: 28.3	Z	2.1160	2.0277
	p (1-sided)[a]	0.0172	0.0213
	HR at bound[b]	0.8150	0.8219
	P(Cross) if HR=1[c]	0.0200	0.0250
	P(Cross) if HR=0.725[d]	0.9000	0.9150

Abbreviations: HR=hazard ratio; IA=interim analysis.
*Percentage of expected number of events at final analysis.
[a] p (1-sided) is the nominal α for testing.
[b] HR at bound is the approximate HR required to reach an efficacy bound.
[c] P(Cross if HR=1) is the cumulative probability of crossing a bound under the null hypothesis.
[d] P(Cross if HR=0.725) is the cumulative probability of crossing a bound under the alternative hypothesis.

9.8.3 TFST

The key secondary TFST hypothesis will be tested at the time of IA1. The TFST hypothesis is initially allocated a Type I error α=0% and thus cannot be tested unless the rPFS null hypothesis has been rejected. If the rPFS null hypothesis has been rejected and the OS null hypothesis has not been rejected, then the TFST hypothesis will be tested at a Type I error of 0.5%. If both the rPFS and OS null hypotheses have been rejected, then the TFST hypothesis will be tested at a Type I error level of α=2.5%.

Table 18 shows the boundary properties for TFST. Note that the final row indicates the total power to reject the null hypothesis for TFST superiority. In addition, if testing of TFST is not positive at IA1 but retesting of rPFS at IA1 is positive, then TFST at IA1 will be retested.

Table 18 Efficacy Boundaries and Properties for TFST

Analysis	Value	α=0.005	α=0.025
IA1: N: 780 Events: 432[a] Month: 16.7	Z	2.576	1.96
	p (1-sided)[b]	0.005	0.025
	HR at bound[c]	0.769	0.819
	P(Cross) if HR=1[d]	0.005	0.025
	P(Cross) if HR=0.65[e]	95%	98.8%

Abbreviations: HR=hazard ratio; IA=interim analysis; TFST=time to initiation of the first subsequent anticancer therapy or death.
[a] Projected TFST events.
[b] p (1-sided) is the nominal α for testing.
[c] HR at bound is the approximate HR required to reach an efficacy bound.
[d] P(Cross if HR=1) is the cumulative probability of crossing a bound under the null hypothesis.
[e] P(Cross if HR=0.725) is the cumulative probability of crossing a bound under the alternative hypothesis.

9.8.4 Safety Analyses

The eDMC has responsibility for assessment of overall risk/benefit. When prompted by safety concerns, the eDMC can request corresponding efficacy data. External DMC review of efficacy data to assess the overall risk/benefit to study participants will not require a multiplicity adjustment typically associated with a planned efficacy IA. However, to account for any multiplicity concerns raised by the eDMC review of unplanned efficacy data prompted by safety concerns, a sensitivity analysis for efficacy endpoints adopting a conservative multiplicity adjustment will be prespecified in the sSAP. This analysis will be performed if requested by the eDMC.

9.9 Sample Size and Power Calculations

NOTE: As of Amendment 06, the prespecified 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 primary endpoint OS.

A total of approximately 780 participants will be randomized in a 2:1 ratio to the pembrolizumab and olaparib arm and the abiraterone/enzalutamide arm; approximately 520 and 260 participants, respectively.

The final analysis of OS is event-driven and will be conducted after at least 482 OS events (target number of OS events) have been observed between the 2 treatment arms unless OS is proven at an earlier IA. It is expected to occur around 29 months after the first participant is randomized (depending on enrollment rate and event accumulation rate). The final analysis should be conducted at least 12 months after the last participant is randomized to maintain sufficient minimal follow-up duration.

With 482 OS events, the study has approximately 90% (91.5%) power to demonstrate that men treated with pembrolizumab and olaparib have a longer median OS than do those treated with abiraterone acetate or enzalutamide at a 1-sided significance level of 0.020 (0.025) if the underlying constant HR is 0.725. Sample size and power calculations are based on the following assumptions: 1) an HR of 0.725 where OS follows an exponential distribution with a median of 14.5 months in the pembrolizumab and olaparib arm and a median of 10.5 months in the control arm; 2) IAs for efficacy evaluation as outlined in Section 9.7, 3) an enrollment rate of 60 participants per month with a 6-month ramp-up time; and 4) an approximately monthly dropout rate of 0.2%.

The final analysis of rPFS will be conducted when (1) enrollment is complete, (2) at least 360 rPFS events are observed, and (3) at least 241 OS events (target number of OS events) are observed. If rPFS event number achieves but OS event number does not achieve, IA1 may be delayed for up to 3 months. It is expected to occur around 17 months after the first participant is randomized (depending on enrollment rate and event accumulation rate), with about 432 rPFS events.

