Official Protocol Title:	A Phase 3, Randomized, Double-blind Study of Pembrolizumab (MK-3475) Plus Docetaxel Plus Prednisone versus Placebo Plus Docetaxel Plus Prednisone in Participants with Chemotherapy-naïve Metastatic Castration-Resistant Prostate Cancer (mCRPC) who have Progressed on a Next Generation Hormonal Agent (NHA)(KEYNOTE-921)
NCT number:	NCT04907227
Document Date:	29-SEP-2022

Title Page

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Protocol Title: A Phase 3, Randomized, Double-blind Study of Pembrolizumab (MK-3475) Plus Docetaxel Plus Prednisone versus Placebo Plus Docetaxel Plus Prednisone in Participants with Chemotherapy-naïve Metastatic Castration-Resistant Prostate Cancer (mCRPC) who have Progressed on a Next Generation Hormonal Agent (NHA) (KEYNOTE-921)

Protocol Number: 921-06

Compound Number: MK-3475

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	122753
EudraCT	2018-004116-22

Approval Date: 29 September 2022

Sponsor Signatory

Typed Name:
Title:

Date

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

Investigator Signatory

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

Typed Name:
Title:

Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 06 / Global amendment	29-SEP-2022	The study has achieved its prespecified scientific objective to evaluate the combination of pembrolizumab and docetaxel in this setting, and the study will be closed as a result of having completed its final analysis. Added language to state that upon study completion, participants are discontinued from the study and may be enrolled in a pembrolizumab extension study, if available.
Amendment 05 / Global amendment	15-DEC-2021	The TEA survey was added to document the investigator's choice to recruit participants for the MK-3475-921 study rather than using other available treatment options.
Amendment 04 / Global amendment	21-JUN-2021	To update the dose modification and toxicity management guidelines for irAEs.
Amendment 03 / Global amendment	01-SEP-2020	To add an extension portion in China to allow for the required exposure and number of events to investigate efficacy and safety in participants enrolled in China.
Amendment 02 / Global amendment	22-JAN-2020	Changed eligibility criteria to align with latest standard of care (SOC) (NHAs given prior to mCRPC), and amended stratification criteria to reflect this change.
Amendment 01	31-OCT-2019	A new version of Amendment 01 was released to fix an administrative error in the exclusion criteria numbering.
Amendment 01 / Global amendment	17-OCT-2019	Corrections to the Schedule of Activities, Objectives, and Appendices, and minor edits throughout.
Original Protocol	17-JAN-2019	N/A

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 06

Overall Rationale for the Amendments:

The study has achieved its prespecified scientific objective to evaluate the combination of pembrolizumab and docetaxel in this setting, and the study will be closed as a result of having completed its final analysis. Added language to state that upon study completion, participants are discontinued from the study and may be enrolled in a pembrolizumab extension study, if available.

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 4.1 Overall Design	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 local SOC schedule. In addition, ePRO assessments will no longer be performed and biomarker samples will no longer be collected.	Because the final analysis of the efficacy endpoint has been accomplished, further tumor scans and response assessments by BICR, ePRO assessments, and the collection of additional samples for biomarker evaluation are considered unnecessary.
1.1 Synopsis: Estimated Duration of Study	The estimated duration of the study has been changed from approximately 28 months to approximately 36 months.	The actual duration of the study is approximately 36 months.
1.1 Synopsis: Study Governance Committees	Statement added that as of Amendment 06, the Executive Oversight Committee and Data Monitoring Committee are no longer applicable.	These committees will no longer review the study data.

Section # and Name	Description of Change	Brief Rationale
1.3.1 Initial Treatment Phase (Pembrolizumab/Placebo Plus Prednisone)	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 local 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.	As of Amendment 06, these assessments and sample collections are considered unnecessary.
7.1 Discontinuation of Study Intervention	Added the subbullet: As of Amendment 06, central tumor response assessments will no longer be performed. However, participants still on study will be assessed locally by the investigator for disease progression per local SOC schedule.	To clarify that participants still on treatment at the time of Amendment 06, who 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 schedule at the treating physician's discretion for patient management.

Section # and Name	Description of Change	Brief Rationale
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 on treatment and deriving clinical benefit and who will continue on-study intervention until criteria for discontinuation are met, local tumor imaging should continue per local SOC schedule.	As of Amendment 06, further efficacy assessments are considered unnecessary. To clarify that participants still receiving treatment at the time of this amendment who are deriving clinical benefit will continue with local tumor imaging per local SOC schedule.
8.12.4.2 Efficacy Follow-up Visits	Added statement: As of Amendment 06: Efficacy Follow-up will be discontinued. The section below is retained for reference.	As of Amendment 06, these assessments are considered unnecessary.
8.2.4 PROs and Quality of Life Assessments	Added statement: As of Amendment 06: ePROs 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.

Section # and Name	Description of Change	Brief Rationale
8.1.6.1 Treatment Eligibility Assessment (TEA) Form	Added statement: As of Amendment 06: The TEA form will no longer be collected. The subsection below is retained for reference.	As of Amendment 06, this assessment is considered unnecessary.
1.3.2 Second Course Phase 4.1 Overall Design, Second Course Treatment 6.6.4 Second Course 8.2.1.4 Second Course (Retreatment) Tumor Imaging	Added statement: NOTE: As of Amendment 06, the study will be closed 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.
2.3 Benefit/Risk Assessment	Added paragraph describing the safety and efficacy results of the final analysis. 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 discontinue this clinical study.

Section # and Name	Description of Change	Brief Rationale
6.1 Study Intervention(s) Administered	Added statement: As of Amendment 06, participants currently still on treatment may have the option of continuing with study intervention, as appropriate, if they are deriving clinical benefit.	To clarify that participants may continue to receive treatment if deriving clinical benefit.
6.3.3 Blinding 8.1.10 Participant Blinding/Unblinding	Added statement: As of Amendment 06: All participants are to be unblinded. The subsections below are retained for reference.	As of Amendment 06, all participants are to be unblinded.
6.5.1 Prohibited Concomitant Therapy	Added "replication-incompetent" to list of acceptable COVID-19 vaccines.	Added to include Janssen vaccine.
6.7 Intervention After the End of Study 8.1.7 Assignment of Treatment/Randomization Number	Added statement that upon study completion, participants are discontinued from the current study and may be transitioned into a pembrolizumab extension study, if available.	To inform that participants may be enrolled in a pembrolizumab extension study.

Section # and Name	Description of Change	Brief Rationale
8.12.4.3 Survival Follow-up Contacts	Added statement: As of Amendment 06: Survival Follow-up visits will be discontinued. Those participants remaining on study 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.
10.7.3 Japan	Added new subsection to Country-specific Appendix with revision to Table 2 (from Section 6.1 Study Intervention(s) Administered) stating that placebo is not provided by the Sponsor.	Placebo is not categorized as a "product(s) used in the trial" in Japan and therefore, is not supplied by the Sponsor.
Title Page 10.1.1 Code of Conduct for Clinical Trials Throughout	Sponsor entity name and address change.	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp and 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.

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3, Randomized, Double-blind Study of Pembrolizumab (MK-3475) Plus Docetaxel Plus Prednisone versus Placebo Plus Docetaxel Plus Prednisone in Participants with Chemotherapy-naïve Metastatic Castration-Resistant Prostate Cancer (mCRPC) who have Progressed on a Next Generation Hormonal Agent (NHA) (KEYNOTE-921)

Short Title: Phase 3 Study of Pembrolizumab plus Docetaxel in mCRPC

Acronym: KEYNOTE-921

Hypotheses, Objectives, and Endpoints:

In participants with mCRPC who have not received chemotherapy but have progressed on or are intolerant to NHA:

NOTE: As of Amendment 06, all participants will be unblinded. Placebo treatment should stop immediately. All participants should be informed of the results of the trial as described in the investigator memo of 04-AUG-2022. Participants who are deemed to be deriving clinical benefit from treatment may continue at the discretion of the investigator. All other study participants should be discontinued from study and be offered SOC treatment as deemed necessary by the investigator. Participants who are still on treatment and deriving clinical benefit will no longer have tumor response assessments by BICR. However, local tumor imaging assessments should continue per local SOC schedule. In addition, ePRO assessments will no longer be performed and biomarker samples will no longer be collected.

Primary Objectives	Primary Endpoints
- To compare pembrolizumab plus docetaxel plus prednisone to placebo plus docetaxel plus prednisone with respect to OS - Hypothesis 1: The combination of pembrolizumab plus docetaxel plus prednisone is superior to placebo plus docetaxel plus prednisone with respect to OS	- OS: the time from randomization to death due to any cause

- To compare pembrolizumab plus docetaxel plus prednisone to placebo plus docetaxel plus prednisone 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 docetaxel plus prednisone is superior to placebo plus docetaxel plus prednisone 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 docetaxel plus prednisone to placebo plus docetaxel plus prednisone with respect to time to initiation of the first subsequent anti-cancer therapy (TFST) - Hypothesis 3: The combination of pembrolizumab plus docetaxel plus prednisone is superior to placebo plus docetaxel plus prednisone with respect to TFST	- TFST: the time from randomization to initiation of the first subsequent anti-cancer therapy or death, whichever occurs first
- To evaluate pembrolizumab plus docetaxel plus prednisone versus placebo plus docetaxel plus prednisone with respect to - PSA response rate - Objective response rate (ORR) and duration of response (DOR) per PCWG-Modified RECIST 1.1 as assessed by BICR	- PSA Response: a PSA decline of ≥50% from baseline, measured twice at least 3 weeks apart - ORR per PCWG-modified RECIST 1.1 as assessed by BICR - DOR: the time from the earliest date of first documented evidence of CR or PR until earliest date of disease progression or death from any cause, whichever occurs first

- To compare pembrolizumab plus docetaxel plus prednisone versus placebo plus docetaxel plus prednisone with respect to the - Time to pain progression (TTPP) based on the Brief Pain Inventory-Short Form (BPI-SF) item 3 “worst pain in 24 hours” and opiate analgesic use (analgesic quantification algorithm [AQA] score) - Time to first symptomatic skeletal-related event (SSRE) - Time to PSA progression	- TTPP: the time from randomization to pain progression as determined by item 3 of the BPI-SF and AQA score - Time to SSRE: the time from randomization to the first SSRE, defined as - first use of external-beam radiation therapy (EBRT) to prevent or relieve skeletal symptoms - occurrence of new symptomatic pathologic bone fracture (vertebral or non-vertebral) - occurrence of spinal cord compression - or tumor-related orthopedic surgical intervention, whichever occurs first. - 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.
- To compare pembrolizumab plus docetaxel plus prednisone versus placebo plus docetaxel plus prednisone with respect to the time to radiographic soft tissue progression per soft tissue rules of PCWG- Modified RECIST 1.1 as assessed by BICR	- Time to radiographic soft tissue progression: the time from randomization to radiographic soft tissue progression
- To evaluate the safety and tolerability of pembrolizumab plus docetaxel plus prednisone versus placebo plus docetaxel plus prednisone	- Adverse events (AEs) - Study intervention discontinuations due to AEs

Overall Design:

Study Phase	Phase 3
Primary Purpose	Treatment
Indication	Treatment of mCRPC
Population	Participants with mCRPC who have not received chemotherapy but have progressed on next generation hormonal agent (NHA)
Study Type	Interventional
Intervention Model	Parallel This is a multi-site study.
Type of Control	Placebo Control
Study Blinding	Double-blind with in-house blinding
Masking	Participant or Subject, Investigator, and Sponsor
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 36 months from the time the first participant signs the informed consent until the last participant's last study-related telephone call or visit. Extension Portion in China: The Sponsor estimates that the study will require approximately 2 additional years (beyond the global study's last participant last study-related phone call or visit) 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:

Global Portion: Approximately 1000 participants will be randomized in this trial.

Extension Portion in China: Approximately 150 participants overall will be enrolled in China, including participants enrolled in either the global portion or the extension portion.

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	D1 of each 21-day cycle for up to 35 cycles	Experimental
	Docetaxel	75 mg/m^2	Q3W	IV	D1 of each 21-day cycle for up to 10 cycles	SOC
	Prednisone	5 mg	BID	PO	Concomitant with docetaxel	SOC
Arm 2	Placebo	NA	Q3W	IV	D1 of each cycle for 35 cycles	Placebo
	Docetaxel	75 mg/m^2	Q3W	IV	D1 of each 21-day cycle for up to 10 cycles	SOC
	Prednisone	5 mg	BID	PO	Concomitant with docetaxel	SOC

Abbreviations: BID = twice daily; D1 = Day 1; IV = intravenous; NA = not applicable; PO = oral; Q3W = every 3 weeks; SOC = standard of care.

Total Number: 2 arms

Duration of Participation	Each participant may participate in the study for up to approximately 28 months from the time the participant signs the Informed Consent Form (ICF) through the final contact. After a screening phase of 42 days, each participant will be receiving assigned intervention for approximately 2 years. After the end of treatment each participant will be followed up for 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 , when clinically appropriate for participants treated with pembrolizumab, 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 as a result of obtaining an investigator-determined confirmed complete response (CR) or those subjects who stop after receiving 35 cycles of trial treatment may be eligible for up to 17 additional cycles of pembrolizumab (approximately 1 year) upon experiencing disease progression if they meet the criteria for re-treatment (see Section 6.6.4 Second Course) and the study is ongoing. Participants randomized to placebo will not be permitted to cross over to pembrolizumab following progression. 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 confirmed by the site, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. All participants will be followed up by telephone 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. The overall study ends when the last participant completes the last study-related contact or visit, withdraws from the study, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

Study Governance Committees:

Steering Committee	No
Executive Oversight Committee	Yes
Data Monitoring Committee	Yes
Clinical Adjudication Committee	No
Study governance considerations are outlined in Appendix 1. As of Amendment 06, the Executive Oversight Committee and Data Monitoring Committee have fulfilled their responsibilities to the study and will no longer be utilized.	

Study Accepts Healthy Volunteers: No

A list of abbreviations used in this document can be found in Appendix 11.

1.2 Schema

The study design is depicted in Figure 1.

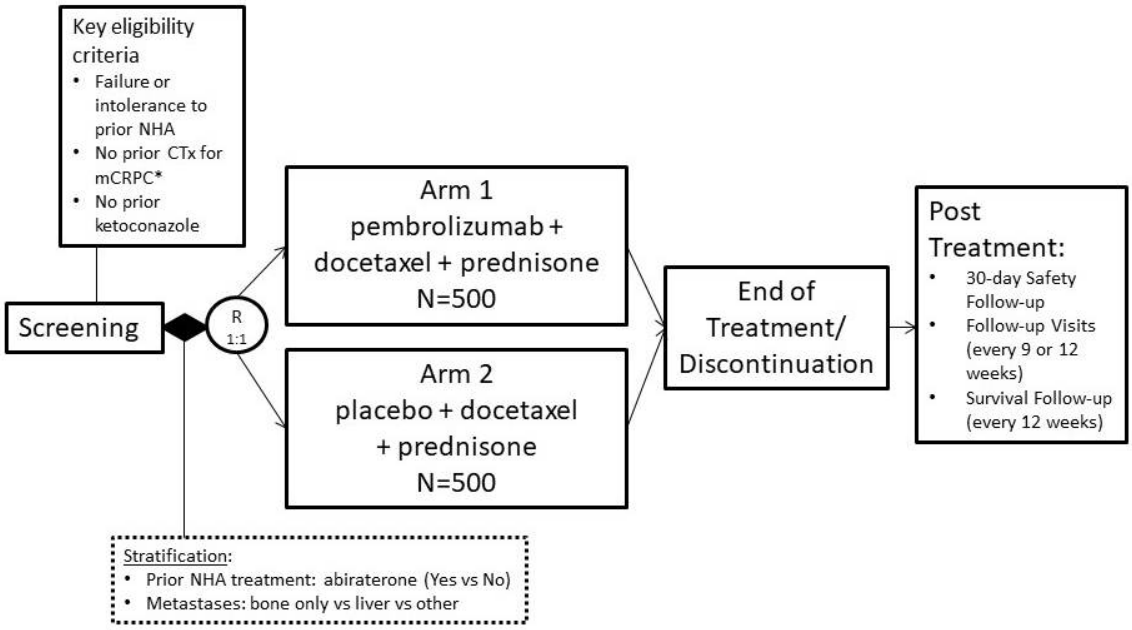

Figure 1 Study Schema

Abbreviations: AE=adverse event; BID=twice daily; CTx=chemotherapy; NHA=next generation hormonal agent; R=randomization.* Participants who received ≥6 cycles of docetaxel for metastatic hormone-sensitive prostate cancer (mHSPC) and did not progress within 1 year after the last dose of docetaxel, are eligible for enrollment.

