Official Protocol Title:	A Phase 3 Study of Pembrolizumab in Combination with Carboplatin/Taxane (Paclitaxel or Nab-paclitaxel) Followed by Pembrolizumab with or without Maintenance Olaparib in the First-line Treatment of Metastatic Squamous Non-small Cell Lung
NCT number:	NCT03976362
Document Date:	31-JANUARY-2024

Title Page

THIS PROTOCOL AMENDMENT AND ALL OF THE INFORMATION RELATING TO IT ARE CONFIDENTIAL AND PROPRIETARY PROPERTY OF MERCK SHARP & DOHME LLC, RAHWAY, NJ, USA (MSD).

Protocol Title: A Phase 3 Study of Pembrolizumab in Combination with Carboplatin/Taxane (Paclitaxel or Nab-paclitaxel) Followed by Pembrolizumab with or without Maintenance Olaparib in the First-line Treatment of Metastatic Squamous Non-small Cell Lung Cancer (NSCLC)

Protocol Number: 008-07

Compound Number: MK-7339

Sponsor Name:

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

Legal Registered Address:

126 East Lincoln Avenue

P.O. Box 2000

Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

IND	140819
Eudra CT	2018-004721-88

Approval Date: 31 January 2024

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
Protocol Amendment 07	31-JAN-2024	Based on the data from an interim safety and efficacy analysis (IA3) for MK-7339-008 (data cutoff 21-SEP-2023), the external Data Monitoring Committee recommended to remove the final analysis. It was extremely unlikely that the efficacy boundary for success for the primary endpoint of OS would be reached by the final analysis. The study will remain open so ongoing participants will have continued access to Olaparib and pembrolizumab if they qualify per protocol or until transferred to an extension study, if applicable.
Protocol Amendment 06	09-SEP-2022	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.
Protocol Amendment 05	18-FEB-2022	The protocol was amended to update the assumptions and timing of the analyses in the SAP to allow reasonable timing for PFS final analysis, and sufficient duration of follow-up based on updated enrollment period and the long-term survival data from the reference study KEYNOTE-407.
Protocol Amendment 04	22-OCT-2021	To update the dose modification and toxicity management guidelines for irAEs. To clarify that participants with PD after the first 4 cycles of induction will not enter the Maintenance Phase, but should enter the Safety Follow-up Visit.
Protocol Amendment 03	08-DEC-2020	To update the RECIST and iRECIST language to make the study intervention decision process following disease progression consistent throughout the protocol, and to update language to improve clarity and decrease redundancy throughout the protocol.

Document	Date of Issue	Overall Rationale
Protocol Amendment 02	04-SEP-2019	To add weekly hematology sample collection during the Induction Phase for participants receiving nab-paclitaxel, further define Inclusion Criterion #5 to ensure adequate tissue collection prior to subject enrollment, change collection times of plasma and serum biomarkers, and clarify that if there is any new diagnosis of MDS or AML this should be reported throughout the Maintenance Phase including the Follow-up Phase.
Protocol Amendment 01	01-JUL-2019	To remove entry into long-term follow-up for participants who discontinue for any reason in the Induction Phase, provide clarity that long-term follow-up for disease status monitoring and overall survival will only be conducted for randomized participants, and to align the time of Long-term Follow-up visits with the imaging schedule.
Original Protocol	24-JAN-2019	Not Applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 07

Overall Rationale for the Amendment:

Based on the data from an interim safety and efficacy analysis (IA3) for MK-7339-008 (data cutoff 21-SEP-2023), the external Data Monitoring Committee recommended to remove the final analysis. It was extremely unlikely that the efficacy boundary for success for the primary endpoint of OS would be reached by the final analysis. The study will remain open so ongoing participants will have continued access to Olaparib and pembrolizumab if they qualify per protocol or until transferred to an extension study, if applicable.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
Section 1.1, Synopsis: Duration of Participation	Added note regarding the study unblinding and the removal of the final analysis. Clarified that there will be no further analyses for efficacy and CCI CCI	This change was made to address a strategy change as a result of the eDMC recommendation to remove the final analysis since the primary endpoint for OS would not be achieved by the final analysis. The rationale is further supported by new data from IA3 of a lack of additional clinical benefit on overall survival of the combination of pembrolizumab plus Olaparib.

Section Number and Name	Description of Change	Brief Rationale
Additional Changes		
CCI [redacted]		

Section Number and Name	Description of Change	Brief Rationale
CCI [redacted]		
Section 4.4, Beginning and End of Study Definition	Added a note that participants may be enrolled in a pembrolizumab extension study.	Refer to Section 1.1 rationale
Section 6.1, Study Intervention(s) Administered	Added a note regarding that final analysis will not be performed.	Refer to Section 1.1 rationale
Section 6.3.2, Stratification	Added a note that disease progression will no longer be centrally verified.	Refer to Section 1.1 rationale
Section 6.3.3, Blinding	Added a note that participant treatment was unblinded.	As part of the eDMC review of IA3 data for futility, the participant treatment data were unblinded.
Section 6.4.1, Olaparib Compliance	Added a note that participants should discontinue taking placebo.	Refer to Section 1.1 rationale
Section 6.5.1, Prohibited Concomitant Medications	Added a bullet that CYP3A4 inhibitors are only prohibited for participants taking Olaparib concomitantly	To clarify CYP3A inhibitors should not be taken with Olaparib.
Section 6.6, Dose Modification (Escalation/Titration/Other)	Added a note that unblinded participants should discontinue taking placebo and the course of action for potential participants undergoing the second course treatment.	Refer to Section 1.1 rationale
Section 7.1, Discontinuation of Study Intervention	Deleted the bullet for the criterion that treatment assignment has been unblinded	Refer to Section 6.3.3 rationale
Section 7.1, Discontinuation of Study Intervention	Removed centrally verified and added a note that disease progression will be assessed locally	Refer to Section 1.1 rationale
Section 8.1.8, Study Intervention Administration	Added a note that unblinded participants should discontinue taking placebo.	Refer to Section 1.1 rationale
Section 8.1.8.1, Timing of Dose Administration	Added a note that unblinded participants should discontinue taking placebo.	Refer to Section 1.1 rationale
Section 8.1.8.1.3, Olaparib or Olaparib Placebo	Added a note that unblinded participants should discontinue taking placebo.	Refer to Section 1.1 rationale
Section 8.1.9, Participant Blinding/Unblinding	Added a note that participant treatment was unblinded and the unblinding processes were no longer relevant.	Refer to Section 6.3.3 rationale
Section 8.2.1, Tumor Imaging and Assessment of Disease	Added a note that tumor response by BICR will not be collected.	Refer to Section 1.1 rationale
Section 8.2.1.4, Second Course (Retreatment) Tumor Imaging	Deleted statement that central reading will be used to determine eligibility.	Refer to Section 1.1 rationale
CCI [redacted]		

Section Number and Name	Description of Change	Brief Rationale
Section 8.4.1, Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information	Added a note for AE assessments when participants roll over into an extension study	Clarify AE collection and reporting criteria during the transition to a pembrolizumab extension study
Section 8.12.5, Second Course Phase (Retreatment Period)	Added note that disease progression will be assessed locally and removed the requirement for BICR determined progression.	Refer to Section 1.1 rationale
Section 9, Statistical Analysis Plan	Added note describing the results of the safety and efficacy IA that led to the determination to stop the final analysis due to futility.	To describe the results of the IA3 and eDMC recommendations. To clarify the prespecified final analysis will not be performed and specify which analyses will be conducted as of Amendment 07.
Section 9, Statistical Analysis Plan	A statement was added that the prespecified final analysis of the study described in the SAP will not be performed.	Refer to Section 9 rationale regarding the IA3 and eDMC recommendation.
CCI [redacted]		
Section 9.1, Statistical Analysis Plan Summary	A statement was added that the prespecified final analysis of the study described in the SAP will not be performed.	Refer to Section 9 rationale regarding the IA3 and eDMC recommendation.
CCI [redacted]		
Section 9.7, Interim Analyses	A statement was added that the prespecified final analysis of the study described in the SAP will not be performed.	Refer to Section 9 rationale regarding the IA3 and eDMC recommendation.
Section 9.8, Multiplicity	A statement was added that the prespecified final analysis of the study described in the SAP will not be performed.	Refer to Section 9 rationale regarding the IA3 and eDMC recommendation.
Section 9.9, Sample Size and Power Calculations	A statement was added that the prespecified final analysis of the study described in the SAP will not be performed.	Refer to Section 9 rationale regarding the IA3 and eDMC recommendation.
Throughout document	Minor typographical and/or editorial changes were made throughout.	To ensure clarity and consistency.

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3 Study of Pembrolizumab in Combination with Carboplatin/Taxane (Paclitaxel or Nab-paclitaxel) Followed by Pembrolizumab with or without Maintenance Olaparib in the First-line Treatment of Metastatic Squamous Non-small Cell Lung Cancer (NSCLC)

Short Title: Phase 3 Study of Pembrolizumab with or without Maintenance Olaparib in First-line Metastatic Squamous NSCLC

Acronym: Not applicable

Hypotheses, Objectives, and Endpoints:

In male and female participants with Stage IV squamous non–small-cell lung cancer (NSCLC) with stable disease (SD), partial response (PR), or complete response (CR) following induction treatment with pembrolizumab combined with carboplatin and a taxane (paclitaxel or nab-paclitaxel):

Primary Objectives	Primary Endpoints
- Objective: To compare pembrolizumab plus maintenance olaparib with pembrolizumab plus placebo with respect to progression-free survival (PFS) assessed according to RECIST 1.1 (Section 4.2.1.1) by blinded independent central review (BICR). - Hypothesis (H1): Pembrolizumab plus maintenance olaparib is superior to pembrolizumab plus placebo with respect to PFS per RECIST 1.1 (Section 4.2.1.1) by BICR.	- PFS, the time from the date of randomization until either documented disease progression or death due to any cause, whichever occurs first.
- Objective: To compare pembrolizumab plus maintenance olaparib with pembrolizumab plus placebo with respect to overall survival (OS). - Hypothesis (H2): Pembrolizumab plus maintenance olaparib is superior to pembrolizumab plus placebo with respect to OS.	- OS, the time from the date of randomization to death due to any cause.

Secondary Objectives	Secondary Endpoints
- Objective: To evaluate the safety and tolerability of pembrolizumab plus maintenance olaparib compared to pembrolizumab plus placebo.	- Adverse events (AEs) - Discontinuation of study intervention due to AEs
- Objective: To evaluate the change from baseline (at randomization) and the time to true deterioration (TTD) in global health status/quality of life (QoL), cough, chest pain, dyspnea and physical functioning following treatment with pembrolizumab plus maintenance olaparib compared to pembrolizumab plus placebo.	- Change from baseline (at randomization) and the time to true deterioration (TTD) defined as the time from baseline (at randomization) to the first onset of a ≥10-point deterioration with confirmation by the subsequent visit of a ≥10-point deterioration in the following European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ) and QLQ Lung Cancer Module 13 (LC13) scales/items: - Global health status/QoL (C30/Items 29 and 30) - Cough (LC13/Item 1) - Chest pain (LC13/Item 10) - Dyspnea (C30/Item 8) - Physical functioning (C30/Items 1 – 5)

Overall Design:

Study Phase	Phase 3
Primary Purpose	Treatment
Indication	Treatment with pembrolizumab and maintenance olaparib in participants with stable disease, PR or CR upon completion of 4 cycles of induction pembrolizumab with carboplatin/taxane chemotherapy in participants with Stage IV squamous NSCLC in need of first-line therapy
Population	Adult participants with treatment-naïve Stage IV squamous NSCLC
Study Type	Interventional
Intervention Model	Parallel This is a multisite study.
Type of Control	Placebo control
Study Blinding	Double-blind with In-House Blinding Procedures
Masking	Participant or Subject Investigator Sponsor
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 60 months from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Approximately 857 participants will be enrolled into an Induction Phase, with approximately 590 required for randomization, as described in Section 9.9.

Intervention Groups and Duration:

Intervention Groups	**Induction Phase (4 Cycles)** All participants will receive the study intervention (pembrolizumab + carboplatin/taxane-based chemotherapy) in a nonrandomized Induction Phase: • Pembrolizumab 200 mg IV every 3 weeks (Q3W) on Day 1 (Cycles 1-4) • Carboplatin titrated to an area under the plasma drug concentration-time curve (AUC) of 6 mg/mL/min IV Q3W on Day 1 (Cycles 1-4) • Taxane, investigator's choice (paclitaxel or nab-paclitaxel) Paclitaxel 200 mg/m^2 Q3W on Day 1 (Cycles 1-4) OR Nab-paclitaxel 100 mg/m^2 (D1, D8, D15) Q3W for (Cycles 1-4) **Maintenance Phase (Up to 31 Cycles of Pembrolizumab)**: Participants with a partial or complete disease response or with stable disease who meet eligibility criteria after the fourth cycle of the Induction Phase will be randomly assigned to pembrolizumab + maintenance olaparib or pembrolizumab + matching maintenance olaparib placebo (P) (see study schema in Figure 1). • Pembrolizumab 200 mg IV Q3W for a maximum of 31 cycles or until specific discontinuation criteria are met (Section 7.1) • Olaparib 300 mg twice daily (BID) will continue until specific discontinuation criteria are met (Section 7.1). • Olaparib placebo BID will continue until specific discontinuation criteria are met (Section 7.1). *Note: Eligible participants who enter the Maintenance Phase may receive a maximum of 35 cycles of pembrolizumab during the study (4 cycles during the Induction Phase and 31 cycles during the Maintenance Phase). If pembrolizumab is stopped due to toxicity or completion of 31 cycles during the Maintenance Phase, the participant may continue with olaparib/olaparib placebo until specific discontinuation criteria are met (Section 7.1). If olaparib/olaparib placebo is stopped due to toxicity, the participant may continue to receive pembrolizumab for a maximum of 31 cycles during the Maintenance Phase or until specific discontinuation criteria are met (Section 7.1).*

Note: Consultation with the Sponsor is required if a participant receives fewer than 4 cycles of study intervention during the Induction Phase without progressive disease, and the investigator would like to randomize the participant to the Maintenance Phase.

Note: The study has been unblinded as of 15-DEC-2023. Participants who are confirmed to be actively taking placebo should discontinue taking the placebo intervention and continue in the study.

End-of-Treatment and Long-term Follow-up

After the End-of-Treatment (EOT) visit, those randomized participants who discontinue for reasons other than radiographic progressive disease will have long-term follow-up for disease status (every 6 weeks up to 48 weeks post-randomization and, thereafter, every 9 weeks) until experiencing progressive disease, initiating a non-study cancer treatment, withdrawal of consent, becoming lost to follow-up, or end of study (EOS). All participants will be followed by telephone for OS every 3 months, until death, withdrawal of consent, or EOS.

A summary of the study interventions, including dose formulation, dose strength, dose frequency, route of administration, treatment period, and use is presented in Table 1.

Table 1 Summary of Study Interventions

Drug Name	Dose Formulation	Dose Strength	Dose Frequency	Route of Admin.	Treatment Period	Use
Olaparib	Tablet	300 mg	BID	Oral	Maintenance Phase	Experimental
Olaparib placebo	Tablet	N/A	BID	Oral	Maintenance Phase	Experimental
Pembrolizumab	Solution for infusion	200 mg	Q3W	IV	Induction and Maintenance Phases	Experimental
Paclitaxel	Solution for infusion	200 mg/m^2	Q3W	IV	Induction Phase	SOC
Nab-paclitaxel	Solution for infusion	100 mg/m^2	Q3W	IV	Induction Phase	SOC
Carboplatin	Solution for infusion	AUC 6 mg/mL/min	Q3W	IV	Induction Phase	SOC

Abbreviations: AUC=area under the plasma drug concentration-time curve; BID=twice daily; IV=intravenous; N/A=not applicable; Q3W=every 3 weeks; SOC=standard of care.

Total Number	2 arms

Duration of Participation	Each participant will participate in the study from the time the participant provides documented informed consent through the final protocol-specified contact. **Induction Phase**: After a Screening Phase, each participant will enter into the nonrandomized Induction Phase and will receive 4 cycles of assigned study intervention for approximately 3 months: pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel. **Maintenance Phase:** Only participants who have received 4 cycles of study treatment during the Induction Phase, have at least one evaluable imaging timepoint during the Induction Phase, have no imaging visit with an overall response of PD (as verified by BICR, are clinically stable, and meet eligibility criteria to participate in the Maintenance Phase will be randomized to receive either pembrolizumab plus olaparib or pembrolizumab plus placebo. Participants will receive randomly assigned study intervention during the Maintenance Phase until disease progression is radiographically documented per RECIST 1.1 (verified by BICR) and, when clinically appropriate, confirmed by the site per modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics (iRECIST), unacceptable 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. Eligible participants who enter the Maintenance Phase may receive a maximum of 35 cycles of pembrolizumab during the study (4 cycles during the Induction Phase and 31 cycles during the Maintenance Phase). If pembrolizumab is stopped due to toxicity or completion of 31 cycles, the participant may continue with maintenance olaparib until specific discontinuation criteria are met (Section 7.1). If maintenance olaparib is stopped due to toxicity, the participant may continue to receive pembrolizumab for a maximum of 31 cycles during the Maintenance Phase or until specific discontinuation criteria are met (Section 7.1). **End-of-Treatment and Long-term Follow-up:** After the EOT visit, each participant will be followed for the occurrence of AEs and spontaneously reported pregnancy as described under Section 8.4. Randomized participants who discontinue for reasons other than radiographic disease progression will have long-term follow-up imaging for disease status until disease progression is documented radiographically per RECIST 1.1, initiating a non-study cancer treatment, withdrawal of consent, becoming lost to follow up, or EOS. All

	randomized participants will be followed by telephone every 3 months for overall survival until death, withdrawal of consent, or the end of the study. Randomized participants are expected to participate in the study for approximately 60 months including the Long-term Follow-up Phase. **Second Course Phase** Participants in each arm who stop study intervention after receiving 35 cycles of pembrolizumab for reasons other than disease progression or intolerability, may be eligible for up to an additional 1 year (17 cycles) of pembrolizumab after experiencing disease progression (Second Course Phase; Section 8.12.5). Note: Based on the data from an interim safety and efficacy analysis (IA3), the external Data Monitoring Committee recommended to remove the Final Analysis. All study participants still receiving study treatment will be informed of the analysis and should continue to receive therapy on study and undergo modified protocol study procedures as specified in Amendment 07. There were no new safety signals identified in the IA3 analysis. Participants who are confirmed to be actively taking placebo should discontinue taking the placebo intervention and continue in the study. Participants currently on study treatment with Olaparib may continue treatment per Investigator's discretion after discussion with their physician. Participants who are potential candidates for Second Course treatment will continue in Efficacy Follow-up. Participants currently undergoing or who will undergo Second Course treatment with pembrolizumab monotherapy can continue or start treatment per Investigator's discretion under this protocol or under an extension study.

Study Governance Committees:

Executive Oversight Committee	Yes
Data Monitoring Committee	Yes
Clinical Adjudication Committee	No
Study governance considerations are outlined in Appendix 1.	

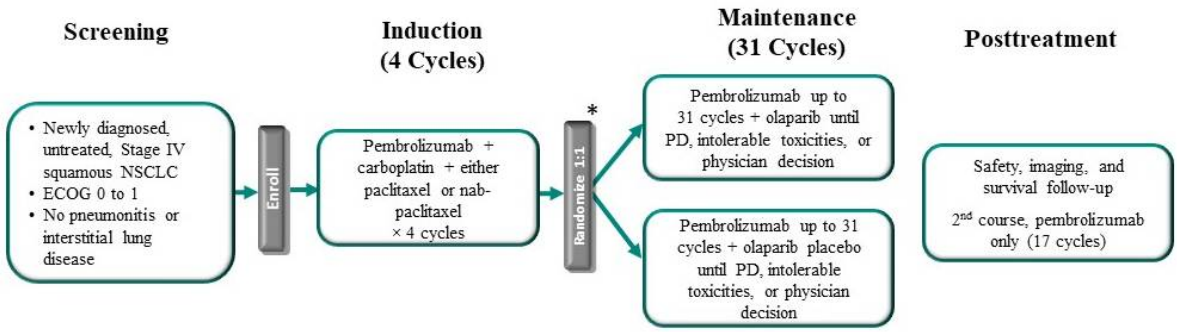
Study Accepts Healthy Volunteers: No

A list of abbreviations used in this document can be found in Appendix 9.

1.2 Schema

The study design (Screening, Induction Phase, and Maintenance Phase) is depicted in Figure 1.

Figure 1 Study Design Overview



* Participants with SD/PR/CR after receiving 4 induction cycles will be randomized to receive pembrolizumab plus maintenance olaparib, or pembrolizumab plus maintenance olaparib placebo.

Note: Participants may receive a maximum of 35 cycles of pembrolizumab treatment during the study (4 cycles during the Induction Phase and 31 cycles during the Maintenance Phase). If pembrolizumab is stopped due to toxicity or completion of 31 cycles during Maintenance Phase, the participant may continue with maintenance olaparib or maintenance olaparib placebo, until specific discontinuation criteria are met (Section 7.1). If maintenance olaparib or maintenance olaparib placebo is stopped due to toxicity, the participant may continue to receive pembrolizumab for a maximum of 31 cycles during the Maintenance Phase, or until specific discontinuation criteria are met (Section 7.1).

In the Posttreatment Phase, participants who discontinue study intervention for reasons other than PD will move into Follow-up (Section 8.12.6). All participants who receive 35 cycles of pembrolizumab with SD, PR, or CR in either arm may be eligible for up to 1 additional year (17 cycles) of pembrolizumab if they progress after having received 35 cycles of pembrolizumab and with SD, PR, or CR in either arm. (Section 8.12.5). Second-course pembrolizumab is optional.

Abbreviations: ECOG=Eastern Cooperative Oncology group; NSCLC=non-small cell lung cancer; PD=progressive disease; SD/PR/CR=stable disease/partial response/complete response.

1.3 Schedule of Activities (SoA)

1.3.1 Screening and Induction Phases – ALL PARTICIPANTS

Study Period	**Screening Phase**	**Induction Phase (3 –Week Cycles)[a]**												Notes
Cycle		**1**			**2**			**3**			**4**			
Day (in Cycle)		**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	
Visit Number/Title	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	
Scheduling Window (Days):	**-28 to -1**	**+3**	**-**	**-**	**±3**	**-**	**-**	**±3**	**-**	**-**	**±3**	**-**	**-**	
Administrative Procedures														
Informed Consent	X													Consent must be obtained prior to performing any protocol-specific procedures.
FBR ICF (optional)	X													Participants can still participate in the study if they decline to sign the Future Biomedical Research ICF.
Inclusion/Exclusion Criteria	X													
Participant Identification Card	X	X												At the time of Visit Number 2/Cycle 1, Day 1, site personnel should add the screening number to the Participant ID card.
Demographics and Medical History	X													
History of blood transfusions	X													Include history of blood transfusion within previous 120 days from start of study intervention and the reasons, eg, bleeding or myelosuppression
Prior/Concomitant Medication Review	X	←----------											----------→	Include blood transfusions during review of concomitant medications
NSCLC Disease Details	X													
Obtain Study Treatment Assignment using IRT		X												Cycle 1, Day 1 study intervention must be administered within 3 days of enrolling the participant in the study.

Study Period	**Screening Phase**	**Induction Phase (3 –Week Cycles)[a]**												Notes
Cycle		**1**			**2**			**3**			**4**			
Day (in Cycle)		**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	
Visit Number/Title	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	
Scheduling Window (Days):	**-28 to -1**	**+3**	**-**	**-**	**±3**	**-**	**-**	**±3**	**-**	**-**	**±3**	**-**	**-**	
Administration of Study Intervention														
Pembrolizumab		X			X			X			X			200 mg Q3W for a maximum of 4 cycles
Carboplatin		X			X			X			X			AUC 6 mg/mL/min Q3W
Paclitaxel		X			X			X			X			200 mg/m^2 Q3W
Nab-paclitaxel[b]		X	X	X	X	X	X	X	X	X	X	X	X	100 mg/m^2 on Days 1, 8, and 15 of Cycles 1-4. Day 8 and 15 window ± 1 day.
Tumor Tissue Collection														
Archival or Newly Obtained Tissue Collection for PD-L1 IHC and other Biomarkers	X													A **new** incisional or core biopsy will be required if archival tissue is not available. PD-L1 IHC will be mandatory to stratify participants prior to randomization for the Maintenance Phase.

Study Period	**Screening Phase**	**Induction Phase (3 –Week Cycles)[a]**												Notes
Cycle		**1**			**2**			**3**			**4**			
Day (in Cycle)		**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	
Visit Number/Title	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	
Scheduling Window (Days):	**-28 to -1**	**+3**	**-**	**-**	**±3**	**-**	**-**	**±3**	**-**	**-**	**±3**	**-**	**-**	
Efficacy Procedures[c]														
CT/MRI imaging of chest, abdomen, and pelvis	X						X						X[d]	The first on study imaging visit has a window of +7 days. All other imaging visits have a visit window of ±7 days. Screening images are to be captured within 28 days of first dose. During the Induction Phase, images will be captured every Q6W from the date of the first dose (Cycle 1). Imaging timing should follow calendar days and should not be adjusted for delays in study intervention. All imaging must be submitted to central imaging vendor as soon as possible for expedited central review to determine eligibility for randomization into Maintenance Phase
MRI of Brain	X						X						X	Participants with treated brain lesions and participants with known, asymptomatic, untreated brain lesions at diagnosis may participate, but require regular imaging of the brain as a site of disease. Participants without brain lesions at baseline should be imaged as clinically indicated.

Study Period	**Screening Phase**	**Induction Phase (3 –Week Cycles)[a]**												Notes
Cycle		**1**			**2**			**3**			**4**			
Day (in Cycle)		**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	
Visit Number/Title	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	
Scheduling Window (Days):	**-28 to -1**	**+3**	**-**	**-**	**±3**	**-**	**-**	**±3**	**-**	**-**	**±3**	**-**	**-**	
Safety Procedures														
AE Monitoring	X	←----------											→	AEs: Report all AEs occurring from the start of study treatment through 30 days following the last dose of study intervention. SAEs: Report all SAEs from the start of study intervention through 90 days following the last dose of study intervention, or 30 days following the last dose of study intervention if the participant initiates new anticancer therapy, whichever is earlier. New diagnoses of MDS and AML should be reported throughout the study, including the follow-up period.
Complete Physical Examination (including height)	X													Height at screening only
Directed Physical Examination		X			X			X			X			Directed physical exam performed as clinically indicated prior to treatment administration.
Weight	X	X			X			X			X			
Vital Signs (HR, DBP, SBP, RR, temperature)	X	X	X	X	X	X	X	X	X	X	X	X	X	Assessments performed prior to treatment administration. The Day 8 and Day 15 evaluations apply only to nab-paclitaxel.
12-lead ECG	X													12-lead ECG performed using local standard procedures. Additional ECGs performed as clinically indicated.

Study Period	**Screening Phase**	**Induction Phase (3 –Week Cycles)[a]**												Notes
Cycle		**1**			**2**			**3**			**4**			
Day (in Cycle)		**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	
Visit Number/Title	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	
Scheduling Window (Days):	**-28 to -1**	**+3**	**-**	**-**	**±3**	**-**	**-**	**±3**	**-**	**-**	**±3**	**-**	**-**	
Hematology	X	X	X[b]	X[b]	X	X[b]	X[b]	X	X[b]	X[b]	X	X[b]	X[b]	Screening samples to be collected within 10 days prior to first dose of treatment intervention. On-treatment samples to be collected within 72 hours prior to the first dose of study intervention in each cycle.
Urinalysis	X													
Chemistry	X	X			X			X			X			
Thyroid Function Tests (total T3 or free T3, FT4, TSH)		X						X						Cycle 1, Day 1 tests may be performed within 10 days prior to first dose of study intervention. On-treatment tests performed every other cycle. Participants may be dosed while thyroid function tests are pending.
HBV, HCV, and HIV testing	X													HBV and HCV screening tests are not required unless participant has a known history of infection or as mandated by local health authority. No HIV testing is required unless mandated by local health authority. Refer to Appendix 7 for country-specific requirements.
Urine Pregnancy Test (WOCBP only)	X													WOCBP require a negative highly sensitive urine test within 24 hours (72 hours for serum) prior to the first dose of study intervention. Testing during the Induction Phase must be conducted as clinically indicated and as per local regulations where applicable. Serum test is only required if urine test is positive or is not evaluable.