With 432 rPFS events, the study has approximately 95% (98%) power to demonstrate that men treated with pembrolizumab + olaparib have a longer median rPFS than do those treated with abiraterone or enzalutamide at a 1-sided significance level of 0.005 (0.025) if the underlying constant HR is 0.65. These calculations are based on the following assumptions: 1) an HR of 0.65 where rPFS follows an exponential distribution with a median of 4.6 months in the pembrolizumab and olaparib arm and a median of 3 months in the control group, 2) IAs for efficacy evaluation as outlined in Section 9.7, 3) an enrollment rate of 60 participants per month with a 6-month ramp-up time; and 4) a monthly dropout rate of 5%.

The final analysis of TFST will be conducted at IA1, and approximately 432 TFST events are expected. With 432 TFST events, the study has approximately 95% (98%) power to demonstrate that men treated with pembrolizumab and olaparib have a longer median TFST than do those treated with abiraterone or enzalutamide at a 1-sided significance level of 0.005 (0.025) if the underlying constant HR is 0.65. These calculations are based on the following assumptions: 1) an HR of 0.65 where TFST follows an exponential distribution with a median of 4.6 months in the pembrolizumab and olaparib arm and a median of 3 months in the control arm, 2) IAs for efficacy evaluation as outlined in Section 9.7, 3) an enrollment rate of 60 participants per month with a 6-month ramp-up time; and 4) a monthly dropout rate of 5%.

The sample size and power calculations for rPFS, TFST, and OS were performed using software R (package “gsDesign”) and EAST 6.4.

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:

- Age group: <65 years versus ≥65 years
- Race: white versus nonwhite
- ECOG performance status: 0 versus 1
- Measurable disease at baseline: yes versus no
- Prior NHA treatment: abiraterone acetate versus enzalutamide

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

If there are a small number of responses/events in one or more strata, then, for analysis, strata will be combined to ensure a sufficient number of responses/events in each stratum. Details regarding the combining of strata will be specified in the sSAP before 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 olaparib, abiraterone, and enzalutamide will be summarized as duration of treatment in days. The extent of exposure for pembrolizumab will be summarized as duration of treatment in cycles. Dose interruption for each drug and dose reduction or dose increase for olaparib will be summarized. Summary statistics will be provided for 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 composed of members of Sponsor Senior Management. The EOC will receive and decide on 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 eDMC will monitor the interim data from this study. The voting members of the committee are external to the Sponsor. The members of the eDMC 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 eDMC will make recommendations to the EOC regarding steps to ensure both participant safety and the continued ethical integrity of the study. Also, the eDMC will

review interim study results, consider the overall risk and benefit to study participants (Section 9.7) 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 eDMC reports, minutes, and recommendations will be described in the eDMC charter that is reviewed and approved by all eDMC 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 signed ICF, 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 19 will be performed by the central laboratory.
- Results of predose laboratory procedures must be reviewed by the investigator or qualified designee and found acceptable before each dose of study intervention. Local laboratory results are permitted if the central laboratory results are not available in time for study intervention administration and/or response evaluation. If a sample for local analysis is used, it is important that the sample for central analysis is obtained in parallel. Additionally, if the use of local laboratory tests results in a change in participant management or is considered clinically significant by the investigator (eg, SAE, AE, or dose modification), the results must be recorded in the appropriate CRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Sections 5.1 and 5.2.
- 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, and CTC results are not reported to sites, to prevent early withdrawal of participants from study intervention.

Table 19 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet count	RBC indices: MCV MCH % reticulocytes		WBC count with differential: Neutrophils (ANC) Lymphocytes Monocytes Eosinophils Basophils
	RBC count			
	Hemoglobin			
	Hematocrit			
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	Phosphorus
	Creatinine	Sodium	Alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase (SGPT)	Total Protein
	Glucose (fasting or nonfasting)	Calcium	Alkaline phosphatase	

Laboratory Assessments	Parameters
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, (bilirubin, urobilinogen, nitrite, leukocyte esterase) • Microscopic examination (if blood or protein is abnormal)
Other tests	Serology (HIV antibody, hepatitis B surface antigen, and hepatitis C virus antibody), if required by local regulations • Testosterone • Thyroid function tests • PT or INR and PTT/aPTT

The investigator (or medically qualified designee) must document his or her 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 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, 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.

10.3.2 Definition of SAE

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

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

1. **Results in death**

2. **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.

3. **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.

4. **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.

5. **Is a congenital anomaly/birth defect**

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

6. 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.

10.3.3 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

10.3.4 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.

10.3.5 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

Definition

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.