Study intervention will begin on Day 1 of each 3-week pembrolizumab/placebo + docetaxel dosing cycle. Participants should receive docetaxel (with prednisone 5 mg BID) for up to a maximum of 10 cycles, unless specific discontinuation criteria are met. Pembrolizumab/placebo will continue for up to 35 cycles (approximately 2 years) unless specific withdrawal/discontinuation criteria are met. Participants who must discontinue 1 of the 2 treatments due to drug-related AEs may continue with the other combination partner until criteria for discontinuation are met (eg, disease progression).

1.3 Schedule of Activities (SoA)

1.3.1 Initial Treatment Phase (Pembrolizumab/Placebo Plus Docetaxel Plus Prednisone)

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 local 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.

Trial Period	**Screening Phase**	**Treatment Cycles (21-day Cycles)**								**End of Treatment**	**Post-Treatment**			**Notes**
Treatment Cycle/Title	Screening (Visit 1)	1	2	3	4	5	6	7 to 10	11 up to 35	End of Treatment Visit	Safety Follow-up	Follow-up Visits	Survival Follow-up	**The Safety Follow-up Visit is not needed if the Discontinuation Visit occurs ≥30 days after the last dose.**
Scheduling Window (Days)	-42 to -1	+3	±3	±3	±3	±3	±3	±3	±3	At time of Discon	30 days from last dose (+ 7days)	Q9W to W54, then Q12W (± 7 days)	Q12W (± 7 days)	
Administrative Procedures														
Informed consent	X													Obtain written consent prior to performing any protocol-specific procedures. Additional consent may be required after initial 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													

Trial Period	**Screening Phase**	**Treatment Cycles (21-day Cycles)**								**End of Treatment**	**Post-Treatment**			**Notes**
Treatment Cycle/Title	Screening (Visit 1)	1	2	3	4	5	6	7 to 10	11 up to 35	End of Treatment Visit	Safety Follow-up	Follow-up Visits	Survival Follow-up	**The Safety Follow-up Visit is not needed if the Discontinuation Visit occurs ≥30 days after the last dose.**
Scheduling Window (Days)	-42 to -1	+3	±3	±3	±3	±3	±3	±3	±3	At time of Discon	30 days from last dose (+ 7days)	Q9W to W54, then Q12W (± 7 days)	Q12W (± 7 days)	
Participant identification card	X													The identification card will be updated at randomization.
Demographics and medical history	X													
Prior and concomitant medication review	X	X	X	X	X	X	X	X	X	X	X			Abiraterone acetate or enzalutamide washout period: ≥4 weeks; no prednisone washout period. Report medications started 28 days prior to the first dose and up to 30 days after last dose of study intervention.
SSRE Evaluation	X	X	X	X	X	X	X	X	X	X	X	X		
HIV, Hep B, and Hep C status	X													No testing is required unless mandated by the local health authority. Refer to Appendix 7 for country-specific requirements.
Randomization		X												
Telephone contact or visit		X												Telephone contact or visit on C1D8 (±3 days) will assess participants for development of early toxicity. An unscheduled visit can occur at any time if deemed necessary by the investigator.

Trial Period	**Screening Phase**	**Treatment Cycles (21-day Cycles)**								**End of Treatment**	**Post-Treatment**			**Notes**
Treatment Cycle/Title	Screening (Visit 1)	1	2	3	4	5	6	7 to 10	11 up to 35	End of Treatment Visit	Safety Follow-up	Follow-up Visits	Survival Follow-up	**The Safety Follow-up Visit is not needed if the Discontinuation Visit occurs ≥30 days after the last dose.**
Scheduling Window (Days)	-42 to -1	+3	±3	±3	±3	±3	±3	±3	±3	At time of Discon	30 days from last dose (+ 7days)	Q9W to W54, then Q12W (± 7 days)	Q12W (± 7 days)	
Clinical Procedures/Assessments														
AE monitoring	X	X	X	X	X	X	X	X	X	X	X	X		AEs must be recorded up to 30 days after last dose of study intervention. SAEs must be recorded up to 90 days after the last dose of study intervention or 30 days following cessation of 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.
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				Vital signs (weight, temperature, blood pressure, respiratory and heart rate) are measured after 5 min rest, prior to study administration. Height will be measured at screening only.

Trial Period	**Screening Phase**	**Treatment Cycles (21-day Cycles)**								**End of Treatment**	**Post-Treatment**			**Notes**
Treatment Cycle/Title	Screening (Visit 1)	1	2	3	4	5	6	7 to 10	11 up to 35	End of Treatment Visit	Safety Follow-up	Follow-up Visits	Survival Follow-up	**The Safety Follow-up Visit is not needed if the Discontinuation Visit occurs ≥30 days after the last dose.**
Scheduling Window (Days)	-42 to -1	+3	±3	±3	±3	±3	±3	±3	±3	At time of Discon	30 days from last dose (+ 7days)	Q9W to W54, then Q12W (± 7 days)	Q12W (± 7 days)	
12-lead ECG	X													
ECOG performance status	X	X	X	X	X	X	X	X	X	X				Obtain within 7 days of randomization. Obtain prior to 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 course of the study.
Study Intervention Administration														**Begin within 3 days of randomization.**
Pembrolizumab/ placebo		X	X	X	X	X	X	X	X					Pembrolizumab/placebo IV infusion on Day 1 of each cycle Q3W up to a maximum 35 cycles.
Docetaxel & Prednisone/ prednisolone		X	X	X	X	X	X	X						Docetaxel to be administered Q3W with prednisone/ prednisolone (5 mg BID) for up to 10 cycles. Docetaxel should begin 30 mins after the pembrolizumab/ placebo infusion.

Trial Period	**Screening Phase**	**Treatment Cycles (21-day Cycles)**								**End of Treatment**	**Post-Treatment**			**Notes**
Treatment Cycle/Title	Screening (Visit 1)	1	2	3	4	5	6	7 to 10	11 up to 35	End of Treatment Visit	Safety Follow-up	Follow-up Visits	Survival Follow-up	**The Safety Follow-up Visit is not needed if the Discontinuation Visit occurs ≥30 days after the last dose.**
Scheduling Window (Days)	-42 to -1	+3	±3	±3	±3	±3	±3	±3	±3	At time of Discon	30 days from last dose (+ 7days)	Q9W to W54, then Q12W (± 7 days)	Q12W (± 7 days)	
Laboratory Procedures/Assessments: analysis performed by CENTRAL laboratory														**Screening labs are to be performed within 10 days of first study intervention.** **After Cycle 1, predose laboratory tests may be performed up to 72 hours predose. Unresolved abnormal laboratory results associated with drug-related AEs should be followed until resolution.**
PT or INR and PTT/aPTT	X													PT or INR and aPTT/PTT should be monitored more closely in participants receiving anticoagulant therapy during treatment and safety follow-up period.
Complete blood count with differential	X		X	X	X	X	X	X	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 functions tests are performed every other cycle (ie, Cycle 2, 4, 6, etc.).
T3 or FT3, FT4, and TSH	X		X		X		X	X	X	X	X			
Testosterone	X				X			X	X	X				Testosterone is determined every 4 cycles.

Trial Period	**Screening Phase**	**Treatment Cycles (21-day Cycles)**								**End of Treatment**	**Post-Treatment**			**Notes**
Treatment Cycle/Title	Screening (Visit 1)	1	2	3	4	5	6	7 to 10	11 up to 35	End of Treatment Visit	Safety Follow-up	Follow-up Visits	Survival Follow-up	**The Safety Follow-up Visit is not needed if the Discontinuation Visit occurs ≥30 days after the last dose.**
Scheduling Window (Days)	-42 to -1	+3	±3	±3	±3	±3	±3	±3	±3	At time of Discon	30 days from last dose (+ 7days)	Q9W to W54, then Q12W (± 7 days)	Q12W (± 7 days)	
Procedures/Assessments: analysis performed CENTRALLY														**Schedule of scans, PSA, and CTC count are calculated from the date of randomization and should not be adjusted for dose delays or cycle starts.**
Efficacy Measurements														**PD-L1, PSA, and CTC results are not reported back to sites to prevent early withdrawal of participants from study intervention.**
PSA by central laboratory	X		← Q3W (± 7 days) from randomization →							X	X	X		Screening PSA is performed within 10 days prior to randomization. The window for other PSA collections is ±7 days. Only during Screening, if central laboratory result for PSA is not expected prior to randomization the investigator may also perform the test locally and use the result to determine eligibility. Local laboratory may not be used in lieu of central laboratory.

Trial Period	**Screening Phase**	**Treatment Cycles (21-day Cycles)**								**End of Treatment**	**Post-Treatment**			**Notes**
Treatment Cycle/Title	Screening (Visit 1)	1	2	3	4	5	6	7 to 10	11 up to 35	End of Treatment Visit	Safety Follow-up	Follow-up Visits	Survival Follow-up	**The Safety Follow-up Visit is not needed if the Discontinuation Visit occurs ≥30 days after the last dose.**
Scheduling Window (Days)	-42 to -1	+3	±3	±3	±3	±3	±3	±3	±3	At time of Discon	30 days from last dose (+ 7days)	Q9W to W54, then Q12W (± 7 days)	Q12W (± 7 days)	
Tumor imaging (CT/MRI) and Bone Scan	X		← Q9W (± 7 days) through Week 54, then Q12W (± 7 days) thereafter →							X		X		Baseline CT/MRI chest/abdomen/pelvis and whole-body bone scan must be performed within 28 days prior to randomization. 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. If a scan was obtained within 4 weeks prior to discontinuation, another scan at discontinuation is not mandatory.
Blood for CTC count by central laboratory		X	← W9 (± 7 days) and W18 (± 7 days) from randomization →							X				Collect predose Cycle 1 Day 1.

Trial Period	**Screening Phase**	**Treatment Cycles (21-day Cycles)**								**End of Treatment**	**Post-Treatment**			**Notes**
Treatment Cycle/Title	Screening (Visit 1)	1	2	3	4	5	6	7 to 10	11 up to 35	End of Treatment Visit	Safety Follow-up	Follow-up Visits	Survival Follow-up	**The Safety Follow-up Visit is not needed if the Discontinuation Visit occurs ≥30 days after the last dose.**
Scheduling Window (Days)	-42 to -1	+3	±3	±3	±3	±3	±3	±3	±3	At time of Discon	30 days from last dose (+ 7days)	Q9W to W54, then Q12W (± 7 days)	Q12W (± 7 days)	
Tumor Tissue Collection/Correlative and Biomarker Studies performed by CENTRAL laboratory														**Timing should not be adjusted for dose delays or cycle starts**
Tumor tissue collection (recent biopsy)	X													Obtain within 12 months of screening. Site required to submit 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 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.

Trial Period	**Screening Phase**	**Treatment Cycles (21-day Cycles)**								**End of Treatment**	**Post-Treatment**			**Notes**
Treatment Cycle/Title	Screening (Visit 1)	1	2	3	4	5	6	7 to 10	11 up to 35	End of Treatment Visit	Safety Follow-up	Follow-up Visits	Survival Follow-up	**The Safety Follow-up Visit is not needed if the Discontinuation Visit occurs ≥30 days after the last dose.**
Scheduling Window (Days)	-42 to -1	+3	±3	±3	±3	±3	±3	±3	±3	At time of Discon	30 days from last dose (+ 7days)	Q9W to W54, then Q12W (± 7 days)	Q12W (± 7 days)	
Patient-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 surveys prior to dosing and before other assessments and procedures. Complete on site prior to study intervention on Day 1 of every cycle through Cycle 8, then every 2 cycles through Cycle 24, then every 4 cycles thereafter up to 2 years or until discontinuation and at Safety Follow-up Visit.
BPI-SF Patient Analgesic Log	X	← Q3W until W24, then Q6W until W72, thereafter Q12W up to 2 years →								X	X			Complete at home daily for any 7 consecutive days from Day -10 of screening. At each timepoint after randomization complete for 7 consecutive days (eg, days 15 – 21). A 3-day window will be permitted to begin completing the BPI-SF and analgesic log prior to the expected 7 days.

Trial Period	**Screening Phase**	**Treatment Cycles (21-day Cycles)**								**End of Treatment**	**Post-Treatment**			**Notes**
Treatment Cycle/Title	Screening (Visit 1)	1	2	3	4	5	6	7 to 10	11 up to 35	End of Treatment Visit	Safety Follow-up	Follow-up Visits	Survival Follow-up	**The Safety Follow-up Visit is not needed if the Discontinuation Visit occurs ≥30 days after the last dose.**
Scheduling Window (Days)	-42 to -1	+3	±3	±3	±3	±3	±3	±3	±3	At time of Discon	30 days from last dose (+ 7days)	Q9W to W54, then Q12W (± 7 days)	Q12W (± 7 days)	

Abbreviations: AE= adverse event; aPTT = activated partial thromboplastin time; BPI-SF = Brief Pain Inventory-Short Form; C1D8 = Cycle 1 Day 8; CT = computed tomography; CTC = circulating tumor cell; ctDNA = circulating tumor deoxyribonucleic acid; Discon = discontinuation; ECG = electrocardiogram; ECI = events of clinical interest; 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; FBR=Future Biomedical Research; FT3 = free triiodothyronine; FT4=free thyroxine; Hep = hepatitis; HIV = human immunodeficiency virus; ICF = informed consent form; ICG = informed consent form; IEC=Independent Ethics Committee; INR = international normalized ratio; IRB = Institutional Review Board; MRI = magnetic resonance imaging; PK = pharmacokinetic; 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; 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 (Pembrolizumab ONLY)

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

Trial Period	Treatment Cycles (21-day Cycles)					End of Treatment	Post-Treatment			Notes
Treatment Cycle/Title	1	2	3	4	5 up to 17	Discon	Safety Follow-up	Follow-up Visits	Survival Follow-up	**The safety follow-up is not needed if the DC visit occurs ≥30 days after the last dose**
Scheduling Window (Days)		± 3	± 3	± 3	± 3	At time of Discon	30 days from last dose (+ 7 days)	Q12W (± 7 days)	Q12W (± 7 days)	
Administrative Procedures										
Eligibility criteria	X									
Concomitant medication review	X	X	X	X	X	X	X			Report new medications started 28 days prior to the first retreatment dose and up to 30 days after last dose of trial treatment. All medications related to reportable SAEs and ECIs should be recorded.
Clinical Procedures/Assessments										
AE monitoring	X	X	X	X	X	X	X	X		AEs must be recorded up to 30 days after last dose of study intervention. SAEs must be recorded up to 90 days after the last dose of study intervention or 30 days following cessation of 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.
Full physical examination	X					X				
Directed physical examination		X	X	X	X		X			Perform as clinically indicated.
Vital signs and weight	X	X	X	X	X	X				
ECOG performance status	X	X	X	X	X	X				After Cycle 8, conduct every other cycle.
Pembrolizumab	X	X	X	X	X					
Subsequent anticancer therapy status							X	X	X	Safety Follow-up visit must occur before the start of the new therapy.