Study Period	**Screening Phase**	**Induction Phase (3 –Week Cycles)[a]**												Notes
Cycle		**1**			**2**			**3**			**4**			
Day (in Cycle)		**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	
Visit Number/Title	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	
Scheduling Window (Days):	**-28 to -1**	**+3**	**-**	**-**	**±3**	**-**	**-**	**±3**	**-**	**-**	**±3**	**-**	**-**	
PT or INR and aPTT	X													Screening samples collected within 10 days of treatment initiation. PT or INR and aPTT should be monitored more closely in participants receiving anticoagulant therapy during treatment and Safety Follow-up Period.
Creatinine clearance calculation	X	X			X			X			X			Creatinine Clearance is calculated using the Cockcroft-Gault method (Table 3).
ECOG performance status	X	X			X			X			X			Screening assessment to be performed within 7 days prior to administration of study intervention.
CCI [redacted]														

Study Period	**Screening Phase**	**Induction Phase (3 –Week Cycles)[a]**												Notes
Cycle		**1**			**2**			**3**			**4**			
Day (in Cycle)		**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	
Visit Number/Title	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	
Scheduling Window (Days):	**-28 to -1**	**+3**	**-**	**-**	**±3**	**-**	**-**	**±3**	**-**	**-**	**±3**	**-**	**-**	
CCI [redacted]														

Abbreviations: AE = adverse event; aPTT = activated partial thromboplastin time; CCI [redacted] DBP = diastolic blood pressure; DC = discontinuation; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FBR = Future Biomedical Research; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HR = heart rate; ICF = informed consent form; ID = identification; IHC = immunohistochemistry; INR = International Normalized Ratio; IRT = interactive response system; PD = progressive disease; PD-L1 = programmed death ligand 1; PRO = patient-reported outcome; PT = prothrombin time; Q3W = every 3 weeks; Q6W = every 6 weeks; RR = respiratory rate; SBP = systolic blood pressure; TSH = thyroid-stimulating hormone; WOCBP = women of childbearing potential.

a. Participants who do not continue to the randomization phase are to complete the 30-day safety follow-up assessments; refer to Section 1.3.3.
b. Day 8 and 15 only apply if Nab-paclitaxel is given instead of paclitaxel. Days 8 and 15 are based on Day 1 of each cycle.
c. Imaging should continue to be performed until PD is verified, the start of new anticancer treatment, withdrawal of consent, pregnancy, or death, whichever occurs first.
d. Imaging must occur at Week 12. Imaging should be performed within 28 days of entering the Maintenance Phase.

1.3.2 Maintenance Phase

Study Period	**Post-induction/Pre-randomization Visit[a]**	**Maintenance Phase[b] (3–Week Cycles)**	Notes
Cycle	**-**	**1+**	As of Amendment 07, tumor imaging will be assessed locally based on the site's standard of care imaging schedule. Also, participants who are still on study treatment will no longer require ePRO assessments.
Day (in Cycle)	**-**	**1**	
Visit Number/Title	**14**	**15+**	
Scheduling Window (Days):	**±3**	**±3**	
Administrative Procedures			
Maintenance Phase Checklist	X		Pre-randomization visit is to occur 4 weeks ± 7 days from Cycle 4, Day 1 of induction. Checklist must be reviewed by Sponsor. Participants with PD must be excluded from the Maintenance Phase and should enter the Safety Follow-up Visit (refer to Section 1.3.3).
Inclusion/exclusion criteria	X		
Prior/Concomitant Medication Review	X	X	Include blood transfusions during review of concomitant medication.
Randomization		X	Study drug administration should begin on the day of randomization, but no later than 3 days after randomization. At this time, the participant will receive an allocation number.
Administration of Study Intervention			
Olaparib		X	To initiate maintenance olaparib, creatinine clearance (CrCl) must be ≥51 mL/min. Continuous daily dose of 300 mg BID until progression of disease, intolerable toxicities, or physician decision. Maintenance olaparib to start at least 4 weeks and no later than 6 weeks from Cycle 4, Day 1 of study medication in the Induction Phase. Participants will self-administer olaparib except on Day 1 of first cycle, when the dose will be given at the study site clinic prior to the infusion of pembrolizumab.
Pembrolizumab		X	Participants will need to return to the site Q3W for dosing at 200 mg for a maximum of 31 cycles or until progression of disease, intolerable toxicities, or physician decision. Pembrolizumab to restart at least 4 weeks and no later than 6 weeks from Cycle 4, Day 1 of study medication in the Induction Phase.
Olaparib or Olaparib Placebo Container Returned		X	

Study Period	**Post-induction/Pre-randomization Visit[a]**	**Maintenance Phase[b] (3–Week Cycles)**	Notes
Cycle	**-**	**1+**	As of Amendment 07, tumor imaging will be assessed locally based on the site's standard of care imaging schedule. Also, participants who are still on study treatment will no longer require ePRO assessments.
Day (in Cycle)	**-**	**1**	
Visit Number/Title	**14**	**15+**	
Scheduling Window (Days):	**±3**	**±3**	
Efficacy Procedures			Imaging should continue to be performed until PD is verified, the start of new anticancer treatment, withdrawal of consent, pregnancy, or death, whichever occurs first. Imaging can continue to be performed after PD is verified if the investigator elects to continue treatment and follow iRECIST. See Section 8.2.1.5.
CT/MRI imaging of chest, abdomen, and pelvis		X	The first imaging visit has a visit window of +7 days, all subsequent imaging visits have a visit window of ±7 days. During the Maintenance Phase, images will be captured Q6W for the first 48 weeks from the date of randomization, followed by Q9W thereafter until disease progression, or the start of new anticancer treatment. A new baseline CT scan of the chest/abdomen/pelvis will be needed prior to initiating Cycle 1 of the Maintenance Phase if the last imaging was obtained >28 days before the date of randomization. Imaging timing should follow calendar days and should not be adjusted for delays in study intervention. Note: As of Amendment 07, tumor imaging will be assessed locally based on the site's standard of care schedule.
MRI of Brain[c]		X	
Safety Procedures			
AE Monitoring	X	X	AEs: Report all AEs occurring from the start of study intervention through 30 days following the last dose of study intervention. SAEs: Report all SAEs occurring from the start of study intervention through 90 days following the last dose of study invention, or 30 days following the last dose of study intervention if the participant initiates new anticancer therapy, whichever is earlier. New diagnoses of MDS and AML should be reported throughout the study, including the follow-up period.
Directed Physical Examination	X	X	Directed physical exam performed as clinically indicated prior to treatment administration.
Weight	X	X	
Vital Signs (HR, DBP, SBP, RR, temperature)	X	X	Assessments performed prior to treatment administration.

Study Period	**Post-induction/Pre-randomization Visit[a]**	**Maintenance Phase[b] (3–Week Cycles)**	Notes
Cycle	**-**	**1+**	As of Amendment 07, tumor imaging will be assessed locally based on the site's standard of care imaging schedule. Also, participants who are still on study treatment will no longer require ePRO assessments.
Day (in Cycle)	**-**	**1**	
Visit Number/Title	**14**	**15+**	
Scheduling Window (Days):	**±3**	**±3**	
Hematology	X	X	Laboratory tests performed within 3 days of Cycle 1 (ie, pre-randomization) do not need to be repeated at Cycle 1. On-treatment samples collected prior to administration of study intervention.
Chemistry	X	X	
Thyroid Function Tests Total or Free T3 FT4 TSH		X	Thyroid function tests at Cycle 1 followed by every other cycle through Cycle 31. Participants may be dosed while thyroid function tests are pending.
Urine Pregnancy Test (WOCBP only)	X	X	WOCBP require a negative highly sensitive urine test at the pre-randomization visit and within 24 hours (72 hours for serum) prior to first dose of study intervention. Serum test only required if urine test is positive or not evaluable. Testing during Maintenance Phase must be conducted as clinically indicated and as per local regulations, where applicable. More frequent pregnancy testing may be indicated, as dictated by local regulations.
Creatinine clearance calculation	X	X	CrCl is calculated using the Cockcroft-Gault method (Table 3). As an alternative, CrCl can be determined from a 24-hour urine collection. To initiate maintenance olaparib, CrCl must be ≥51 mL/min.
ECOG performance status	X	X	ECOG performance status will be evaluated within 7 days of the first administration of study intervention and before administration of each cycle.
Patient-Reported Outcomes			
CCI [redacted]			

Study Period	Post-induction/Pre-randomization Visit[a]	Maintenance Phase[b] (3–Week Cycles)	CCI
Cycle	-	1+	
Day (in Cycle)	-	1	
Visit Number/Title	14	15+	
Scheduling Window (Days):	±3	±3	

CCI

Abbreviations: AE = adverse event; BID = twice daily; CrCl = creatinine clearance; ctDNA = circulating tumor DNA; DBP = diastolic blood pressure; DC = discontinuation; ECOG = Eastern Cooperative Oncology Group; CCI

CCI

CCI HR = heart rate; ICF = informed consent form; PD = progressive disease; PRO = patient-reported outcome; Q3W = every 3 weeks; Q6W = every 6 weeks; Q9W = every 9 weeks; RR = respiratory rate; SBP = systolic blood pressure; SoA = schedule of activities; WOCBP = women of childbearing potential.

a. Participants who do not qualify for the Maintenance Phase will proceed to the 30-day Safety Follow-up (refer to Section 1.3.3).
b. Study drug administration should begin on the day of randomization, but no later than 3 days after randomization.
c. Participants with treated brain lesions and participants with known, asymptomatic, untreated brain lesions at diagnosis will require regular imaging of the brain during the Maintenance Phase as a site of disease. Participants without brain lesions at baseline should be imaged as clinically indicated.

1.3.3 End-of-Treatment and Long-term Follow-up

	Participants Who Receive Induction Phase Treatment and are Not Randomized	**Participants Randomized to Maintenance Phase**				**Notes:** * Participants who discontinue study treatment in the Induction Phase will proceed directly to Safety Follow-up.
Study Period	**Safety Follow-up**	**EOT**	**Long-term Follow-up**			
Visit Number/Title	**Safety***	**DC**	**Safety[a]**	**Follow-up[a,b]**	**Survival Follow-up[c]**	
Scheduling Window (Days):	**30 Days After Last Dose (+ 7 days)**	**At time of DC (± 3 days)**	**30 Days After Last Dose (+7 days)**	**Q6W for 48 weeks Post-randomization, thereafter Q9W post DC (± 7 days)**	**Q12W (±14 days)**	
Administrative Procedures						
Prior/Concomitant Medication Review	X	X	X	X		Include blood transfusions during review of concomitant medication
Survival status		←----------			----------→	Continued after verified PD or start of new anticancer treatment. In addition, upon Sponsor request, participants may be contacted for survival status at any time during the course of the study

	Participants Who Receive Induction Phase Treatment and are Not Randomized	**Participants Randomized to Maintenance Phase**				**Notes:** * Participants who discontinue study treatment in the Induction Phase will proceed directly to Safety Follow-up.
Study Period	**Safety Follow-up**	**EOT**	**Long-term Follow-up**			
Visit Number/Title	**Safety***	**DC**	**Safety[a]**	**Follow-up[a,b]**	**Survival Follow-up[c]**	
Scheduling Window (Days):	**30 Days After Last Dose (+ 7 days)**	**At time of DC (± 3 days)**	**30 Days After Last Dose (+7 days)**	**Q6W for 48 weeks Post-randomization, thereafter Q9W post DC (± 7 days)**	**Q12W (±14 days)**	
Efficacy Procedures						Imaging should continue to be performed until PD is verified, the start of new anticancer treatment, withdrawal of consent, pregnancy, or death, whichever occurs first.
CT/MRI imaging of chest, abdomen, and pelvis		X[d]		X		All imaging visits have a visit window of ±7 days. Imaging will be captured Q6W for the first 48 weeks from the date of randomization, followed by Q9W thereafter until verified disease progression, or the start of new anticancer treatment. Imaging timing should follow **calendar days** and should not be adjusted for delays in study intervention. As of Amendment 07, tumor imaging will be assessed locally based on the site's standard of care imaging schedule.
MRI of Brain[e]		X[d]		X		

	Participants Who Receive Induction Phase Treatment and are Not Randomized	Participants Randomized to Maintenance Phase				Notes: * Participants who discontinue study treatment in the Induction Phase will proceed directly to Safety Follow-up.
Study Period	**Safety Follow-up**	**EOT**	**Long-term Follow-up**			
Visit Number/Title	**Safety***	**DC**	**Safety[a]**	**Follow-up[a,b]**	**Survival Follow-up[c]**	
Scheduling Window (Days):	**30 Days After Last Dose (+ 7 days)**	**At time of DC (± 3 days)**	**30 Days After Last Dose (+7 days)**	**Q6W for 48 weeks Post-randomization, thereafter Q9W post DC (± 7 days)**	**Q12W (±14 days)**	
Safety Procedures						
AE Monitoring	X	X	X	X		AEs: Report all AEs occurring through 30 days following the last dose of study intervention. SAEs: Report all SAEs occurring through 90 days following the last dose of study intervention, or 30 days following the last dose of study intervention if the participant initiates new anticancer therapy, whichever is earlier. New diagnoses of MDS and AML should be reported throughout the study, including the follow-up period.
Complete Physical Examination		X				
Directed Physical Examination	X		X			Directed physical examination performed as clinically indicated prior to treatment administration.
Weight	X	X				
Vital Signs (HR, DBP, SBP, RR, temperature)	X	X	X			
12-lead ECG		X				12-lead ECG performed using local standard procedures. Additional ECGs performed as clinically indicated.

	Participants Who Receive Induction Phase Treatment and are Not Randomized	**Participants Randomized to Maintenance Phase**				**Notes:** * Participants who discontinue study treatment in the Induction Phase will proceed directly to Safety Follow-up.
Study Period	**Safety Follow-up**	**EOT**	**Long-term Follow-up**			
Visit Number/Title	**Safety***	**DC**	**Safety[a]**	**Follow-up[a,b]**	**Survival Follow-up[c]**	
Scheduling Window (Days):	**30 Days After Last Dose (+ 7 days)**	**At time of DC (± 3 days)**	**30 Days After Last Dose (+7 days)**	**Q6W for 48 weeks Post-randomization, thereafter Q9W post DC (± 7 days)**	**Q12W (±14 days)**	
Hematology	X	X	X			
Urinalysis			X			
Chemistry	X	X	X			
Thyroid Function Tests Total or Free T3 FT4 TSH	X	X	X			
Urine Pregnancy Test (WOCBP only)	X	X	X			Testing during EOT and Long-term Follow-up must be conducted as clinically indicated and as per local regulations where applicable. Serum test is only required if urine test is positive or is not evaluable.
Creatinine clearance calculation	X	X	X			Creatinine clearance is calculated using the Cockcroft-Gault method (Table 3).
ECOG performance status	X	X	X			

	Participants Who Receive Induction Phase Treatment and are Not Randomized	Participants Randomized to Maintenance Phase				Notes: * Participants who discontinue study treatment in the Induction Phase will proceed directly to Safety Follow-up.
Study Period	**Safety Follow-up**	**EOT**	**Long-term Follow-up**			
Visit Number/Title	**Safety***	**DC**	**Safety[a]**	**Follow-up[a,b]**	**Survival Follow-up[c]**	
Scheduling Window (Days):	**30 Days After Last Dose (+ 7 days)**	**At time of DC (± 3 days)**	**30 Days After Last Dose (+7 days)**	**Q6W for 48 weeks Post-randomization, thereafter Q9W post DC (± 7 days)**	**Q12W (±14 days)**	
CCI [redacted]						
CCI [redacted]						

	Participants Who Receive Induction Phase Treatment and are Not Randomized	Participants Randomized to Maintenance Phase				Notes:
Study Period	**Safety Follow-up**	**EOT**	**Long-term Follow-up**			* Participants who discontinue study treatment in the Induction Phase will proceed directly to Safety Follow-up.
Visit Number/Title	**Safety***	**DC**	**Safety[a]**	**Follow-up[a,b]**	**Survival Follow-up[c]**	
Scheduling Window (Days):	**30 Days After Last Dose (+ 7 days)**	**At time of DC (± 3 days)**	**30 Days After Last Dose (+7 days)**	**Q6W for 48 weeks Post-randomization, thereafter Q9W post DC (± 7 days)**	**Q12W (±14 days)**	

Abbreviations: AE = adverse event; aPTT = activated partial thromboplastin time; BID = twice daily; CCI [redacted]; DBP = diastolic blood pressure; DC = discontinuation; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; CCI [redacted] CCI [redacted] HR = heart rate; ICF = informed consent form; ID = identification; PD = progressive disease; PRO = patient-reported outcome; RR = respiratory rate; SBP = systolic blood pressure; SoA = schedule of activities; WOCBP = women of childbearing potential.

a. If the DC visit occurs ≥30 days from last dose of study intervention, a Safety Follow-up Visit is not required.
b. Follow-up visits may be scheduled to coincide with Follow-Up imaging. For participants who DC for reasons other than PD, imaging continues until verified PD or initiation of a new antineoplastic therapy.
c. Participants who either DC for documented PD or start a new anticancer therapy will enter the Survival Follow-up Phase and will be monitored approximately every 12 weeks by telephone call to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.
d. Imaging to be performed at DC (±4 weeks [28 days]). If an imaging assessment was obtained within 4 weeks (28 days) prior to the date of DC, imaging is not required at the EOT visit. For participants who DC for PD, this is the final required tumor imaging.
e. Participants with treated brain lesions and participants with known, asymptomatic, untreated brain metastases at diagnosis, will require imaging of the brain as a site of disease at DC (±4 weeks [28 days]). If an imaging assessment was obtained within 4 weeks (28 days) prior to the date of DC, imaging is not required at the EOT visit. For participants who DC for PD, this is the final required tumor imaging.

1.3.4 Second Course Treatment Phase

Study Period	**Second Course Treatment**						**End-of-Treatment**	**Posttreatment**			**Comments**
Treatment Cycle	**C1**	**C2**	**C3**	**C4**	**C5**	**C6+**		**Safety Follow-up[a]**	**Imaging Follow-up[b]**	**Survival Follow-up**	
Cycle Day	**1**	**1**	**1**	**1**	**1**	**1**	At time of discon-tinuation	30 days from last dose (+7)	Q12W (±7)	Q12W (±7)	
Scheduled Days		**±3**	**±3**	**±3**	**±3**	**±3**					
Administrative Procedures											
Review eligibility criteria	X										
Review Concomitant Medication	X	X	X	X	X	X	X	X			
Review new anticancer treatment							X	X	X	X	All anticancer therapy will be recorded until time of death or termination of survival follow-up. If a clinical visit is not feasible, this information may be obtained via telephone or email.
Survival status	←----------									----------→	X	All participants may be contacted for survival status at any time during the course of the study.

Study Period	Second Course Treatment						End-of-Treatment	Posttreatment			Comments
Treatment Cycle	**C1**	**C2**	**C3**	**C4**	**C5**	**C6+**		**Safety Follow-up[a]**	**Imaging Follow-up[b]**	**Survival Follow-up**	
Cycle Day	**1**	**1**	**1**	**1**	**1**	**1**	At time of discon-tinuation	30 days from last dose (+7)	Q12W (±7)	Q12W (±7)	
Scheduled Days		**±3**	**±3**	**±3**	**±3**	**±3**					
Clinical Assessments or Procedures											
Review adverse events	X	X	X	X	X	X	X	X	X		Report all AES occurring through 30 days following the last dose of study intervention. SAEs: Report all SAEs occurring through 90 days following the last dose of study intervention, or 30 days following the last dose of study intervention if the participant initiates new anticancer therapy, whichever is earlier. New diagnoses of MDS and AML should be reported throughout the study, including the follow-up period.
Full physical exam	X						X				
Directed physical exam		X	X	X	X	X		X			
Vital signs	X	X	X	X	X	X	X	X			
12-Lead Electrocardiogram	X										
ECOG performance status	X	X	X	X	X	X	X	X			Perform within 3 days prior to Second Course Cycle 1 and prior to treatment during treatment visits.

Study Period	Second Course Treatment						End-of-Treatment	Posttreatment			Comments
Treatment Cycle	**C1**	**C2**	**C3**	**C4**	**C5**	**C6+**		**Safety Follow-up[a]**	**Imaging Follow-up[b]**	**Survival Follow-up**	
Cycle Day	**1**	**1**	**1**	**1**	**1**	**1**	At time of discon-tinuation	30 days from last dose (+7)	Q12W (±7)	Q12W (±7)	
Scheduled Days		**±3**	**±3**	**±3**	**±3**	**±3**					
Laboratory Assessments or Procedures											
Pregnancy Test (WOCBP only) - urine or β-HCG	X	X	X	X	X	X	X	X	X		WOCBP require a negative highly sensitive urine test within 24 hours (72 hours for serum) prior to first dose of Second Course study intervention. Serum test only required if urine test is positive or not evaluable. Testing during Second Course must be conducted as clinically indicated and as per local regulations, where applicable. More frequent pregnancy testing may be indicated, as dictated by local regulations.
PT/INR and aPTT/PTT	X										Perform within 3 days prior to Second Course Cycle 1 Participants receiving coumarin-based anticoagulants should have more frequent INR monitoring as clinically indicated.
Chemistry panel	X	X	X	X	X	X	X	X			Perform within 3 days prior to Second Course Cycle 1
Hematology panel	X	X	X	X	X	X	X	X			Perform within 3 days prior to Second Course Cycle 1.

Study Period	Second Course Treatment						End-of-Treatment	Posttreatment			Comments
Treatment Cycle	**C1**	**C2**	**C3**	**C4**	**C5**	**C6+**		**Safety Follow-up[a]**	**Imaging Follow-up[b]**	**Survival Follow-up**	
Cycle Day	**1**	**1**	**1**	**1**	**1**	**1**	At time of discon-tinuation	30 days from last dose (+7)	Q12W (±7)	Q12W (±7)	
Scheduled Days		**±3**	**±3**	**±3**	**±3**	**±3**					
T3/FT3, FT4, and TSH	X		X		X		X	X			Perform within 3 days prior to Second Course Cycle 1 and every other cycle thereafter (C3, C5, C7).
Efficacy Measurements											
CT/MRI imaging of chest, abdomen, and pelvis	X			X		X	X		X[c]		Perform within 28 days prior to Second Course Cycle 1. Q12W (±7 days) from Second Course Cycle 1 onwards or more frequently as clinically indicated. If imaging was obtained within 28 days prior to discontinuation, an additional scan is not needed at discontinuation. As of Amendment 07, tumor imaging will be assessed locally based on the site's standard of care imaging schedule.

Study Period	Second Course Treatment						End-of-Treatment	Posttreatment			Comments
Treatment Cycle	**C1**	**C2**	**C3**	**C4**	**C5**	**C6+**		**Safety Follow-up[a]**	**Imaging Follow-up[b]**	**Survival Follow-up**	
Cycle Day	**1**	**1**	**1**	**1**	**1**	**1**	At time of discon-tinuation	30 days from last dose (+7)	Q12W (±7)	Q12W (±7)	
Scheduled Days		**±3**	**±3**	**±3**	**±3**	**±3**					
MRI Brain	X			X		X	X		X[c]		Perform within 28 days prior to Second Course Cycle 1 for participants known to be positive for brain metastases or who are clinically symptomatic. If positive for brain metastases at the start of Second Course, continue imaging Q12W from Second Course Cycle 1 onwards or more frequently as clinically indicated. If imaging was obtained within 28 days prior to discontinuation, an additional scan is not needed at discontinuation.
Dispensing and Administration of Study Intervention											
Pembrolizumab	X	X	X	X	X	X					200 mg IV Q3W

Abbreviations: AE=adverse event; C1=Cycle 1; C2=Cycle 2; CT=computed tomography; DC=discontinuation; ECOG=Eastern Cooperative Oncology Group; FT4=free thyroxine; MRI=magnetic resonance imaging; Q12W=every 12 weeks; SAE=serious adverse event; T3=triiodothyronine; TSH=thyroid-stimulating hormone; WOCBP=women of childbearing potential.

a. If Discontinuation visit occurs ≥30 days from last dose of study intervention, a Safety Follow-up Visit is not required. All procedures for both visits will be performed at the Discontinuation Visit.
b. Follow-up visits to be scheduled to coincide with Follow-up imaging.
c. Participants who discontinue for reasons other than radiographic disease progression will have posttreatment follow-up imaging for disease status until disease progression is documented radiographically per RECIST 1.1, confirmed by the site per iRECIST when clinically appropriate, initiating a new anticancer treatment, withdrawing consent, becoming lost to follow-up, pregnancy or death.

2 INTRODUCTION

This clinical trial will study the combination of pembrolizumab and the polyadenosine 5′ diphosphoribose (polyADP ribose) polymerization (PARP) inhibitor, olaparib, in the treatment of squamous non-small cell lung cancer (NSCLC).

2.1 Study Rationale

Squamous NSCLC accounts for approximately 30% to 35% of all NSCLC, with the majority of patients having advanced disease at diagnosis that is not amenable to surgical resection. There remains a high unmet medical need for patients with previously untreated metastatic squamous NSCLC. Although squamous cell lung cancers harbor putative oncogenic drivers, these have little clinical relevance and cannot be targeted. Unlike non-squamous NSCLC, no agent has been approved for maintenance therapy in squamous cell NSCLC. Consequently, platinum doublets had remained the standard of care in the first-line treatment in this disease until most recently when immunotherapy with the use of anti-PD-1/anti-PD-L1 antibodies has begun to change outcomes in this patient population.

Pembrolizumab monotherapy did change the treatment paradigm for those patients with NSCLC whose tumors express PD-L1 ≥50% in the Phase 3 study, KEYNOTE-024. In this study, pembrolizumab showed statistically significant increases in OS and PFS compared with platinum-based chemotherapy for treatment-naïve participants with metastatic NSCLC whose tumors expressed high levels of the PD-L1 (tumor proportion score [TPS] ≥50%) with no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations, leading to regulatory approval for this indication in the US and other countries around the world. Approximately 30% of patients with newly diagnosed, advanced NSCLC highly express PD-L1 to a TPS ≥50% [Reck, M., et al 2016]; therefore, only a subset of patients with metastatic squamous NSCLC are potential candidates. With the findings from KEYNOTE-042, the TPS cutoff has been lowered, as pembrolizumab monotherapy significantly improved OS for participants with NSCLC who had TPS ≥1% (16.7 months vs 12.1 months; hazard ratio [HR]: 0.81) and TPS ≥20% (17.7 months vs. 13.0 months; HR: 0.77), compared with chemotherapy alone, while continuing to demonstrate an OS benefit in those with TPS ≥50% (20.0 months vs. 12.2 months; HR: 0.69). Thus, both KEYNOTE-024 and KEYNOTE-042 showed that pembrolizumab monotherapy is effective in participants with PD-L1 positive metastatic NSCLC, including in participants with squamous histology. Yet, despite these encouraging data, there is still substantial room for improvement of the treatment options available to these patients.

KEYNOTE-407 was designed to expand upon the efficacy of pembrolizumab by combining it with carboplatin and a taxane (paclitaxel or nab-paclitaxel) in patients with metastatic squamous NSCLC, as chemotherapy has been shown to augment the antitumor immune response. The study was a global, multicenter, placebo-controlled trial that randomized 559 participants with untreated Stage IV squamous NSCLC in a 1:1 fashion to receive carboplatin and investigator's choice of either paclitaxel or nab-paclitaxel in combination with pembrolizumab for 4 cycles followed by pembrolizumab monotherapy for up to 31 cycles or saline placebo plus carboplatin/paclitaxel or nab-paclitaxel for 4 cycles followed by

saline placebo [Paz-Ares, L., et al 2018]. Patients in the saline placebo arm had the option to cross over to pembrolizumab monotherapy if progressive disease had been verified by BICR and other safety criteria were met. In the original analysis, the study demonstrated a clinically meaningful and statistically significant improvement in OS with an HR of 0.64 (95% CI: 0.49-0.85, p=0.008) and a median OS of 15.9 months in the pembrolizumab combination arm compared to 11.3 months in the chemotherapy alone arm. Similarly, there was significant PFS benefit with an HR of 0.56 (95% CI: 0.45-0.70, p<0.0001) with a median PFS of 6.4 months and 4.8 months in the pembrolizumab combination arm vs chemotherapy alone arm, respectively. ORR also was significantly improved in the pembrolizumab combination arm (58.4%) compared with chemotherapy alone (35%), p=0.0004. Importantly all subgroups benefited from pembrolizumab in combination with carboplatin and taxane-based chemotherapy, including patients whose tumors did not express PD-L1; therefore, extending the benefit of pembrolizumab to those with PD-L1 negative tumors.

Unfortunately, while these results have changed the paradigm in lung cancer treatment, patients with squamous cell NSCLC continue to progress and succumb to this disease and as such, there can be further improvement upon the therapeutic options available.

As PARP inhibition has been established as maintenance therapy in platinum-sensitive ovarian cancer, there is potential for improved outcomes in lung cancers by adding maintenance olaparib to pembrolizumab in those demonstrating platinum-sensitivity after induction pembrolizumab with chemotherapy, especially in squamous cell NSCLC where no maintenance agent is approved. Non-small cell lung cancer also is a prime candidate for olaparib use as HRD-LOH (homologous recombination deficiency loss of heterozygosity) scores are as high as in breast and ovarian cancers, as per The Cancer Genome Atlas. Furthermore, preclinical data indicate that olaparib and anti-PD(L)-1 inhibitors demonstrate improved therapeutic benefit than each alone, likely being synergistic effects. Therefore, adding olaparib as maintenance therapy to pembrolizumab in the treatment of patients with platinum-sensitive squamous NSCLC has the potential for further treatment benefit, which is clearly necessary.