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

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens consented and/or collected in this study as outlined in Section 8.8 will be used in various experiments to understand:

- The biology of how drugs/vaccines work
- Biomarkers responsible for how a drug/vaccine enters and is removed by the body
- Other pathways drugs/vaccines may interact with
- The biology of disease

The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

3. Summary of Procedures for Future Biomedical Research.

a. Participants for Enrollment

All participants enrolled in the clinical study will be considered for enrollment in the future biomedical research

b. Informed Consent

Informed consent for specimens (ie, DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all participants or legal guardians, at a study visit by the investigator or his or her designate. Informed consent for future biomedical research should be presented to the participants on the visit designated in the SoA. If delayed, present consent at next possible Participant Visit. Consent forms signed by the participant will be kept at the clinical study site under secure storage for regulatory reasons.

A template of each study site's approved informed consent will be stored in the Sponsor's clinical document repository.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of participant consent for future biomedical research will be captured in the eCRFs. Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)

Collection of specimens for future biomedical research will be performed as outlined in the SoA. In general, if additional blood specimens are being collected for future biomedical research, these will usually be obtained at a time when the participant is having blood drawn for other study purposes.

4. Confidential Participant Information for Future Biomedical Research

In order to optimize the research that can be conducted with future biomedical research specimens, it is critical to link participant' clinical information with future test results. In fact little or no research can be conducted without connecting the clinical study data to the specimen. The clinical data allow specific analyses to be conducted. Knowing participant characteristics like gender, age, medical history and intervention outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for future biomedical research, the Sponsor has developed secure policies and procedures. All specimens will be single-coded per ICH E15 guidelines as described below.

At the clinical study site, unique codes will be placed on the future biomedical research specimens. This code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between participant identifiers and this unique code will be held at the study site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses utilizing the future biomedical research specimens may be performed by the Sponsor, or an additional third party (eg, a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third-party analyses will conform to the specific scope of analysis outlined in the FBR. FBR specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research

Participants may withdraw their consent for future biomedical research and ask that their biospecimens not be used for future biomedical research. Participants may withdraw consent at any time by contacting the principal investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to main study use only. If specimens were collected from study participants specifically for future biomedical research, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main study records) or the specimens have been completely anonymized, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for withdrawal of consent and/or destruction cannot be processed.

7. Retention of Specimens

Future biomedical research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the main study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the study site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not utilized in a particular study, the study site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according

to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated study administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Participants

No information obtained from exploratory laboratory studies will be reported to the participant, family, or physicians. Principle reasons not to inform or return results to the participant include: Lack of relevance to participant health, limitations of predictive capability, and concerns regarding misinterpretation.

If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and participants. Participants will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population

Every effort will be made to recruit all participants diagnosed and treated on Sponsor clinical studies for future biomedical research.

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the participant have been minimized and are described in the future biomedical research informed consent.

The Sponsor has developed strict security, policies, and procedures to address participant data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation, there is risk that the information, like all medical information, may be misused.

12. Questions

Any questions related to the future biomedical research should be emailed directly to clinical.specimen.management@MSD.com.

13. References

1. National Cancer Institute [Internet]: Available from https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45618

2. International Conference on Harmonization [Internet]: E15: Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. Available from http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html

3. Industry Pharmacogenomics Working Group [Internet]: Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

4. Industry Pharmacogenomics Working Group [Internet]: Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

10.7 Appendix 7: Country-specific Requirements

10.7.1 Laboratory Testing

HIV Status

While the protocol does not require specific testing for HIV at screening, it does require testing if required by the local health authority. Sites should check with their local health authority to inquire if country-specific guidance regarding mandatory HIV testing at screening is required. This can also be performed per the discretion of the investigator, if desired. Perform this testing locally if required.

Hepatitis B/C Status

While the protocol does not require specific testing for hepatitis B/C at screening, it does require testing if required by the local health authority. Sites should check with their local health authority to inquire if country-specific guidance regarding mandatory hepatitis B/C testing at screening is required. This can also be performed per the discretion of the investigator, if desired. Perform this testing locally if required.

10.7.2 Country-specific Requirements

10.7.2.1 Germany

Section 5.2: Exclusion Criteria

HIV testing and hepatitis B/C screening are required evaluations for study entry and must be performed to evaluate eligibility. This testing can be performed at any time during the screening period. Perform this testing locally if required.

Section 6.5.1: Rescue Medications and Supportive Care

Live vaccines should not be administered to participants for 90 days after the last dose of study intervention is administered.

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 Prostate Cancer Working Group 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 radionuclide (^{99m}Tc) bone scintigraphy. Other modalities, including fluorodeoxyglucose positron emission tomography (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 these methods 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 time points, 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
Non-PD	**Nonprogressive disease:** At least 1 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 1 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 2 new lesions present.

10.8.4.3 Unconfirmed Progressive Disease (PDu)

At least 2 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 2 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 1 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.