Trial Period	Treatment Cycles (21-day Cycles)					End of Treatment	Post-Treatment			Notes
Treatment Cycle/Title	1	2	3	4	5 up to 17	Discon	Safety Follow-up	Follow-up Visits	Survival Follow-up	**The safety follow-up is not needed if the DC visit occurs ≥30 days after the last dose**
Scheduling Window (Days)		± 3	± 3	± 3	± 3	At time of Discon	30 days from last dose (+ 7 days)	Q12W (± 7 days)	Q12W (± 7 days)	
Survival status	←	—	—	—	—	—	→		X	Updated survival status may be requested by the Sponsor at any time during the course of the study
Laboratory Procedures/Assessments: analysis performed by CENTRAL laboratory										**Perform within 10 days prior to the participant's receiving the first retreatment infusion.** **After C1, predose laboratory tests may be performed up to 72 hours predose. Unresolved abnormal laboratory results associated with drug-related AEs should be followed until resolution.**
PT or INR and PTT/aPTT	X									PT or INR and aPTT/PTT should be monitored more closely in participants receiving anticoagulant therapy during treatment and safety follow-up period.
Complete blood count with differential	X	X	X	X	X	X	X			After Cycle 1, predose laboratory procedures may be conducted up to 72 hours predose. Unresolved abnormal lab results associated with drug-related AEs should be followed until resolution.
Comprehensive chemistry panel	X	X	X	X	X	X	X			
Urinalysis	X		X		X	X	X			Urinalysis and thyroid function tests are performed every other cycle (ie, Cycle 5, 7, 9, etc.).
T3 or FT3, FT4, and TSH	X		X		X	X	X			
Testosterone	X			X	X	X				Testosterone is to be tested every 4 cycles.
Efficacy Measurements										**Schedules of PSA determinations and scans are calculated from the date of first re-treatment infusion. The timing of assessments should not be adjusted for dose delays or cycle starts.**
PSA (central laboratory)	X	← Q3W (±7 days) from first retreatment infusion →				X	X	X		Collect predose on study intervention days.

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

Abbreviations: AE = adverse event; aPTT = activated partial thromboplastin time; CT = computed tomography; CTC = circulating tumor cell; Discon = discontinuation; ECI = events of clinical interest; ECOG = Eastern Cooperative Oncology Group; FBR = Future Biomedical Research; FT4 = free thyroxine; INR = international normalized ratio; MRI = magnetic resonance imaging; PSA = prostate-specific antigen; PT = prothrombin time; PTT = partial thromboplastin time; Q12W = every 12 weeks; SAE = serious adverse event; T3 = total triiodothyronine; TSH = thyroid-stimulating hormone; W = week.

2 INTRODUCTION

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

While many men diagnosed with locally confined disease may be treated definitively with radiation or surgery, men who go on to develop or are diagnosed with metastatic prostate cancer, an incurable entity, are typically treated first with androgen-deprivation therapy (ADT), usually with a gonadotropin-releasing hormone 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 in spite of ADT alone it is referred to as castration resistant. The disease at this point is known as mCRPC and requires the addition of systemic therapies to re-establish control of disease. A number of important systemic therapies for mCRPC now comprise the current therapeutic landscape. These include the next generation hormonal agents (NHAs), abiraterone acetate and enzalutamide, and the taxanes, docetaxel and cabazitaxel.

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 after docetaxel, and it too was found to be associated with superior survival (median 15.1 months versus 12.7 months with mitoxantrone) [de Bono, J. S., et al 2010]. However, cabazitaxel can be a toxic therapy, and 4.9% of participants died from 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 participants ≥65 years of age. Thus, an unmet need remains for participants after treatment in the mCRPC setting with targeted endocrine therapy and docetaxel.

2.1 Study Rationale

Interim results from Cohort B of KEYNOTE-365 (data cutoff 03-APR-2018), which evaluated the combination of pembrolizumab and docetaxel/prednisone in the population intended for the current study, showed a response (at least 50% reduction in prostate-specific antigen [PSA] from baseline) in 26.8% (95% CI: 16.9%, 38.6%) of participants with a baseline PSA measurement available, and 28.8% (95% CI: 18.3%, 41.3%) in those with an elevated PSA at baseline. While an objective response (complete response [CR] + partial response [PR]) was observed in 5.6% (95% confidence interval [CI]: 1.5%, 13.6%) of participants, the disease control rate (DCR) for the cohort was 84.7% (95% CI: 74.3%, 92.1%) driven primarily by the large proportion of participants who had stable disease for at least 24 weeks (79.2%) prior to disease progression. Approximately half of the participants had a reduction in tumor size, of which nearly a third had a reduction of >30%. These results

provide support for further evaluation of the combination of pembrolizumab and docetaxel plus prednisone/prednisolone in patients with mCRPC.

The present study, KEYNOTE-921 (KN921), is a randomized, multicenter, double-blind, placebo-controlled, Phase 3 study in participants with mCRPC who have received prior NHA. Participants will be randomly assigned 1:1 to study intervention with either pembrolizumab +docetaxel + prednisone/prednisolone or with placebo + docetaxel + prednisone/prednisolone.

2.2 Background

Pembrolizumab is a potent humanized 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).

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 8 (CD8) + T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [Dudley, M. E., et al 2005] [Hunder, N. N., et al 2008].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene *Pdcd1*) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [Greenwald, R. J., et al 2005] [Okazaki, T., et al 2001].

The structure of murine PD-1 has been resolved [Zhang, X., et al 2004]. PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type (IgV-type)

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

2.2.1.2 Overview of Prostate Cancer

Prostate cancer represents one of the most commonly diagnosed cancer malignancies and the second leading cause of cancer-related deaths in men worldwide [Center, M. M., et al 2012] [Torre, L. A., et al 2015]. According to the Global Burden of Disease Study [Fitzmaurice, C., et al 2018], there were 1.4 million new prostate cancer cases and 381,000 deaths from the disease globally in 2016. These statistics highlight the socioeconomic burden prostate cancer poses worldwide. In the United States (US), analysts estimated that there will be 164,690 new cases of prostate cancer (19% of all new cases in males) and 29,430 deaths caused by prostate cancer (9% of all new deaths of males) in 2018 [Siegel, R. L., et al 2018]. Since the advent of PSA screening about 3 decades ago, the prostate cancer death rate had been falling until it stabilized between 2013 and 2015 [Negoita, S., et al 2018]. Additionally, following the US Preventive Services Task Force's recommendation against routine PSA-based screening regardless of age in 2012, incidence of late-stage disease has increased [Negoita, S., et al 2018]. Although identifying cause and effect is difficult, this change in the national trend in late-stage prostate cancer incidence may portend future increases in the number of men requiring treatment for advanced disease. Therefore, there is an urgent need to develop new therapeutic strategies, including combination therapies for prostate cancer.

2.2.1.3 Unmet Medical Need in Prostate Cancer

Patients with mCRPC have a high unmet medical need. The prognosis for men diagnosed with locally confined disease is favorable, and such cases may be treated definitively with radiation therapy or surgery [Gray, P. J., et al 2017]. In fact, prostate cancer has been a prime example of an indolent cancer, with the majority of men found to have localized disease at diagnosis [Loeb, S., et al 2015]. For that reason, in the last decade physicians have increasingly adopted active surveillance as a management option for low-risk prostate cancer, reflecting the low rate of disease progression and enthusiasm for avoiding harms associated with overtreatment (eg, incontinence and impotence) [Loeb, S., et al 2015] [Resnick, M. J., et al 2013]. Additionally, metastatic prostate cancer evolves molecularly during disease progression and/or therapy through an adaptive response, which may result in emergence of

histologic variants that are biologically more aggressive and resistant to therapy [Vlachostergios, P. J., et al 2017].

Androgen signaling mediated through the androgen receptor is a critical factor for promotion and growth of prostate cancer [Knudsen, K. E. 2010]. Therefore, until 2015 the standard of care for initial first-line therapy for metastatic prostate cancer (either recurrent or de novo metastatic tumors, heretofore called castration-sensitive prostate cancer [CSPC]) consisted of ADT (eg, a gonadotropin-releasing hormone agonist or antagonist). However, a great stride in treatment of CSPC was made over the last few years. The Chemohormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer (CHAARTED [Sweeney, C. J., et al 2015] [James, N. D., et al 2016]) study demonstrated significant survival benefit with the addition of docetaxel to ADT. In a 2018 follow-up analysis [Kyriakopoulos, C. E., et al 2018], investigators extended the original median duration of follow-up from 28.9 months to 53.7 months and confirmed the median overall survival (OS) advantage in the ADT plus docetaxel group (57.6 vs. 47.2 months; hazard ratio (HR), 0.72; 95% CI, 0.50 to 0.79; p<001). In a similar comparison from the STAMPEDE study [James, N. D., et al 2017], researchers recommended docetaxel become part of the standard of care after a 43-month follow-up found superior results with it against ADT in median OS (81 vs. 71 months; HR, 0.78; 95% CI, 0.66 to 0.93; p=.006) [James, N. D., et al 2016].

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

In spite of these recent advances, treatment options for men with mCRPC progressing after NHA therapy and docetaxel are limited and provide 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 showed significant improvement in median OS in the cabazitaxel group (15.1 months [95% CI, 14.1 to 16.3] vs. 12.7 months [95% CI, 11.6 to 13.7]; HR, 0.70 [95% CI, 0.59 to 0.83]; p<0.0001). Also, cabazitaxel maintained its antitumor activity following treatment with docetaxel and abiraterone or docetaxel and enzalutamide [Pezaro, C. J., et al 2014]. However, cabazitaxel can be a toxic therapy, and consequently it is not utilized widely. Retrospective studies suggest that either abiraterone or

enzalutamide may be an option; however, with previous therapies [Handy, C. E. 2016] the potential for developing cross-resistance [Zhang, T., et al 2015] and for the emergence of a more aggressive form of prostate cancer following prolonged treatment [Roubaud, G., et al 2017] must be considered and could be limiting factors. Thus, there remains an unmet medical need for patients with mCRPC with disease progression following treatment with an NHA and/or docetaxel-based chemotherapy.

2.2.1.4 Preclinical and Clinical Studies

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

2.2.1.5 Pembrolizumab in mCRPC

Participants with PD-L1-positive mCRPC have been treated with pembrolizumab monotherapy in the Phase 1b KEYNOTE-028 (KN028) study (Cohort E3: advanced [unresectable and/or metastatic] prostate adenocarcinoma). The primary end point was the objective response rate (ORR), according to the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1), which was determined by investigator review. Participants with PD-L1-positive (defined by PD-L1 expression in >1% tumor or stroma cells) mCRPC were enrolled and treated with pembrolizumab monotherapy. All had treatment with at least 1 prior antineoplastic therapy, and 17 of 23 (73.9%) and 7 of 23 (30%) had been treated with 2 or more or 5 or more lines of therapy, respectively. Of the 23 participants, only 1 patient remained on treatment at the time of last published analysis. [Hansen, A. R., et al 2018]. Twenty-one (91.3%) had 1 or more post-baseline PSA level determinations; 5 of these participants (24%) had a PSA level decline of 50%. There were 4 confirmed PRs, according to RECIST 1.1 guidelines, for an ORR at that time of 17.4% (95% CI, 5.0 to 38.8%). Responses were durable (median duration of response [DOR], 13.5 months), and treatment was well tolerated.

2.2.1.6 Ongoing Clinical Trials in mCRPC

KEYNOTE-199 (KN199) was designed to further evaluate the positive signal of activity seen in KN028 with pembrolizumab monotherapy in participants with mCRPC who previously received docetaxel-based chemotherapy and underwent abiraterone acetate or enzalutamide treatment. The ORR was 4.5% (cohorts 1 and 2) at the second interim database lock with a data cutoff date of 13-OCT-2017. However, the DCR suggested a durable response and potential OS benefit, regardless of PD-L1 status, that warranted further evaluation. Additionally, early unpublished results from Graff, et al. suggest a potential survival benefit in the advanced mCRPC population with pembrolizumab monotherapy [Graff, J. N., et al 2016].

Graff et al. [Graff, J. N., et al 2016] initially enrolled 10 men in 2015 to 2016 who had mCRPC with evidence of progression on enzalutamide, and subsequently enrolled a total of 28. Because of previous immunotherapies (nivolumab, ipilimumab) had failed to produce an objective response in mCRPC [Topalian, S. L., et al 2012] [Kwon, E. D., et al 2014], interest in pursuing further studies waned. Nonetheless, after some success, Graff et al., undertook

the Phase 2 study adding pembrolizumab to enzalutamide for men with mCRPC and reported a decline in PSA ≥50% (primary endpoint) in 5 of 28 patients (17.9%) and an ORR (secondary endpoint) in 3 of 12 patients (25.0%) who had measurable disease at baseline. At 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 to 28.4 months).

KN365, a Phase 2 umbrella study evaluating pembrolizumab combination therapies in mCRPC participants, included a cohort for the evaluation of pembrolizumab in combination with up to 10 cycles of docetaxel (Cohort B). Participants in this cohort were required to have had previously received either abiraterone acetate or enzalutamide. The primary endpoint is the percentage of participants with a decrease in PSA level of ≥50%. In a recent amendment of the protocol, ORR based on RECIST 1.1 by BICR was changed from a secondary endpoint to a (dual) primary endpoint. Additionally, the target enrollment in each of the 3 cohorts was expanded to 100, and a new cohort for pembrolizumab in combination with abiraterone acetate with target enrollment of 100 mCRPC participants was added. See Section 2.1 for a summary of interim results.

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

2.2.2 Information on Other Study-related Therapy

2.2.2.1 Docetaxel

Docetaxel is a microtubule inhibitor indicated for locally advanced or metastatic breast cancer, non-small cell lung cancer (NSCLC), mCRPC, gastric adenocarcinoma, and squamous cell carcinoma of the head and neck. Docetaxel is an antineoplastic agent that acts by disrupting the microtubular network in cells that is essential for mitotic and interphase cellular functions. Docetaxel binds to free tubulin and promotes the assembly of tubulin into stable microtubules while simultaneously inhibiting their disassembly. This leads to the production of microtubule bundles without normal function and to the stabilization of microtubules, which results in the inhibition of mitosis in cells. The binding of docetaxel to microtubules does not alter the number of protofilaments in the bound microtubules, a feature which differs from most spindle poisons currently in clinical use.

The safety and efficacy of docetaxel in combination with prednisone in participants with mCRPC were evaluated in a randomized, multicenter, active control trial [Tannock, I, et al 2004]. A total of 1006 participants with Karnofsky Performance Status ≥60 were randomized to the following treatment groups:

- Docetaxel 75 mg/m^2 every 3 weeks (Q3W) for 10 cycles
- Docetaxel 30 mg/m^2 administered weekly for the first 5 weeks in a 6-week cycle for 5 cycles
- Mitoxantrone 12 mg/m^2 Q3W for 10 cycles

All 3 regimens were administered in combination with prednisone 5 mg twice daily (BID), continuously. In the docetaxel Q3W arm, a statistically significant OS advantage was demonstrated compared to mitoxantrone. Median OS was 18.9 months (95% CI, 17.0 to 21.2 months) versus 16.5 months (95% CI, 14.4 to 18.6 months) in the docetaxel and mitoxantrone arms, respectively. In the docetaxel weekly arm, no OS advantage was demonstrated compared to the mitoxantrone control arm.

Refer to the approved labeling for detailed background information on docetaxel.

Concomitant treatment with prednisone prior to and during docetaxel treatments is recommended per docetaxel labeling. Corticosteroids provide palliation and tumor responses in prostate cancer patients [Montgomery, B., et al 2014]. Docetaxel was approved in the US in combination with prednisone as the first treatment shown to prolong survival in men with mCRPC.

2.3 Benefit/Risk Assessment

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

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

Docetaxel has been approved by regulatory agencies globally for the treatment of mCRPC and have been recommended for treatment for mCRPC by NCCN and European Society for Medical Oncology guidelines [Parker, C., et al 2015].