Based on a critical need for new therapies in 1L treatment of Stage IV squamous NSCLC, we are undertaking this Phase 3 study of pembrolizumab plus standard-of-care chemotherapy (carboplatin/paclitaxel or nab-paclitaxel) followed by pembrolizumab and maintenance olaparib.

2.2 Background

2.2.1 Olaparib

Olaparib (AZD2281, KU-0059436) is a potent PARP inhibitor (PARP1, 2, and 3) that is being developed as a monotherapy as well as for combination with chemotherapy, ionizing radiation and other anticancer agents including novel agents and immunotherapy.

PARP inhibition is a novel approach to targeting tumors with deficiencies in DNA repair mechanisms. PARP enzymes are essential for repairing DNA single strand breaks (SSBs). Inhibiting PARPs leads to the persistence of SSBs, which are then converted to the more

serious DNA double strand breaks (DSBs) during the process of DNA replication. During the process of cell division, DSBs can be efficiently repaired in normal cells by HRR. Tumors with HRD, such as ovarian cancers in patients with breast cancer susceptibility gene 1/2 (BRCA1/2) mutations (BRCAm), cannot accurately repair the DNA damage, which may become lethal to cells as it accumulates. In such tumor types, olaparib may offer a potentially efficacious and less toxic cancer treatment compared with currently available chemotherapy regimens.

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

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on olaparib.

2.2.2 Pembrolizumab

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

2.2.3 Non-small Cell Lung Cancer (NSCLC)

Lung cancer is the most common malignancy in the world, with an estimated incidence in 2012 of 2.1 million and an associated 1.76 million deaths [Bray, F., et al 2018]. Among males, the estimated incidence rates of new diagnoses are highest in Central and Eastern Europe (53.5 per 100,000/year) and Eastern Asia (50.4), while the incidence rates among females are highest in North America (33.8), Northern Europe (23.7), and Eastern Asia (19.2) [Ferlay, J., et al 2015].

Non-small cell lung cancer represents approximately 80% to 85% of all lung cancer [National Cancer Institute 2016] and consists of 2 major types: non-squamous carcinoma (~65%-70% of cases) and squamous carcinoma (~30%-35% of cases) [Ferlay, J., et al 2015] [Arnold, M., et al 2015]. At the time of diagnosis, approximately 80% of patients with lung cancer have locally advanced or metastatic disease that is not amenable to surgical resection [National Cancer Institute 2012]. Of those patients diagnosed with early stage NSCLC and treated with surgery, a significant percentage subsequently develop distant recurrence [Pisters, K. M. W. and Le Chevalier, T. 2005]. These factors contribute to the dismal 5-year

relative survival rates of 17.7% in patients diagnosed with NSCLC, and a mere 4.3% in those with advanced/metastatic disease [National Cancer Institute 2016a].

2.2.4 Current Treatment Options and Unmet Medical Need

There remains a high unmet medical need for patients with previously untreated metastatic squamous NSCLC.

Prior to the use and availability of pembrolizumab, limited therapeutic options were available for first-line treatment of metastatic squamous NSCLC beyond standard platinum-based chemotherapy. Regimens have included cisplatin or carboplatin in combination with paclitaxel, gemcitabine, pemetrexed, or docetaxel [Peters, S., et al 2012]. Multiple Phase 3 studies have shown similar efficacy for most platinum-based chemotherapies in participants with metastatic NSCLC [Schiller, J. H., et al 2002] [Socinski, Mark A., et al 2012] [Scagliotti, G. V., et al 2008] [Thatcher, N., et al 2015]. Carboplatin with either paclitaxel or nab-paclitaxel is one of the most widely accepted regimens for chemotherapy-naïve patients with metastatic squamous NSCLC [National Comprehensive Cancer Network 2015]. In a randomized, Phase 3 study that compared the efficacy and safety of albumin-bound paclitaxel (nab-paclitaxel) plus carboplatin with solvent-based paclitaxel plus carboplatin in advanced NSCLC, the ORR (primary endpoint) was 33% in the nab-paclitaxel group and 25% in the paclitaxel group. For participants with squamous histology, the ORR was 41% and 24%, respectively. However, neither PFS (median, 6.3 vs 5.8 months) nor OS (median, 12.1 vs 11.2 months) differed significantly between the nab-paclitaxel and paclitaxel groups. Significantly less AEs of neuropathy, neutropenia, arthralgia, and myalgia of at least Grade 3 severity occurred among participants on nab-paclitaxel and less thrombocytopenia and anemia occurred among participants on paclitaxel [Socinski, Mark A., et al 2012].

While squamous cell lung cancers harbor putative oncogenic drivers, these have little clinical relevance and cannot be targeted, unlike non-squamous lung cancers. Two agents efficacious in treating non-squamous NSCLC are the anti-metabolite, pemetrexed, and the anti-angiogenic agent, bevacizumab, neither of which is used to treat squamous NSCLC [Thatcher, N., et al 2015]. For patients with squamous NSCLC, pemetrexed-based therapies result in shorter survival times compared with patients with non-squamous NSCLC [Scagliotti, G., et al 2009], and bevacizumab has the toxicity concern of pulmonary hemorrhage [Sandler, A., et al 2006]. Necitumumab in combination with gemcitabine and cisplatin was approved by the US FDA and the EMA in squamous NSCLC based on the SQUIRE trial study [Thatcher, N., et al 2015]; however, because the absolute benefit from the addition of necitumumab to platinum-based chemotherapy remains small, this combination does not have widespread use.

Pembrolizumab has led to a paradigm shift from standard platinum-based doublets for the first-line treatment of NSCLC. KEYNOTE-024 showed statistically significant increases in OS and PFS for pembrolizumab compared with platinum-based chemotherapy in treatment-naïve participants with metastatic NSCLC whose tumors expressed high levels of the PD-L1 (TPS ≥50%) with no EGFR or ALK genomic tumor aberrations. With the findings from KEYNOTE-042, the TPS cutoff has been lowered, as pembrolizumab monotherapy significantly improved OS for participants with NSCLC who had TPS ≥1% (16.7 months vs

12.1 months; HR: 0.81) and TPS ≥20% (17.7 months vs. 13.0 months; HR: 0.77), compared with chemotherapy alone, while continuing to demonstrate an OS benefit in those with TPS ≥50% (20.0 months vs 12.2 months; HR: 0.69). Thus, both KEYNOTE-024 and KEYNOTE-042 showed that pembrolizumab monotherapy is effective in participants with PD-L1 positive metastatic NSCLC, including those with squamous histology.

KEYNOTE-407 has further redefined the standard of care for patients with squamous NSCLC. In the original report with a medial follow-up of 7.8 months (range, 0.1 to 19.1), the study demonstrated a clinically meaningful and statistically significant improvement in OS with an HR of 0.64 (95% CI: 0.49-0.85, p=0.008) and a median OS of 15.9 months in the pembrolizumab combination arm compared to 11.3 months in the chemotherapy alone arm. Similarly, there was significant PFS benefit with an HR of 0.56 (95% CI: 0.45-0.70, p<0.0001) with a median PFS of 6.4 months and 4.8 months in the pembrolizumab combination arm vs chemotherapy alone arm, respectively. ORR also was significantly improved in the pembrolizumab combination arm (58.4%) compared with chemotherapy alone (35%), p=0.0004. In a subsequent 3-year OS analysis from KEYNOTE-407 (median time from randomization to data cutoff, 40.1 months; range 33.1–49.4 months), pembrolizumab plus platinum-doublet chemotherapy demonstrated long-term OS (HR, 0.71 [95% CI, 0.59–0.86]; estimated 3-year OS rates, 29.7% vs 18.2%), PFS (HR, 0.59 [95% CI, 0.49–0.71]; estimated 3-year PFS rates, 16.1% vs 6.5%), ORR (62.6% vs 38.8%), and DOR (medians, 9.0 vs 4.9 months) benefits compared with placebo plus chemotherapy in patients with previously untreated metastatic squamous NSCLC regardless of PD-L1 expression [Robinson, A. G., et al 2021]. Importantly, all subgroups benefited from pembrolizumab in combination with carboplatin and taxane-based chemotherapy, including patients whose tumors did not express PD-L1; therefore, extending the benefit of pembrolizumab to those with PD-L1 negative tumors.

Despite these impressive results, patients with advanced squamous NSCLC still have an urgent need for new agents that can be combined with a pembrolizumab backbone to increase response rates, decrease the risk of progression, and decrease the risk of death [Gandhi, L., et al 2018].

2.2.5 Pharmaceutical and Therapeutic Background

2.2.5.1 Inhibition of PARP as a Target for Cancer Therapy

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

Under normal conditions, HRR is the preferred pathway for repairing DNA damage as it is associated with a lower rate of errors compared with other forms of DNA repair

[Prakash, R., et al 2015]. During DNA replication (S phase), pre-existing or chemotherapy-induced SSBs are converted to DSBs if not adequately repaired by intracellular mechanisms [Fong, Peter C., et al 2009], such as HRR. Cells unable to perform HRR (eg, due to inactivation of genes required for homologous recombination, such as BRCA1 or BRCA2) are more likely to use the error-prone non-homologous end-joining (NHEJ) or alternative (alt)-NHEJ pathways to repair these DSBs and risk accumulating multiple lesions or loss of heterozygosity (LOH) due to an increase in deletions and accompanying genomic instability. Over time, the accumulation of excessive DNA errors in combination with the inability to complete S phase (ie, because of stalled replication forks due to PARP inhibitor administration), leads to cell death demonstrating that PARP inhibition is synthetically lethal in the context of BRCAm [Farmer, H., et al 2005] [Bryant, H. E., et al 2005]. Cells without SSBs or with intact HRR, such as somatic tissue, replicate normally in the presence of a PARP inhibitor, thereby minimizing toxicity.

Treatment with PARP inhibitors could represent a novel opportunity to selectively kill cancer cells with deficiencies in DNA repair pathways.

Additionally, PARP inhibitors, by causing DNA damage can activate the cGAS-STING pathway, increasing type I interferons, immunomodulatory molecules (eg, CXCL10, CCL5), and CD4+/CD8+ lymphocytes and upregulating PD-L1 and other checkpoint inhibitors in both *BRCA*-proficient and *BRCA*-deficient cells. Preclinically, the combination of olaparib and anti-PD(L)1 inhibitors demonstrate improved therapeutic benefit than each alone, likely being synergistic [Higuchi, T., et al 2015] [Huang, J., et al 2015] [Jiao, S., et al 2017] [Parkes, E. E., et al 2017]; therefore, there is a rationale for the combination of olaparib and pembrolizumab.

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

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

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

The structure of murine PD-1 has been resolved [Zhang, X., et al 2004]. PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type (IgV type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKC-θ), 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 squamous NSCLC.

2.2.5.3 Homologous Recombination Repair in Solid Tumors

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

Normally, the process of HRR corrects DSBs using proteins such as BRCA1 and BRCA2; however, the HRR armamentarium includes proteins coded by at least 13 other genes including *ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D,* and *RAD54L*. For example, the protein coded by the *ATM* gene also is involved in the repair of DSB. *ATM* is activated by DSB and phosphorylates diverse cellular proteins, leading to cell-cycle arrest (eg, mediator of DNA damage checkpoint 1 [MDC1], checkpoint kinase 2), activates the tumor suppressor p53, contributes to chromatin relaxation and remodeling, and activates nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB). Defective *ATM* increases the risk of breast, gastrointestinal, lung, and lymphoid cancers. Moreover, defective *ATM* also appears to correlate with a poor prognosis, but the conferred risk has not been quantified.

A small percentage of tumors have loss-of-function mutations in HRR genes, with *BRCA1, BRCA2*, and *ATM* being the best characterized and most frequently mutated [Watkins, J. A., et al 2014] [Marquard, A. M., et al 2015] [Choi, M., et al 2016] [Lord, C. J. 2016]. Approximately half of the detected HRRm are germline mutations [Mateo, J., et al 2015]. While an adverse prognostic impact of germline *BRCA2* mutations has been described in prostate cancer [Castro, E., et al 2015], it is less clear if other germline or somatic HRR gene

mutations are associated with similar adverse clinical outcomes. To date, HRRm has not been associated with specific patient or tumor characteristics.

Notably, in NSCLC, HRD-LOH scores are as high as in breast and ovarian cancers, as per The Cancer Genome Atlas data [Cerami, E., et al 2012] [Gao, J., et al 2013].

2.2.6 Preclinical and Clinical Studies

For a summary of preclinical and clinical study data for pembrolizumab and olaparib, refer to their respective IBs.

2.2.7 Ongoing Clinical Studies

For a summary of ongoing clinical study data for pembrolizumab and olaparib, refer to their respective IBs.

2.2.7.1 Information on Other Trial-related Therapy

A platinum doublet with a taxane is the most commonly used 1L chemotherapy for chemo-naïve metastatic squamous NSCLC patients, respectively. Pembrolizumab in combination with carboplatin and paclitaxel or nab-paclitaxel is also being evaluated in a randomized Phase 3 study, KN407, and data were positive at the interim analysis [Paz-Ares, L., et al 2018]. Based on safety and efficacy data from these combination studies with pembrolizumab and other PD-1/PD-L1 inhibitors, the current study will use pembrolizumab in combination with carboplatin plus paclitaxel or nab-paclitaxel at approved doses.

2.3 Benefit/Risk Assessment

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

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 male and female participants with Stage IV squamous NSCLC with stable disease, partial response, or complete response following induction treatment with pembrolizumab combined with carboplatin and a taxane (paclitaxel or nab-paclitaxel):

Objectives	Endpoints
Primary	
• Objective: To compare pembrolizumab plus maintenance olaparib with pembrolizumab plus placebo with respect to progression-free survival (PFS) assessed according to RECIST 1.1 (Section 4.2.1.1) by blinded independent central review (BICR). • Hypothesis (H1): Pembrolizumab plus maintenance olaparib is superior to pembrolizumab plus placebo with respect to PFS per RECIST 1.1 (Section 4.2.1.1) by BICR.	• PFS, the time from the date of randomization until either documented disease progression or death due to any cause, whichever occurs first.
• Objective: To compare pembrolizumab plus maintenance olaparib with pembrolizumab plus placebo with respect to overall survival (OS). • Hypothesis (H2): Pembrolizumab plus maintenance olaparib is superior to pembrolizumab plus placebo with respect to OS.	• OS, the time from the date of randomization to death due to any cause.
As of Interim Analysis 3, this study did not meet its primary objective (pembrolizumab plus maintenance Olaparib is superior to pembrolizumab plus placebo with respect to OS). The final analysis will not be performed.	

Objectives	Endpoints
Secondary	
• Objective: To evaluate the safety and tolerability of pembrolizumab plus maintenance olaparib compared to pembrolizumab plus placebo.	• Adverse events (AEs) • Discontinuation of study intervention due to AEs
• Objective: To evaluate the change from baseline (at randomization) and the time to true deterioration (TTD) in global health status/quality of life (QoL), cough, chest pain, dyspnea and physical functioning following treatment with pembrolizumab plus maintenance olaparib compared to pembrolizumab plus placebo.	• Change from baseline (at randomization) and the time to true deterioration (TTD) defined as the time from baseline (at randomization) to the first onset of a ≥10-point deterioration with confirmation by the subsequent visit of a ≥10-point deterioration in the following European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ) and QLQ Lung Cancer Module 13 (LC13) scales/items: - Global health status/QoL (C30/Items 29 and 30) - Cough (LC13/Item 1) - Chest pain (LC13/Item 10) - Dyspnea (C30/Item 8) - Physical functioning (C30/Items 1 – 5)
CCI [redacted]	
CCI [redacted]	

Objectives	Endpoints
CCI [redacted]	

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 3, randomized, placebo-controlled, multisite, double-blind study of the combination of pembrolizumab plus carboplatin/taxane (paclitaxel or nab-paclitaxel) followed by continued pembrolizumab and olaparib maintenance compared with continued pembrolizumab and placebo in participants with metastatic squamous NSCLC in need of first-line treatment.

This study will be conducted in 4 phases: Screening, an Induction Phase, a Maintenance Phase, and Long-term Follow-up. An optional Second Course Phase is also available. The study design overview is presented in Figure 1 and described below.

The Induction Phase is an open-label, 12-week period during which approximately 857 eligible participants will be enrolled to receive 4 cycles of pembrolizumab and carboplatin plus paclitaxel or nab-paclitaxel; refer to Table 2. During the Induction Phase, participants will have study visits every 3 weeks for assessments. Tumor response during the Induction Phase will be evaluated using RECIST 1.1, with radiographic imaging at Weeks 6 and 12 (±7 days) from the date of the first dose (Cycle 1) of study intervention. All imaging must be submitted to the central imaging vendor as soon as possible for expedited BICR to determine overall responses for each Induction Phase scan prior to randomization into the Maintenance Phase.

Note: As of Amendment 07, disease progression will no longer be centrally verified; participants will only be assessed locally.

The Maintenance Phase is a randomized, double-blind period during which approximately 590 participants will be eligible for randomization to pembrolizumab combined with maintenance olaparib or pembrolizumab combined with maintenance olaparib placebo (Table 2), CCI

CCI

A detailed list of inclusion criteria specific for entering the Maintenance Phase is provided in Section 5.1.

Randomization will be stratified by Eastern Cooperative Oncology Group (ECOG) performance status score (0 or 1) at Pre-randomization Visit, PD-L1 expression (TPS <50% vs ≥50%), and response at the latest evaluable scan obtained prior to randomization (CR/PR vs SD).

Eligible participants who enter the Maintenance Phase may receive a maximum of 35 cycles of pembrolizumab during the study (4 cycles during the Induction Phase and 31 cycles during the Maintenance Phase). If pembrolizumab is stopped due to toxicity or completion of 35 cycles, the participant may continue with olaparib until specific discontinuation criteria are met (Section 7.1). If olaparib is stopped due to toxicity, the participant may continue to receive pembrolizumab for a maximum of 31 cycles during the Maintenance Phase or until specific discontinuation criteria are met (Section 7.1).

Table 2 Treatment Plan

Induction Phase (Cycles 1 to 4)	**Maintenance Phase (Up to 31 Cycles)**
• Pembrolizumab 200 mg IV Q3W on Day 1 • Carboplatin titrated to an AUC of 6 mg/mL/min IV Q3W on Day 1 • Paclitaxel 200 mg/m^2 IV Q3W OR Nab-paclitaxel 100 mg/m^2 on Day 1, Day 8, and Day 15	• Pembrolizumab 200 mg IV Q3W on Day 1 -for a maximum of 31 cycles or until specific discontinuation criteria are met (Section 7.1) • Olaparib 300 mg BID daily - will continue until specific discontinuation criteria are met (Section 7.1). • OR • Pembrolizumab 200 mg IV Q3W on Day 1 -for a maximum of 31 cycles or until specific discontinuation criteria are met (Section 7.1) • Olaparib placebo BID daily - will continue until specific discontinuation criteria are met (Section 7.1).
Abbreviations: AUC=area under the concentration-time curve; BID= twice daily; Q3W=every 3 weeks. Note: As of Amendment 07, participants who are confirmed to be actively taking placebo should discontinue taking the placebo intervention and continue in the study.	

Efficacy will be evaluated using PFS per RECIST 1.1, as determined by BICR, and OS.

Participants randomized into Maintenance Phase will be evaluated with radiographic imaging to assess response to treatment at regular intervals throughout the study as described in Section 8.2.1. The images prior to initiating the Maintenance Phase should be performed within 28 days of the date of randomization; these imaging studies will serve as the new baseline. All imaging obtained on study, including imaging showing Investigator-assessed progressive disease (PD), will be submitted to the central imaging vendor for review, which

will assess images using RECIST 1.1 for verification of PD and for determination of ORR (Section 8.2.1.4). Initial tumor imaging showing site-assessed PD should be submitted immediately for verification by BICR prior to discontinuation of study intervention.

Participants in the Maintenance Phase will receive randomly assigned study intervention until disease progression is radiographically documented and, when clinically appropriate, confirmed by the site per modified Response Evaluation Criteria in Solid Tumors 1.1, for immune-based therapeutics (iRECIST), or unacceptable AEs, intercurrent illness that prevents further administration of study intervention, investigator's decision to discontinue the participant, noncompliance with study intervention or procedure requirements, or administrative reasons requiring cessation of treatment (Section 7.1). Pembrolizumab will continue for a maximum of 31 cycles, or until specific discontinuation criteria are met (Section 7.1). Olaparib will continue until specific discontinuation criteria are met (Section 7.1).

Participants treated with pembrolizumab who complete 35 cycles of pembrolizumab during the study (4 cycles during the Induction Phase and 31 cycles during the Maintenance Phase) with SD, CR, or PR, and without a current AE, may be eligible for retreatment with up to an additional 17 cycles (approximately 1 year) of pembrolizumab if they experience radiographic disease progression after stopping treatment in the Maintenance Phase. This retreatment is termed Second Course Treatment and is only available if the study remains open and the participant meets the criteria listed in Section 8.12.5. Responses or events of progression that occur during Second Course Treatment will not be counted toward the ORR and PFS endpoints in this study.

Adverse event (AE) monitoring will be ongoing throughout the trial and graded in severity according to the guidelines outlined in the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.0 (Section 8.4). Adverse events will be reported by the Investigator or delegate from randomization through 30 days following cessation of study Intervention. Serious AEs (SAEs) will be reported by the investigator or delegate from the start of Induction Phase treatment through either 90 days following cessation of study intervention or 30 days following cessation of study intervention if the

CCI [redacted]

Participants who discontinue treatment for reasons other than verified PD will have Long-term Follow-up for disease status (including imaging) until PD, initiating a new anticancer therapy, withdrawing consent for study participation, or becoming lost to follow up. After documented PD, each participant will be contacted by telephone approximately every 12 weeks (84 ±14 days) for survival until withdrawal of consent to participate in the study, becoming lost to follow up, death, or end of the study, whichever occurs first.

Three interim efficacy analyses and 1 final analysis are planned in this study. Details regarding interim analyses are provided in Section 9.7. An external data monitoring committee (eDMC) will serve as the primary reviewer of the treatment-level results and will make recommendations for discontinuation of the study or modification to an Executive Oversight Committee (see Section 10.1.4 Committees Structure) of the Sponsor. The eDMC responsibilities and review schedules will be outlined in the eDMC charter.

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.

Note: Based on the data from an interim safety and efficacy analysis (IA3) (data cutoff 21-SEP-2023), the external Data Monitoring Committee recommended to remove the final analysis. The pembrolizumab plus Olaparib arm did not meet the statistical criterion for success for the primary endpoint of OS at Interim Analysis 3, nor is it expected to meet the endpoint at the planned prespecified final analysis. Based on these data, the study was unblinded as of 15-DEC-2023. The prespecified final analysis of the study described in the SAP will not be performed. Selected analyses of safety endpoints will be performed at the end of the study; there will be no further analyses for efficacy and ePRO endpoints.

Note: In alignment with the study-specific investigator letter dated 07-DEC-2023, all study participants still receiving study treatment will discuss next steps with the Investigator. They should continue to receive therapy on study and undergo modified protocol study procedures. There were no new safety signals identified in the IA3 analysis. Participants who are confirmed to be actively taking placebo should discontinue taking the placebo intervention and continue in the study. Participants currently on study treatment with Olaparib will be able to continue treatment per Investigator's discretion after discussion with their physician. Participants who are potential candidates for Second Course treatment will continue in Efficacy Follow-up. Participants currently undergoing or who will undergo Second Course with pembrolizumab monotherapy can continue or start treatment per investigator’s discretion under this protocol or under an extension study.

4.2 Scientific Rationale for Study Design

In contrast to non-squamous NSCLC, no agent has been approved for maintenance therapy in squamous NSCLC. The results of KEYNOTE-407 have led to a paradigm shift in the treatment of front-line treatment of patients with Stage IV squamous NSCLC and the new standard of care in this population is 4 cycles of pembrolizumab combined with carboplatin and paclitaxel (or nab-paclitaxel) followed by pembrolizumab for up to a total of 35 cycles.

Unfortunately, while these results have changed the paradigm in squamous NSCLC, patients with this disease progress with first-line therapy and ultimately succumb to this malignancy. A potential opportunity for improvement in this high area of unmet medical need is by adding a PARP inhibitor to pembrolizumab in the maintenance setting. PARP inhibition has been established as a maintenance therapy for platinum-sensitive populations in ovarian cancer, regardless of *BRCA* status. Clinical benefit from platinum may predict for sensitivity to Olaparib maintenance, which may extend beyond ovarian cancer. Olaparib, when added to pembrolizumab, may continue to induce DNA damage and upregulate PD-L1, leading to synergism and further delaying progressive disease in squamous NSCLC. Notably, in the MEDIOLA trial, a Phase 2 basket study that included patients with SCLC, an improvement in overall survival was demonstrated when olaparib-durvalumab was administered following olaparib in those with relapsed disease.

Importantly, olaparib in combination with pembrolizumab is being evaluated in an ongoing nonrandomized, multicenter, multicohort, open-label, Phase 1b/2 study (KEYNOTE-365) in participants with metastatic castration-resistant prostate cancer (mCRPC) and the combination has been generally well tolerated, with no new safety signals identified for either compound.

A recently published Phase 2 trial of the PARP inhibitor veliparib in combination with carboplatin and paclitaxel vs carboplatin and paclitaxel alone as first-line therapy in patients with advanced NSCLC showed clinically meaningful, but not statistically significant, benefit [Ramalingam, S. S., et al 2017]. This benefit was more pronounced in patients with squamous histology, with a median PFS of 6.5 months in the group of patients treated with veliparib vs 4.1 months in the placebo group, HR 0.54, 95% CI, 0.26-1.12; p=0.098.

This trial is a Phase 3, double-blind study designed and powered to determine whether continued pembrolizumab with maintenance olaparib leads to improved PFS and OS when compared with continued pembrolizumab and maintenance olaparib placebo in participants with stable disease or partial/complete response to 4 cycles of induction pembrolizumab combined with chemotherapy. Randomization to the Maintenance Phase after all participants complete induction therapy, isolates the treatment effect of the combination of continued pembrolizumab and maintenance olaparib compared with pembrolizumab alone.

Based on a critical need for new therapies in 1L treatment of Stage IV squamous NSCLC and the growing scientific evidence for the potential synergism for the combination of pembrolizumab and olaparib in NSCLC, we are undertaking this Phase 3, double-blind study of pembrolizumab plus chemotherapy (carboplatin/paclitaxel or nab-paclitaxel) followed by pembrolizumab and maintenance olaparib. Adding olaparib as maintenance therapy to pembrolizumab in platinum-sensitive squamous NSCLC likely has the potential for further improvements in this malignancy.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

This study has dual primary endpoints of PFS and OS.

This study will use PFS as assessed by BICR according to RECIST 1.1 (see Section 4.2.1.1.1) as a primary endpoint. Progression-free survival is an acceptable measure of clinical benefit for a late-stage study that demonstrates superiority of a new antineoplastic therapy, especially if the magnitude of the effect is large and the therapy has an acceptable risk/benefit profile. The use of BICR and RECIST 1.1 to assess PFS is typically considered acceptable by regulatory authorities. Images will be submitted to a central imaging vendor and read by independent central reviewers blinded to treatment assignment to minimize bias in the response assessments. In addition, the final determination of radiologic progression will be based on the central assessment of progression, rather than a local site investigator/radiology assessment. Expedited verification of radiologic progression by BICR will be communicated to the site by email.

Overall survival has been recognized as the gold standard for the demonstration of superiority of a new antineoplastic therapy in randomized clinical studies.

4.2.1.1.1 RECIST 1.1

RECIST 1.1 will be used by the BICR when assessing images for efficacy measures and by the local site when determining eligibility (Section 8.2.1.5). Although traditional RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, this protocol has implemented a modification to RECIST 1.1 to allow a maximum of 10 target lesions in total and 5 per organ.

4.2.1.1.2 iRECIST

RECIST 1.1 will be adapted to account for the unique tumor response characteristics seen following treatment with pembrolizumab (Section 8.2.1.5). Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and patients treated with pembrolizumab may manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Thus, standard RECIST 1.1 may not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab. Based on an analysis of participants with melanoma enrolled in KEYNOTE-001 (KN001), 7% of evaluable participants experienced delayed or early tumor pseudo-progression. Of note, participants who had PD by RECIST 1.1, but not by the immune-related response criteria [Wolchok, J. D., et al 2009], had longer overall survival than participants with PD by both criteria [Hodi, F. S., et al 2014]. Additionally, the data suggest that RECIST 1.1 may underestimate the benefit of pembrolizumab in approximately 15% of participants. These findings support the need to apply a modification to RECIST 1.1 that considers the unique

patterns of atypical responses in immunotherapy and enables treatment beyond initial radiographic progression, if the participant is clinically stable.