10.8.4.6 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 2 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 is 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 2 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 time points, since they were not new. This may be called "rebaselining".

10.8.4.7 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 rebaselining of lesions will occur in this scenario.

10.8.5 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 increased 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 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.

10.8.6 Management After 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 is achieving a clinically meaningful benefit, an exception to continue study intervention may be considered after 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
ADP	adenosine diphosphate
ADT	androgen deprivation therapy
AE	adverse event
ALT	alanine aminotransferase
AML	acute myeloid leukemia
APaT	all participants as treated
AQA	Analgesic Quantification Algorithm
AST	aspartate aminotransferase
ATM	ataxia-telangiectasia mutated
BICR	blinded independent central review
BID	twice daily
BP	blood pressure
BPI-SF	Brief Pain Inventory-Short Form
BRCAm	breast cancer susceptibility gene 1/2 mutations
CD28	cluster of differentiation 28
CD3 ζ	cluster of differentiation 3 zeta
CI	confidence interval
CNS	central nervous system
CR	complete response
CrCl	creatinine clearance
CRF	case report form
CT	computed tomography
CTC	circulating tumor cell
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor cell deoxyribonucleic acid
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
CYP	cytochrome P450
DCR	disease control rate
DNA	deoxyribonucleic acid
DOR	duration of response
DSB	double strand break
EBRT	external-beam radiation therapy
ECG	electrocardiogram
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data collection
eDMC	external Data Monitoring Committee
EMA	European Medicines Agency
EOC	Executive Oversight Committee
ePRO	electronic patient-reported outcome
EQ-5D-5L	EuroQoL 5- dimension, 5-level health state utility
ESMO	European Society for Medical Oncology
FAS	final analysis set
FACT-G	Functional Assessment of Cancer Therapy-General
FACT-P	Functional Assessment of Cancer Therapy-Prostate
FDAAA	Food and Drug Administration Amendments Act
FT3	free triiodothyronine
FT4	free thyroxine

Abbreviation	Expanded Term
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GnRH	gonadotropin-releasing hormone
HIV	human immunodeficiency virus
HR	hazard ratio
HRD	homologous repair deficiency
HRQoL	health-related quality of life
HRR	homologous recombination repair
IA	interim analysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
iCRO	imaging contract research organization
IEC	Independent Ethics Committee
Ig	immunoglobulin
IgV	immunoglobulin-variable
IHC	immunohistochemistry
IMP	investigational medicinal product
irAE	immune-related adverse event
IRB	Institutional Review Board
IRT	interactive response technology
ITT	intent to treat
IV	intravenous(ly)
KN	Keynote
LHRH	luteinizing hormone-releasing hormone
LOH	loss of heterozygosity
mAb	monoclonal antibody
mCRPC	metastatic castration-resistant prostate cancer
MDS	myelodysplastic syndrome
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	nonevaluable
NED	no evidence of disease
NF-κB	nuclear factor kappa light chain enhancer of activated B-cells
NHA	next-generation hormonal agent
NHEJ	nonhomologous end-joining
NIMP	noninvestigational medicinal product
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
OR	objective response
ORR	objective response rate
OS	overall survival
PARP	polyadenosine 5' diphosphoribose (polyADP ribose) polymerization
PBPK	physiologically based pharmacokinetics
PCWG	Prostate Cancer Working Group
PD	progressive disease
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PDu	progressive disease unconfirmed

Abbreviation	Expanded Term
PET	positron emission tomography
PFS	progression-free survival
PIN	personal identification number
PK	pharmacokinetics
PKCθ	protein kinase C-theta
PO	oral(ly)
PR	partial response
PRES	posterior reversible encephalopathy syndrome
PRO	patient-reported outcome
PSA	prostate-specific antigen
Q2W	every 2 weeks
Q3W	every 3 weeks
Q9W	every 9 weeks
Q12W	every 12 weeks
QD	once daily
RBC	red blood cell
RECIST 1.1	Response Evaluation Criteria in Solid Tumors Version 1.1
RMST	Restricted Mean Survival Time
RNA	ribonucleic acid
rPFS	radiologic progression-free survival
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCF	Sponsor Communication Form
SD	stable disease
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SoA	schedule of activities
SOC	standard of care
SOP	standard operating procedure
sSAP	sSupplemental Statistical Analysis Plan
SSB	single strand break
SSRE	symptomatic skeletal-related event
STAMPEDE	Systemic Therapy in Advancing or Metastatic Prostate Cancer
T1DM	type 1 diabetes mellitus
TFST	time to initiation of the first subsequent anticancer therapy
TOPARP-A	Trial of PARP Inhibition in Prostate Cancer
TTPP	time to pain progression
ULN	upper limit of normal
US	United States
WBC	white blood cell
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 predisease 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 housework, 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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