Preliminary results from Cohort B of KEYNOTE-365 (see Section 2.1), in which participants have been treated with a combination of pembrolizumab and docetaxel, show a modest objective response, although the DCR for the cohort was 84.7% with a large proportion of participants with stable disease for at least 24 weeks (79.2%) prior to disease progression. Two thirds of the participants had a reduction in tumor size, of which nearly a third had a reduction of >30%. Participants in this cohort reported Grade 3 to 5 AEs in 42 of 72 (58.3%) participants, and SAEs in 30 of 72 (41.7%).

NOTE: At the final analysis, the combination of pembrolizumab and docetaxel plus prednisone did not demonstrate a benefit in OS, one of the study's dual primary endpoints, compared to placebo and docetaxel plus prednisone. The study's other dual primary endpoint, rPFS, was evaluated at an earlier interim analysis and did not demonstrate improvement compared to the control arm. There were trends toward an improvement in both OS and rPFS for participants who received pembrolizumab plus chemotherapy compared with chemotherapy alone; however, these results did not meet statistical significance per the prespecified statistical plan.

The combination was associated with a slightly higher incidence of AEs compared to docetaxel alone, however the safety profile of pembrolizumab in combination with docetaxel in this study appears consistent with that observed in previously reported studies for the individual therapies.

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.

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

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

In participants with mCRPC who have not received chemotherapy but have progressed on or are intolerant to NHA:

NOTE: As of Amendment 06, all participants will be unblinded. Placebo treatment should stop immediately. All participants should be informed of the results of the trial as described in the investigator memo of 04-AUG-2022. Participants who are deemed to be deriving clinical benefit from treatment may continue at the discretion of the investigator. All other study participants should be discontinued from study and be offered SOC treatment as deemed necessary by the investigator. Participants who are still on treatment and deriving clinical benefit will no longer have tumor response assessments by BICR. However, local tumor imaging assessments should continue per local SOC schedule. In addition, ePRO assessments will no longer be performed and biomarker samples will no longer be collected.

Objectives	Endpoints
Primary	
• To compare pembrolizumab plus docetaxel plus prednisone to placebo plus docetaxel plus prednisone with respect to overall survival (**OS)** • Hypothesis 1: The combination of pembrolizumab plus docetaxel plus prednisone is superior to placebo plus docetaxel plus prednisone with respect to OS	• **OS**: the time from randomization to death due to any cause

Objectives	Endpoints
• To compare pembrolizumab plus docetaxel plus prednisone to placebo plus docetaxel plus prednisone 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 docetaxel plus prednisone is superior to placebo plus docetaxel plus prednisone 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	
• To compare pembrolizumab plus docetaxel plus prednisone to placebo plus docetaxel plus prednisone with respect to time to initiation of the first subsequent anti-cancer therapy（**TFST)** • Hypothesis 3: The combination of pembrolizumab plus docetaxel plus prednisone is superior to placebo plus docetaxel plus prednisone with respect to **TFST**	• **TFST:** the time from randomization to initiation of the first subsequent anti-cancer therapy or death, whichever occurs first
• To evaluate pembrolizumab plus docetaxel plus prednisone versus placebo plus docetaxel plus prednisone with respect to ○ **PSA response rate** ○ **Objective response rate (ORR)** and **duration of response** (**DOR**) per PCWG-Modified RECIST 1.1 as assessed by BICR	• **PSA Response:** a PSA decline of ≥50% from baseline, measured twice at least 3 weeks apart • **ORR** per PCWG-modified RECIST 1.1 as assessed by BICR • **DOR:** the time from the earliest date of first documented evidence of CR or PR until earliest date of disease progression or death from any cause, whichever occurs first

Objectives	Endpoints
• To compare pembrolizumab plus docetaxel plus prednisone versus placebo plus docetaxel plus prednisone with respect to the ○ **Time to pain progression (TTPP)** based on the Brief Pain Inventory-Short Form (BPI-SF) item 3 "worst pain in 24 hours" and opiate analgesic use (analgesic quantification algorithm [AQA] score) ○ **Time to first symptomatic skeletal-related event (SSRE)** ○ **Time to PSA progression**	• **TTPP**: the time from randomization to pain progression as determined by item 3 of the BPI-SF and AQA score • **Time to SSRE**: the time from randomization to the first SSRE, 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 non-vertebral) 3) occurrence of spinal cord compression 4) or tumor-related orthopedic surgical intervention whichever occurs first. • **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.
• To compare pembrolizumab plus docetaxel plus prednisone versus placebo plus docetaxel plus prednisone with respect to the **time to radiographic soft tissue progression** per soft tissue rules of PCWG-Modified RECIST 1.1 as assessed by BICR	• **Time to radiographic soft tissue progression**: the time from randomization to radiographic soft tissue progression
• To evaluate the safety and tolerability of pembrolizumab plus docetaxel plus prednisone versus placebo plus docetaxel plus prednisone	• Adverse events (AEs) • Study intervention discontinuations due to AEs

Objectives	Endpoints
Tertiary/Exploratory	
• To evaluate efficacy with respect to OS, rPFS, ORR and DOR in participants with positive PD-L1 (combined positive score >1%) versus all- comers	• OS, rPFS, OR, DOR
• To compare pembrolizumab plus docetaxel plus prednisone versus placebo plus docetaxel plus prednisone 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 assess the effect of the combination of pembrolizumab plus docetaxel plus prednisone versus placebo plus docetaxel plus prednisone on disease-related symptoms and health-related quality of life (HRQoL) using **BPI-SF**, **Functional Assessment of Cancer Therapy (FACT) - Prostate Cancer (FACT-P)** and **EuroQoL Five-Dimension Five-Level Health State Utility Index (EQ-5D-5L)** questionnaires in patients with mCRPC	• **BPI-SF**: progression in pain severity domain, change in pain interference domain, and pain palliation • **FACT-P** total score, FACT-G total score, trial outcome index, functional well-being, physical well-being, prostate cancer subscale, and FACT Advanced Prostate Symptom Index 6 (FAPSI6) • **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 in participants following administration of pembrolizumab plus docetaxel plus prednisone versus placebo plus docetaxel plus prednisone	• **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 treatments	• Molecular (genomic, metabolic and/or proteomic) determinants of response or resistance to study interventions, using blood and/or tumor tissue

4 STUDY DESIGN

4.1 Overall Design

NOTE: As the study has completed its final analysis, the study has achieved its prespecified scientific objective to evaluate the combination of pembrolizumab and docetaxel in this setting, and the study will be closed.

All participants will be unblinded. Placebo treatment should stop immediately. Investigators should inform all participants of the study results as described in the investigator memo of 04-AUG-2022; participants who are deemed to be deriving clinical benefit from treatment may continue at the discretion of the investigator. All other study participants should be discontinued from study and be offered SOC treatment as deemed necessary by the investigator. Upon study completion, participants are discontinued from the current study and may be transitioned into a pembrolizumab extension study, if available.

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

After a screening phase of up to 42 days, approximately 1000 eligible participants will be randomly assigned in a 1:1 ratio to 1 of the following 2 study intervention arms:

- Arm 1: pembrolizumab plus docetaxel plus prednisone/prednisolone
- Arm 2: placebo plus docetaxel plus prednisone/prednisolone

Participants must have previously received treatment with a NHA (but not more than one) and failed treatment or become intolerant of the drug. Participants who progressed must have received at least 8 weeks (minimum 14 weeks for those with bone progression) of treatment. Participants who became intolerant of NHA must have had a minimum of 4 weeks exposure. Prior docetaxel chemotherapy in the hormone-sensitive setting is allowed.

Participants must provide tumor tissue from a new core or excisional biopsy from soft tissue not previously irradiated (samples from tumors progressing in a prior site of radiation are allowed; other exceptions may be considered after Sponsor consultation). For participants with bone only or bone predominant disease may provide a bone biopsy sample (decalcification not allowed). However, if obtaining a new biopsy is not feasible, then participants may provide an archival tumor tissue sample after Sponsor consultation. Adequacy of these specimens for biomarker analysis will be evaluated by a central laboratory prior to randomization. For complete details about entrance criteria, please see Section 5.1 – Inclusion Criteria.

Prior to randomization, participants will be stratified by prior NHA treatment (abiraterone: Yes vs. No) and metastases (bone only vs. liver vs. other). Pembrolizumab/placebo administration will occur on Day 1 of each 3-week dosing cycle and will continue for a maximum of 35 cycles (approximately 2 years starting with the first infusion in Cycle 1) or until specific withdrawal/discontinuation criteria are met (Section 7.1). Participants should

receive a maximum of 10 cycles of docetaxel Q3W with prednisone/prednisolone BID; a minimum of 6 cycles of docetaxel is recommended, unless specific withdrawal/study intervention discontinuation criteria are met. Prior to docetaxel treatments, participants may be premedicated with dexamethasone or per local standard of care, and will be treated concomitantly with prednisone/prednisolone per docetaxel labeling. Participants who must discontinue either pembrolizumab/placebo or docetaxel due to drug-related AEs, may continue with the other combination partner following consultation with the Sponsor until criteria for discontinuation of study intervention are met (eg, disease progression). After cessation of docetaxel treatment, prednisone/prednisolone should be discontinued (tapering is acceptable).

This trial will use an independent, external Data Monitoring Committee (eDMC) to 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] scans of the chest, abdomen, and pelvis) every 9 weeks for approximately 1 year (through Week 54) and every 12 weeks thereafter.

Participants will be evaluated with radiologic imaging to assess response to treatment at regular intervals during the study (Section 8.2.1).

Participants who attain an investigator-determined confirmed complete response (CR) may receive up to 35 cycles of pembrolizumab/placebo. If a participant with radiographic progression is clinically stable or clinically improved, an exception may be considered to continue study intervention upon consultation with the Sponsor. Participants showing clinical benefit in the trial will be allowed to continue study intervention per protocol regardless of any decision to stop enrollment or suspend the study.

Adverse events (AEs) will be monitored throughout the trial 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 the study intervention, each participant will be followed for 30 days for AE monitoring (all serious AEs [SAEs] will be collected for 90 days after the end of study intervention or 30 days after the end of study intervention if the participant initiates new anticancer therapy, whichever is earlier). Treatment-related SAEs must be reported regardless of when they occur. Participants who discontinue study intervention for reasons other than radiographic disease progression will stay on study and continue study-related disease assessments until radiographic disease progression, initiation of a non-study cancer treatment, participant discontinuation from the trial, or if the participant becomes lost to follow-up. All participants will be followed up for survival. This may be done in a variety of ways including phone, email, chart review, or review of public records in compliance with local practices or regulations.

Second Course Treatment:

NOTE: As of Amendment 06, second course treatment is not an option for participants. There are currently no participants in the Second Course Phase.

Participants who stop study intervention as a result of obtaining an investigator-determined confirmed CR or those participants who stop after receiving 35 cycles may be eligible, at the discretion of the investigator, for an additional 17 cycles (approximately 1 year) of pembrolizumab after BICR-verified progressive disease if they meet the criteria for re-treatment (see 6.6.4 Second Course) and the study is ongoing. Participants who receive pembrolizumab after progression as described above will not receive further treatment with docetaxel plus prednisone/prednisolone. The decision to retreat with pembrolizumab will be at the discretion of the investigator only if no cancer treatment was administered since the last dose of pembrolizumab/placebo, the participant still meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial remains open.

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

This study will use a group sequential design, using an independent eDMC to monitor safety and efficacy during the course of the study. There will be 2 planned interim analyses conducted. The final OS analysis will be conducted when approximately 549 OS events (target number of OS events) have been observed. There will be only 1 PFS analysis conducted, which is at the time of first interim analysis (IA1) when at least 468 rPFS events have been observed. The results of the interim analyses will be reviewed by the eDMC, which will provide recommendations for the study in accordance with the eDMC Charter and the Statistical Analysis Plan (SAP) described in detail in Section 9.0 - Statistical Analysis Plan.

Extension Portion in China:

Approximately 150 participants in China will be randomized overall in the global portion and the China Extension Portion of the study. After enrollment of the global portion is closed, participants in China will continue to be enrolled and randomized in a 1:1 ratio in the Extension Portion designed to meet local regulatory requirements. The Extension Portion will be identical to the global portion (eg, double-blinded, with identical inclusion and exclusion criteria, study endpoints, primary and secondary objectives, and study procedures), with the exception of an additional supplemental statistical analysis plan (sSAP) section for participants enrolled in China. Details of the analysis will be provided in the sSAP.

4.2 Scientific Rationale for Study Design

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

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

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

Radiographic PFS is an acceptable measure of clinical benefit for a late stage study that demonstrates superiority of a new antineoplastic therapy, especially if the magnitude of the effect is large and the therapy has an acceptable risk/benefit profile. Radiographic progression for soft tissue lesions will be determined as assessed by BICR according to PCWG-Modified RECIST 1.1 (Section 8.2).

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

4.2.1.2 Safety Endpoints

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

4.2.1.3 Patient-reported Outcomes

The EuroQoL-5D (EQ-5D-SL), BPI-SF, and FACT-P patient-reported outcomes (PROs) are not pure efficacy or safety endpoints because they are affected by both disease progression and study intervention tolerability.

The EQ-5D-SL 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. and de Charro, F. 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 FACT-P is a disease-specific 39-item questionnaire included for the purpose of assessing HRQoL and prostate cancer-specific symptoms. It is a well-established measure of HRQoL/health status commonly 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 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 functions [Cleeland, C. S. and Ryan, K. M. 1994].

The Patient Analgesic Log will be used to capture all analgesic medication dosages and dose times. Both the BPI-SF and Patient Analgesic Log will be used over a 7-day period each treatment cycle.

4.2.1.4 Planned Exploratory Biomarker Research

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

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

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

Genetic (DNA) analyses from tumor

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

Tumor and blood RNA analyses

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

Proteomics and immunohistochemistry (IHC) using blood or tumor

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

Other blood-derived biomarkers

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

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

4.2.1.4.1 Planned Genetic Analysis

Genetic variation may impact a participant's response to therapy, susceptibility to, severity, and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a sample will be collected for DNA analysis from consenting participants.

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

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

4.2.1.5 Future Biomedical Research

The Sponsor will conduct future biomedical research 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 future biomedical research.

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 future biomedical research 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 future biomedical research are presented in Appendix 6.

4.2.2 Rationale for the Use of Placebo

Normal saline or dextrose infusion Q3W will be used as placebo for pembrolizumab. The use of saline or dextrose placebo in combination with chemotherapy will ensure the objectivity of the investigator. The use of a placebo-controlled trial will allow for testing the hypotheses that OS for participants treated with pembrolizumab and chemotherapy is superior to the combination of placebo and chemotherapy in participants with mCRPC to be tested.

4.3 Justification for Dose

4.3.1 Pembrolizumab

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

- Clinical data from 8 randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg Q2W,

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

- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [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 (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5- fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also 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 the 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 KN001 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 the fixed-dosing provides similar control of PK variability as weight-based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics and given that fixed-dose 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 Docetaxel

The recommended dose of docetaxel for mCRPC is 75 mg/m^2 Q3W as a 1-hour IV infusion for a maximum of 10 cycles. The recommended premedication with dexamethasone is 8 mg PO at 12 hours, 3 hours, and 1 hour before the start of the docetaxel infusion. Steroid pretreatment prior to docetaxel administration as per local standard of care is allowed. Prednisone/prednisolone 5 mg PO BID is administered continuously according to the docetaxel prescribing information for the treatment of mCRPC. After cessation of docetaxel treatment, prednisone/prednisolone should be discontinued.

Refer to Section 6.6.3 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 signs the ICF. The overall study ends when the last participant completes the last study-related telephone call or visit, 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

Male participants with mCRPC in the pre-chemotherapy state who have been previously treated with an NHA and have failed treatment or become intolerant of the drug and meet the following inclusion criteria will be enrolled in this study.

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. Diagnosis must be stated in a pathology report and confirmed by the investigator.

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

    a. PSA progression using local laboratory values as defined by a minimum of 2 consecutive rising PSA levels with an interval of ≥1 week between each assessment

where the PSA value at screening should be ≥1 ng/mL – See Section 8.2.2 – Prostate-specific Antigen Assessment for further details.