Modified RECIST 1.1 for immune-based therapeutics (iRECIST) assessment has been developed and published by the RECIST Working Group, with input from leading experts from industry and academia, along with participation from the US Food and Drug Administration and the European Medicines Agency [Seymour, L., et al 2017]. The unidimensional measurement of target lesions, qualitative assessment of nontarget lesions, and response categories are identical to RECIST 1.1, until progression is seen by RECIST 1.1. However, if a participant is clinically stable, additional imaging may be performed to confirm radiographic progression. iRECIST will be used by investigators to assess tumor response and progression and make treatment decisions.

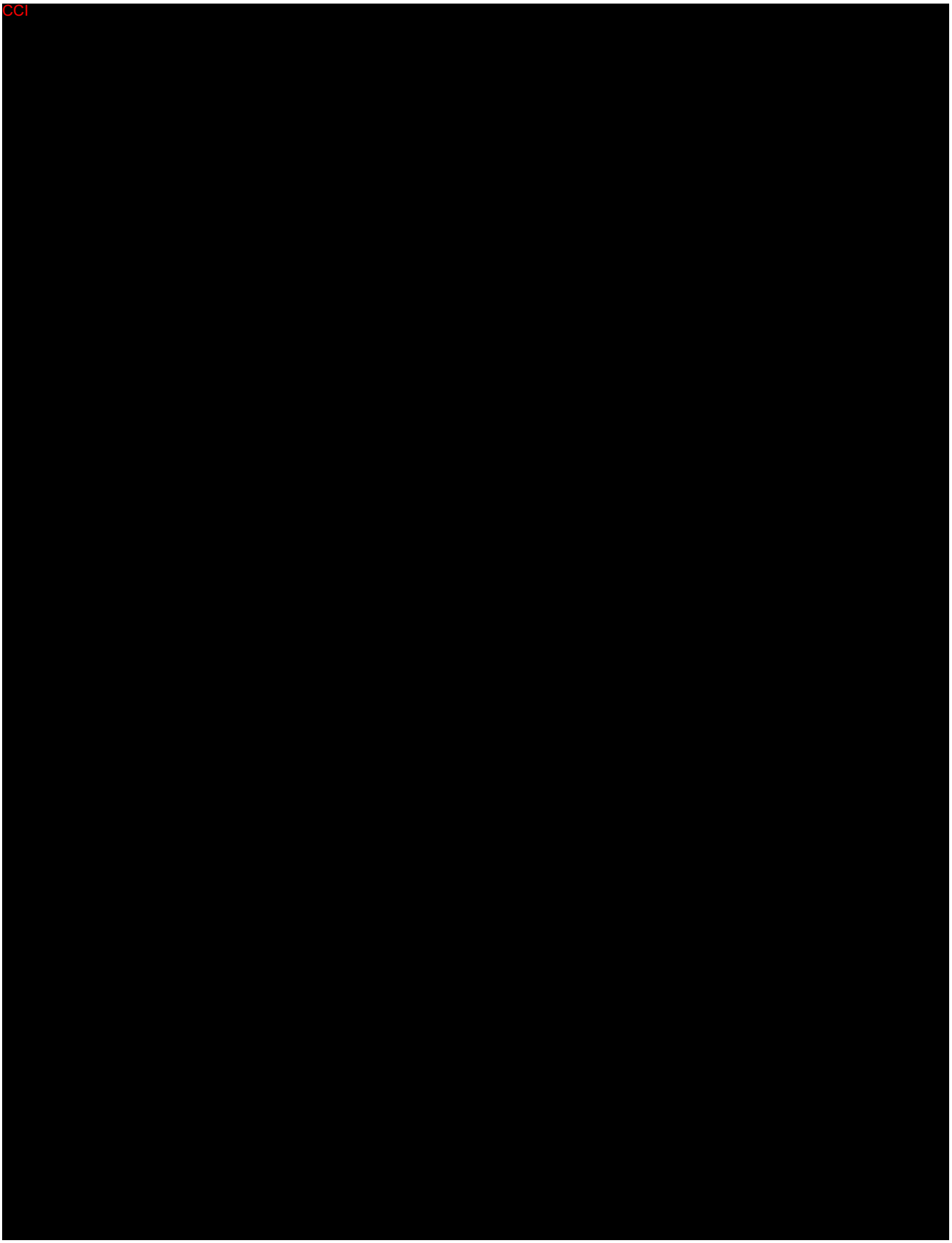
4.2.1.2 Safety Endpoints

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. Adverse events will be assessed as defined by CTCAE, Version 4.0.

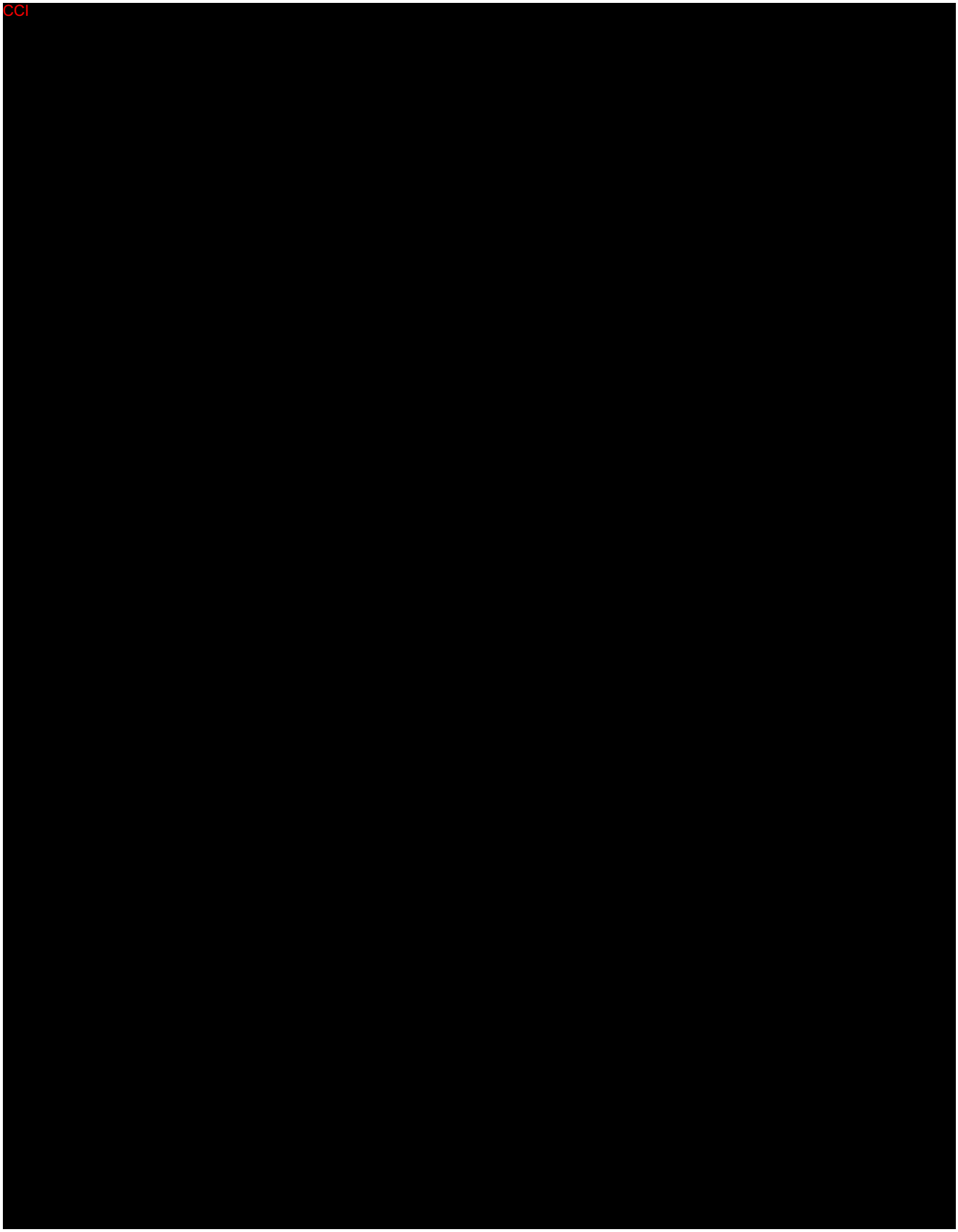
CCI

[redacted]

CCI



CCI



CCI

[redacted]

CCI [redacted]

4.2.2 Rationale for the Use of Comparator/Placebo

The use of a placebo for olaparib will ensure the objectivity of Investigator-assessed progression, as well as any decisions to interrupt/discontinue therapy.

Note: The study has been unblinded. Participants who are confirmed to be actively taking placebo should discontinue taking the placebo intervention and continue in the study. Participants taking Olaparib should continue receiving it per Investigator's discretion after discussion.

4.3 Justification for Dose

4.3.1 Starting Dose for Olaparib

The safety and efficacy of olaparib have been demonstrated in the clinical programs using predominantly the capsule formulation (400 mg [8 capsules] twice daily); however, an improved tablet formulation (2 tablets twice daily) has been developed and will be used in this study. The recommended tablet formulation of olaparib as monotherapy is 300 mg twice daily, which is considered similar in terms of efficacy and safety to the capsule 400 mg twice daily dose. CCI [redacted] The tolerability profile of the 300 mg BID tablet dose in Study 24 was considered similar to the 400 mg BID capsule formulation. The most common AEs were consistent with the known safety profile of olaparib, namely low-grade nausea, vomiting, fatigue, and anemia. The tablet formulation is used across the olaparib Phase III program.

Olaparib, when given via the tablet formulation has a t_{max} typically between 0.5 and 2 hours and mean terminal half-life of approximately 12 to 15 hours. Based on the average single dose $t_{½}$, it would be expected that steady state exposure would be achieved within approximately 3 days of commencing dosing with olaparib. It is metabolized primarily by the CYP3A4 enzyme and is excreted through the urine (35% to 50%) and feces (12% to 60%).

Further information is provided in the olaparib Investigator's Brochure.

4.3.2 Starting Dose for Pembrolizumab

The planned dose of pembrolizumab for this study is 200 mg every 3 weeks (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 every 2 weeks (Q2W),

- Clinical data showing meaningful improvement in benefit-risk including overall survival 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 (TMDD) 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.

4.3.2.1 Rationale for Carboplatin With Paclitaxel/nab-Paclitaxel Dosing Regimen

The platinum doublet (carboplatin with paclitaxel or nab-paclitaxel) used in this study is a well-established regimen for squamous NSCLC.

4.3.3 Maximum Dose/Exposure for This Study

4.3.3.1 Pembrolizumab

The maximum duration of exposure for pembrolizumab is 35 administrations (~2 years).

4.3.3.2 Olaparib

There is no maximum duration of exposure for olaparib.

4.4 Beginning and End of Study Definition

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent. The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

Upon study completion, participants are discontinued and may be enrolled in a pembrolizumab extension study, if available.

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 particular study sites 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.

5 STUDY POPULATION

Male and female participants with untreated Stage IV squamous NSCLC 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:

Type of Participant and Disease Characteristics

1. Have a histologically or cytologically confirmed diagnosis squamous NSCLC. Patients with mixed histology (eg, adenosquamous) are allowed if there is squamous component in the specimen.

2. Have Stage IV (T any, N any, M1a, M1b, or M1c as per AJCC 8th edition) squamous NSCLC.

3. Have measurable disease based on RECIST 1.1, as determined by the local site investigator/radiology assessment. Target lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.

4. Have not received prior systemic treatment for their advanced/metastatic NSCLC. Participants who received adjuvant or neoadjuvant therapy are eligible if the adjuvant/neoadjuvant therapy was completed at least 12 months prior to the development of metastatic disease.

5. Have provided archival tumor tissue sample or newly obtained core or incisional biopsy of a tumor lesion not previously irradiated. Formalin-fixed, paraffin embedded (FFPE) tissue blocks are preferred to slides. Newly obtained biopsies are preferred to archived tissue.

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

   Note: Adequacy of biopsy specimen for the above analyses must be confirmed by the central laboratory before the participant can start the Induction Phase. Submission of another tumor specimen may be required prior to enrolling the participant, if adequate tumor tissue was not provided the first time.

6. Have a performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) Performance Status assessed within 7 days prior to the administration of study intervention.

7. Have a life expectancy of at least 3 months.

8. Has adequate organ function, as detailed in Table 3; all screening laboratory tests should be performed within 10 days prior to initiation of study treatment.

Table 3 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500 cells/µL
Platelets	≥100 000 cells/µL
Hemoglobin	≥9.0 g/dL[1]
Renal	
Estimated creatinine clearance using the Cockcroft-Gault equation test[2] or a 24-hour urine test	>51 mL/min
Hepatic	
Total bilirubin	≤1.5 × ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)
Coagulation (only required at Screening)	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants

Abbreviations: ALT (SGPT)=alanine aminotransferase (serum glutamic-pyruvic transaminase); aPTT=Activated partial thromboplastin time; AST (SGOT)=aspartate aminotransferase (serum glutamic-oxaloacetic transaminase); ANC=Absolute neutrophil count; CrCl=creatinine clearance; GFR=glomerular filtration rate; INR=international normalized ratio; PT=prothrombin time; ULN=upper limit of normal.

1. For Screening, criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 28 days prior to initiation of study intervention. For post-Induction/pre-Randomization, criteria must be met without erythropoietin dependency within last 14 days prior to randomization.
2. Estimated creatinine clearance using Cockcroft-Gault:

$$\frac{(140\text{-age [years]} \times \text{weight (kg)}}{\text{Serum creatinine (mg/dL)} \times 72} \quad (\times F)^*$$

*where F = 0.85 for females and F = 1 for males

As an alternative, the creatinine clearance can be determined from a 24-hour urine collection.

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. Be at least 18 years of age on day of signing informed consent.

Male Participants

10. Male participants are eligible to participate if they agree to the following during the intervention period for at least 180 days after the last dose of study intervention:

    - Refrain from donating sperm
    - 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

- Agree to use contraception, unless confirmed to be azoospermic (vasectomized or secondary to medical cause [Appendix 5]), as detailed below:

- Agree to use 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.

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

Female Participants

11. A female participant is eligible to participate if she is not pregnant (Appendix 5), not breastfeeding, and at least 1 of the following conditions applies:

    a. Not a woman of childbearing potential (WOCBP) as defined in Appendix 5.

        OR

    b. A WOCBP who agrees to follow the contraceptive guidance in Appendix 5 during the treatment period and for at least 180 days following the last dose of pembrolizumab and olaparib or at least 180 days following the last dose of cytotoxic chemotherapy and agrees not to donate eggs (ova, oocytes) to others or freeze/store for her own use for the purpose of reproduction during this period. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention.

    – A WOCBP must have a negative highly sensitive urine pregnancy test as required by local regulations) within 24 hours (72 hours for serum) before the first dose of study intervention.

    – Additional requirements for pregnancy testing during and after study intervention are in Appendix 5.

    – The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

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

Informed Consent

12. Has (or legally acceptable representative) provided documented 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 trial without participating in Future Biomedical Research.

Additional Criteria Applicable to Maintenance Phase Only - Prior to Randomization

13. Has a CR/PR or stable disease of their NSCLC as determined by central imaging review after completion of study-specified Induction Phase.

14. Have an ECOG performance status score of 0 or 1 as assessed at Pre-randomization visit (most recent assessment within this visit).

15. All AEs (with the exception of alopecia, Grade 2 fatigue, and Grade ≤2 endocrine-related AEs requiring treatment or hormone replacement. For anemia and creatinine clearance, the guidelines provided in Table 3 may be followed) resolved to Grade ≤1 or baseline following Induction Phase treatment.

16. Have adequate organ function, as indicated by the laboratory values in Table 3 above.

17. Are not taking medications or vaccinations specifically prohibited in the Exclusion Criteria (Section 5.2).

18. Are not pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the study, starting from the pre-randomization visit through 180 days after the last dose of study intervention.

19. Have not withdrawn consent to continue treatment.

20. Continue to derive clinical benefit from study participation according to investigator's discretion.

5.2 Exclusion Criteria

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

Medical Conditions

1. Has non-squamous histology NSCLC. Mixed tumors will be categorized by the predominant cell type; if small cell elements are present, the participant is ineligible; for non-small cell histology if there is any squamous element is present (example adenosquamous), the participant is eligible; the squamous element does not have to be predominant.

2. Has a known additional malignancy that is progressing or has progressed within the past 3 years requiring active treatment.

   Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin or carcinoma in situ (eg, breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.

3. Has known active central nervous system metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are clinically stable for at least 2 weeks and, have no evidence of new or enlarging brain metastases and also are off steroids 3 days prior to dosing with study medication. Stable brain metastases by this definition should be established prior to the first dose of study medication. Participants with known untreated, asymptomatic brain metastases (ie, no neurological symptoms, no requirements for corticosteroids, no or minimal surrounding edema, and no lesion >1.5 cm) may participate, but will require regular imaging of the brain as a site of disease.

4. Has a known hypersensitivity to any components or excipients of carboplatin, paclitaxel or nab-paclitaxel, or olaparib.

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

6. 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.

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

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

9. Has an active infection, requiring systemic therapy.

10. Has known history of human immunodeficiency virus (HIV) infection. No HIV testing is required unless mandated by local health authority.

11. Has a known history of Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection.

    Note: No testing for Hepatitis B or Hepatitis C is required unless mandated by local health authority.

12. Participant has a known history of active tuberculosis (TB, *Mycobacterium tuberculosis*).

13. Has a known history of interstitial lung disease. Lymphangitic spread of the NSCLC is not exclusionary.

14. Has symptomatic ascites or pleural effusion. A participant who is clinically stable following treatment for these conditions (including therapeutic thoraco- or paracentesis) is eligible.

15. Has a known psychiatric or substance abuse disorder that would interfere with the participant's ability to cooperate with the requirements of the study.

16. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 180 days after the last dose of study intervention.

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

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. Note: For post-Induction/pre-Randomization, within 14 days prior to randomization.

19. Is considered a poor medical risk in the opinion of the treating Investigator due to a serious, uncontrolled medical disorder or non-malignant systemic disease. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, or superior vena cava syndrome.

20. Is unable to swallow orally administered medication or has a gastrointestinal disorder affecting absorption (eg, gastrectomy, partial bowel obstruction, malabsorption).

Prior/Concomitant Therapy

21. Has received prior therapy with olaparib or with any other PARP inhibitor.

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. Before the first dose of study treatment:

    a) Has received prior systemic cytotoxic chemotherapy for metastatic disease

    b) Has received other targeted or biological antineoplastic therapy (eg, erlotinib, crizotinib, cetuximab) for metastatic disease

    c) Had major surgery (<3 weeks prior to study intervention) or has not recovered from any effects of any major surgery.

24. Received radiation therapy to the lung that is > 30 Gy within 6 months of the first dose of trial treatment.

25. Completed palliative radiotherapy within 7 days of the first dose of trial treatment. Participants must have recovered from all radiation-related toxicities and not require corticosteroids

26. Is expected to require any other form of antineoplastic therapy while on study

27. Has received a live or live attenuated vaccine within 30 days prior to the first dose of study drug. Note: Killed vaccines are allowed.

28. Is currently receiving either strong (eg, itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate (eg, ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil) inhibitors of cytochrome P450 (CYP)3A4 that cannot be discontinued for the duration of the study. The required washout period prior to starting olaparib is 2 weeks.

    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

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

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

Prior/Concurrent Clinical Study Experience

30. 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 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

31. The presence of uncontrolled, potentially reversible cardiac conditions, as judged by the Investigator (eg, unstable ischemia, uncontrolled symptomatic arrhythmia, congestive heart failure, electrolyte disturbances, etc.), or participant has congenital long QT syndrome.

Other Exclusions

32. Has had an allogeneic tissue/solid organ transplant.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

During the Maintenance Phase, participants should avoid grapefruit, grapefruit juice, and St. John's Wort (tablet or tea) while receiving study intervention. Otherwise, participants should maintain a normal diet unless modifications are required to manage AEs such as diarrhea, nausea, or vomiting.

5.3.2 Contraception

The study intervention 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 intervention may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the trial. To participate in the trial, participants of childbearing potential must adhere to the contraception requirement (Appendix 5) from the day of study intervention initiation (or 14 days prior to the initiation of study intervention for oral contraception) throughout the trial period up to 180 days after the last dose of study intervention. If there is any question that a participant 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 inadvertently becomes pregnant during the study, the participant will be immediately discontinued from study intervention. The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor as described in Section 8.4.5.

5.3.4 Use in Nursing Women

It is unknown whether any of the study medications are excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, participants who are breastfeeding are not eligible for enrollment.

5.3.5 Activity Restrictions

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

5.4 Screen Failures

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

5.5 Participant Replacement Strategy

A participant who discontinues from study intervention OR withdraws 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 as required. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study intervention(s) to be used in this study are outlined in Table 4.

In the Induction Phase, pembrolizumab should be given prior to chemotherapy; carboplatin and either paclitaxel or nab-paclitaxel should be given as per SOC.

For the Maintenance Phase, Olaparib on Day 1 should be given prior to pembrolizumab.

Note: Based on the data from an interim safety and efficacy analysis (IA3), the external Data Monitoring Committee recommended to remove the final analysis. Participants will be unblinded. Participants who are confirmed to be actively taking placebo should discontinue taking the placebo intervention and continue in the study. Participants taking Olaparib should continue receiving it per the investigator's discretion after discussion. Participants currently undergoing or who will undergo Second Course with pembrolizumab monotherapy can continue or start treatment per investigator's discretion under this protocol or under an extension study. Participants who are potential candidates for Second Course treatment will continue in Efficacy Follow-up.

Table 4 Study Interventions

Drug Name	Drug 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
Pembrolizumab	Experimental	Active	Drug	Solution for Infusion	25 mg/mL	200 mg	IV Infusion	Q3W/Induction and Maintenance Phases for a maximum of 35 cycles	Experi-mental	IMP	Central
Carboplatin	Other	Chemo-therapy	Drug	Solution for Infusion	10 mg/mL (60 mL)	AUC 6 mg/mL/min	IV Infusion	Q3W/Induction Phase (4 cycles)	SOC	NIMP	Local or Central
Paclitaxel	Other	Chemo-therapy	Drug	Solution for Infusion	6 mg/mL (16.7 mL)	200 mg/m^2	IV Infusion	Q3W/Induction Phase (4 cycles)	SOC	NIMP	Local or Central
Nab-paclitaxel	Other	Chemo-therapy	Drug	Solution for Infusion	5 mg/mL	100 mg/m^2	IV Infusion	Q3W/Induction Phase (Days 1,8 and 15 for 4 cycles)	SOC	NIMP	Local or Central
Olaparib	Experimental	Active	Drug	Tablet	150 mg; 100 mg	300 mg	Oral	BID/Maintenance Phase	Experi-mental	IMP	Central
Placebo	Control	Placebo	Other	Tablet	150 mg; 100 mg	N/A	Oral	BID/Maintenance Phase	Placebo	IMP	Central

Abbreviations: AUC=area under the plasma drug concentration time curve; BID=twice daily; IMP=Investigational Medicinal Product; IV=intravenous; N/A=not applicable; NIMP=Non-investigational Medicinal Product; Q3W=every 3 weeks; SOC=standard of care.

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

Note: For locally sourced supplies, the unit dose strength may vary, depending on market availability.

Note: The Olaparib 300-mg dose should be made up of 2 × 150 mg tablets; 100 mg tablets and matching placebo are provided for dose reductions as outlined in Section 6.6.1.

Placebo for Olaparib was created to match the active product.

All supplies indicated in Table 4 will be provided per the "Sourcing" column depending upon local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number where possible (eg, not applicable in the case where multiple lots or batches may be required due to the length of the study, etc.).

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

The Pembrolizumab Pharmacy Manual contains specific instructions for pembrolizumab preparation and administration.

Olaparib and Olaparib placebo are tablets for oral administration; no preparation is required (see Olaparib Pharmacy Manual). Olaparib and matching placebo will be provided in high-density polyethylene (HDPE) bottles with child-resistant closures. Each bottle will be labeled in accordance with Good Manufacturing Practice (GMP) Annex 13 and per country regulatory requirement.

Carboplatin and paclitaxel/nab-paclitaxel should be prepared per local and institutional guidelines according to the approved product labels.

The rationale for selection of doses to be used in this study is provided in Section 4.3.

6.2.2 Handling, Storage, and Accountability

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

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

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

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

investigator is responsible for ensuring that a local discard/destruction procedure is documented.

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Treatment allocation will occur centrally using an interactive response technology (IRT) system. The allocation numbers will be given to each participant at the time of randomization.

There are 2 study intervention arms. Participants will be assigned randomly in a 1:1 ratio to receive either pembrolizumab plus olaparib or pembrolizumab plus placebo.

Randomization will occur after participants complete the Induction Phase and imaging shows SD, PR, or CR, as verified by central vendor. All participants will undergo a pre-randomization visit during which a checklist will be completed by the investigator and approved by the Sponsor. Randomization will be done via the IRT system.

CCI

6.3.3 Blinding

The Induction Phase of this study is conducted as open-label; therefore, the Sponsor, investigator, and participant will know the intervention administered.

The Maintenance Phase of this study will make use of a double-blinding technique and in-house blinding will be used. Olaparib and its placebo will be packaged identically so that the blind is maintained. The participant, the investigator, and Sponsor personnel or delegates who are involved in the study intervention administration or clinical evaluation of the participants are unaware of the intervention assignments.

Note: Based on the IA3 data, the study was unblinded on 15-DEC-2023.

6.4 Study Intervention Compliance

6.4.1 Olaparib Compliance

Note: As of Amendment 07, participants who are confirmed to be actively taking placebo should discontinue taking the placebo intervention and continue in the study. The protocol content has been retained for reference.

Participants will take their dose of olaparib/olaparib placebo BID without regard to food. Participants will self-administer olaparib/olaparib placebo except on Day 1 of the first cycle, when the dose will be given at the study site clinic prior to the infusion of pembrolizumab. For all other cycles, olaparib will be given prior to pembrolizumab infusion.

Site staff will make tablet counts at regular intervals during treatment. After the tablet count has been performed, the remaining tablets will not be returned to the participant, but will be retained by the investigative site until reconciliation is completed by the study monitor. Olaparib/olaparib placebo compliance will be calculated by the Sponsor based on the drug accountability documented by the site staff and monitored by the Sponsor/designee. All participants will be instructed to return their bottle of olaparib or olaparib placebo at the appropriate scheduled visit, when a new bottle will be dispensed. Participants will be instructed to notify study site personnel of missed doses.

Interruptions from the protocol-specified olaparib/olaparib placebo treatment plan for >21 consecutive days require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

6.4.2 Pembrolizumab and Chemotherapy Compliance

Pembrolizumab and chemotherapy will be administered on an out-patient basis.

Interruptions from either the protocol-specified pembrolizumab or chemotherapy (carboplatin, paclitaxel or nab-paclitaxel) treatment plan require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management (Section 7.1).

If there are interruptions in the study intervention schedule or injection was stopped, the details of reason for any interruption or infusion cessation of study intervention will be documented in the participant's medical record.

Refer to Section 6.6.3 for dose modification and toxicity management for irAEs associated with pembrolizumab and for other allowed dose interruption of pembrolizumab.

6.5 Concomitant Therapy

All concomitant medications received within 28 days prior to the first dose of study intervention and up to 30 days after the last dose of study intervention should be recorded. If participants experience an SAE or ECI, all concomitant medications administered >30 days after the last dose of study intervention are to be recorded as defined in Section 8.4.7.

Based on in vitro data, olaparib may increase the exposure to substrates of CYP3A4, organic-anion-transporting polypeptide (OATP)1B1, organic cation transporter (OCT)1/2/3, and multidrug and toxic compound extrusion (MATE)1/2 and reduce exposure to substrates of CYP2B6. Caution should be observed if substrates of these isoenzymes or transporter proteins are co-administered. A current list of substrates can be found at the following website:
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

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 electronic case report form (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.

6.5.1 Prohibited Concomitant Medications

Medications or vaccinations specifically prohibited in the exclusion criteria (Section 5.2) are not allowed during Screening Phase and administration of study intervention. If there is a clinical indication for any medication or vaccination specifically prohibited, discontinuation from study intervention may be required. The investigator should discuss any questions regarding this with the Sponsor 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.

Listed below are specific concomitant therapies or vaccinations that are prohibited during the study (exceptions noted):

1. Antineoplastic systemic chemotherapy, immunotherapy, or biological therapy not specified in this protocol.

2. Investigational agents other than pembrolizumab and olaparib.

3. Surgery for tumor control.

4. Radiation therapy for disease control.

   - Note: Participants are allowed to receive palliative radiotherapy for painful bone lesions. Targeted external beam irradiation should not be used in the primary lung field where assessment for tumor is indicated. Radiation therapy to the brain may be allowed following Sponsor consultation.

5. Live or live attenuated vaccines while participating in the trial, and within 30 days of the last dose of study intervention. See Appendix 7 for country-specific requirements.

   - Note: killed vaccines are 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, adenoviral vaccines, or inactivated vaccines. These vaccines will be treated just as any other concomitant therapy.