Note: A PSA level obtained during the Screening Period can count as the confirmatory second rising PSA.

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

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

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

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

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

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

5. Have received prior treatment with one (but not more than one) NHA (eg, abiraterone acetate, enzalutamide, apalutamide, or darolutamide) for mHSPC or CRPC and either:

   a) progressed through treatment after a minimum of 8 weeks treatment (minimum 14 weeks for those with bone progression).

   OR

   b) have become intolerant of the drug (minimum 4 weeks treatment).

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

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

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

Table 1 Laboratory Values for Adequate Organ Function

System	Laboratory Value
Hematological	
ANC	>1,500/μL
Platelets[a]	≥100,000/μL
Hemoglobin[a]	≥9.0 g/dL or ≥5.6 mmol/L
Renal	
Serum creatinine **OR** Measured or calculated[b] creatinine clearance (GFR can also be used in place of creatinine or creatinine clearance)	≤1.5 × ULN **OR** ≥60.0 mL/min for participant with creatinine levels >1.5 × ULN
Hepatic	
Serum total bilirubin	Total bilirubin ≤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 therapeutic range of intended use of anticoagulants ≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

a. Hemoglobin and platelet requirements cannot be met by use of recent transfusion or growth factor support (GCSF or erythropoietin) within 28 days prior to treatment randomization.

b. Creatinine clearance should be calculated per institutional standard.

Abbreviations: ALT=alanine aminotransferase; ANC=absolute neutrophil count; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; GCSF=granulocyte colony-stimulating factor; GFR=glomerular filtration rate; 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.

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

Demographics

9. Participant is male.

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

Male Participants

Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

11. Male participants are eligible to participate if they agree to the following during the intervention period and for at least 120 days after the last dose of pembrolizumab or 180 days after the last dose of docetaxel, whichever is longer:

    - 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 [Appendix 5]) as detailed below:

    - Agree to use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a woman of childbearing potential (WOCBP) who is not currently pregnant. Note: Men 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.

12. Male participants must agree to use male condom when engaging in any activity that allows for passage of ejaculate to another person of any sex.

Female Participants

Not applicable.

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 future biomedical research. However, the participant may participate in the main study without participating in future biomedical research.

Additional Categories

14. Have provided newly obtained core or excisional biopsy (obtained within 12 months of screening) from soft tissue not previously irradiated (samples from tumors progressing in a prior site of radiation are allowed; other exceptions may be considered after Sponsor consultation). Participants with bone only or bone predominant disease may provide a

bone biopsy sample. However, if obtaining a fresh biopsy is not feasible, then participants may provide an archival tumor tissue sample after Sponsor consultation (SCF). Formalin-fixed, paraffin embedded (FFPE) tissue blocks are preferred to slides. Newly obtained biopsies are preferred to archive tissue.

Note: If submitting unstained cut slides, newly cut slides should be submitted to the testing laboratory within 14 days from the date slides are cut (details pertaining to tumor tissue submission can be found in the Procedures Manual).

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

5.2 Exclusion Criteria

The participant must be excluded from the study if the participant:

Medical Conditions

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

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

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

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

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

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

7. Is unable to swallow tablets/capsules.

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

9. Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.

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

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

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

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

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

15. Has ascites and/or clinically significant pleural effusion.

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

Prior/Concomitant Therapy

17. Has received a whole blood transfusion in the last 120 days prior to entry into the study. Packed red blood cells and platelet transfusions are acceptable if not given within 28 days of the first dose of study intervention.

18. 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 prior to the first dose of study intervention.

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

    Note: Treatment with denosumab as standard of care for bone metastases is permitted if the participant has been on a stable dose for ≥4 weeks prior to randomization.

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

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

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

23. Has received prior treatment with docetaxel or another chemotherapy agent for metastatic prostate cancer. NOTE: Participants who received docetaxel for mHSPC are permitted provided they received ≥6 cycles and did not progress within 1 year after the last dose of docetaxel.

24. Has hypersensitivity to docetaxel or polysorbate 80.

25. Participant is currently receiving either strong or moderate inhibitors of cytochrome P450 (CYP)3A4 that cannot be discontinued for the duration of the study.

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

26. Has received prior targeted small molecule therapy or abiraterone acetate, enzalutamide, apalutamide or darolutamide within 4 weeks prior to the first dose of study intervention, or has not recovered (ie, Grade ≤1 or at baseline) from AEs due to a previously administered agent.

    Note: Participants with Grade ≤2 alopecia may be eligible.

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

28. Has received a live vaccine within 30 days prior to randomization. Examples of live vaccines include, but are not limited to, the following: 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.

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

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

30. Has received prior treatment with ketoconazole for prostate cancer.

Prior/Concurrent Clinical Study Experience

31. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study intervention.

    Note: Participants who have entered the non-treatment 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

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

Other Exclusions

33. Is expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 120 days after the last dose of study intervention.

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

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

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

5.3.2 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Refer to Appendix 5 for approved methods of contraception.

Participants should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study, participants with a partner of childbearing potential must adhere to the contraception requirement (Appendix 5) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of pembrolizumab/placebo or 180 days after the last dose of docetaxel, whichever is longer. If there is any question that a participant with a

partner of childbearing potential will not reliably comply with the requirements for contraception, that participant should not be entered into the study.

5.3.3 Pregnancy

If a participant impregnates his female partner, the study personnel at the site must be informed immediately, and the pregnancy must be reported to the Sponsor and followed up as described in Section 8.4.

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 the study intervention or withdraws consent 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 will be packaged to support enrollment. When a replacement participant is required, the Sponsor or designee needs to be contacted prior to dosing the replacement supplies. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

As of Amendment 06, placebo treatment should stop immediately. Investigators should inform all participants of the study results; participants who are deemed to be deriving clinical benefit from treatment may continue at the discretion of the investigator. All other study participants should be discontinued from study and be offered SOC treatment as deemed necessary by the investigator. The study intervention(s) 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/ Treatment Period/ Vaccination Regimen	Use	IMP/ NIMP	Sourcing
Arm 1	Experi-mental	pembrolizumab	Biological/ Vaccine	Solution for Infusion	25 mg/mL	200 mg	IV Infusion	Day 1 of each 21-day cycle	Experimental	IMP	Central or Local
Arm 1, Arm 2	Other	docetaxel	Drug	Solution for Infusion	10 or 20 mg/mL[a]	75 mg/m^2	IV Infusion	Day 1 of each 21-day cycle	Standard of Care	NIMP	Central or local
Arm 1, Arm 2	Other	prednisone (or equivalent dose of prednisolone[b])	Drug	Tablet	5 mg	5 mg	Oral	BID	Standard of Care	NIMP	Local
Arm 1, Arm 2	Other	Recommended dexamethasone (or equivalent dose of another corticosteroid[c]) premedication. Local SOC premedication allowed	Drug	Tablet	8 mg	8 mg	Oral	12, 3, and 1 hour prior to docetaxel administration	Standard of Care	NIMP	Local
Arm 2	Placebo	Normal saline or dextrose[d]	Other	Solution for Infusion	N/A	N/A	IV infusion	Day 1 of each 21-day cycle	Placebo	IMP	Local

BID= twice daily; IMP = Investigational Medicinal Product; IV = intravenous; NIMP = Non-Investigational Medicinal Product; SOC = Standard of care.

Note: Definition IMP and 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.

[a] When locally supplied, docetaxel unit vial strength is based on region.

[b] Prednisone is the preferred steroid to be used in the study. Prednisolone should only be used when prednisone is unavailable.

[c] Dexamethasone, or the equivalent dose of another steroid, is the preferred corticosteroid to be used in the study. Local standard of care premedication prior to docetaxel infusion is allowed

[d] Normal saline is the primary diluent/placebo for pembrolizumab; use dextrose only if saline is not available.

All study interventions will be administered on an outpatient basis.

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

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

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

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Details on preparation and administration of pembrolizumab/placebo are provided in the Pharmacy Manual. Concomitant chemotherapeutic agents will be prepared and administered as per the approved product labels.

6.2.2 Handling, Storage, and Accountability

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

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

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

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

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

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

6.3.2 Stratification

Participants will be stratified according to the following factors:

- Prior NHA treatment: abiraterone (Yes vs. No)
- Metastases: bone only versus liver versus other

NOTE: for metastases, if there are only bone metastases, it will be categorized as bone only; otherwise (ie, not bone only), if there are liver metastases, then participants will be categorized as liver. All other participants will be categorized as other.

6.3.3 Blinding

As of Amendment 06: all participants will be unblinded. The subsections below are retained for reference.

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

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

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

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

6.4 Study Intervention Compliance

Administration of study medication(s) will be monitored by the investigator and/or study staff. The total volume of study medication infused will be compared with the total volume prepared to determine compliance with each dose administered.

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

For prednisone/prednisolone taken at home, the site will validate compliance with study intervention at each site visit according to their standard operating procedure.

6.5 Concomitant Therapy

6.5.1 Prohibited Concomitant Therapy

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

In addition, the following concomitant medications/vaccinations are not permitted:

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

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

- Radiation therapy

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

- Live vaccines within 30 days prior to randomization and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, 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.

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

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

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

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an AE that is suspected to have an immunologic etiology or that are listed as permitted below. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

Note: The following uses of systemic glucocorticoids **are permitted** without Sponsor consultation:

    - Concomitant prednisone/prednisolone 5 mg PO BID during treatment with docetaxel.

    - Standard dexamethasone (or equivalent) premedication prior to administration of docetaxel.

    - Inhaled steroids for management of asthma.

    - Intranasal steroids for allergies.

    - Use of prophylactic corticosteroids to avoid allergic reactions (eg, IV contract dye).

    - Treatment with palliative prednisone up to 10 mg daily or corticosteroid equivalent in the manner used to treat men with prostate cancer.

- Physiologic doses of corticosteroids for adrenal insufficiency.

- Strong or moderate inhibitors of cytochrome CYP3A4.

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

In addition to the medications listed here, site staff should refer to the local approved product label for permitted and prohibited medications, as well as drug-drug interactions for docetaxel and prednisone.

The Exclusion Criteria describe other medications which are prohibited in this study.

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

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the eCRF including all prescription, over-the-counter (OTC) products, herbal supplements, and IV medications and fluids. If changes occur during the study period, documentation of drug dosage, frequency, route, and date should also be included on the eCRF.

All concomitant medications received within 28 days prior to the first dose of study intervention and up to 30 days after the last dose of study intervention should be recorded. All concomitant medications administered during SAEs or ECIs are to be recorded. SAEs and ECIs are defined in Section 8.4.

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 6.6.2, Table 3. 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 3 in Section 6.6.2 for guidelines regarding dose modification and supportive care.

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

6.5.3 Radiotherapy

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

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

6.6 Dose Modification (Escalation/Titration/Other)

6.6.1 Concomitant Combination Therapy

If either pembrolizumab/placebo is interrupted for >12 weeks, the site must gain approval via Sponsor consultation form (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 following consultation with the Sponsor until criteria for discontinuation of treatment are met (eg, disease progression). A maximum of 10 cycles of docetaxel + prednisone/prednisolone is allowed. It is recommended that participants receive a minimum of 6 cycles of docetaxel, unless specific withdrawal/treatment discontinuation criteria are met.

In response to AEs that occur during combination therapy, refer to the approved labeling for docetaxel for more detailed information regarding dose regimen/modification, and refer to Table 3 for pembrolizumab dose modification. Additionally, refer to the respective product information/labeling for additional information about avoidance of concomitant medications or foods that may affect the metabolism of these drugs.

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

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

AEs associated with pembrolizumab exposure may represent an immune-related response. These irAEs may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be

included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids.

Dose Modification and Toxicity Management Guidelines for irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations are provided in Table 3.

Table 3 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		

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

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

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

Dose Modification and Toxicity Management of Infusion Reactions Related to Pembrolizumab

Pembrolizumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 4.

Table 4 Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

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

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

Other Allowed Dose Interruption for Pembrolizumab/Placebo

Pembrolizumab/placebo may be interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to study therapy. Participants should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the participant's study record.

6.6.3 Dose Modification for Docetaxel

Adverse events due to docetaxel will be managed as shown in Table 5.

Table 5 Docetaxel Dose Modification Guidelines for Drug-related Adverse Events

Toxicity	Hold Treatment	Docetaxel Timing for Restarting Treatment	Action
Diarrhea/Colitis	Grade 2 or 3	Toxicity resolves to Grade 0 or 1	Reduce subsequent doses
	Grade 4	Discontinue docetaxel	Discontinue docetaxel
AST (SGOT), ALT (SGPT)	Grade 2	Toxicity resolves to Grade 0 or 1	Reduce subsequent doses
	Grade 3 or 4	Discontinue docetaxel	Discontinue docetaxel
Bilirubin	>ULN	<ULN	Reduce subsequent doses
ANC	<1500	>1500	See footnote[a]
Febrile neutropenia	Grade 3 with fever[b]	See footnote[c]	Reduce dose
Platelet count	<100,000	>100,000	See footnote[d]
Peripheral neuropathy	Grade 2	Grade ≤1	Reduce subsequent doses
	Grade ≥3	Discontinue docetaxel	Discontinue docetaxel
Other grade ≥3 toxicities attributed to docetaxel except for Grade 3 lymphopenia	Grade ≥3	Grade ≤1 or baseline	Reduce subsequent doses

[a] If on Day 1 of the next cycle, the ANC is <1500, hold docetaxel. Recheck ANC weekly. Hold docetaxel until recovery to ANC 1500. If neutrophil count is <500 cells/mm^3 for a sustained period of at least 1 week from the preceding cycle, the dose of docetaxel should be reduced in successive cycles. If the ANC does not recover to >1500 in 3 weeks from the previously scheduled Day 1, discontinue docetaxel and continue with pembrolizumab monotherapy.

[b] Grade 3 neutropenia associated with fever (one reading of oral temperature of >38.5 or 3 readings of oral temperature >38.0 in a 24-hour period.

[c] For retreatment, fever must have resolved and infection be adequately treated and clinically resolved before next dose. If bacteremia blood cultures must be negative on recheck.

[d] If on Day 1 of the next cycle the platelet count is less than 100,000, hold docetaxel. Recheck platelet count weekly. Hold docetaxel until recovery to platelet count 100,000. Reduce dose of docetaxel in successive cycles. If the platelet count does not recover to >100,000 in 3 weeks from the previously scheduled Day 1, discontinue docetaxel and continue with pembrolizumab monotherapy.

Abbreviations: ALT= alanine aminotransferase; ANC=absolute neutrophil count; AST=aspartate aminotransferase; SGOT=serum glutamic oxaloacetic transaminase; SGPT=serum glutamic pyruvic transaminase; ULN=upper limit of normal.

After resolution of the toxicity, the subject can resume treatment with docetaxel with a dose reduction according to Table 6. Once the dose has been reduced, it may not be escalated up to a previous dose level.

Table 6 Docetaxel Dose Reduction Guidelines

Drug	Dose/Potency	Regimen
Initial docetaxel dose	75 mg/m^2	Every 3 weeks
Dose reduction	60 mg/m^2	Every 3 weeks

If a scheduled docetaxel dose must be delayed for 3 consecutive weeks, docetaxel must be discontinued.

Other Allowed Dose Interruption for Docetaxel

Docetaxel may be interrupted for situations other than treatment-related AEs such as medical/surgical events or logistical reasons not related to study therapy. Participants should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the participant's study record.

6.6.4 Second Course

NOTE: As of Amendment 06, second course treatment is not an option for participants. There are currently no participants in the Second Course Phase.