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

6. Anticancer hormonal therapy (eg, androgen deprivation, androgen receptor blockade, anti-estrogens)

   - *Note: Hormonal replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is allowed.*

7. Strong and moderate inducers or inhibitors of CYP3A4 that cannot be discontinued for the duration of the study.

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

   - Note: Exceptions are outlined in Section 6.6.2.5.

   - Note: Only applicable to participants taking Olaparib concomitantly.

8. Systemic glucocorticoids are permitted for the following purposes:

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

   - As needed for the prevention of emesis

- Premedication for IV contrast allergies
- Short-term oral or IV use in doses >10 mg/day prednisone equivalent for COPD exacerbations
- For chronic systemic replacement not to exceed 10 mg/day prednisone equivalent

In addition, the following glucocorticoid use is allowed:

- For topical use or ocular use
- Intraarticular joint use
- For inhalation in the management of asthma or chronic obstructive pulmonary disease

9. Phenytoin during therapy with carboplatin.

In addition to the medications listed here, study site staff should refer to the approval product labels for prohibited medications, as well as drug-drug interactions for each chemotherapeutic agent used in this study.

If the investigator determines that a participant requires any of the aforementioned treatments for any reason, all study intervention must be discontinued.

There are no prohibited therapies during the Long-term Follow-up Phase.

6.5.2 Rescue Medications and Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating Investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 6.6.3, Table 9. 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 9 in Section 6.6.3 for guidelines regarding dose modification and supportive care.

Participants should receive appropriate supportive care measures as deemed necessary by the treating Investigator.

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

6.6 Dose Modification (Escalation/Titration/Other)

Note: As of Amendment 07, participants will be unblinded. Participants who are confirmed to be actively taking placebo should discontinue taking the placebo intervention and continue in the study. Participants taking Olaparib should continue receiving it per investigator's discretion after discussion. Participants who are potential candidates for Second Course treatment will continue in Efficacy Follow-up. Participants currently undergoing or who will undergo Second Course with pembrolizumab monotherapy can continue or start treatment per investigator's discretion under this protocol or under an extension study.

6.6.1 Management of Overlapping Toxicities of Olaparib and Pembrolizumab

Both olaparib and pembrolizumab treatment may be associated with the development of pneumonitis and renal toxicity.

For renal dysfunction, follow the dose modification guidelines provided in Table 7 (Olaparib) and Table 9 (pembrolizumab). A kidney biopsy is strongly recommended to help to determine etiology of renal dysfunction.

If pneumonitis is confirmed, treatment with olaparib/olaparib placebo must be withheld. Olaparib/olaparib placebo may be restarted once pneumonitis has completely resolved. Treatment with pembrolizumab must be withheld for pneumonitis ≥Grade 2 (Table 9). When the pneumonitis resolves to <Grade 2, then pembrolizumab may be resumed as per guidelines in Table 9. Sponsor consultation is recommended if there are any doubts. Study intervention must be discontinued for recurrent Grade 2 pneumonitis (Section 7.1).

6.6.2 Olaparib Dose Modifications

The dose of olaparib can be reduced to 250 mg BID initially and then to 200 mg BID as needed. If the 200 mg BID dose is not tolerable, no further dose reduction is allowed and study intervention should be discontinued. Once the dose has been reduced, escalation is not permitted.

The reason for the dose interruption or reduction should be captured on the appropriate eCRF.

During the Maintenance Phase, if, in the opinion of the investigator, a toxicity is related to the combination of both olaparib and pembrolizumab, both drugs should be interrupted and/or discontinued according to the recommendations listed in this section. If the toxicity can be attributable to olaparib or pembrolizumab, the respective agent may be reduced (if applicable), interrupted, or discontinued according to the recommendations listed in this section; in such situations, the other agent can continue to be administered.

6.6.2.1 Management of Hematological Toxicities

Any hematological toxicity observed during the study could be managed by a brief interruption of study intervention or a dose reduction of Olaparib (Table 5 and Table 6). Repeated interruptions, not exceeding 3 weeks (21 days) duration, are allowed as required. If the interruption is any longer, the Sponsor must be informed.

Table 5 Management of Anemia

Toxicity	NCI CTCAE Grade	Action Taken
Hemoglobin (Hb)	Grade 2 (<9.0 but ≥8.0 g/dL)	**First Occurrence:** Give appropriate supportive treatment and investigate causality. • Investigator judgment to either continue maintenance olaparib with supportive treatment (eg, transfusion) or interrupt maintenance olaparib dosing for a maximum of 3 weeks (21 days). Study intervention can be restarted if Hb has recovered to >9.0 g/dL. **Subsequent Recurrence:** • **Hb <9.0 but ≥8.0 g/dL**: Interrupt maintenance olaparib for a maximum of 3 weeks (21 days) until Hb improves to >9.0 g/dL. Upon recovery, reduce the dose of olaparib to 250 mg BID. A second dose reduction to 200 mg BID may be considered if additional decreases in Hb occur
	Grade 3 (<8.0 g/dL)	Give appropriate supportive treatment (eg, transfusion) and investigate causality. • Interrupt olaparib, for a maximum of 3 weeks (21 days), until Hb improves to ≥9.0 g/dL. • Upon recovery, reduce the dose of maintenance olaparib to 250 mg BID. A second dose reduction to 200 mg BID may be considered if additional decreases in Hb occur.
Abbreviations: BID=twice daily; CTCAE=Common Terminology Criteria for Adverse Events; Hb = hemoglobin; NCI = National Cancer Institute. Note: Common treatable causes of anemia (eg, iron, vitamin B12 or folate deficiencies and hypothyroidism) should be investigated and appropriately managed. In some cases, management of anemia may require blood transfusions. The management of prolonged hematological toxicities is detailed in Section 6.6.2.2.		

Table 6 Management of Neutropenia, Leukopenia, and Thrombocytopenia

Toxicity	NCI CTCAE Grade	Action Taken
Neutropenia, Leukopenia, or Thrombocytopenia	Grades 1 or 2	Investigator judgment to either continue maintenance olaparib or interrupt dosing for a maximum of 3 weeks (21 days). Give appropriate supportive treatment and investigate causality.
	Grades 3 or 4	• Interrupt olaparib, for a maximum of 3 weeks (21 days), until event recovers to ≤Grade 1. • Repeated incidence: reduce the dose of olaparib to 250 mg BID. A second dose reduction to 200 mg BID may be considered if additional Grade 3 or 4 events occur.
• AEs of neutropenia and leukopenia should be managed as deemed appropriate by the investigator with close follow-up and interruption of study intervention if CTCAE Grade 3 or worse neutropenia occurs. • Primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) is not recommended; however, if a participant develops febrile neutropenia, study intervention should be stopped and appropriate management including G-CSF should be given according to local hospital guidelines. Please note that G-CSF should not be used within at least 24 hours (7 days for pegylated G-CSF) of the last dose of study intervention unless absolutely necessary. • Platelet transfusions, if indicated, should be done according to local hospital guidelines. • The management of prolonged hematological toxicities is detailed in Section 6.6.2.2.		

6.6.2.2 Management of Prolonged Hematological Toxicities

If a participant develops prolonged hematological toxicity such as:

- ≥2-week interruption/delay in study intervention due to NCI CTCAE Grade 3 or worse anemia and/or the development of blood transfusion dependence
- ≥2-week interruption/delay in study intervention due to NCI CTCAE Grade 3 or worse neutropenia (ANC $<1 \times 10^9$/L)
- ≥2-week interruption/delay in study intervention due to NCI CTCAE Grade 3 or worse thrombocytopenia and/or development of platelet transfusion dependence (platelets $<50 \times 10^9$/L)

Differential blood count, including reticulocytes and peripheral blood smear, should be checked weekly. If any blood parameters remain clinically abnormal after the dosing of maintenance olaparib has been interrupted for ≥3 weeks (≥21 days), the participant should be referred to a hematologist for further investigations. Bone marrow analysis and/or blood cytogenetic analysis should be considered, according to local regulation and/or standard institutional hematological practice. Study intervention should be discontinued if blood counts do not recover to NCI CTCAE Grade 1 or better within 3 weeks (21 days) of dose interruption.

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

6.6.2.3 Management of Nonhematologic Toxicity

Repeated dose interruptions, not exceeding 3 weeks (21 days) duration, are allowed as required. If toxicity reoccurs following rechallenge with study intervention, and where further dose interruptions are considered inadequate for management of toxicity, either a dose reduction should be considered (Section 6.6.1) or the participant must permanently discontinue study intervention.

Treatment must be interrupted if any NCI CTCAE Grade 3 or 4 AE occurs that the Investigator considers to be related to administration of olaparib.

6.6.2.3.1 Management of New or Worsening Pulmonary Symptoms

If new or worsening pulmonary symptoms (eg, dyspnea) or radiological abnormalities occur in the absence of a clear diagnosis, an interruption in study intervention dosing is recommended and further diagnostic workup (including a high resolution computed tomography [CT] scan) should be performed to exclude pneumonitis. Please refer to Table 9 as well, which outlines the Toxicity Management Guidelines for pembrolizumab as it can cause pneumonitis.

Following investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, then study intervention can be restarted, if deemed appropriate by the Investigator. If significant pulmonary abnormalities are identified, these need to be discussed with the Clinical Director. If pneumonitis is confirmed while on study, refer to Section 6.6.1 for guidance on the management of olaparib and pembrolizumab.

6.6.2.3.2 Management of Nausea and Vomiting

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

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

As per international guidance on antiemetic use in cancer patients (ESMO, NCCN), generally a single agent antiemetic should be considered (eg, dopamine receptor antagonist, antihistamines).

6.6.2.3.3 Management of Renal Impairment

To initiate maintenance olaparib, creatinine clearance (CrCl) must be ≥51 mL/min.

If subsequent to study, entry and/or while still on study therapy, a participant's estimated creatinine clearance (CrCl) falls below the threshold for study inclusion (≥51 ml/min), retesting should be performed promptly.

A dose reduction is recommended for participants who develop moderate renal impairment (calculated CrCl between 31 to 50 mL/min as calculated by either Cockcroft-Gault equation or based on a 24 hour urine test) for any reason during the course of the study (Table 7).

Table 7 Dose Reduction of Olaparib to Manage Moderate Renal Impairment

Initial Dose	**Moderate Renal Impairment[a]**
300 mg BID	200 mg BID
Abbreviation: BID = twice daily. a. Creatinine clearance of 31 to 50 mL/min as calculated by either Cockcroft-Gault equation. As an alternative, the creatinine clearance can be determined from a 24-hour urine collection.	

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

Please refer to Table 9, as well, which outlines the Toxicity Management Guidelines for pembrolizumab as it also can cause renal toxicity. For renal toxicity, a biopsy to determine the etiology of the toxicity and to determine if the renal toxicity is related to olaparib or pembrolizumab should be performed.

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

6.6.2.4 Interruptions for Intercurrent Non-toxicity-related Events

Olaparib dose interruption for conditions other than toxicity resolution should be kept as short as possible. If a participant cannot restart study intervention within 3 weeks (21 days) for resolution of intercurrent conditions not related to disease progression or toxicity, the case should be discussed with the Clinical Director, and approved via a Sponsor Communication Form.

All dose reductions and interruptions (including any missed doses), and the reasons for the reductions/interruptions, per drug accountability and participant feedback reconciliation, are to be recorded in the eCRF.

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

Maintenance olaparib should be discontinued for a minimum of 3 days before a participant undergoes radiation treatment and should be restarted within 3 weeks (21 days) as long as any bone marrow toxicity has recovered.

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

6.6.2.5 Dose Reductions for Concurrent CYP3A4 Inhibitor Use

Strong or moderate CYP3A inhibitors should not be taken with olaparib. If there is no suitable alternative concomitant medication then the dose of olaparib should be reduced for the period of concomitant administration as described in Table 8. After the washout of the inhibitor is complete (Section 5.2), the olaparib dose cannot be re-escalated. The dose reduction of olaparib should be recorded in the eCRF with the reason documented as concomitant CYP3A4 inhibitor use.

Table 8 Dose Reduction of Olaparib with a Strong or Moderate CYP3A4 Inhibitor

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

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

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 9.

Table 9 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab Monotherapy, Coformulations or IO Combinations

General instructions:

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

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Recurrent Grade 2 or Grade 3 or 4	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
AST / ALT Elevation or Increased Bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5-1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [a]	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [a]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or Permanently discontinue [a]		

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

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

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

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

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

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 10.

Table 10 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 h	**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 treatment.**	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 treatment.**	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

Other Allowed Dose Interruption for Pembrolizumab

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

6.6.4 Carboplatin and Paclitaxel or Nab-paclitaxel Dose Modification

If a participant experiences a ≥10% weight change during Cycles 1 to 4, the doses of carboplatin and paclitaxel/nab-paclitaxel should be recalculated.

Dose modifications due to AEs will depend on the investigator's assessment of causality. If appropriate, the investigator may attribute each toxicity event to carboplatin, paclitaxel/nab-paclitaxel, and pembrolizumab alone or to the combination and use a stepwise dose reduction according to approved product labels for dose modifications regarding this regimen. Dose modifications must be based on the maximum toxicity experienced during a cycle. Toxicity must resolve to Grade ≤1 or baseline prior to resuming the subsequent cycle, with the exception of alopecia, Grade 2 fatigue, and Grade ≤ 2 endocrine-related AEs requiring treatment or hormone replacement; for anemia and creatinine clearance, the guidelines provided in Table 3 may be followed.

If a dose reduction for toxicity occurs with any agent, the dose may not be re-escalated. Participants can have a maximum of 2 dose modifications (if applicable) to each of the components of study therapy throughout the course of the study for toxicities. If a participant experiences several toxicities and there are conflicting recommendations, the most conservative dose adjustment recommended should be followed (ie, dose reduction appropriate to the most severe toxicity). Participants who require a third dose modification to any particular component will have that agent discontinued. In the absence of the agent thought to be causing toxicity, treatment can continue with pembrolizumab and the remaining chemotherapeutic drug. Once the dose has been decreased, it should remain reduced for all subsequent administrations or be further reduced, if necessary. There will be no dose escalations in this study.

Reduction of one chemotherapy agent and not the other agent is appropriate if, in the opinion of the investigator, the toxicity is clearly related to one of the treatments. If, in the opinion of the investigator, the toxicity is related to the combination of both chemotherapy agents, both drugs should be reduced according to recommended dose modifications. If the toxicity is related to the combination of 3 agents, all 3 agents should be reduced (if applicable), interrupted, or discontinued according to the recommended dose modifications. If all 3 agents are discontinued due to a toxicity without completing 4 cycles of the Induction Phase, the participant cannot proceed to the Maintenance Phase.

Pembrolizumab dose reductions are not permitted. Pembrolizumab treatment may be delayed/interrupted for a maximum of 12 weeks. However, for participants to proceed to the Maintenance Phase, the toxicity must resolve to Grade ≤1 or baseline prior to resuming the subsequent cycle, with the exception of alopecia, Grade 2 fatigue, and Grade ≤ 2 endocrine-related AEs requiring treatment or hormone replacement; for anemia and creatinine clearance, the guidelines provided below may be followed.

During the Induction Phase, study drug-related toxicities must be resolved to baseline or Grade ≤1 (with the exception of alopecia, Grade 2 fatigue, and Grade ≤ 2 endocrine-related AEs requiring treatment or hormone replacement; for anemia and creatinine clearance, the guidelines provided below may be followed) prior to administering the next dose. Participants must not receive the next cycle of chemotherapy if any of the following apply:

- Absolute neutrophil count (ANC) <1,500/mm^3
- Platelet count <100,000/mm^3
- Hemoglobin level <9 g/dL
- Total bilirubin level >1.5 × ULN
- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels ≥2.5 × ULN, or ≥5 × ULN if liver metastases are present
- CrCl <51 mL/min (CrCl will be based the Cockcroft-Gault formula

During Cycles 1 through 4 of carboplatin plus paclitaxel/nab-paclitaxel:

- If paclitaxel/nab-paclitaxel dosing is delayed or interrupted on Day 1, the platinum agent and pembrolizumab should also be delayed/interrupted. If carboplatin plus paclitaxel/nab-paclitaxel is delayed or interrupted during Cycles 1 through 4, participants should be seen weekly until toxicity resolves.
- If carboplatin dosing is delayed or interrupted on Day 1, paclitaxel/nab-paclitaxel and pembrolizumab should also be delayed/interrupted. If carboplatin plus paclitaxel/nab-paclitaxel is delayed or interrupted during Cycles 1 through 4, participants should be seen weekly until toxicity resolves.
- If pembrolizumab dosing is delayed or interrupted, carboplatin plus paclitaxel/nab-paclitaxel therapy can continue as scheduled. Pembrolizumab administration should be attempted at the next cycle of therapy.
- Each chemotherapy cycle may not be delayed by more than 3 weeks (>21 consecutive days) despite supportive treatment. If only one of the agents is thought to be causing the specified toxicity leading to a 21-day delay of administration of the next cycle, that chemotherapeutic agent can be withheld and treatment can continue with pembrolizumab and the remaining chemotherapy drug.

The CTCAE 4.0 must be used to grade the severity of AEs. All dose modifications should be based on the AE requiring the greatest dose modification. Dose modifications are detailed in Table 5 through Table 11. These serve as a guide and do not replace investigator judgment and applicable local label recommendations, if more stringent.

Table 11 Dose Modification for Chemotherapeutic Agents

Drug	Dose Level-0	Dose Level-1	Dose Level-2	Dose Level-3
Carboplatin	AUC 6 mg/mL/min Maximum dose 900 mg	AUC 4.5 mg/mL/min Maximum dose 675 mg	AUC 3 mg/mL/min Maximum dose 450 mg	Discontinue
Paclitaxel	200 mg/m^2	150 mg/m^2	100 mg/m^2	Discontinue
Nab-Paclitaxel	100 mg/m^2	75 mg/m^2	50 mg/m^2	Discontinue
Abbreviation: AUC=area under the concentration-time curve; BID=twice daily Note: For olaparib/olaparib placebo, follow dose modifications as outlined in Section 6.6.2 (and all of its subsections). For pembrolizumab, follow dose modifications as outlined in Section 6.6.3.				

Recommended dose modifications for key chemotherapy toxicities are outlined in Table 12 and Table 13. These serve as a guide and do not replace investigator judgment and applicable local label recommendations, if more stringent. These data are based on Day 1 cell counts.

Table 12 Recommended Chemotherapy Dose Modifications for Hematological Toxicity

Platelets	ANC	Carboplatin	Paclitaxel	Nab-Paclitaxel
		Dose Level (DL) from Table 11		
≥50,000/mcL AND	≥ 500/mcL	DL 0	DL 0	DL-0 [a]
≥50,000/mcL AND	< 500/mcL without fever	DL -1	DL -1	DL-1
<50,000/mcL without significant bleeding nor requiring blood transfusions AND	ANY	DL -1	DL -1	DL-1
<50,000/mcL with Grade ≥2 hemorrhage or requiring blood transfusions AND	ANY	DL -2	DL -2	DL-2
ANY AND	< 1,000/mcL + fever ≥ 38.5°C (101°F)	DL -1	DL -1	DL-1

Abbreviations: ANC = absolute neutrophil counts; DL = dose level; mcL = microliter(s).

Should the hematologic toxicity recur; the dose of the agent could be reduced further. However, not more than 2 dose reductions per chemotherapy agent are permitted.

a. Do not administer nab-paclitaxel on Day 1 of a cycle until ANC is at least 1500 cells/mm^3 and platelet count is at least 100,000 cells/mm^3. In participants who develop severe neutropenia or thrombocytopenia withhold treatment until counts recover to an absolute neutrophil count of at least 1500 cells/mm^3 and platelet count of at least 100,000 cells/mm^3 on Day 1 or to an absolute neutrophil count of at least 500 cells/mm^3 and platelet count of at least 50,000 cells/mm^3 on Days 8 or 15 of the cycle.

Table 13 Recommended Dose Modifications for Chemotherapy Nonhematological Toxicity

Event	CTCAE Grade	Carboplatin	Paclitaxel	Nab-Paclitaxel
		Dose Level (DL) from Table 11		
Nausea or Vomiting	Grade 3 or 4	DL-1	DL-1	DL-0
Diarrhea	Grade 3 or 4	DL -1	DL -1	DL 0
Mucositis	Grade 3 or 4	DL -1	DL-1	DL 0
Neurotoxicity	Grade 2	DL 0	DL -2	DL 0
	Grade 3 or 4	DL -1	Discontinue	DL -1
Total Bilirubin Elevation	Grade 2	DL-0	DL-2	DL-0
	Grade 3 or 4	DL-0	Discontinue	DL-0
Transaminase Elevation	Grade 3	DL -1	Discontinue	DL -1
	Grade 4	Discontinue	Discontinue	Discontinue
Other Nonhematological Toxicity (except fatigue and transient arthralgia and myalgia)	Grade 3 or 4	DL -1	DL -1	DL -1

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; DL = dose level.

6.7 Intervention After the End of the Study

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

6.8 Clinical Supplies Disclosure

The emergency unblinding call center will use the intervention randomization schedule for the study to unblind participants and to unmask study intervention identity for the Maintenance Phase of this study. The emergency unblinding call center should only be used in cases of emergency (see Section 8.1.10). Participants whose treatment assignment has been unblinded by the investigator/delegate and/or non-study treating physician must be discontinued from study drug, but should continue to be monitored in the trial. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

6.9 Standard Policies

At the close of the study after unblinding, a letter is to be sent by the investigator to those participants who received placebos in the image of the competitor's product to provide the following advice: "You have participated in a study conducted by the Sponsor. This letter is to advise you that you were among those who received a look-alike tablet created by the

Sponsor to resemble the drug Olaparib as much as possible. You did not receive the active drug Olaparib as manufactured by Astra Zeneca."

6.9.1 Study Site Retention Samples

Not applicable.

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 8.12.4.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study intervention discontinuation are provided in Section 8.1.8.2 and Section 8.12.4.

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.
- Radiographic disease progression outlined in Section 8.2 (exception if the Sponsor approves treatment continuation following confirmed PD per iRECIST).

  Note: As of Amendment 07, central tumor response assessments will no longer be performed. Participants on study treatment will be assessed locally by the investigator for disease progression, based on the site's standard of care imaging schedule. Participants with PD per local investigator assessment should be discontinued (except if the Sponsor approves treatment continuation following PD).
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires treatment.
- Unacceptable AEs or toxicities (Section 6.6).

- Any study intervention-related toxicity specified as a reason for permanent discontinuation as defined in the guidelines for dose modification due to AEs in Section 6.6 (eg, recurrent Grade 2 pneumonitis, recurrent Grade 3 colitis, recurrent Grade 3 diarrhea).

- If a participant with liver metastasis has Grade 2 AST or ALT at the start of study treatment, and the AST or ALT value increases by ≥50% relative to baseline and lasts for ≥1 week, then the participant should permanently discontinue study intervention.

- Bone marrow findings consistent with MDS or AML.

- Interruption of carboplatin/taxane (paclitaxel/nab-paclitaxel) for more than 6 weeks without Sponsor consultation.

- Interruption of pembrolizumab administration for more than 12 consecutive weeks for an AE/toxicity or for more than 3 weeks for administrative reasons without Sponsor consultation.

- Interruption of administration of olaparib or olaparib placebo for more than 21 consecutive days without Sponsor consultation.

- Intercurrent illness other than another malignancy as noted above that prevents further administration of treatment.

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

- The participant has a confirmed positive serum pregnancy test.

- Prohibited medication or vaccination required, and agreement between Sponsor, Investigator, and participant to discontinue (Section 6.5.1).

Any prolonged interruption of study intervention beyond the permitted periods, for irAE management or other allowed dose interruptions, as noted in Section 6.6.3 require Sponsor consultation prior to restarting treatment. If treatment will not be restarted, the participant will continue to be monitored in the study and the reason for discontinuation of study intervention will be recorded in the medical record.

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

Discontinuation from study intervention is “permanent.” Once a participant is discontinued, he/she shall not be allowed to restart study intervention.

Participants in this study may discontinue in the Induction Phase due to progression of disease or not meeting eligibility criteria to proceed to the Maintenance Phase (as listed in

Section 5.1). Upon completion of the End-of-Treatment/Safety Follow-up Visit, these participants are to be discontinued from the study and are no longer followed.

7.2 Participant Withdrawal From the Study

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

If a participant withdraws consent, 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 8.1.8.2 and 8.1.8.3. If a participant fails to return for scheduled visits and/or if the study site is unable to contact the participant after multiple attempts (ie, is lost to follow-up), the procedures to be performed are outlined in Section 7.3.

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

7.3 Lost to Follow-up

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

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

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

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

8 STUDY ASSESSMENTS AND PROCEDURES

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

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

- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified or trained 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 providing documented informed consent 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.

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

8.1 Administrative and General Procedures

8.1.1 Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented informed consent from each potential participant (or their legally acceptable representative) prior to participating in this clinical study 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 documented informed consent is in place.

8.1.1.1 General Informed Consent

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

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

The initial ICF, any subsequent revised ICF, and any written information provided to the participant must receive the 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 or the participant's legally acceptable representative's dated signature.

The participant (or their legally acceptable representative) will be asked to provide documented informed consent at the point of initial radiographic disease progression. Specifics about a study and the study population will be added to the consent form.

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 or the participant's legally acceptable representative, answer all of his/her questions, and obtain documented informed consent before performing any procedure related to future biomedical research. A copy of the informed consent will be given to the participant before performing any procedure related to future biomedical research.

8.1.2 Inclusion/Exclusion Criteria

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

8.1.3 Participant Identification Card

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

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

8.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. The medical history will collect all active conditions and any condition diagnosed within the prior 10 years that the investigator considers to be clinically important. Include history of blood transfusion within previous 120 days from start of study intervention and the reasons, eg, bleeding or myelosuppression. Details regarding the disease for which the participant has enrolled in this study will be recorded separately and not listed as medical history.

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

8.1.4.1 Non-small Cell Lung Cancer History

The investigator or qualified designee will obtain prior and current details regarding the participant's NSCLC.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 28 days before first dose of study intervention.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication (including blood transfusions), if any, taken by the participant during the study.

8.1.5.3 Subsequent Antineoplastic Therapy

Details of subsequent therapies for cancer and/or details of radiation therapy and surgery for the treatment of the cancer, after discontinuation of study intervention, will be collected. Reasons for starting subsequent antineoplastic therapies including access to other PARP inhibitors, PD-1/PD-L1 inhibitors, or investigational drugs will be collected.

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 intervention allocation. 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 time will retain the original screening number assigned at the initial screening visit.

Specific details on the screening visit requirements (screening/rescreening) are provided in Section 8.12.1.

8.1.7 Assignment of Treatment/Randomization Number

All participants eligible for study intervention will continue to be treated using the initial assigned screening number. All participants eligible for the Maintenance Phase who are

randomized will receive an allocation/randomization number. The allocation/randomization number identifies the participant for all procedures occurring after randomization to the Maintenance Phase. Once a treatment/randomization number is assigned to a participant, it can never be re-assigned to another participant.

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

For those participants that are treated as per the Induction Phase and are not randomized to the Maintenance Phase, a separately devised allocation number will be assigned.

8.1.8 Study Intervention Administration

Administration of pembrolizumab, carboplatin, and paclitaxel or nab-paclitaxel during the Induction Phase will be monitored by the investigator and/or study staff.

During the Maintenance Phase, administration of pembrolizumab will be monitored by the investigator and/or study staff on Day 1 of each cycle; olaparib or olaparib placebo will be monitored by the investigator and/or study staff on Day 1 of the first cycle according to the specifications within the pharmacy manual. Participants will then self-administer olaparib or olaparib placebo orally for the remainder of the 21-day treatment cycle.

Study intervention should begin within 3 days of treatment allocation for the Induction Phase and within 3 days of treatment randomization in the Maintenance Phase.

Note: As of Amendment 07, participants who are confirmed to be actively taking placebo should discontinue taking the placebo intervention and continue in the study. Participants taking Olaparib should continue receiving it per investigator's discretion after discussion. Participants who are potential candidates for Second Course treatment will continue in Efficacy Follow-up. Participants currently undergoing or who will undergo Second Course with pembrolizumab monotherapy can continue or start treatment per investigator's discretion under this protocol or under an extension study.

8.1.8.1 Timing of Dose Administration

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

Cycles 1 – 4 (Induction Phase):

Participants will receive pembrolizumab 200 mg (Day 1) together with carboplatin AUC 6 mg/mL/min and investigator's choice of paclitaxel 200 mg/m^2 or nab-paclitaxel 100 mg/m^2 for 4 cycles.

Cycle 1 onwards (Maintenance Phase):

Participants will continue pembrolizumab 200 mg and begin maintenance therapy with either olaparib 300 mg or olaparib placebo BID.

Note: As of Amendment 07, participants who are confirmed to be actively taking placebo should discontinue taking the placebo intervention and continue in the study. The protocol content has been retained for reference.

8.1.8.1.1 Pembrolizumab

Pembrolizumab will be administered as a 30-minute IV infusion Q3W. Pembrolizumab will be administered prior to chemotherapy. 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 minutes/+ 10 minutes).

8.1.8.1.2 Paclitaxel or Nab-paclitaxel

Paclitaxel or nab-paclitaxel will be administered approximately 30 minutes after pembrolizumab and should be completely administered prior to initiating the carboplatin dose.

- Paclitaxel (200 mg/m^2 Q3W) will be administered as an IV infusion over 3 hours for 4 cycles as per local practice and labels. All participants should be premedicated with oral or IV steroid and antihistamines according to the approved product label and/or standard practice. Additional premedications should be administered as per standard practice.

- Nab-paclitaxel will be administered at 100 mg/m^2 as an IV infusion over 30 minutes for 4 cycles as per local practice and labels. Participants will be dosed on Day 1, 8 and 15 of each Q3W cycle.

Participants are allowed to switch from paclitaxel to nab-paclitaxel if the participant experiences an infusion reaction to paclitaxel and the investigator considers switching to be in the best interest of the participant. Switching from paclitaxel to nab-paclitaxel requires consultation between the investigator and the Sponsor and written documentation of the collaborative decision.

8.1.8.1.2.1 Carboplatin

Carboplatin (AUC 6 [mg/mL/min]) will be administered as an IV infusion over approximately 60 minutes Q3W on Day 1 for each of the 4 cycles (Induction Phase) and after paclitaxel or nab-paclitaxel as per local practice and labels. The carboplatin dose should be calculated using the Calvert formula (see below) and should not exceed 900 mg.

Calvert Formula:

- Total dose (mg) = (target AUC) × (CrCl + 25)

- The estimated CrCl in the Calvert formula should not exceed 125 mL/min

- Maximum carboplatin dose (mg) = target AUC 6 × (125 + 25)

$$= 6 \times 150$$
$$= 900 \text{ mg}$$

Creatinine clearance must be calculated using either the Cockcroft-Gault formula or another acceptable standard formula for estimating CrCl in mL/min based on serum creatinine:

- Men: [(140 - age (y)) × weight (kg)]/[72 × serum creatinine (mg/dL)]
- Women: [(140 - age (y)) × weight (kg)] × 0.85/[72 × serum creatinine (mg/dL)]

Note: Dose may be rounded to the nearest 50 mg at the discretion of the investigator, and according to institutional standards.

Unless there is a change in weight ≥10%, the same dose of carboplatin can be used throughout the 4 cycles of the Induction Phase (provided there are no additional toxicities).

Additional premedications should be administered as per standard practice.

8.1.8.1.3 Olaparib or Olaparib Placebo

Participants must have at least one evaluable imaging timepoint and no overall response of PD prior to starting either olaparib or olaparib placebo in the Maintenance Phase. To initiate or continue with olaparib or olaparib placebo, CrCl must be ≥51 mL/min. During the Maintenance Phase, ingestion of olaparib or olaparib placebo will be monitored by the investigator and/or study staff on Day 1 of first cycle and participants will then self-administer olaparib orally for the remainder of the 21-day treatment cycle. Participants will be instructed to self-administer olaparib or olaparib placebo at approximately the same time of day. If vomiting occurs within 2 hours after the olaparib or olaparib placebo tablets are swallowed, the dose should only be replaced if all of the intact tablets can be seen and counted.

If a participant misses a scheduled dose for any reason (eg, as a result of forgetting to take the tablets or vomiting), the participant will be allowed to take the scheduled dose up to a maximum of 2 hours after that scheduled dose time. If greater than 2 hours after the scheduled dose time, the missed dose is not to be taken and the participant should take their allotted dose at the next scheduled time.

Refer to the Olaparib Pharmacy Manual for further details on dose administration.

Note: As of Amendment 07, participants who are confirmed to be actively taking placebo should discontinue taking the placebo intervention and continue in the study. Participants taking Olaparib should continue receiving it per Investigator's discretion after discussion. Participants taking or will take pembrolizumab monotherapy (Second Course), should/will continue receiving it if they qualify per protocol. The protocol content has been retained for reference.

8.1.8.1.4 Colony-stimulating Factors

During the Induction Phase, the use of CSFs is highly recommended as primary prophylaxis to reduce the risk of febrile neutropenia in this participant population, especially as many participants have multiple comorbidities and advanced disease. G-CSF should not be used within 14 days prior to randomization.

During the Maintenance Phase, primary prophylaxis with G-CSF is not recommended; however, if a participant develops febrile neutropenia, study intervention should be interrupted and appropriate management including G-CSF should be given according to local hospital guidelines. Please note that G-CSF should not be used within at least 24 hours (7 days for pegylated G-CSF) of the last dose of study intervention unless absolutely necessary.

The American Society of Clinical Oncology guidelines for use of CSFs should be followed for this study [Smith, T. J., et al 2015].

8.1.8.1.5 Antiemetic Therapy

Antiemetic therapy should follow the Multinational Association of Supportive Care in Cancer (MASCC) guidelines [Roila, F., et al 2016]. In each cycle of treatment during the Induction Phase, antiemetic therapy should include a 5-HT3 receptor antagonist, dexamethasone (or equivalent), and/or aprepitant [Roila, F., et al 2016]. Some antiemetics are inducers/inhibitors of CYP3A4 (e.g., aprepitant); consider the required washout period before starting olaparib/olaparib placebo.

8.1.8.2 Discontinuation and Withdrawal

Section 7.2 provides a complete description of withdrawal of consent from the study.

Participants who withdraw consent from the study should be encouraged to complete all applicable activities scheduled for the final study visit at the time of withdrawal.

8.1.8.3 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.

8.1.9 Participant Blinding/Unblinding

The study intervention during the Induction Phase is open-label.

During the Maintenance Phase, when the investigator or delegate needs to identify the drug used by a participant and the dosage administered in case of emergency, eg, the occurrence of serious AEs, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or delegate 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 patient's treatment assignment, the investigator or delegate must enter the toxicity grade of the AEs observed, the relation to study drug, the reason thereof, etc., in the medical chart, etc.

Participants whose treatment assignment has been unblinded by the investigator/delegate and/or non-study treating physician must be discontinued from study drug, but should continue to be monitored in the trial.

Treatment identification information is to be unmasked ONLY if necessary for the welfare of the participant. Every effort should be made not to unblind the participant unless necessary.

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 or a non-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 patient.

Note: Based on the IA3 data, the study was unblinded on 15-DEC-2023. The unblinding processes are no longer relevant. Original protocol text has been retained for reference.

8.1.10 Calibration of Equipment

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

8.1.11 Tumor Tissue for Biomarker Status

During the screening period, a tumor sample for each participant is required and is to be:

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

Or

- An archival tumor tissue sample if a new biopsy is unavailable (depending on protocol requirements)

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

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

The central laboratory will use the tissue sample to ascertain PD-L1 status using the PD-L1 IHC 22C3 pharmDx (Investigational Use Only) diagnostic kit. The diagnostic test is identical to the US FDA-approved PD-L1 IHC 22C3 pharmDx diagnostic kit except it is labeled IUO. The PD-L1 IHC 22C3 pharmDx assay kit is currently approved to assess PD-L1 status in participants with NSCLC for treatment with pembrolizumab.

The PD-L1 result will be masked to the site.

8.2 Efficacy/Immunogenicity Assessments

Immunogenicity assessments will not be performed in this study.

8.2.1 Tumor Imaging and Assessment of Disease

Note: As of Amendment 7, participants who are still on study treatment will no longer require tumor response assessments by BICR to be performed. Scans will not be submitted to the iCRO. Participants who are still on study treatment and who have not experienced radiographic disease progression will be assessed locally by the investigator for disease progression, based on the site's standard of care imaging schedule. Original protocol text in this section has been retained for reference.

The process for image collection and transmission to the central imaging vendor can be found in the Site Imaging Manual (SIM). Tumor imaging is strongly preferred as follows

- CT with IV and oral contrast (preferred) of the chest, abdomen and pelvis for all participants, or non-contrast CT of the chest and MRI of the abdomen and pelvis with IV gadolinium for participants in whom iodinated contrast is contraindicated

- MRI (strongly preferred) or CT with contrast (when MRI is medically contraindicated) of 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. 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.

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 captures radiologic progression based on investigator assessment, should also be submitted to the central imaging vendor.

When the investigator identifies radiographic progression per RECIST 1.1, the central imaging vendor will perform expedited verification of radiologic disease progression and communicate the results to the study site and Sponsor. Progression of disease should be verified centrally before intervention is discontinued if the participant is clinically stable. If the participant is clinically stable, treatment should continue until PD has been centrally verified. Regardless of whether PD is verified, if the investigator considers the participant has progressed but elects to implement iRECIST, the investigator will assess for confirmation of progression by iRECIST at subsequent time points. Images should continue to be submitted to the central imaging vendor until VOP is confirmed centrally.

8.2.1.1 Initial Tumor Imaging

Initial tumor imaging at screening must be performed within 28 days prior to the date of the first dose of study intervention.

Tumor imaging performed as part of routine clinical management is acceptable for use as screening tumor imaging if it is of diagnostic quality and performed within 28 days prior to first treatment dose.

Participants with previously treated brain metastases may participate provided they are clinically stable for at least 2 weeks and have no evidence of new or enlarging brain metastases and also are off steroids 3 days prior to dosing with study medication. Stable brain metastases by this definition should be established prior to the first dose of study medication. Participants with known untreated, asymptomatic brain metastases (ie, no neurological symptoms, no requirements for corticosteroids, no or minimal surrounding edema, and no lesion >1.5 cm) may participate but will require regular imaging of the brain as a site of disease. This exception does not include carcinomatous meningitis, as participants with carcinomatous meningitis are excluded regardless of clinical stability.

CCI

[redacted]

CCI

[redacted]

For participants to proceed to the Maintenance Phase, responses do not need to be confirmed. However, images will need to be reviewed centrally to determine that the participants do not have progressive disease. Further, if the participant is determined to be eligible for maintenance, the latest evaluable imaging time point prior to entering maintenance will serve as the new baseline.

During the Maintenance Phase, objective response should be confirmed by a repeat imaging assessment. Tumor imaging to confirm PR or CR should be performed at least 4 weeks after the first indication of a response is observed. Participants will then return to regular scheduled imaging, starting with the next scheduled imaging time point. Participants who receive additional imaging for confirmation do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point. Note: Response does not typically need to be verified in real time by the central imaging vendor.

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

For randomized 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 due to centrally verified disease progression, this is the final required tumor imaging if the investigator elects not to implement iRECIST.

CCI [redacted]

8.2.1.4 Second Course (Retreatment) Tumor Imaging

Tumor imaging must be performed within 28 days prior to restarting treatment with pembrolizumab.

CCI [redacted]

Per iRECIST (Section 8.2.1.6), if tumor imaging shows initial PD, tumor assessment should be repeated 4 to 8 weeks later to confirm PD with the option of continuing treatment while awaiting radiologic confirmation of progression. Participants who obtain confirmatory imaging do not need to undergo scheduled tumor imaging if it is less than 4 weeks later and may wait until the next scheduled imaging time point, if clinically stable.

Imaging should continue to be performed until locally verified disease progression, the start of a new anticancer treatment, withdrawal of consent, death, or notification by MSD, whichever occurs first. In clinically stable participants, disease progression may be confirmed by the investigator using iRECIST 4 to 8 weeks after the first tumor imaging indicating PD.

CCI [redacted]

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

CCI [redacted]

CCI [redacted]

CCI

[redacted]

8.2.1.5 RECIST 1.1 Assessment of Disease

CCI

[redacted]

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

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

- If participant is clinically stable, continue study intervention per protocol
    - Continue scans per protocol schedule (the next scheduled scan should be ≥4 weeks from most recent scan acquired)
    - Send scan(s) to iCRO
    - Continue local assessment
    - Do not change investigator assessment of progression
    - If subsequent scan(s) indicate progression, submit scan(s) to iCRO to request verification
- If the participant is not clinically stable, the best medical practice is to be applied.

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

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

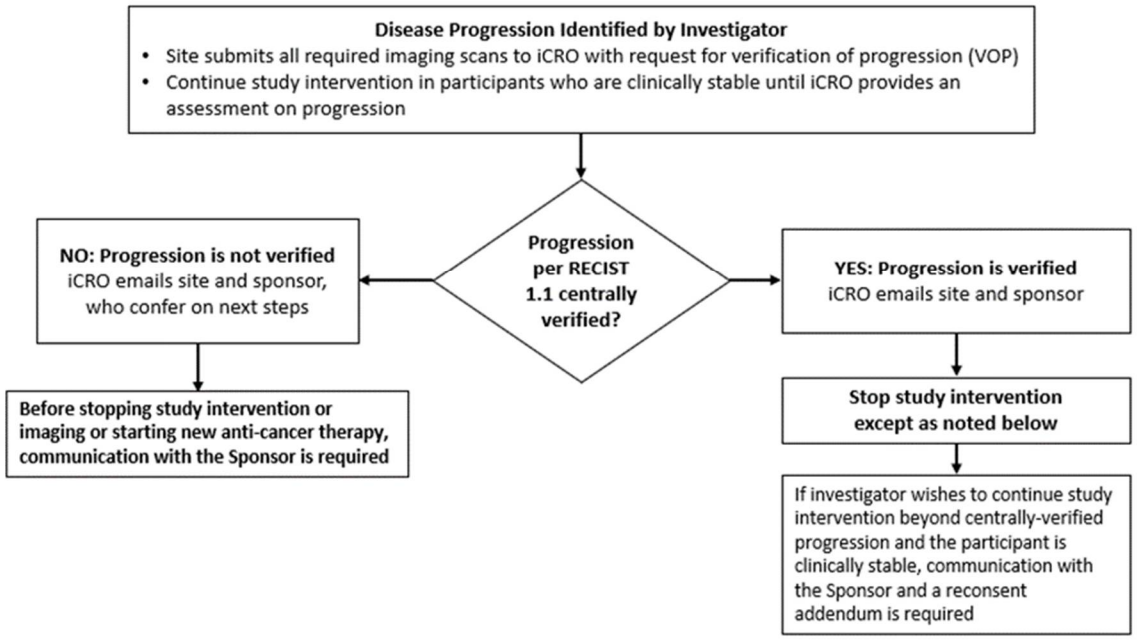
- Investigator judgment will determine action
- If participant is clinically stable and study intervention is to continue, communication with the Sponsor is required and a reconsent addendum must be signed
- Obtain scan(s) locally per original protocol schedule
- Do not send scan(s) to iCRO

Figure 2 illustrates the study intervention decision process involving verification of disease progression for participants.

For the purpose of this decision process, lack of clinical stability is defined as:

- Unacceptable toxicity
- Clinical signs or symptoms indicating clinically significant disease progression
- Decline in performance status
- Rapid disease progression or threat to vital organs or critical anatomical sites (eg, CNS metastasis, respiratory failure due to tumor compression, spinal cord compression) requiring urgent alternative medical intervention

Figure 2 Study Intervention Decision-making Process When Progression per RECIST 1.1 is Observed by Investigator



iCRO=imaging Contract Research Organization; VOP=verification of progression

8.2.1.6 iRECIST Assessment of Disease

iRECIST is based on RECIST 1.1, but it is adapted to account for the unique tumor response seen with immunotherapeutic drugs. iRECIST will be used by the investigator to assess tumor response and progression and make treatment decisions [Seymour, L., et al 2017]. When clinically stable, participants may continue study intervention beyond RECIST 1.1 progression with continued assessment of response according to the rules outlined in Appendix 8. iRECIST reflects that some participants can have a transient tumor flare after the start of immunotherapy then experience subsequent disease response. This data will be captured in the clinical database.

- If participant is clinically stable and VOP is not centrally verified (refer to Section 8.2.1.5), continue study intervention per protocol
  - Perform scans 4 to 8 weeks after RECIST 1.1 progression
  - Continue investigator assessment per iRECIST
  - Send scans to iCRO
  - If progression is BICR-verified, stop sending scans to iCRO
- If the participant is not clinically stable, best medical practice is to be applied.

CCI

[redacted]

8.3 Safety Assessments

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

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

8.3.1 Physical Examinations

At the initial visit, a complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) as per institutional standard. Clinically significant abnormal findings should be recorded as medical history. Height and weight will also be measured and recorded.

A brief directed physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard prior to trial treatment administration and at other times according to the SoA. 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

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and during the follow-up period as specified in the Schedule of Activities. Vital signs include temperature, pulse, respiratory rate, and blood pressure. Weight will be monitored as per vital signs. Height will be measured at Visit 1 only.

8.3.3 Electrocardiograms

A standard 12-lead ECG will be performed using local standard procedures. The timing of ECG is specified in the schedule of activities in Section 1.3. Clinically significant abnormal findings should be recorded as medical history. Additional ECGs may be performed as clinically necessary.

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.

8.3.4.1 Bone Marrow or Blood Cytogenetic Samples

Bone marrow or blood cytogenetic samples may be collected for participants with prolonged hematological toxicities as defined in Section 6.6.2.1.

Bone marrow analysis should include an aspirate for cellular morphology, cytogenetic analysis and flow cytometry, and a core biopsy for bone marrow cellularity. If it is not possible to conduct cytogenetic analysis or flow cytometry on the bone marrow aspirate, then attempts should be made to carry out the tests on a blood sample.

8.3.5 Performance Assessments

8.3.5.1 Eastern Cooperative Oncology Group Performance Status

The ECOG Performance Status is standardized criteria to measure how cancer impacts level of functioning (performance status) in terms of ability to care for oneself, daily activity, and physical ability (walking, working, etc.) with Grades 0 to 5.

The investigator or qualified designee will assess ECOG status at screening, prior to the administration of each dose of study intervention and during the follow-up 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 participant provides documented consent but before intervention allocation/randomization must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event 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.
- Any SAE of MDS/AML or new primary malignancy should be reported regardless of the investigator's assessment of causality or knowledge of the treatment arm.
- 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 14.

Exception: A positive pregnancy test at the time of initial screening is not a reportable event unless the participant has received study intervention.

Extension Study: Upon study completion, participants are discontinued and may be enrolled in a pembrolizumab extension study, if available. From the time of intervention randomization through up to documentation of consent to the extension study, all AEs, SAE, and other reportable safety events must be reported by the investigator in this protocol (parent study). Laboratory values that meet criteria for reporting as AEs performed during parent study will be collected in the parent study. Once consented to the extension study, AEs and other reportable events meeting the criteria of the extension study, including those considered related to study intervention, will be collected as instructed in the extension study.

Table 14 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: - participant has been exposed to any protocol-specified intervention (eg, procedure, washout or run-in treatment including placebo run-in) Exception: A positive pregnancy test at the time of initial screening is not a reportable event.	Report all	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event

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:
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 toward the safety of participants and the safety of a study intervention under clinical investigation are met.

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

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

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

8.4.5 Pregnancy and Exposure During Breastfeeding

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

All reported pregnancies must be followed to the completion/termination of the pregnancy.

Any pregnancy complication will be reported as an AE or SAE.

The medical reason (example: maternal health or fetal disease) for an elective termination of a pregnancy will be reported as an AE or SAE. Prenatal testing showing fetus will be born with severe abnormalities/congenital anomalies that leads to an elective termination of a pregnancy will be reported as an SAE for the fetus.

Pregnancy outcomes of ectopic pregnancy, 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.

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 products, as defined in Section 8.5, that is not associated with clinical symptoms or abnormal laboratory results.

2. An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less

than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

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

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

8.5 Treatment of Overdose

Olaparib must only be used in accordance with the dosing recommendations in this protocol. Any dose or frequency of dosing that exceeds the dosing regimen specified in this protocol should be reported as an overdose. 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 olaparib or pembrolizumab. In the event of overdose, the study intervention should be discontinued, and the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

8.6 Pharmacokinetics

PK parameters will not be evaluated in this study.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

CCI

[redacted]

CCI

[redacted]

8.12 Visit Requirements

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

8.12.1 Screening

Approximately 28 days prior to treatment allocation, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.

Documented informed consent must be provided before performing any protocol-specific procedure. Results of a test performed prior to the participant signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 28 days prior to the first dose of study treatment except for the following:

- Laboratory tests are to be performed within 10 days prior to the first dose of study intervention. An exception is hepatitis and HIV testing which may be done up to 28 days prior to the first dose of study intervention if required by the local health authority.
- Evaluation of ECOG is to be performed within 7 days prior to the first dose of study intervention.
- For WOCBP, a urine pregnancy test will be performed within 72 hours prior to the first dose of study treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local trial site laboratory). Additional pregnancy testing can be conducted if required by local regulations or clinically indicated.

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. Rescreening is permitted as long as the study is open for enrollment.

8.12.2 Pre-randomization Visit

All participants will be evaluated at a Pre-Randomization visit, which will occur 4 weeks (±7 days) after Cycle 4, Day 1 of treatment in the Induction Phase and prior to study procedures/intervention in the Maintenance Phase. Investigators will review inclusion/exclusion criteria to ensure eligibility. A checklist will be completed and must be reviewed and approved by Sponsor.

Participants with PD must be excluded from the Maintenance Phase and should enter End-of-Treatment (refer to Section 1.3.2).

8.12.3 Treatment Period

Visit requirements are outlined in the SoA (Section 1.3). Specific procedure-related details are provided in Section 8.1. Assessments/procedures should be performed prior to the administration of study intervention.

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

Randomized participants who discontinue study treatment for reasons other than PD, will move into the Follow-up Phase (Section 8.12.6).

8.12.5 Second Course Phase (Retreatment Period)

Note: Participants are allowed to start Second Course Treatment with locally verified PD. Original protocol text has been retained for reference.

All participants who receive 35 cycles of pembrolizumab with SD, PR, or CR in either arm may be eligible for up to an additional year of treatment with pembrolizumab (17 cycles) if they progress after stopping study treatment from the initial treatment period. 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:

- Experienced radiographic disease progression by RECIST 1.1 after stopping initial treatment with 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.
- AND Had SD, PR or CR and stopped pembrolizumab treatment after completion of 35 administrations (approximately 2 years) of study intervention for reasons other than disease progression or intolerability.

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.

Procedures and visit requirements for the Second Course Phase are outlined in Section 1.3.4.

8.12.6 Posttreatment Visits

8.12.6.1 Safety Follow-up Visit

The mandatory Safety Follow-up Visit should be conducted approximately 30 days after the last dose of study treatment in the Induction Phase or the Maintenance Phase. 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 Phase.

8.12.6.2 Follow-up Visits

Randomized participants who discontinue study treatment for a reason other than PD will move into the Long-term Follow-up Phase and should be assessed approximately Q6W (42 days ± 7 days) during the first 48 weeks following randomization and approximately Q9W (63 days ± 7 days) thereafter. Every effort should be made to collect information regarding disease status until confirmed PD, start of a new anticancer therapy, death,

withdrawal of consent, or the end of the study, whichever occurs first. Information regarding poststudy anticancer treatment will be collected if new treatment is initiated.

8.12.6.3 Imaging Follow-up Visits

All randomized participants who discontinue study intervention prior to disease progression will continue to undergo tumor assessments as per SoA (see Section 1.3.2) until centrally verified disease progression is documented and confirmed by BICR or a new anticancer therapy is initiated, unless the participant withdraws consent.

Participants who are eligible for retreatment with pembrolizumab according to the criteria in Section 8.12.5 will move from the Follow-Up Phase to the Second Course Phase when they experience disease progression. Details are provided in the SoA (Section 1.3.4) for retreatment with pembrolizumab.

8.12.6.4 Survival Follow-up Assessments

Randomized participants follow-up status will be assessed approximately every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

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

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

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

8.12.7 Vital Status

To ensure current and complete survival information (vital status) is available at the time of database locks, updated vital status may be requested during the course of the study by the Sponsor. For example, updated vital status may be requested before, but not limited to, an eDMC review, interim and/or final analysis. Upon Sponsor notification, all randomized 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 vital status.

9 STATISTICAL ANALYSIS PLAN

As of Amendment 07: The Statistical Analysis Plan is amended as follows.

Note: Based on the data from an interim safety and efficacy analysis (IA3) for MK-7339-008 (data cutoff 21-SEP-2023), the final analysis will not take place. It has been determined that

it was extremely unlikely that the efficacy boundary for success for the primary endpoint of OS would be reached at the next (final) analysis.

Based upon these data and the recommendation of the eDMC, the study was unblinded. The prespecified final analysis of the study described in the SAP will not be performed. Selected analyses of safety endpoints will be performed at the end of the study; there will be no further analyses of efficacy and ePRO endpoints.

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, changes 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, will be documented in a supplemental Statistical Analysis Plan (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR. Separate analysis plans (ie, separate documents from the sSAP) may be developed to detail other planned analyses (ie, analysis of future biomedical research). The PRO analysis plan will be included in the sSAP.

9.1 Statistical Analysis Plan Summary

Note: As of Amendment 07, the prespecified final analysis of the study described in the SAP will not be performed. Selected analyses of safety endpoints will be performed at the end of the study; there will be no further analyses of efficacy and PRO endpoints. The SAP summary has been updated accordingly.

Key elements of the Statistical Analysis Plan are summarized below; the comprehensive plan is provided in Sections 9.2 to 9.12.

Study Design Overview	A Phase 3 Study of Pembrolizumab in Combination with Carboplatin/Taxane (Paclitaxel or Nab-paclitaxel) Followed by Pembrolizumab with or without Maintenance Olaparib in the First-Line Treatment of Metastatic Squamous Non-Small Cell Lung Cancer (NSCLC)
Treatment Assignment	After completing the Induction Phase of treatment with pembrolizumab in combination with carboplatin with taxane (paclitaxel/nab-paclitaxel), approximately 590 eligible participants will be randomized in a 1:1 ratio to receive pembrolizumab plus maintenance olaparib or pembrolizumab plus maintenance olaparib placebo. Stratification factors are as follows: • PD-L1 TPS <50% vs ≥50% • Response at randomization CR/PR vs SD • ECOG 0 vs 1 at Pre-randomization Visit This is a randomized double-blind study.
Analysis Populations	Efficacy: Intention-to-Treat (ITT) Safety: All Participants as Treated (APaT) PROs: Full Analysis Set (FAS)

Primary Endpoint(s)	• Progression-free Survival (PFS) per RECIST 1.1 (Section 4.2.1.1) assessed by BICR • Overall survival (OS)
Secondary Endpoints	• Safety and tolerability • Patient-report outcomes
Statistical Methods for Key Efficacy Analyses	The dual primary hypotheses on PFS and OS will be evaluated by comparing pembrolizumab plus maintenance olaparib to pembrolizumab plus placebo in Maintenance Phase using a stratified Log-rank test. The hazard ratio will be estimated using a stratified Cox regression model. Event rates over time will be estimated within each treatment group using the Kaplan-Meier method.
Statistical Methods for Key Safety Analyses	The analysis of safety results in the APaT will follow a tiered approach. There are no Tier 1 safety parameters in this trial. All safety parameters are considered either Tier 2 or Tier 3. Tier 2 parameters will be assessed via point estimates with 95% confidence intervals provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters. The between-treatment difference will be analyzed using the Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985].

CCI

[redacted]

CCI

[redacted]

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-blinded 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 Sponsor will generate the randomized allocation schedule(s) for study treatment assignment for this protocol, and the randomization will be implemented in IRT.

Blinding issues related to the planned interim analyses are described in Section 9.7.

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/or between-treatment differences are listed below. Exploratory endpoints will be described in the sSAP.

9.4.1 Efficacy Endpoints

Dual Primary

Progression-free survival (PFS) – RECIST 1.1 assessed by BICR

Progression-free-survival (PFS) is defined as the time from randomization to the first documented disease progression per RECIST 1.1 (Section 4.2.1.1) based on blinded

independent central imaging vendor review or death due to any cause, whichever occurs first. See Section 9.6.1 for the censoring rules.