All participants who received pembrolizumab who stop study intervention with SD or better may be eligible for up to an additional 17 cycles (approximately 1 year) of pembrolizumab monotherapy treatment if they progress after stopping study intervention from the initial treatment phase. 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

- Stopped initial study intervention after attaining an investigator determined confirmed CR based on RECIST 1.1, and
- Was treated with at least 8 cycles of study intervention before discontinuing treatment, and
- Received at least 2 cycles with pembrolizumab beyond the date when the initial CR was declared

OR

- 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

- Experienced BICR-verified radiographic disease progression by RECIST 1.1 after stopping initial treatment, and
- Upon unblinding at the time of centrally verified disease progression were found to have received pembrolizumab, and
- No new anticancer treatment was administered after the last dose of study intervention, and
- The participant meets all of the safety parameters listed in the inclusion criteria and none of the safety parameters listed in the exclusion criteria, and
- The study is ongoing

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

6.6.5 Management of Overlapping Toxicities

Based on the known toxicity profiles of pembrolizumab and docetaxel, certain treatment-related AEs are uniquely associated with one drug versus the other. For example, neutropenia, anemia, thrombocytopenia, peripheral neuropathy, alopecia, nail disorders, and fluid retention are known risks for docetaxel treatment, while irAEs are risks for pembrolizumab treatment. However, certain AEs, such as such as skin reactions, infusion-related reactions and liver enzyme elevation, 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 proper clinical management.

If an AE is suspected to be treatment related and is severe/life threatening at the time of onset or is rapidly worsened, action including interrupting both drugs and initiating treatment with a corticosteroid and other supportive care should be taken promptly.

6.7 Intervention After the End of the Study

Upon study completion, participants are to be discontinued and may be enrolled in an extension study using pembrolizumab monotherapy, if available.

6.8 Clinical Supplies Disclosure

The emergency unblinding call center will use the intervention/randomization schedule for the study to unblind participants and to unmask study intervention identity . The emergency unblinding call center should only be used in cases of emergency (see Section 8.1.10). In the event that the emergency unblinding call center is not available for a given site in this study, the central electronic intervention allocation/randomization system (IRT) should be used to

unblind participants and to unmask study intervention identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

6.9 Standard Policies

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

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

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

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

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

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

- The participant or participant's legally acceptable representative requests to discontinue study intervention.

- The participant interrupts study intervention administration for more than 12 consecutive weeks of pembrolizumab or has missed 2 consecutive cycles of docetaxel.
  NOTE: Interruptions from the protocol-specified treatment plan for more than 12 weeks between pembrolizumab doses or 6 weeks between docetaxel 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.

- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.

- Recurrent Grade 3 colitis/diarrhea.

- Confirmed BICR-verified radiographic disease progression outlined in Appendix 8 (exception if the Sponsor approves treatment continuation).

  - As of Amendment 06, central tumor response assessments will no longer be performed. However, participants still on study will be assessed by the investigator for disease progression per local SOC schedule.

- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment

- Recurrent Grade 2 pneumonitis

- Completion of 35 cycles (approximately 2 years) with pembrolizumab

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

- Discontinuation of treatment may be considered for participants who have attained a confirmed CR and have been treated for at least 8 cycles (at least 24 weeks), receiving 2 cycles of the combination including 2 doses of pembrolizumab or placebo and at least 80% of the planned doses of docetaxel beyond the date when the initial CR was declared. These participants may be eligible for second course treatment described in Section 6.6.4.

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/her 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 future biomedical research consent to the participant, answer all of his/her questions, and obtain written informed consent before performing any procedure related to future biomedical research. 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 significant. In addition, significant and potentially relevant conditions that occurred >10 years should also 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 prior to randomization. Treatment for the disease for which the participant has enrolled in this study will be recorded separately and not listed as a prior medication.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study through the Safety Follow-up visit. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 8.4.2. In addition, new medications started during the Second Course Phase through the Second Course Safety Follow-up visit should be recorded.

8.1.6 Assignment of Screening Number

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

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

8.1.6.1 Treatment Eligibility Assessment (TEA) Form

As of Amendment 06: The TEA form will no longer be collected. The subsection below is retained for reference.

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

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

8.1.7 Assignment of Treatment/Randomization Number

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

Upon study completion, participants are discontinued from the current study and may be transitioned into a pembrolizumab extension study, if available. All participants in the extension study will be allocated by non-random assignment and will receive a treatment/randomization number. The treatment/randomization number identifies the participant for all procedures occurring after treatment allocation. This number will be unique from the treatment/randomization number in the parent study.

8.1.8 Study Intervention Administration

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

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

8.1.8.1 Timing of Dose Administration

8.1.8.1.1 Pembrolizumab/Placebo

Pembrolizumab or placebo will be administered as a 30-minute IV infusion on Day 1 of each cycle. Pembrolizumab or placebo will be administered prior to docetaxel. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of –5 minutes and +10 minutes is permitted (ie, infusion time is 30 minutes: –5 min/+10 min).

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

8.1.8.1.2 Docetaxel

Docetaxel, at a dose of 75 mg/m^2, will be administered as an IV infusion on Day 1 of each cycle for up to 10 cycles. Docetaxel administration should begin 30 minutes after the end of the pembrolizumab IV infusion per local practice and product label. The recommended premedication with dexamethasone is 8 mg at 12 hours, 3 hours, and 1 hours prior to docetaxel infusion. Steroid pretreatment prior to docetaxel administration as per local standard of care is allowed. Participants should be treated concomitantly with prednisone/prednisolone (5 mg BID) according to the approved product label and/or standard of practice. After cessation of docetaxel treatment, prednisone/prednisolone should be discontinued (tapering is acceptable per standard of care).

8.1.9 Discontinuation and Withdrawal

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

When a participant withdraws from participation in the study, all applicable activities scheduled for the 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

As of Amendment 06: all participants will be unblinded. The subsections below are retained for reference.

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

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

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

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

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

8.1.10.1 Non-emergency Unblinding

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

8.1.11 Calibration of Equipment

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

8.2 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 treatment until criteria for discontinuation are met, tumor imaging should continue per local SOC schedule.

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

Tumor imaging should be to be acquired by computed tomography (CT is strongly preferred) and radionuclide bone scan. For the abdomen and pelvis, contrast-enhanced magnetic resonance imaging (MRI) may be used when CT with iodinated contrast is contraindicated, or when mandated by local practice. Magnetic resonance imaging is the strongly preferred modality for imaging the brain. The same imaging technique regarding modality, ideally the same scanner, and the use of contrast should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the assessment of response or progression based on imaging. Tumor imaging by both CT (or MRI) chest, abdomen, pelvis and whole-body radionuclide bone scan is required at every scheduled imaging time point. MRI (or CT) brain imaging is only as clinically indicated at baseline and on study.

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

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

When the investigator identifies radiographic progression, the central imaging vendor will perform expedited verification of radiologic PD and communicate the results to the study site and Sponsor. Treatment should continue until PD has been verified. Once disease progression is verified centrally, subsequent imaging (if acquired) should not be submitted to the iCRO.

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

Assessment of treatment response in soft tissues will be according to soft tissue rules of PCWG-Modified RECIST 1.1, modified to follow a maximum of 10 target 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 rules, as described in Appendix 8.

Soft tissue and bone response assessments will be combined to produce an overall radiographic response, as shown in Table 7.

Table 7 Overall Radiographic Response per PCWG-modified RECIST

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

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

8.2.1.1 Initial Tumor Imaging

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

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

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

MRI of the brain at screening should be performed only if clinically indicated.

8.2.1.2 Tumor Imaging During the Study

In the first year, on-study imaging assessments must be performed every 9 weeks (63 days ± 7 days) from the date of randomization (through Week 54). Participants who remain on treatment beyond Week 54 will have imaging performed every 12 weeks (84 days ± 7 days). Imaging should continue to be performed until disease progression is identified by the investigator and verified by the BICR, the start of new anticancer treatment, withdrawal of consent, or death, whichever occurs first. All supplemental imaging must be submitted to the central imaging vendor.

Timing of imaging should follow calendar days from date of randomization and should not be adjusted for delays in cycle starts.

Response must be confirmed at least 4 weeks later to be considered for best overall response.

Radiographic progression will be determined according to PCWG-modified RECIST 1.1. Disease progression in bone lesions should be confirmed by another bone scan ≥6 weeks after site-assessed first 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 prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory.

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

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

- Disease progression as defined by PCWG Modified RECIST 1.1 as 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, 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 prior to restarting treatment with pembrolizumab. Local reading (investigator assessment with site radiology reading) will be used to determine eligibility. All second course imaging should be performed locally.

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

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

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

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

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.

8.2.2 Prostate-specific Antigen Assessments

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

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

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]

Figure 2 Change in Prostate-specific Antigen

The screening value performed during the Screening Period can count as the confirmatory second rising PSA compared to a prior single increased PSA value. If a PSA value during screening is used as the second data point to confirm rising PSA and it 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.

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

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

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

In participants who discontinue study intervention without documented disease progression, every effort should be made to continue monitoring their disease status by PSA assessments until: 1) the start of new anticancer treatment, 2) disease progression, 3) death or 4) the end

of the study, whichever occurs first. In these participants, PSA will be measured by a central laboratory at the same time points as imaging.

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

8.2.3 Tumor Tissue Collection

Baseline tumor tissue for biomarker analysis must be sent to the testing laboratory and analyzed for adequacy prior to enrollment. (Details pertaining to tumor tissue submission can be found 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 EuroQoL EQ-5D-SL, FACT-P, and the BPI-SF and analgesic questionnaires should be administered per the SoA in Section 1.3. Both the EQ-5D-SL and the FACT-P will be administered at the site, while the BPI-SF and analgesic questionnaires 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 prior to drug 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 the assessment was not performed. Site staff must not read, administer or complete the PRO questionnaires on behalf of 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 EQ-5D-SL

The 5 health state dimensions in the EQ-5D-SL include the following: 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-SL also includes a graded (0 to 100) vertical visual analog scale on which the participant rates his or her general state of health at the time of the assessment.

8.2.4.2 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 contains a 27-item self-report questionnaire measuring general health-related quality of life 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.

8.2.4.3 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). It does not have to be completed at the site.

The BPI-SF has 15 items that are rate 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 consists of 4 items (Items 3, 4, 5, and 6) which assess pain at its "worst," "least," "average," and "now" (current pain) respectively on the 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 the 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.

Patient 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). Participants will record all analgesic medication dosages and dosage times. All medications captured in ePRO database will be reconciled periodically with the concomitant medications data to address any discrepancies. The Analgesic Log is study specific (not generic).

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 exam during the Screening Period. Clinically significant abnormal findings should be recorded as medical history. The time points for full physical exams are described in Section 1.3. After the first dose of study intervention, new clinically significant abnormal findings should be recorded as AEs.

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

8.3.1.2 Directed Physical Examination

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

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

8.3.2 Vital Signs

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

8.3.3 Electrocardiograms

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

8.3.4 Clinical Safety Laboratory Assessments

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

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

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

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

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

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

8.3.4.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

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

8.3.5 Performance Assessments

8.3.5.1 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status at screening (within 7 days of randomization) and prior to dosing during the treatment period, as specified in the SoA (Section 1.3).

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

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

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

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

The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity and causality.

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.

- 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 8.

Table 8 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 and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

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

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

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, and investigators.

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

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

8.4.5 Pregnancy and Exposure During Breastfeeding

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

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

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

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

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

8.4.7 Events of Clinical Interest (ECIs)

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

Events of clinical interest for this study include:

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).

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.

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 Future Biomedical Research:

- 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 local IRB/Independent Ethics Committee [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 future biomedical research only if participant signs the Future Biomedical Research consent.

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 (eg, protein, RNA, DNA, 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

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

Health Economics and Medical Resource Utilization are not evaluated in this study.

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

- Laboratory tests are to be performed within 10 days prior to the first dose of study intervention. An exception is HIV and hepatitis testing which may be done up to 28 days prior to randomization if required by local regulations. Refer to Appendix 7 for country-specific requirements.

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

- Imaging for screening assessments is to be performed within 28 days prior to randomization.

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

- 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 is 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 8.1.

8.12.3 Discontinued Participants Continuing to be Monitored in the Study

The Discontinuation Visit should occur at the time study treatment is discontinued. If the Discontinuation Visit occurs 30 after the last dose of study treatment, at the time of the mandatory Safety Follow-up visit, procedures do not need to be repeated. Visit requirements are outlined in Section 1.3 – Schedule of Activities. Prior to discontinuing participants from therapy, submit the Treatment Termination & Disease Assessment Termination Form.

8.12.4 Post-treatment Visits

8.12.4.1 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 the Second Course Treatment.

8.12.4.2 Follow-up Visits

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

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

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

8.12.4.3 Survival Follow-up

As of Amendment 06: Survival Follow-up visits will be discontinued. Those participants remaining on study 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.

8.12.5 Survival Status

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

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any unblinding/final database lock, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to unblinding/final database lock, will be documented in a sSAP and referenced in the Clinical Study Report for the study. Post hoc exploratory analyses will be clearly identified in the Clinical Study Report. Other planned analyses (ie, those specific to the analysis of PK data, patient-reported outcomes, and future biomedical research) 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 statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 9.2 through 9.12.

Study Design Overview	A Phase 3, Randomized, Double-blind Treatment Study of Pembrolizumab (MK-3475) Plus Docetaxel versus Placebo Plus Docetaxel in Participants with Chemotherapy-naïve Metastatic Castration-Resistant Prostate Cancer (mCRPC) who have Progressed on Next Generation Hormonal Therapy
Treatment Assignment	Approximately 1000 eligible participants will be randomized in a 1:1 ratio to one of the following 2 treatment arms: • Arm 1: pembrolizumab plus docetaxel plus prednisone/prednisolone • Arm 2: placebo plus docetaxel plus prednisone/prednisolone Randomization stratification factors are: • Prior NHA treatment: abiraterone (Yes vs. No) • Metastases: bone only versus liver versus other
Analysis Populations	Efficacy: Intent to Treat (ITT) Safety: All Participant as Treated (APaT)
Primary Endpoint(s)	1. Overall Survival (OS) 2. Radiographic Progression-Free Survival (rPFS)
Key Secondary Endpoints	1. Time to initiation of the first subsequent anti-cancer therapy or death (TFST)
Statistical Methods for Key Efficacy Analyses	The primary hypotheses will be evaluated by comparing pembrolizumab plus docetaxel plus prednisone/prednisolone with placebo plus docetaxel plus prednisone/prednisolone arm with respect to OS, TFST, and rPFS using a stratified log-rank test. The hazard ratio will be estimated using a Cox regression model. Event rates over time will be estimated within each treatment group using the Kaplan-Meier method.
Statistical Methods for Key Safety Analyses	The analysis of safety results will follow a tiered approach. The tiers differ with respect to the analyses that will be performed. There are no events of interest that warrant elevation to Tier 1 events in this study. Tier 2 parameters will be assessed via point estimates with 95% CIs provided for between-group comparison; only point estimates by treatment group are provided for Tier 3 safety parameters. The 95% CIs for the between-treatment differences in percentages will be provided using the Miettinen and Nurminen method.
Interim Analyses	Two interim analyses (IAs) will be performed in this study. Results will be reviewed by an external data monitoring committee. These interim analyses are summarized below. Details are provided in Section 9.7. • Interim Analysis 1: ◦ Timing: To be performed when at least 468 rPFS events and approximately 302 OS events (target number of OS events) are observed (approximately 18 months after the first participant is randomized). ◦ Testing: final analysis for rPFS, final analysis for TFST, and interim analysis for OS • Interim Analysis 2: ◦ Timing: To be performed when approximately 439 OS events (target number of OS events) are observed (approximately 23 months after the first participant is randomized). ◦ Testing: interim analysis 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. and Bretz, F. 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	The planned sample size is approximately 1000 participants. For rPFS, the trial has approximately 93% power to demonstrate that pembrolizumab plus docetaxel plus prednisone/prednisolone is superior to placebo plus docetaxel plus prednisone/prednisolone (HR: 0.70) at an overall 1-sided 0. 5% alpha-level. For OS, the trial has about 90% power to demonstrate that pembrolizumab plus docetaxel plus prednisone/prednisolone is superior to placebo plus docetaxel plus prednisone/prednisolone (HR: 0.75) at an initial overall 1-sided 2.0% alpha-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.

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

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

Extension Portion in China:

For all participants in China, including participants randomized in the global portion and the extension portion, participant level treatment randomization information will be blinded to the statistician(s)/programmer(s) responsible for the analysis of the Extension Portion in China until the extension portion database lock is achieved. The extent to which individuals are unblinded to the results will be limited. Blinded and unblinded members will be clearly 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.

9.4.1 Efficacy Endpoints

9.4.1.1 Primary

Overall Survival (OS)

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

9.4.1.3 Secondary

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

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

Duration of Response (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 until the earliest date of disease progression or death from any cause, whichever occurs first.

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

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

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

3) occurrence of spinal cord compression

4) a tumor-related orthopedic surgical intervention, whichever occurs first

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

Time to PSA progression is defined as the time from randomization to PSA progression. Participants without PSA progression will be censored at the last PSA assessment date. The

PSA progression date is defined as the date that 1) ≥25% increase and ≥2 ng/mL above the nadir, and which is confirmed by a second value ≥3 weeks later if there is PSA decline from baseline 2) or ≥25% increase and ≥2 ng/mL increase from baseline beyond 12 weeks if there is no PSA decline from baseline.

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 adverse events, laboratory values and vital signs.

9.4.3 Patient-Reported Outcome Endpoints

9.4.3.1 Time to Pain Progression (TTPP)

Time to pain progression 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 to 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 are randomized for the analysis of efficacy data using the ITT population.

Extension Portion in China:

After enrollment of the global portion is closed, the study will continue to randomize participants in China until the sample size for participants in China reaches approximately 150. The participants in China who are randomized in the extension portion will not be included in the primary efficacy analysis population for the global portion. The China ITT population, including all participants in China randomized in the global portion and the extension portion, will be analyzed separately.

9.5.2 Safety Analysis Populations

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

At least 1 laboratory, vital sign, or ECG measurement obtained subsequent to 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.

Extension Portion in China:

The participants in China randomized and treated in the extension portion after completion of the global enrollment will not be included in the primary safety analysis population for the global portion. The China APaT population, including all participants in China randomized in the global portion and the extension portion who received at least 1 dose of study treatment, will be analyzed separately.

9.5.3 PRO Analysis Population

The PRO analyses are based on the PRO full analysis set 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

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

combining of strata will be specified in the sSAP prior to database lock based on a blinded review of response counts by stratum.

9.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary and key secondary objectives. Methods related to other objectives will be described in the sSAP.

9.6.1.1 Overall Survival

The non-parametric Kaplan-Meier method will be used to estimate the survival curves. The treatment difference in survival will be assessed by the stratified log-rank test (based on the stratification factors defined in Section 6.3.2). A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, the 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. Restricted Mean Survival Time method proposed by Uno et al. [Uno, H., et al 2014] may be conducted for OS to account for the possible non-proportional hazards effect.

9.6.1.2 Radiographic Progression-free Survival (rPFS)

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

Since disease progression is assessed periodically, PD can occur any time in the time interval 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 a rPFS event will be censored at the last disease assessment. Sensitivity analyses will be performed for comparison of rPFS based on investigator's assessment.

In order 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 prior to missing visits. Also, data after new anti-

cancer therapy are censored at the last disease assessment prior to the initiation of new anti-cancer therapy. The first sensitivity analysis follows the intention-to-treat principle. That is, PDs/deaths are counted as events regardless of missed study visits or initiation of new anti-cancer therapy. The second sensitivity analysis considers discontinuation of treatment or initiation of an anti-cancer treatment subsequent to discontinuation of study-specified treatments due to reasons other than complete response, 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 9.

Table 9 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 anti-cancer 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 immediately after ≥2 consecutive missed disease assessments, or after new anti-cancer therapy	Censored at last disease assessment prior to the earlier date of ≥2 consecutive missed disease assessment and new anti-cancer 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 complete response; 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

In case the proportional hazards assumption is not valid, supportive analyses using Restricted Mean Survival Time method may be conducted for rPFS to account for the possible non-proportional hazards effect.

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

9.6.1.3 TFST

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

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

9.6.1.4 Analysis Strategy for Key Efficacy Endpoints

Table 10 summarizes the primary analysis approach for key efficacy endpoints.

Table 10 Efficacy Analysis Methods for Key Efficacy Endpoints

Endpoint/Variable	Statistical Method †	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 9
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 anti-cancer therapy

Abbreviations: BICR=blinded independent central review; ITT=Intent to treat; OS=Overall survival; PCWG=Prostate Cancer Working Group; rPFS= radiographic progression-free survival; TFST=Time to initiation of the first subsequent anti-cancer therapy or death.

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

The strategy to address multiplicity issues with regard to multiple efficacy endpoints, and interim analyses is described in Section 9.7 - Interim Analyses and in Section 9.8 - Multiplicity.

9.6.2 Statistical Methods for Safety Analyses

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

The analysis of safety results will follow a tiered approach (Table 11). 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 pre-specified as Tier-1 endpoints or will be classified as belonging to "Tier 2" or "Tier 3", based on observed proportions of participants with an event.

Tier 1 Events

Safety parameters or AEs of special interest that are identified a priori constitute “Tier 1” safety endpoints that will be subject to inferential testing for statistical significance. AEs that are immune-mediated or potentially immune-mediated are well documented and will be evaluated separately; however, these events have been characterized consistently throughout the pembrolizumab clinical development program, and determination of statistical significance is not expected to add value to the safety evaluation. Similarly, the combination of pembrolizumab and docetaxel has not been associated with any new safety signals. Finally, there are no known AEs associated with participants with prostate 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. and Nurminen, M. 1985].

Membership in Tier 2 requires that at least 10% of participants in any treatment group exhibit the event; all other AEs and predefined limits of change will belong to Tier 3. The threshold of at least 10% of participants was chosen for Tier 2 events because the population enrolled in this study are in critical conditions and usually experience various AEs of similar types regardless of treatment; events reported less frequently than 10% of participants would obscure the assessment of the overall safety profile and add little to the interpretation of potentially meaningful treatment differences. Because many 95% CIs may be provided without adjustment for multiplicity, the CIs should be regarded as a helpful descriptive measure to be used in safety review, not a formal method for assessing the statistical significance of the between-group differences in adverse events and safety parameters that meet predefined limits of change.

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

Tier 3 Events

Safety endpoints that are not Tier 1 or 2 events are considered Tier 3 events. Only point estimates by treatment group are provided for Tier 3 safety parameters (Table 11).

Continuous Safety Measures

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

Table 11 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	Any AE	X	X
	Any Grade 3 to 5 AE	X	X
	Any Serious AE	X	X
	Any Drug-Related AE	X	X
	Any Drug-Related and Serious AE	X	X
	Any Drug-Related and Grade 3-5 AE	X	X
	Discontinuation due to AE	X	X
	Dose modification due to AE	X	X
	Death	X	X
	Specific AEs, SOCs, or PDLCs‡ (incidence ≥10% of participants in one of the treatment groups)	X	X
Tier 3	Specific AEs, SOCs or PDLCs† (incidence <10% of participants in all of the treatment groups)		X
	Change from baseline results (laboratory test toxicity grade, vital signs, ECGs)		X

† Includes only those endpoints not pre-specified as Tier 1 or not already pre-specified as Tier 2 endpoints.

‡ Indicates broad AE category of the number of participants reporting any adverse event

Abbreviations: AE = adverse event; CI = confidence interval; ECG=electrocardiogram; PDLC=Pre-Defined Limit of Change; SOC=System Organ Class; X = results will be provided.

9.6.3 Analysis Methods for PRO Endpoints

For time to pain progression, the Kaplan Meier method will be used to estimate the survival curves for TTPP, separately, in each treatment arm. In addition, corresponding survival curves will be estimated by treatment 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 treatment groups for each relevant demographic and baseline characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants screened and randomized and the primary reason for screening failure and discontinuation will be displayed. Demographic variables, baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

9.7 Interim Analyses

Blinding to treatment assignment will be maintained at all investigational sites. The results of interim analyses will not be shared with the investigators prior to the completion of the study. Participant-level unblinding will be restricted to an external unblinded statistician and scientific programmer performing the interim analysis, who will have no other responsibilities associated with the study.

An eDMC will serve as the primary reviewer of the results of the interim analysis (analyses) of the study and will make recommendations for discontinuation of the study or protocol modifications to an executive oversight committee (EOC) of the Sponsor. If the eDMC recommends modifications to the design of the protocol or discontinuation of the study, this executive oversight committee (and potentially other limited Sponsor personnel) may be unblinded to results at the participant level in order to act on these recommendations. The extent to which individuals are unblinded with respect to results of interim analyses will be documented by the external unblinded statistician. Additional logistical details will be provided in the DMC Charter.

Treatment-level results from the interim analysis will be provided to the eDMC by the external unblinded statistician. Prior to final study unblinding, the external unblinded statistician will not be involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol deviations, or data validation efforts after the interim analyses.

9.7.1 Efficacy Interim Analyses

Two interim analyses 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. Final analysis is to be performed approximately 28 months after the first participant is randomized.

The analyses planned, endpoints evaluated, and drivers of the timing are summarized in Table 12. Type I error control for the efficacy analyses as well as efficacy bounds are described in Section 9.8 – Multiplicity.

Table 12 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 468 rPFS events to achieve 90% power • Approximate 302 OS events (target number of OS events)	~18 months	rPFS FA, TFST FA OS IA
IA 2: Interim OS analysis	OS	Approximately 439 OS events (target number of OS events)	~23 months	OS IA
FA: Final OS analysis	OS	Approximately 549 OS events (target number of OS events) and at least 12 months after the last participant is randomized	~28 months	OS FA
Abbreviations: rPFS = FA = final analysis; IA = interim analysis; OS = overall survival; radiographic progression-free survival; TFST = Time to initiation of the first subsequent anti-cancer therapy or death.				

9.7.2 Safety Interim Analyses

The eDMC will conduct regular safety interim analyses. The timing of these safety interim analyses will be specified in the eDMC charter.

9.8 Multiplicity

The study uses the graphical method of Maurer and Bretz [Maurer, W. and Bretz, F. 2013] to strongly control multiplicity for multiple hypotheses as well as interim analyses. Figure 3 shows the initial 1-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 hypotheses.

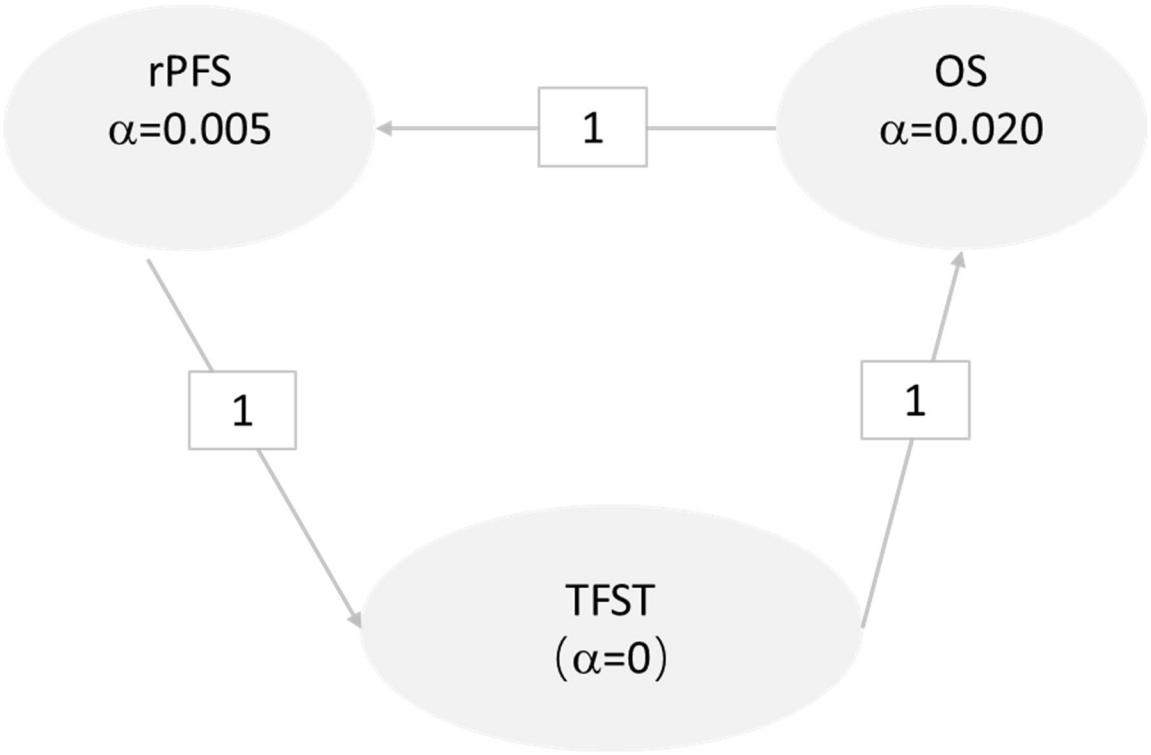

Figure 3 Multiplicity Graph for One-sided Alpha Reallocation Strategy

9.8.1 Radiographic Progression-free Survival (rPFS)

This study initially allocates one-sided $\alpha = 0.005$ for superiority test of rPFS between 2 treatment groups. If OS null hypothesis has been rejected, then rPFS hypothesis will be tested at a Type I error level of $\alpha=0.025$.

Table 13 shows the boundary properties for the rPFS. Note that the final row indicates the total power to reject the null hypothesis for rPFS superiority. In addition, if the testing of rPFS is not positive at IA1 but the testing of OS is positive at IA2 or FA, then re-testing of rPFS at IA1 will be conducted.

Table 13 Efficacy Boundaries and Properties for rPFS

Analysis	Value	α =0.005	α =0.025
IA 1: N: 1000 Events: 468 Month: 16	Z	2.5760	1.9600
	p (1-sided) §	0.0050	0.0250
	HR at bound%	0.7881	0.8343
	P(Cross) if HR=1†	0.0050	0.0250
	P(Cross) if HR=0.70#	0.9000	0.9710
IA 1: N: 1000 Events: 516 Month: 18	Z	2.5760	1.9600
	p (1-sided)§	0.0050	0.0250
	HR at bound%	0.7970	0.8420
	P(Cross) if HR=1†	0.0050	0.0250
	P(Cross) if HR=0.70#	0.9300	0.9820

§p (1-sided) is the nominal alpha for testing.
%HR at bound is the approximate HR required to reach an efficacy bound
†P(Cross if HR=1) is the cumulative probability of crossing a bound under the null hypothesis
#P(Cross if HR=0.70) is the cumulative probability of crossing a bound under the alternative hypothesis

9.8.2 Overall Survival

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

Table 14 shows the boundary properties for the interim analyses 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 the table, the bounds will be adjusted using the Lan-DeMets O'Brien-Fleming alpha-spending function accordingly. Cumulative alpha spent in the interim analysis will not exceed the pre-specified level based on the projected number of events as shown in below table. That is, if the number of observed events exceeds the pre-specified number of events in the interim analysis, then the pre-specified cumulative alpha spent in the interim analysis based on the projected number of events will be used. Otherwise, cumulative alpha 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 interim analyses and final analysis.