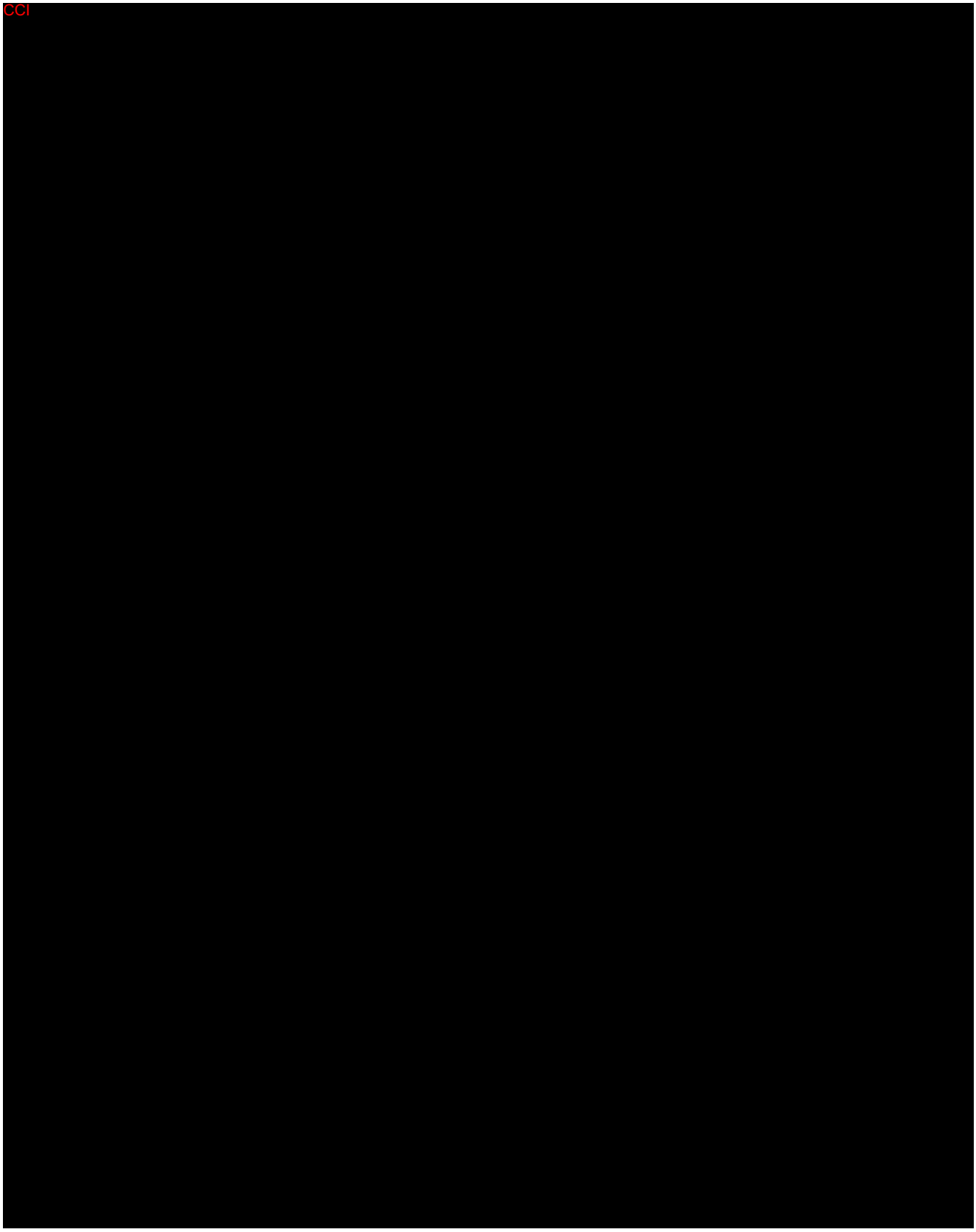
Overall Survival

Overall Survival (OS) is defined as the time from randomization to death due to any cause. Participants without documented death at the time of analysis will be censored at the last date known to be alive.

9.4.2 Safety Endpoints

Safety measurements are described in Section 4.2.1.2, and Section 8.3 and Section 8.4.

CCI



CCI

[redacted]

9.6 Statistical Methods

9.6.1 Statistical Methods for Efficacy Analyses

Note: As of Amendment 07, the prespecified final analysis of the study described in the SAP will not be performed. Selected analyses of safety endpoints will be performed at the end of the study; there will be no further analyses of efficacy and PRO endpoints. The subsections below are retained for reference.

This section describes the statistical methods that address the primary objectives. Methods related to exploratory objectives will be described in the supplemental SAP.

Efficacy results that will be deemed to be statistically significant after consideration of the Type I error control strategy are described in Section 9.8. Nominal p values will be computed for other efficacy analyses but should be interpreted with caution due to potential issues of multiplicity. Response or progression in the Second Course Phase will not count toward the PFS of the primary endpoint in this trial.

The stratification factors used for randomization (see Section 6.3.2) will be applied to all stratified analyses, in particular, the stratified log-rank test, stratified Cox model, and stratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985a]. In the event that there are small strata, for the purpose of analysis, strata will be combined to ensure sufficient number of participants, responses and events in each stratum. Details regarding the pooling strategy will be prespecified in the sSAP.

9.6.1.1 Progression-free Survival

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

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 RECIST 1.1 via BICR by the

imaging vendor. Death is always considered as a confirmed PD event. Participants who do not experience a PFS event will be censored at the last disease assessment. Sensitivity analyses will be performed for comparison of PFS based on investigator's assessment.

CCI

[redacted]

CCI

[redacted]

9.6.1.2 Overall Survival (OS)

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 factor defined in Section 6.3.2). A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, the hazard ratio). The hazard ratio and its 95% confidence interval from the stratified Cox model 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. Participants without documented death at the time of analysis will be censored at the date of last known to be alive.

The RMST method may be conducted for OS as a sensitivity analysis to account for the possible non-proportional hazards effect and to estimate the absolute benefit of experimental treatment.

9.6.1.3 Analysis Strategy for Key Efficacy Endpoints

The primary analysis approach for the primary and key secondary efficacy endpoints are summarized in Table 16. Sensitivity analysis methods are described above for each endpoint as applicable.

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.

Table 16 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable (Description, Time Point)	Statistical Method[a]	Analysis Population	Missing Data Approach
Dual Primary Endpoints			
PFS per RECIST 1.1 by blinded independent central review (BICR) by the imaging vendor	Test: Stratified Log-rank test to assess the treatment difference Estimation: Stratified Cox model with Efron's tie handling method to assess the magnitude of treatment difference	ITT	• Primary censoring rule • Sensitivity analysis 1 • Sensitivity analysis 2
OS	Test: Stratified Log-rank test to assess the treatment difference Estimation: Stratified Cox model with Efron's tie handling method to assess the magnitude of treatment difference	ITT	Model based (censored at the last date the participant was known to be alive)

[a] Statistical models are described in further detail in the text. For stratified analyses, the stratification factors used for randomization (Section 6.3.2) will be applied to the analysis.

Abbreviations: ITT=intention-to-treat; OS=overall survival; PFS=progression-free survival; RECIST 1.1=Response Evaluation Criteria in Solid Tumors 1.1;

9.6.2 Statistical Methods for Safety Analyses

Adverse events occurring in participants treated during the induction phase will be collected and reported, which will be detailed in the sSAP.

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests, vital signs, and ECG measurements after randomization. The analysis of safety results in the APaT will follow a tiered approach (Table 17). 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 parameters are either prespecified as Tier-1 endpoints or will be classified as belonging to "Tier 2" or "Tier 3", based on the number of events observed.

Tier 1 Events

Safety parameters or adverse experiences of special interest that are identified a priori constitute "Tier 1" safety endpoints that will be participant to inferential testing for statistical significance with p values and 95% confidence intervals to be provided for between-treatment comparisons. Those AEOSIs that are immune-mediated or potentially immune-mediated are well documented and will be separately evaluated; however, these events have been consistently characterized throughout the pembrolizumab clinical development program, and determination of statistical significance is not expected to add value to the

safety evaluation. In addition, there are no known AEs associated with participants with NSCLC for which determination of a p-value is expected to impact the safety assessment. Thus, there are no AEs that warrant elevation to Tier 1 in this study.

Tier 2 Events

Tier 2 parameters will be assessed via point estimates with 95% confidence intervals provided for between-treatment differences in the proportion of participants with events using the Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985], an unconditional, asymptotic method.

Membership in Tier 2 requires that at least 10% of participants in any treatment group exhibit the event. The threshold of at least 10% participants was chosen because the patient population enrolled in this study are in critical conditions and usually experience various adverse events of similar types regardless of treatment, events reported less frequent than 10% of participants would obscure the assessment of overall safety profile and add little to the interpretation of potentially meaningful treatment differences. In addition, Grade 3 to 5 AE (≥5% of participants in one of the treatment groups) and SAE (≥5% of participants in one of the treatment groups) will be considered Tier 2 endpoints. Because many 95% confidence intervals may be provided without adjustment for multiplicity, the confidence intervals should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in adverse experiences and safety parameters that meet predefined limits of change.

Tier 3 Events

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

Continuous Safety Measures

For continuous measures such as changes from baseline in laboratory and vital signs and ECG parameters that are not prespecified as Tier 1 endpoints will be considered Tier 3 safety parameters. Summary statistics for baseline, on treatment, and change from baseline values will be provided by treatment group in table format.

Table 17 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	Any AE (≥10% of participants in one of the treatment arms)	X	X
	Any Serious AE (≥5% of participants in one of the treatment arms)	X	X
	Any Grade 3-5 AE (≥5% of participants in one of the treatment arms)	X	X
Tier 3	AEs, Specific AEs, SOCs	-	X
	Discontinuation due to AE	-	X
	Dose interruption due to AE	-	X
	Change from Baseline[a] Results (Labs, ECGs, Vital Signs)	-	X

Abbreviations: AE=adverse event; CI=confidence interval; ECG=electrocardiogram; PDLC=predefined limit of change; SOC= system organ class.

[a] The baseline value is defined as last available measurement on or before the first study intervention during Maintenance Phase.

CCI

CCI

[redacted]

9.6.4 Summaries of Baseline Characteristics, Demographics, and Other Analyses

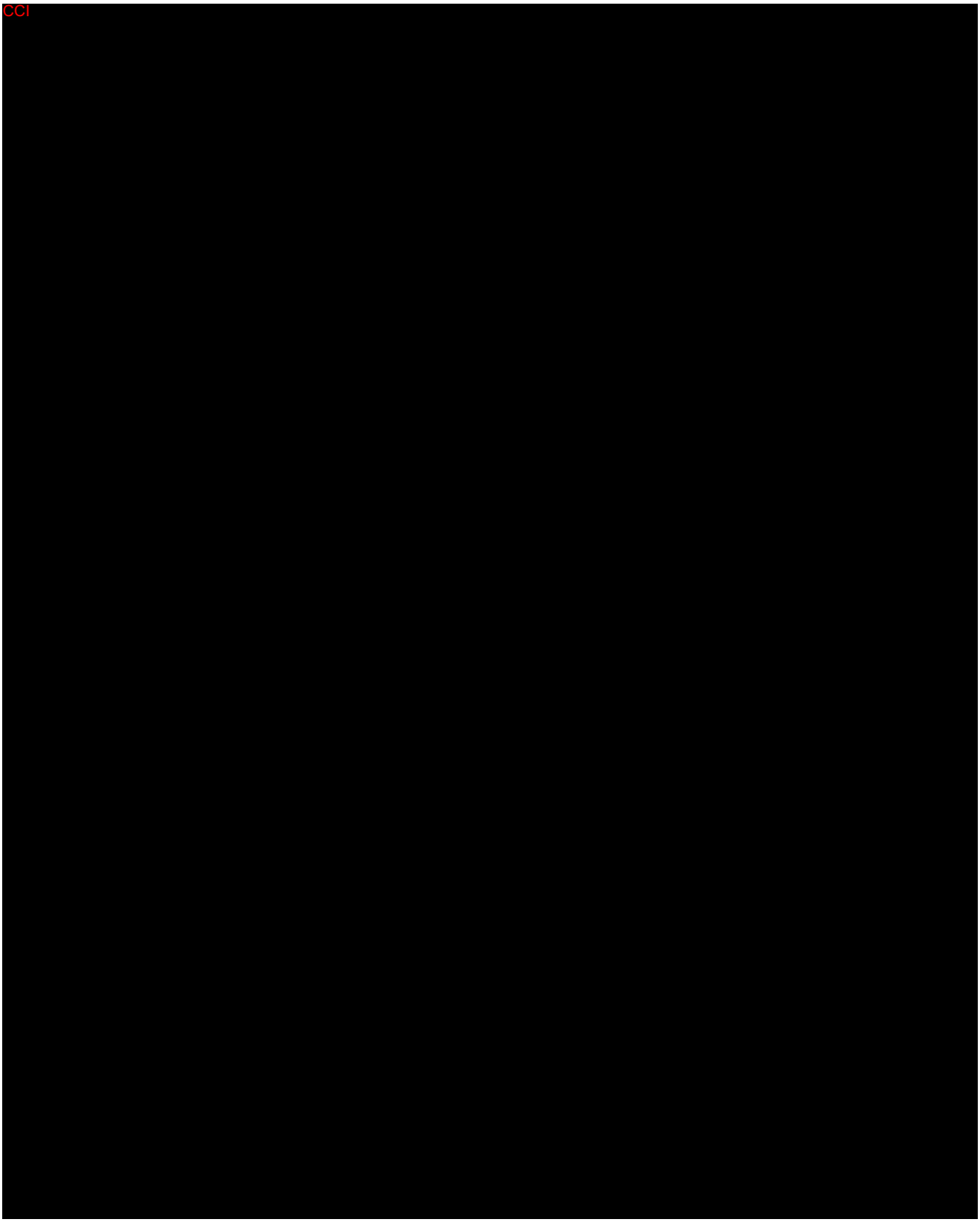
9.6.4.1 Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant demographic and baseline characteristic will be assessed using tables and/or graphs (ie, baseline values will be the last available measurement on or before randomization). No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants screened, randomized, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables (eg, age, gender), baseline characteristics, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

CCI

[redacted]

CCI



CCI

[redacted]

9.8 Multiplicity

Note: As of Amendment 07, the prespecified final analysis of the study described in the SAP will not be performed. This section is retained for reference.

The trial uses the graphical method of Maurer and Bretz [Bretz, F., et al 2011] to provide strong multiplicity control for multiple hypotheses as well as interim analyses. According to Maurer and Bretz approach, study hypotheses may be tested more than once, and when a particular null hypothesis is rejected, the α allocated to that hypothesis can be reallocated to other hypothesis tests. CCI

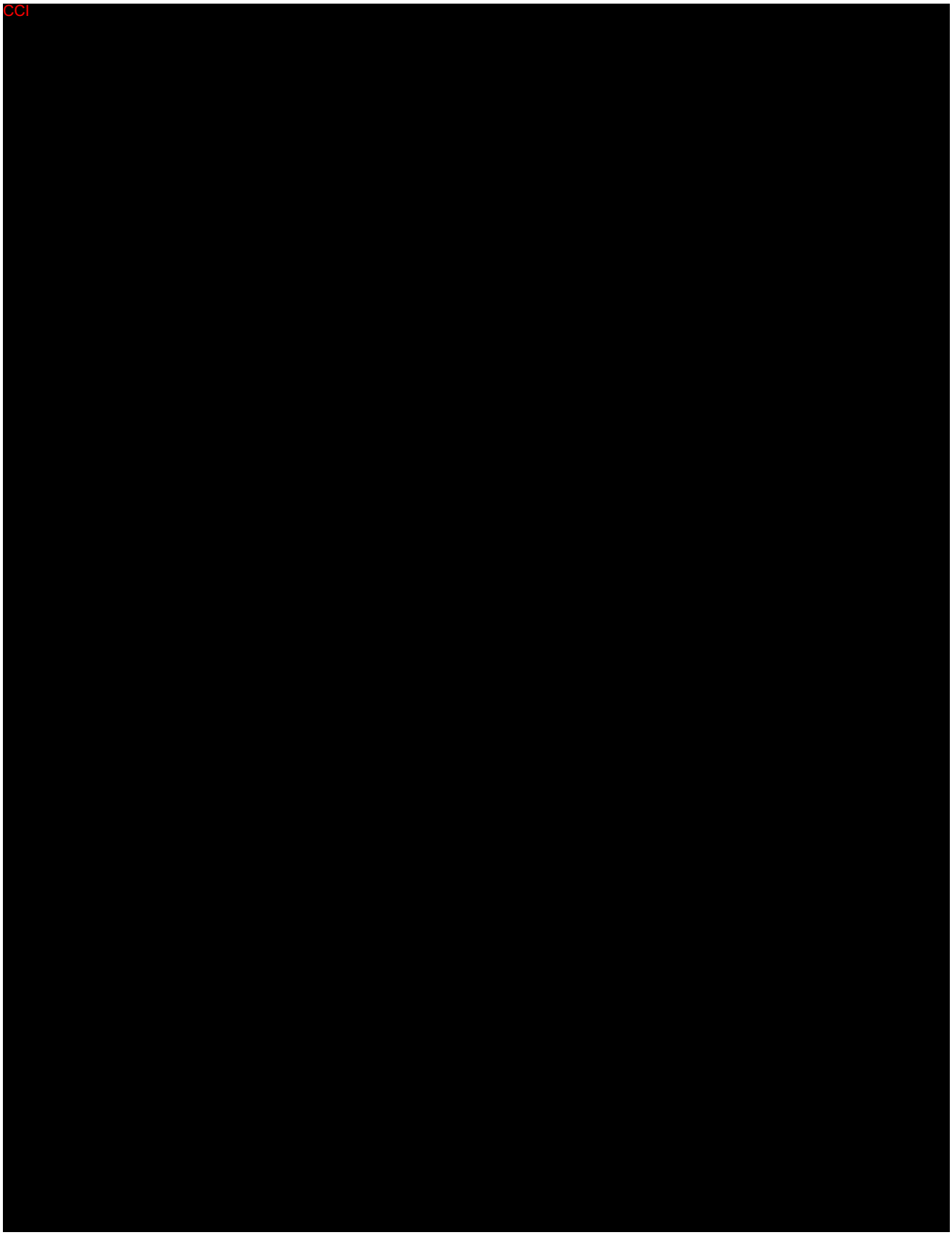
CCI

CCI

CCI

[redacted]

CCI



CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

9.8.3 Safety Analyses

The external DMC has responsibility for assessment of overall risk:benefit. When prompted by safety concerns, the external DMC 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 external DMC 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 external DMC.

9.9 Sample Size and Power Calculations

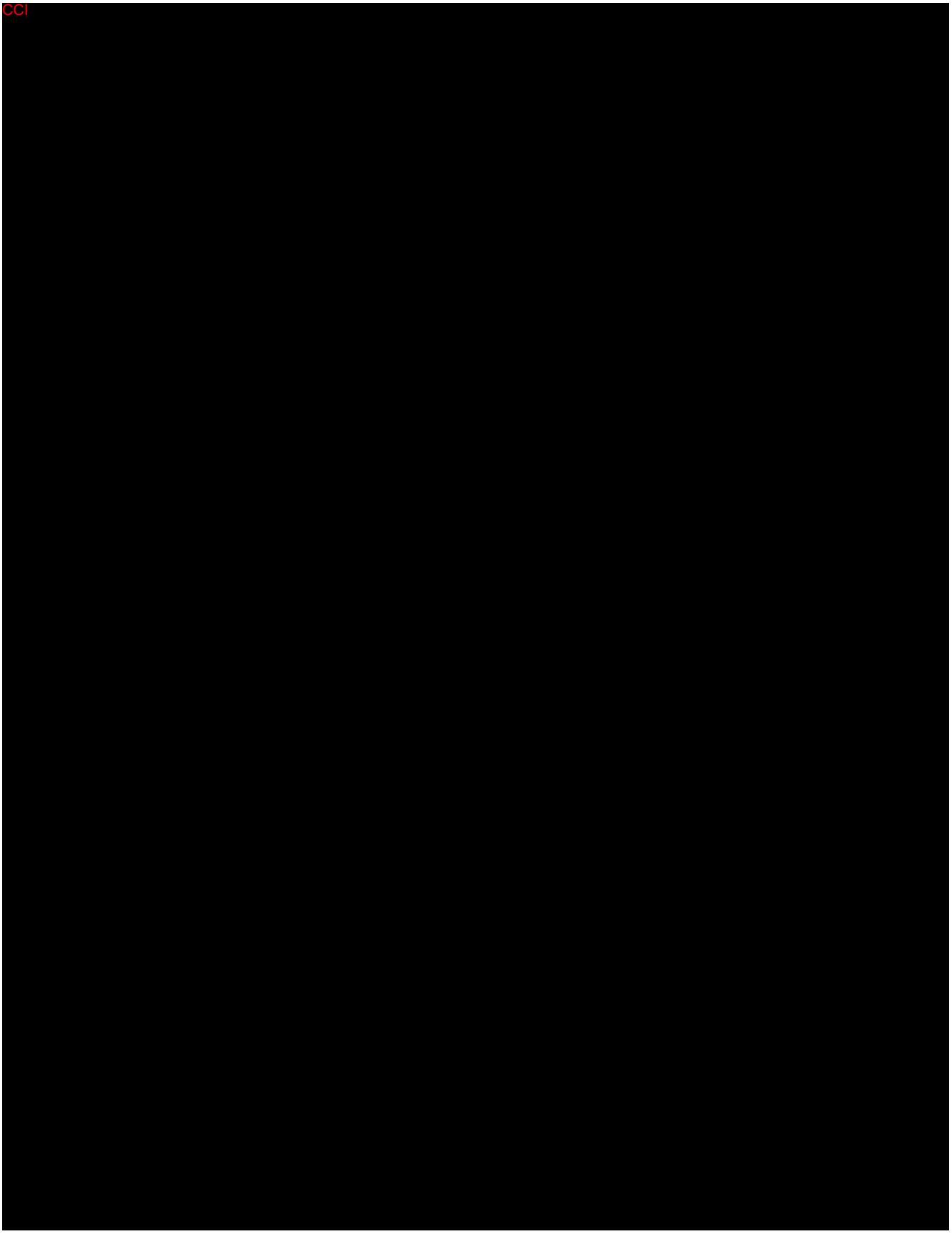
Note: As of Amendment 07, the prespecified final analysis of the study described in the SAP will not be performed. This section is retained for reference.

The study will randomize approximately 590 participants in a 1:1 ratio into the 2 study interventions, pembrolizumab combined with maintenance olaparib and pembrolizumab combined with placebo. PFS and OS are dual primary endpoints for the study.

CCI

[redacted]

CCI



CCI

[redacted]

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 will be summarized as duration of treatment in cycles. Summary statistics will be provided on extent of exposure for the APaT population.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Code of Conduct for Clinical Trials

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

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

The design (ie, participant population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. All trial protocols are and will be assessed for the need and capability to enroll underrepresented groups. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD's clinical trials are conducted globally in many different countries and in diverse populations, including people of varying age, race, ethnicity, gender, and accounting for other potential disease related factors. 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 (or individuals acting on behalf of MSD) to assess the ability to successfully conduct the trial.

Where appropriate, and in accordance with regulatory authority guidance, MSD will make concerted efforts to raise awareness of clinical trial opportunities in various communities. MSD will seek to engage

underrepresented groups and those disproportionately impacted by the disease under study. MSD will support clinical trial investigators to enroll underrepresented groups and expand access to those who will ultimately use the products under investigation.

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 composed of members of Sponsored Senior Management. The EOC will receive and decide on any recommendations made by the DMC or Steering Committee regarding the study.

10.1.4.2 Data Monitoring Committee

To supplement the routine study monitoring outlined in the protocol, an external DMC will monitor the interim data from the 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 this 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 eDMC 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 Council for Harmonisation of Technical Requirements for 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 participant's documented informed consent, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.9 Source Documents

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

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

10.1.10 Study and Site Closure

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

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

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 21 will be performed by the local laboratory.
- All on-treatment samples will be collected prior to administration of study intervention.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.1 and Section 5.2 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 21 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology Chemistry	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
	Blood Urea Nitrogen (BUN) or urea[a]	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the upper limit of normal)
	Albumin	Carbon dioxide (CO_2 or bicarbonate)[b]	Chloride	Phosphorous
	Creatinine or creatinine clearance[c]	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose (nonfasting)	Calcium	Alkaline phosphatase	Lactate dehydrogenase
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of nonchildbearing potential only). • Serum or urine β human chorionic gonadotropin (β-hCG) pregnancy test (as needed for WOCBP). • Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody) as required by local health authority or institutional regulations. Refer to Appendix 7 for country-specific information. • Coagulation factors (PT or INR, and aPTT/PTT). Additional testing to be conducted as clinically indicated for participants taking anticoagulation therapy. • Thyroid-stimulating hormone (TSH), free thyroxine (FT4), triiodothyronine (T3)			

Laboratory Assessments	Parameters
Other Tests	• Bone marrow or blood cytogenetic analysis for prolonged hematological toxicities (Section 6.6.2.2). This should include an aspirate for cellular morphology, cytogenetic analysis and flow cytometry, and a core biopsy for bone marrow cellularity.

Abbreviations: aPTT=activated partial thromboplastin time; FT4=free thyroxine; HIV=human immunodeficiency virus; INR=international normalized ratio; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; PT=prothrombin time; PTT=partial thromboplastin time; RBC = red blood cell; T3 = triiodothyronine; TSH=thyroid-stimulating hormone; WBC=white blood cell.

Notes:

a. BUN is preferred; if not available, urea may be tested.

b. Performed only if considered the local standard of care.

c. GFR (measured or calculated) or creatinine clearance can be used in place of creatinine.

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:

1. **Results in death**

2. **Is life-threatening**

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

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

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

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

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

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

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

6. Other important medical events

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.

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

10.3.3 Additional Events Reported in the Same Manner as SAE

Additional events that require reporting in the same manner as SAE

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

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

10.3.4 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity/toxicity

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

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

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (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, (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 IRB/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 email 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 2 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 non-hormonal 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

Male participants with female partners of childbearing potential are eligible to participate if they agree to 1 of the following during the protocol-defined time frame in Section 5.1:

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.
- 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.
  - The following are not acceptable methods of contraception:
    - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM).
    - Male condom with cap, diaphragm, or sponge with spermicide.
    - Male and female condom cannot be used together.

- 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 penetration.
- Note: Male participants must refrain from donating sperm during treatment and for at least 180 days after the last dose of study intervention.

Female Participants

Female participants of childbearing potential are eligible to participate if they agree to consistent and correct use of a highly effective method of contraception as described in Table 22 during the protocol-defined time frame in Section 5.1.

Table 22 Highly Effective Contraception Methods

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only subdermal contraceptive implant[b] • IUS[c] • Non-hormonal IUD • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
[a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. [b] If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. [c] IUS is a progestin releasing IUD. Note: The following are not acceptable methods of contraception: - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM. - Male condom with cap, diaphragm, or sponge with spermicide. - Male and female condom should not be used together (due to risk of failure with friction).

10.5.3 Pregnancy Testing

- Pregnancy testing requirements for study inclusion are described in Section 5.1.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted as indicated in the SoA.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted for the time required to eliminate systemic exposure after the last dose of each study interventions as noted in Section 5.1. The length of time required to continue pregnancy testing for each study intervention is 180 days following the last dose of pembrolizumab, olaparib, or cytotoxic chemotherapy.
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

CCI

[redacted]

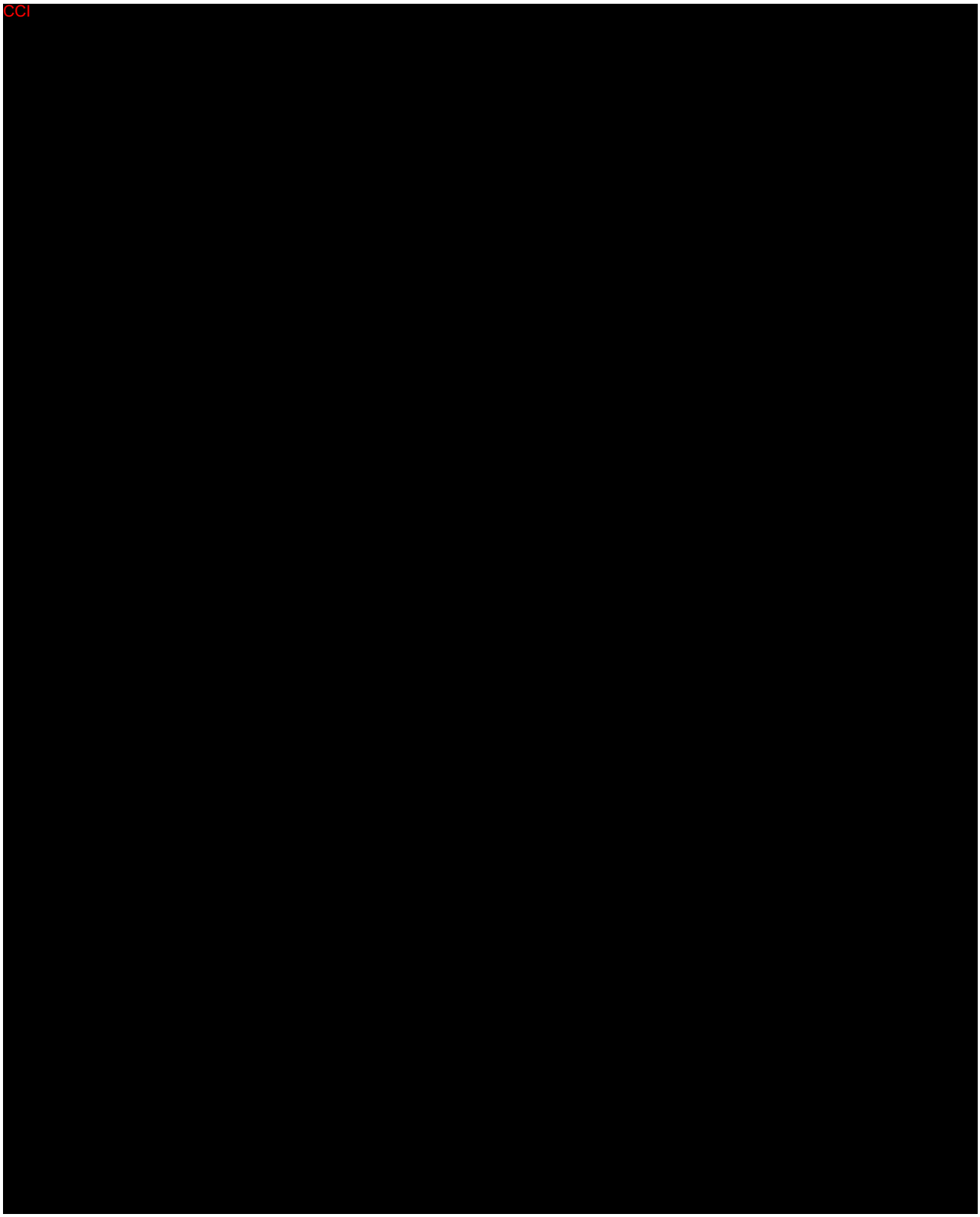
CCI

[redacted]

CCI

[redacted]

CCI



CCI

[redacted]

10.7 Appendix 7: Country-specific Requirements

10.7.1 France-specific Requirements

- Section 1.3.1 Schedule of Activities for Screening and Induction Phases

  Pregnancy testing must be performed at each cycle during treatment as well as at the end of study treatment.