Table 14 Efficacy Boundaries and Properties for Overall Survival Analyses

Analysis	Value	α =0.020	α =0.025
IA 1: 55%* N: 1000 Events: 302 Month: 18	Z	2.9276	2.8059
	p (1-sided) §	0.0017	0.0025
	HR at bound%	0.7138	0.7239
	P(Cross) if HR=1†	0.0017	0.0025
	P(Cross) if HR=0.75#	0.3338	0.3791
IA 2: 80%* N: 1000 Events: 439 Month: 23	Z	2.3758	2.2759
	p (1-sided) §	0.0088	0.0114
	HR at bound%	0.7970	0.8047
	P(Cross) if HR=1†	0.0093	0.0122
	P(Cross) if HR=0.75#	0.7412	0.7728
Final N: 1000 Events: 549 Month: 28	Z	2.1172	2.0291
	p (1-sided) §	0.0171	0.0212
	HR at bound%	0.8346	0.8409
	P(Cross) if HR=1†	0.0200	0.0250
	P(Cross) if HR=0.75#	0.9000	0.9150

*Percentage of expected number of events at final analysis
§p (1-sided) is the nominal alpha for testing.
%HR at bound is the approximate HR required to reach an efficacy bound
†P(Cross if HR=1) is the cumulative probability of crossing a bound under the null hypothesis
#P(Cross if HR=0.75) is the cumulative probability of crossing a bound under the alternative hypothesis

9.8.3 TFST

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

Table 15 shows the boundary properties for the TFST. Note that the final row indicates the total power to reject the null hypothesis for TFST superiority. In addition, if the testing of TFST is not positive at IA1 but if the retesting of rPFS at IA1 is positive, then re-testing of TFST at IA1 will be conducted.

Table 15 Efficacy Boundaries and Properties for TFST

Analysis	Value	α =0.005	α =0.025
IA 1: N: 1000 Events: 516 Month: 18	Z	2.5760	1.9600
	p (1-sided)[§]	0.0050	0.0250
	HR at bound[%]	0.7970	0.8420
	P(Cross) if HR=1[†]	0.0050	0.0250
	P(Cross) if HR=0.70[#]	0.9300	0.9820

§p (1-sided) is the nominal alpha for testing.
%HR at bound is the approximate HR required to reach an efficacy bound
†P(Cross if HR=1) is the cumulative probability of crossing a bound under the null hypothesis
#P(Cross if HR=0.70) 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 interim analysis. 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

The sample size is estimated based on the primary endpoint OS.

A total of approximately 1000 participants will be randomized in a 1:1 ratio to pembrolizumab plus docetaxel plus prednisone/prednisolone group and placebo plus docetaxel plus prednisone/prednisolone group (approximately 500 participants per group).

The final analysis of OS is event-driven and will be conducted after approximately 549 events (target number of OS events) have been observed between 2 treatment groups and at least 12 months after the last participant is randomized unless OS is proven at an earlier interim analysis. It is expected to occur around 28 months after the first participant is randomized (depending on enrollment rate and event accumulation rate).

With 549 OS events, the study has approximately 90% (91.5%) power to demonstrate that males treated with pembrolizumab + docetaxel have a longer median OS than males treated with docetaxel at a one-sided significance level of 0.020 (0.025) if the underlying constant HR between treatment groups is 0.75. Sample size and power calculations are based on the following assumptions: 1) a HR of 0.75 where the OS follows an exponential distribution

with 18 months in the pembrolizumab + docetaxel group and a median of 13.5 months in the docetaxel group; 2) interim analyses for efficacy evaluation as outlined in Table 14; 3) an enrollment rate of 80 participants per month with a 6-month ramp up time; and 4) an approximately monthly drop-out rate of 0.2%.

The final analysis of rPFS will be conducted when 1) enrollment is complete; 2) At least 468 rPFS events are observed; 3) approximately 302 OS events (target number of OS events) are observed. It is expected to occur around 18 months after the first participant is randomized (depending on enrollment rate and event accumulation rate) with about 516 rPFS events.

With 516 rPFS events, the study has approximately 93% (98.2%) power to demonstrate that males treated with pembrolizumab + docetaxel have a longer median rPFS than males treated with docetaxel at a one-sided significance level of 0.005 (0.025) if the underlying constant HR between treatment groups is 0.70. These calculations are based on the following assumptions: 1) a HR of 0.70 where rPFS follows an exponential distribution with a median of 7 months in the pembrolizumab + docetaxel group and a median of 5 months in the control arm; 2) interim analyses for efficacy evaluation as outlined in Table 14; 3) an enrollment rate of 80 participants per month with a 6-month ramp up time; and 4) an approximately monthly drop-out rate of 5%.

The final analysis of TFST will be conducted at IA1 and approximately 516 TFST are expected. With 516 TFST events, the study has approximately 90% power to demonstrate males treated with pembrolizumab + docetaxel has a longer median TFST than males treated with docetaxel at a one-sided significance level of 0.005 if the underlying constant HR is 0.70. These calculations are based on the following assumptions: 1) a HR of 0.70 where TFST follows an exponential distribution with a median of 7 months in the pembrolizumab + docetaxel group and a median of 5 months in the docetaxel group; 2) IAs for efficacy evaluation as outlined in Section 9.7; 3) an enrollment rate of 80 participants per month with a 6-month ramp up time; and 4) an approximately monthly drop-out rate of 5%.

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

Extension Portion in China:

To evaluate the consistency of efficacy and safety in the population in China compared with the global population, after completion of global portion enrollment, participants in China will continue to be randomized in a 1:1 ratio into the pembrolizumab plus docetaxel plus prednisone/prednisolone arm and the placebo plus docetaxel plus prednisone/prednisolone arm until the planned sample size of approximately 150 participants in China is reached. Participants in China randomized after completion of enrollment in the global portion will not be included in the analysis of the global portion.

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 vs ≥65 years
- Race: white vs non-white
- ECOG status: 0 vs 1
- Prior NHA treatment: abiraterone (Yes vs. No)
- Metastases: bone only vs liver vs other

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.

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

9.11 Compliance (Medication Adherence)

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

9.12 Extent of Exposure

The extent of exposure for pembrolizumab and docetaxel will be summarized as duration of treatment in cycles. Dose interruption for each drug and dose reduction or dose increase for docetaxel will be summarized. Summary statistics will be provided on Extent of Exposure for 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 Executive Oversight Committee (EOC) is comprised of members of Sponsor Senior Management. The EOC will receive and decide upon any recommendations made by the DMC regarding the study.

10.1.4.2 External Data Monitoring Committee

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

The DMC will make recommendations to the EOC regarding steps to ensure both participant safety and the continued ethical integrity of the study. Also, the DMC will review interim study results, consider the overall risk and benefit to study participants (Section 9.7 - Interim Analysis) and recommend to the EOC whether the study should continue in accordance with the protocol.

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

10.1.5 Publication Policy

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

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

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

10.1.6 Compliance with Study Registration and Results Posting Requirements

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

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

10.1.7 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP (eg, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use GCP: Consolidated Guideline and other generally accepted standards of GCP); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical study.

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

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

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

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

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

10.1.8 Data Quality Assurance

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

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

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

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

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the study site upon request for inspection, copying, review, and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor or any regulatory authorities as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/CRFs.

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

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including 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 16 will be performed by the central laboratory during the initial treatment and during the Second Course phase.

- Results of pre-dose laboratory procedures must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

- During initial treatment, local laboratory results are permitted in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is used, it is important that the sample for central analysis is obtained in parallel. Additionally, if the use of local laboratory tests result in a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF. Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.1 and Section 5.2 of the protocol, respectively.

- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

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

Table 16 Protocol-required Safety Laboratory Assessments

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

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

10.3.1 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:

a. **Results in death**

b. **Is life-threatening**

- The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. **Requires inpatient hospitalization or prolongation of existing hospitalization**

- 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.

d. **Results in persistent or significant disability/incapacity**

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza,

and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

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

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

f. **Other important medical events**

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 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 and Pregnancy Testing

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

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

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

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

For individuals with permanent infertility due to an alternate medical cause other than the above (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraception Requirements

Male participants are eligible to participate if they agree to the following during the intervention period and for at least 120 days after the last dose of pembrolizumab/placebo or 180 days after the last dose of docetaxel, whichever is longer:

- 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) 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 who is not currently pregnant. Note: Men 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.

- Male participants must also agree to use male condom when engaging in any activity that allows for passage of ejaculate to another person of any sex.

10.5.3 Pregnancy Testing

Not applicable.

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 with which drugs/vaccines may interact
- 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 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 future biomedical research protocol and consent. Future biomedical research 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 Council on Harmonisation [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.

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.

10.7.2 Country-specific Testing Requirements

10.7.2.1 Germany

HIV testing and hepatitis B/C screening are required evaluations for study entry and need to be performed in order to evaluate eligibility. This testing can be performed at any time during the Screening Period.

10.7.2.2 China

Biomarker sample collection and analysis including tumor tissue collection, blood for genetic analyses, blood for RNA analyses, blood for serum/plasma analyses, and blood for ctDNA analysis, for participants enrolled in China will be dependent on approval by the Human Genetic Resources Administration of China (HGRAC).

10.7.3 Japan

Section 6.1 Study Interventions Administered

Table 2 Study Interventions

Arm Name	Arm Type	Intervention Name	Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Adminis-tration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP/ NIMP	Sourcing
Arm 1	Experi-mental	pembrolizumab	Biological/ Vaccine	Solution for Infusion	25 mg/mL	200 mg	IV Infusion	Day 1 of each 21-day cycle	Experimental	IMP	Central or Local
Arm 1, Arm 2	Other	docetaxel	Drug	Solution for Infusion	10 or 20 mg/mL[a]	75 mg/m^2	IV Infusion	Day 1 of each 21-day cycle	Standard of Care	NIMP	Central or local
Arm 1, Arm 2	Other	prednisone (or equivalent dose of prednisolone[b])	Drug	Tablet	5 mg	5 mg	Oral	BID	Standard of Care	NIMP	Local
Arm 1, Arm 2	Other	Recommended dexamethasone (or equivalent dose of another corticosteroid[c]) premedication. Local SOC premedication allowed	Drug	Tablet	8 mg	8 mg	Oral	12, 3, and 1 hour prior to docetaxel administration	Standard of Care	NIMP	Local
Arm 2	Placebo	Normal saline or dextrose[d]	Other	Solution for Infusion	N/A	N/A	IV infusion	Day 1 of each 21-day cycle	Placebo	IMP	Local[e]

BID= twice daily; IMP = Investigational Medicinal Product; IV = intravenous; NIMP = Non-Investigational Medicinal Product; SOC = Standard of care.

Note: Definition IMP and 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.

[a] When locally supplied, docetaxel unit vial strength is based on region.

[b] Prednisone is the preferred steroid to be used in the study. Prednisolone should only be used when prednisone is unavailable.

[c] Dexamethasone, or the equivalent dose of another steroid, is the preferred corticosteroid to be used in the study. Local standard of care premedication prior to docetaxel infusion is allowed

[d] Normal saline is the primary diluent/placebo for pembrolizumab; use dextrose only if saline is not available.

[e] Intravenous solution, not provided by the Sponsor, as placebo for infusion in this protocol is not categorized as "product(s) used in the clinical trial" in Japan.

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

Only bone lesions seen by bone scan may be followed for assessment of tumor treatment response. Bone disease seen by CT only (not visible on bone scan) is presumed not to represent active disease and should not be documented as a bone lesion (sclerotic lesions seen on CT may represent healed disease or non-malignant 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 non-target 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 (non-evaluable). The definitions are summarized in the following table and described in more detail below.

Bone Response	Definition
PD	**Progressive disease:** 2 new lesions, not flare, persistent
PDu	**Progressive disease unconfirmed:** Temporary marker of possible PD, to be updated to PD or non-PD once a subsequent scan is available. If this is the final visit, the visit response will remain PDu, but is updated to PD during analysis by Sponsor.
Non-PD	**Non progressive disease:** At least 1 bone lesion present, but not enough to trigger PD
NE	**Non-evaluable:** 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 Non-progression (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 (PD-U)

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 PD-U, which marks the possibility of progression that will be resolved by the next scan.

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

After a scan classified as PDu within the first 12 weeks of treatment, if the next bone scan outside the flare window shows at least 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 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 referred to as "re-baselining".

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

After a scan classified as PDu after the first 12 weeks of treatment, if at least 2 of the new lesions seen on that scan persist on the next bone scan performed at least 6 weeks later, this confirms the initial progression. The prior response is then updated to PD. If the new lesions have disappeared on this later scan, the prior response is updated to non-PD because these lesions are presumed to be non-malignant in nature. No re-baselining 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 increase bone uptake may be uniform, but can be distinguished by the faint or absent activity in the kidneys and urinary tract.

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

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

10.8.6 Management Following Confirmed PD

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

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

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

Not applicable.

10.10 Appendix 10: Eastern Cooperative Oncology Group Performance Status

Grade	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light 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

10.11 Appendix 11: Abbreviations

Abbreviation	Expanded Term
ABI	abiraterone acetate
ADL	activities of daily living
ADT	androgen-deprivation therapy
AE	adverse event
APaT	All Participants as Treated
aPTT	activated partial thromboplastin time
AQA	analgesic quantification algorithm
BDS	blood drug screen
BICR	blinded independent central review
BID	twice daily
BPI-SF	Brief Pain Inventory – Short Form
C1D1	Cycle 1 Day 1
CAC	Clinical Adjudication Committee
CD8	cluster of differentiation 8
CD28	cluster of differentiation 28
CI	confidence interval
CNS	central nervous system
CR	complete response
CRF	Case Report Form
CRU	clinical research unit
CSPC	castration-sensitive prostate cancer
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	computed tomography
CTC	circulating tumor cell
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor deoxyribonucleic acid
CTFG	Clinical Trial Facilitation Group
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
CTx	chemotherapy
DC	discontinuation
D1	Day 1
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	duration of response
EBRT	external-beam radiation therapy
ECG	electrocardiogram
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data collection
EMA	European Medicines Agency

Abbreviation	Expanded Term
ENZA	enzalutamide
EOC	Executive Oversight Committee
ePRO	Electronic patient-reported outcome
EQ-5D-5L	EuroQol 5- dimension, 5-level health state utility index
FACT-P, FACT-G	Functional Assessment of Cancer Therapy – Prostate; -General
FAPS16	FACT Advanced Prostate Symptom Index 6
FBR	Future Biomedical Research
FDAAA	Food and Drug Administration Amendments Act
FSH	follicle stimulating hormone
FT3	free triiodothyronine
FT4	free thyroxine
GCP	Good Clinical Practice
GCSF	granulocyte colony-stimulating factor
HGRAC	Human Genetic Resources Administration of China
HR	hazard ratio
HRQoL	health-related quality of life
IA	interim analysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference for Harmonisation
IEC	Independent Ethics Committee
Ig	immunoglobulin
IND	Investigational New Drug
INR	international normalized ratio
irAE	Immune-related Adverse Event
iRECIST	Modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics
IRB	Institutional Review Board
IRT	interactive response technology
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
mCRPC	metastatic castration-resistant prostate cancer
mHSPC	metastatic hormone-sensitive prostate cancer
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NA	not applicable
NCCN	National Comprehensive Cancer Network
NSCLC	non-small cell lung cancer
NDA	New Drug Application
NHA	next generation hormonal agent
NOAEL	no observed adverse effect level
ORR	objective response rate
OS	overall survival

Abbreviation	Expanded Term
PCWG	Prostate Cancer Working Group
PD	progressive disease
PD-1	programmed cell death 1 receptor
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PET	positron emission tomography
PK	pharmacokinetic
PO	by mouth
PR	partial response
PRO	patient-reported outcome
PSA	prostate-specific antigen
PT	prothrombin time
PTT	partial thromboplastin time
Q3W	every 3 weeks
QP2	department of quantitative pharmacology and pharmacometrics
RECIST 1.1	Response Evaluation Criteria in Solid Tumors 1.1
RNA	ribonucleic acid
rPFS	radiographic progression-free survival
SAE	serious adverse event
SCF	Sponsor consultation form
SD	stable disease
SOC	standard of care
SoA	schedule of activities
sSAP	supplemental statistical analysis plan
SSRE	symptomatic skeletal-related event
SUSAR	suspected unexpected serious adverse reaction
T3	total triiodothyronine
TEA	Treatment Eligibility Assessment
TFST	the first subsequent anti-cancer therapy
TSH	thyroid-stimulating hormone
TTBP	time-to bone progression
TTPP	time to pain progression
WOCBP	woman/women of childbearing potential

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