- Section 1.3.2 Schedule of Activities for Maintenance Phase

  Pregnancy testing must be performed at each cycle during treatment as well as at the end of study treatment.

- Section 1.3.4 Schedule of Activities for Second Course Retreatment Phase

  Pregnancy testing must be performed at each cycle during treatment as well as at the end of study treatment.

- Section 10.5 Appendix 5: Contraceptive Guidance and Pregnancy Testing

  Pregnancy testing must be performed at each cycle during treatment as well as at the end of study treatment.

10.7.2 Germany-specific Requirements

- Exclusion Criterion 10: HIV testing is mandatory.
- Exclusion Criterion 11: hepatitis B and C testing is mandatory.
- Section 1.3.1 Schedule of Activities for Screening and Induction Phases

  Monthly urine pregnancy testing is required during treatment as well as at the end of study treatment.

- Section 1.3.2 Schedule of Activities for Maintenance Phase

  Monthly urine pregnancy testing is required during treatment as well as at the end of study treatment.

- Section 1.3.4 Schedule of Activities for Second Course Retreatment Phase

  Monthly urine pregnancy testing is required during treatment as well as at the end of study treatment.

- Section 6.5.1 (Prohibited Concomitant Medications):

  Live vaccines must not be administered for 90 days after the last dose of study intervention.

- Legally Acceptable Representative protocol sections

  In order for a participant to be eligible to participate in Germany, they must be capable of providing documented informed consent; therefore, all references to a participant's "legally acceptable representative" in the protocol are not applicable for participants in Germany.

- Section 10.5 Appendix 5: Contraceptive Guidance and Pregnancy Testing

  Monthly urine pregnancy testing after randomization is required during treatment as well as at the end of study treatment.

10.7.3 Japan-specific Requirements

- For the assistance to early diagnosis of pneumonitis/ILD in study participants, the following items such as pulse oximetry monitoring (SpO_2), CRP, KL-6, and SP-D will be measured in this study. These items should be measured according to the following timing.

  - SpO_2: at the timing of vital sign assessment.

  - CRP, KL-6 and SP-D: at screening*, pre-dose of Day 1 of every cycle, end-of-treatment, and safety follow-up visit (30 days after last dose).

    * should be measured at the timing of clinical laboratory tests (such as hematology/ chemistry).

- In the case that pneumonitis/ILD occurs regardless of causality with study medication, an independent ILD evaluation committee will conduct adjudication of cases of the pneumonitis/ILD. For this purpose, relevant data such as chest imaging (from the baseline to the recovery of pneumonitis/ILD) will be submitted to MSD K.K.

10.7.4 United Kingdom-specific Requirements

- Section 6.5.1 (Prohibited Concomitant Medications): Live vaccines must not be administered for 90 days after the last dose of study intervention. Refer to Section 6.5 for information on COVID-19 vaccines.

- Males are to be advised to seek counseling on sperm storage before starting pemetrexed and platinum-based therapy as per respective SmPCs.

- Section 1.3.1: Schedule of Activities for Screening and Induction Phases

  Monthly urine pregnancy testing is required during treatment as well as at the end of study treatment.

- Section 1.3.2: Schedule of Activities for Maintenance Phase

  Monthly urine pregnancy testing is required during treatment as well as at the end of study treatment.

- Section 1.3.4 Schedule of Activities – Second Course Treatment Phase

  Monthly urine pregnancy testing is required during treatment as well as at the end of study treatment.

- Section 10.5 Appendix 5: Contraceptive Guidance and Pregnancy Testing

  Monthly urine pregnancy testing is required during treatment as well as at the end of study treatment.

10.8 Appendix 8: Description of the iRECIST Process for Assessment of Disease Progression

iRECIST is based on RECIST 1.1 but adapted to account for the unique tumor response seen with immunotherapeutic drugs. iRECIST will be used by the investigator to assess tumor response and progression, and to guide decisions about changes in management.

Assessment at Screening and Before RECIST 1.1 Progression

Until radiographic disease progression based on RECIST 1.1, there is no distinct iRECIST assessment.

Assessment and Decision at RECIST 1.1 Progression

For participants who show radiological PD by RECIST 1.1, the investigator will decide whether to continue a participant on study intervention until repeat scans 4 to 8 weeks later obtained as described in Section 8.2.1.6.

Tumor flare may manifest as any factor causing radiographic progression per RECIST 1.1, including:

- Increase in the sum of diameters of target lesion(s) identified at baseline to ≥20% and ≥5 mm from nadir

  Note: The iRECIST publication uses the terminology "sum of measurements," but "sum of diameters" will be used in this protocol, consistent with the original RECIST 1.1 terminology.

- Unequivocal progression of nontarget lesion(s) identified at baseline

- Development of new lesion(s)

iRECIST defines new response categories, including iUPD (unconfirmed progressive disease) and iCPD (confirmed progressive disease). For purposes of iRECIST assessment, the first visit showing progression according to RECIST 1.1 will be assigned a visit (overall) response of iUPD, regardless of which factors caused the progression.

At this visit, target and nontarget lesions identified at baseline by RECIST 1.1 will be assessed as usual.

New lesions will be classified as measurable or nonmeasurable, using the same size thresholds and rules as for baseline lesion assessment in RECIST 1.1. From measurable new lesions, up to 5 lesions total (up to 2 per organ), may be selected as New Lesions – Target. The sum of diameters of these lesions will be calculated and kept distinct from the sum of diameters for target lesions at baseline. All other new lesions will be followed qualitatively as New Lesions – Nontarget.

Assessment at the Confirmatory Scans

On the confirmatory scans, the participant will be classified as progression confirmed (with an overall response of iCPD), or as showing persistent unconfirmed progression (with an overall response of iUPD), or as showing disease stability or response (iSD/iPR/iCR).

Confirmation of Progression

Progression is considered confirmed, and the overall response will be iCPD, if ANY of the following occurs:

- Any of the factors that were the basis for the iUPD at the previous visit show worsening
  - For target lesions, worsening is a further increase in the sum of diameters of ≥5 mm, compared to any prior iUPD time point
  - For nontarget lesions, worsening is any significant growth in lesions overall, compared to a prior iUPD time point; this does not have to meet the "unequivocal" standard of RECIST 1.1
  - For new lesions, worsening is any of these:
    - An increase in the new lesion sum of diameters by ≥5 mm from a prior iUPD time point
    - Visible growth of new nontarget lesions
    - The appearance of additional new lesions
- Any new factor appears that would have triggered PD by RECIST 1.1

Persistent iUPD

Progression is considered not confirmed, and the overall response remains iUPD, if:

- None of the progression-confirming factors identified above occurs AND
- The target lesion sum of diameters (initial target lesions) remains above the initial PD threshold (by RECIST 1.1)

Additional scans for confirmation are to be scheduled 4 to 8 weeks from the scans on which iUPD is seen. This may correspond to the next visit in the original visit schedule. The assessment of the subsequent confirmation scan proceeds in an identical manner, with possible outcomes of iCPD, iUPD, and iSD/iPR/iCR.

Resolution of iUPD

Progression is considered not confirmed, and the overall response becomes iSD/iPR/iCR, if:

- None of the progression-confirming factors identified above occurs, AND
- The target lesion sum of diameters (initial target lesions) is not above the disease progression threshold.

The response is classified as iSD or iPR (depending on the sum of diameters of the target lesions), or iCR if all lesions resolve.

In this case, the initial iUPD is considered to be pseudo-progression, and the level of suspicion for progression is "reset." This means that the next visit that shows radiographic progression, whenever it occurs, is again classified as iUPD by iRECIST, and the confirmation process is repeated before a response of iCPD can be assigned.

Management Following the Confirmatory Scan

If repeat scans do not confirm disease progression, and the participant continues to be clinically stable, study intervention is to continue. The regular scan schedule is to be followed. If disease progression is confirmed, participants may be discontinued from study intervention.

NOTE: If a participant has confirmed radiographic progression (iCPD) and clinically meaningful benefit, study intervention may be continued, after consultation with the Sponsor. If study intervention is continued, tumor scans are to be performed after the intervals as outlined in Section 1.3.

Detection of Progression at Visits After Pseudo-progression Resolves

After resolution of pseudo-progression (ie, after iSD/iPR/iCR), another instance of progression (another iUPD) is indicated by any of the following events:

- Target lesions
    - Sum of diameters reaches the PD threshold (≥20% and ≥5 mm increase from nadir) either for the first time, or after resolution of previous pseudo-progression. The nadir is always the smallest sum of diameters seen during the entire study, either before or after an instance of pseudo-progression.
- Nontarget lesions
    - If nontarget lesions have never shown unequivocal progression, their doing so for the first-time results in iUPD.

  - If nontarget lesions have shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of nontarget lesions, taken as a whole.

- New lesions

  - New lesions appear for the first time

  - Additional new lesions appear

  - Previously identified new target lesions show an increase of ≥5 mm in the new lesion sum of diameters, from the nadir value of that sum

  - Previously identified nontarget lesions show any significant growth

If any of the events above occur, the overall response for that visit is iUPD, and the iUPD evaluation process (see Assessment at the Confirmatory Scan above) is repeated. Progression must be confirmed before iCPD can occur.

The decision process on the subsequent iUPD is identical to the iUPD confirmation process for the initial disease progression, with one exception, which can occur if new lesions had occurred at a prior instance of iUPD, had not resolved, then worsened (increase in size or number) leading to the second iUPD. If the new lesion worsening has not resolved at the confirmatory scan then iUPD cannot resolve to iSD or iPR. It will remain iUPD until either a decrease in the new lesion burden allows resolution to iSD or iPR, or until new or worsening cause of progression indicates iCPD.

Additional details about iRECIST are provided in the iRECIST publication [Seymour, L., et al 2017].

10.9 Appendix 9: Abbreviations

Abbreviation	Expanded Term
1L	first-line
AE	adverse event
AEOSI	adverse events of special interest
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
APaT	all participants as treated
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATM	ataxia-telangiectasia mutated
AUC	area under concentration-time curve
β-HCG	β-human chorionic gonadotropin
BICR	blinded independent central review
BID	twice daily
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COVID	corona virus disease
CR	complete response
CrCl	creatinine clearance
CRF	Case Report Form
CRU	clinical research unit
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CCI [redacted]	
CTFG	Clinical Trial Facilitation Group
DBP	diastolic blood pressure
DC	discontinuation
DILI	drug-induced liver injury
DL	dose level
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	duration of response
DSB	double strand breaks
ECG	electrocardiogram
ECI	event of clinical interest
ECOG	Eastern Cooperative Cancer Group
eCRF	electronic Case Report Form
EDC	electronic data collection
eDMC	external data monitoring committee
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EOC	Executive Oversight Committee
CCI [redacted]	
EOT	end of therapy
CCI [redacted]	
FAS	full analysis set
FBR	Future Biomedical Research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FSH	Follicle-stimulating hormone

Abbreviation	Expanded Term
FT4	free thyroxine
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GFR	glomerular filtration rate
GM CSF	granulocyte-macrophage colony-stimulating factor
GMP	Good Manufacturing Practice
HA	health authority
Hb	hemoglobin
HBV	hepatitis B virus
HCV	hepatitis C virus
HDPE	high-density polyethylene
HIV	human immunodeficiency virus
HR	heart rate; hazard ratio
HRD	homologous recombination deficiency
HRD-LOH	homologous recombination deficiency loss of heterozygosity
HRQoL	health-related quality of life
HRRm	homologous recombination repair
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
iCPD	iRECIST confirmed progressive disease
iCR	iRECIST complete response
iCRO	imaging contract research organization
ID	identification
IEC	Independent Ethics Committee
IgG4	immunoglobulin G4
IHC	immunohistochemistry
ILD	interstitial lung disease
IMP	Investigational Medicinal Product
IND	Investigational New Drug
INR	International Normalized Ratio
irAEs	immune-related AEs
IRB	Institutional Review Board
iRECIST	modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics
IRT	interactive response system
iSD	iRECIST stable disease
IUD	intrauterine device
iUPD	iRECIST unconfirmed progressive disease
IUS	intrauterine hormone-releasing system
IV	intravenous
LOH	loss of heterozygosity
MATE	multidrug and toxic compound extrusion
MDS	myelodysplastic syndrome
MRI	magnetic resonance imaging
mRNA	messenger RNA
MSI	microsatellite instability
MTD	maximum tolerated dose
Nab-paclitaxel	nano particle albumin-bound paclitaxel
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events

Abbreviation	Expanded Term
NDA	New Drug Application
NHEJ	non-homologous end-joining
NIMP	Non-investigational Medicinal Product
NOAEL	no observed adverse effect level
NSCLC	non-small cell lung cancer
OATP	organic-anion-transporting polypeptide
OCT	organic cation transporter
ORR	objective response rate
OS	overall survival
OTC	over-the-counter
PARP	polyadenosine 5′ diphosphoribose (polyADP ribose) polymerization
PBPK	physiologically based PK
PD	progressive disease
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
CCI	
PT	prothrombin time
Q3W	every 3 weeks
Q8W	every 8 weeks
Q12W	every 12 weeks
QoL	quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
RMST	Restricted Mean Survival Time
RNA	ribonucleic acid
RR	respiratory rate
SAC	Scientific Advisory Committee
SAE	serious adverse event
SAP	
SBP	systolic blood pressure
SD	stable disease
SGOT	serum glutamic-oxaloacetic aminotransferase
SGPT	serum glutamic-pyruvic aminotransferase
SIM	Site Imaging Manual
SoA	schedule of activities
SOC	standard of care
sSAP	
SSB	single strand break
SUSAR	suspected unexpected serious adverse reaction
T3	triiodothyronine
TFST	time to first subsequent anticancer therapy
TMB	tumor mutation burden;
TMDD	target-mediated drug disposition
TPS	tumor proportion score
TSH	Thyroid-stimulating hormone
TSST	time to second subsequent anticancer therapy
UDS	urine drug screen
ULN	upper limit of normal

Abbreviation	Expanded Term
US	United States
VOP	verification of progression
WOCBP	woman/women of childbearing potential

11 REFERENCES

[Aaronson, N. K., et al 1993]	Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85(5):365-76.	[03Q3QL]
[Ame, J. C., et al 2004]	Ame JC, Spenlehauer C, de Murcia G. The PARP superfamily. Bioessays. 2004 Aug;26(8):882-93.	[04PK3D]
[Arnold, M., et al 2015]	Arnold M, Pandeya N, Byrnes G, Renehan AG, Stevens GA, Ezzati M, et al. Global burden of cancer attributable to high body-mass index in 2012: a population-based study. Lancet Oncol. 2015 Jan;16:36-46.	[04YCZY]
[Bergman, B., et al 1994]	Bergman B, Aaronson NK, Ahmedzai S, Kaasa S, Sullivan M. The EORTC QLQ-LC13: a modular supplement to the EORTC core quality of life questionnaire (QLQ-C30) for use in lung cancer clinical trials. Eur J Cancer 1994;30A(5):635-42.	[00VTZB]
[Bray, F., et al 2018]	Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. In press 2018.	[050XQN]
[Bretz, F., et al 2011]	Bretz F, Posch M, Glimm E, Klinglmueller F, Maurer W, Rohmeyer K. Graphical approaches for multiple comparison procedures using weighted Bonferroni, Simes, or parametric tests. Biom J. 2011 Nov;53(6):894-913.	[045QPF]

[Bryant, H. E., et al 2005]	Bryant HE, Schultz N, Thomas HD, Parker KM, Flower D, Lopez E, et al. Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase [Addendum in Nature 2007;447:346]. Nature 2005;434(7035):913-7.	[03R0MK]
[Castro, E., et al 2015]	Castro E, Goh C, Leongamornlert D, Saunders E, Tymrakiewicz M, Dadaev T, et al. Effect of BRCA mutations on metastatic relapse and cause-specific survival after radical treatment for localised prostate cancer. Eur Urol. 2015;68:186-93.	[04Y3PB]
[Cerami, E., et al 2012]	Cerami E, Gao J, Dogrusoz U, Gross BE, Sumer SO, Aksoy BA, et al. The cBio Cancer Genomics Portal: an open platform for exploring multidimensional cancer genomics data. Cancer Discov. 2012 May;2(5):401-4. Erratum in: Cancer Discov. 2012 Oct;2(10):960.	[054MKK]
[Chemnitz, J. M., et al 2004]	Chemnitz JM, Parry RV, Nichols KE, June CH, Riley JL. SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T cell stimulation, but only receptor ligation prevents T cell activation. J Immunol 2004;173:945-54.	[00VMPN]
[Choi, M., et al 2016]	Choi M, Kipps T, Kurzrock R. ATM mutations in cancer: therapeutic implications. Mol Cancer Ther. 2016 Aug;15(8):1781-91.	[04XXYM]
[Disis, M. L. 2010]	Disis ML. Immune regulation of cancer. J Clin Oncol 2010;28(29):4531-8.	[058SQL]
[Dudley, M. E., et al 2005]	Dudley ME, Wunderlich JR, Yang JC, Sherry RM, Topalian SL, Restifo NP, et al. Adoptive cell transfer therapy following non-myeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma. J Clin Oncol 2005;23(10):2346-57.	[00VMPR]

[Farmer, H., et al 2005]	Farmer H, McCabe N, Lord CJ, Tutt AN, Johnson DA, Richardson TB, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature 2005;434(7035):917-21.	[03R2RR]
[Ferlay, J., et al 2015]	Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015 Mar 1;136(5):E359-86.	[043HC4]
[Fong, Peter C., et al 2009]	Fong PC, Boss DS, Yap TA, Tutt A, Wu P, Mergui-Roelvink M, et al. Inhibition of Poly(ADP-Ribose) polymerase in tumors from BRCA mutation carriers. N Engl J Med 2009;361(2):123-34.	[03R858]
[Francisco, L. M., et al 2010]	Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. Immunol Rev 2010;236:219-42.	[058SQP]
[Gandhi, L., et al 2018]	Gandhi L, Rodriguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med. In press 2018.	[04X2M4]
[Gao, J., et al 2013]	Gao J, Aksoy BA, Dogrusoz U, Dresdner G, Gross B, Sumer SO, et al. Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. Sci Signal. 2013 Apr 2;6(269):pl1.	[054MKL]
[Greenwald, R. J., et al 2005]	Greenwald RJ, Freeman GJ, Sharpe AH. The B7 family revisited. Annu Rev Immunol 2005;23:515-48.	[00VMQL]

[Hay, T., et al 2009]	Hay T, Matthews JR, Pietzka L, Lau A, Cranston A, Nygren AOH, et al. Poly(ADP-ribose) polymerase-1 inhibitor treatment regresses Autochthonous Brca2/p53-mutant mammary tumors in vivo and delays tumor relapse in combination with carboplatin. Cancer Res. 2009 May 1;69(9):3850-5.	[04XYQW]
[Helleday, T. 2011]	Helleday T. The underlying mechanism for the PARP and BRCA synthetic lethality: clearing up the misunderstandings. Mol Oncol. 2011;5:387-93.	[04XFRR]
[Higuchi, T., et al 2015]	Higuchi T, Flies DB, Marjon NA, Mantia-Smaldone G, Ronner L, Gimotty PA, et al. CTLA-4 blockade synergizes therapeutically with PARP inhibition in BRCA1-deficient ovarian cancer. Cancer Immunol Res. 2015 Nov;3(11):1257-68.	[04PK3L]
[Hodi, F. S., et al 2014]	Hodi FS, Ribas A, Daud A, Hamid O, Robert C, Kefford R, et al. Patterns of response in patients with advanced melanoma treated with Pembrolizumab (MK-3475) and evaluation of immune-related response criteria (irRC). J Immunother Cancer. 2014;2(Suppl 3):P103.	[0465RW]
[Huang, J., et al 2015]	Huang J, Wang L, Cong Z, Amoozgar Z, Kiner E, Xing D, et al. The PARP1 inhibitor BMN 673 exhibits immunoregulatory effects in a Brca1(-/-) murine model of ovarian cancer. Biochem Biophys Res Commun. 2015 Aug 7;463(4):551-6.	[04PNNZ]
[Hunder, N. N., et al 2008]	Hunder NN, Wallen H, Cao J, Hendricks DW, Reilly JZ, Rodmyre R, et al. Treatment of metastatic melanoma with autologous CD4+ T cells against NY-ESO-1. N Engl J Med 2008;358(25):2698-703.	[00VMPX]

[Jiao, S., et al 2017]	Jiao S, Xia W, Yamaguchi H, Wei Y, Chen MK, Hsu JM, et al. PARP inhibitor upregulates PD-L1 expression and enhances cancer-associated immunosuppression. Clin Cancer Res. 2017 Jul 15;23(14):3711-20.	[0508FD]
[Kaufman, B., et al 2015]	Kaufman B, Shapira-Frommer R, Schmutzler RK, Audeh MW, Friedlander M, Balmana J, et al. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. J Clin Oncol. 2015 Jan 20;33(3):244-50, appendix 1 p.	[04WDM6]
[Lord, C. J. 2016]	Lord CJ, Ashworth A. BRCAness revisited. Nat Rev Cancer. 2016 Feb;16:110-20.	[04Y6FF]
[Marquard, A. M., et al 2015]	Marquard AM, Eklund AC, Joshi T, Krzystanek M, Favero F, Wang ZC, et al. Pan-cancer analysis of genomic scar signatures associated with homologous recombination deficiency suggests novel indications for existing cancer drugs. Biomark Res. 2015;3:9.	[04Y26G]
[Mateo, J., et al 2015]	Mateo J, Carreira S, Sandhu S, Miranda S, Mossop H, Perez-Lopez R, et al. DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer. N Engl J Med. 2015 Oct 29;373(18):1697-708.	[04FKVF]
[Maurer, W. and Bretz, F. 2013]	Maurer W and Bretz F. Multiple testing in group sequential trials using graphical approaches. Stat Biopharm Res 2013;5(4):311-20.	[03XQVB]
[Miettinen, O. and Nurminen, M. 1985]	Miettinen O and Nurminen M. Comparative analysis of two rates. Stat Med. 1985 Apr-Jun;4(2):213-26.	[04J96G]
[Miettinen, O. and Nurminen, M. 1985a]	Miettinen O and Nurminen M. Comparative analysis of two rates. Stat Med 1985;4:213-26.	[00VMQY]

[Murai, J., et al 2012]	Murai J, Huang SY, Das BB, Renaud A, Zhang Y, Doroshow JH, et al. Trapping of PARP1 and PARP2 by clinical PARP inhibitors. Cancer Res. 2012 Nov 1;72(21):5588-99.	[04XY4G]
[National Cancer Institute 2012]	National Cancer Institute. SEER Program: Cancer statistics: SEER stat fact sheets: lung and bronchus [homepage on the internet]. Bethesda, MD. http://seer.cancer.gov/statfacts/html/lungb.html. [accessed 31-Jan-2013].	[00WB92]
[National Cancer Institute 2016]	National Cancer Institute: SEER Cancer Statistics Review 1975-2014. Table 15.28: Cancer of the lung and bronchus (Invasive) [Internet]. Bethesda, MD: National Cancer Institute; [2016]. Available from: https://seer.cancer.Sogov/csr/1975_2014/results_single/sect_15_table.28.pdf.	[04V3HX]
[National Cancer Institute 2016a]	National Cancer Institute. SEER Stat Fact Sheets: Lung and bronchus cancer [Internet]. Bethesda, MD: National Cancer Institute; 2016. Available from: http://seer.cancer.gov/statfacts/.	[04FJVR]
[National Comprehensive Cancer Network 2015]	National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Non-small cell lung cancer: version 7.2015. Fort Washington, PA: National Comprehensive Cancer Network (NCCN); 2015.	[046XP5]
[Okazaki, T., et al 2001]	Okazaki T, Maeda A, Nishimura H, Kurosaki T, Honjo T. PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine. Proc Natl Acad Sci U S A 2001;98(24):13866-71.	[00VMQ6]

[Parkes, E. E., et al 2017]	Parkes EE, Walker SM, Taggart LE, McCabe N, Knight LA, Wilkinson R, et al. Activation of STING-dependent innate immune signaling by S-phase-specific DNA damage in breast cancer. J Natl Cancer Inst. 2017;109(1):djw199.	[050NS7]
[Parry, R. V., et al 2005]	Parry RV, Chemnitz JM, Frauwirth KA, Lanfranco AR, Braunstein I, Kobayashi SV, et al. CTLA-4 and PD-1 receptors inhibit T-cell activation by distinct mechanisms. Mol Cell Biol 2005;25(21):9543-53.	[00VMQ7]
[Paz-Ares, L., et al 2018]	Paz-Ares L, Luft A, Tafreshi A, Gumus M, Mazieres J, Hermes B, et al. KEYNOTE-407: phase 3 study of carboplatin-paclitaxel/nab-paclitaxel with or without pembrolizumab for metastatic squamous NSCLC. Oral session presented at: 2018 ASCO Annual Meeting; 2018 Jun 1-5; Chicago, IL.	[04Y9H7]
[Peters, S., et al 2012]	Peters S, Adjei AA, Gridelli C, Reck M, Kerr K, Felip E, et al. Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals Oncol 2012;23(Supplement 7):vii56-vii64.	[03NFH6]
[Pickard, A. S., et al 2007]	Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. Health Qual Life Outcomes 2007;5:1-8.	[00W0FM]
[Pisters, K. M. W. and Le Chevalier, T. 2005]	Pisters KMW and Le Chevalier T. Adjuvant chemotherapy in completely resected non-small-cell lung cancer. J Clin Oncol 2005;23(14):3270-8.	[03PXJ8]
[Prakash, R., et al 2015]	Prakash R, Zhang Y, Feng W, Jasin M. Homologous recombination and human health: the roles of BRCA1, BRCA2, and associated proteins. Cold Spring Harb Perspect Biol. 2015;7:a016600.	[04XXMT]

[Rabin, R. and de Charro, F. 2001]	Rabin R and de Charro F. EQ-5D: a measure of health status from the EuroQol group. Ann Med 2001;33:337-43.	[03QM46]
[Ramalingam, S. S., et al 2017]	Ramalingam SS, Blais N, Mazieres J, Reck M, Jones CM, Juhasz E, et al. Randomized, placebo-controlled, phase II study of veliparib in combination with carboplatin and paclitaxel for advanced/metastatic non-small cell lung cancer. Clin Cancer Res. 2017 Apr 15;23(8):1937-44.	[052JGG]
[Reck, M., et al 2016]	Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulop A, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2016 Oct 8. [Epub ahead of print].	[04JNM3]
[Riley, J. L. 2009]	Riley JL. PD-1 signaling in primary T cells. Immunol Rev 2009;229:114-25.	[00VMQ9]
[Robinson, A. G., et al 2021]	Robinson AG, Vicente D, Tafreshi A, Parra HS, Mazieres J, Cicin I, et al. First-line pembrolizumab plus chemotherapy for patients with advanced squamous NSCLC: 3-year follow-up from KEYNOTE-407 [abstract]. Presented at: European Lung Cancer Virtual Congress (ELCC) 2021; 2021 Mar 25-27; [online meeting]. J Thorac Oncol. 2021 Apr;16(4 suppl):S748-9.	[07YHXN]
[Roila, F., et al 2016]	Roila F, Molassiotis A, Herrstedt J, Aapro M, Gralla RJ, Bruera E, et al. 2016 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting and of nausea and vomiting in advanced cancer patients. Ann Oncol. 2016 Sep;27(suppl 5):v119-v133.	[04KSW4]

[Rottenberg, S., et al 2008]	Rottenberg S, Jaspers JE, Kersbergen A, van der Burg E, Nygren AO, Zander SA, et al. High sensitivity of BRCA1-deficient mammary tumors to the PARP inhibitor AZD2281 alone and in combination with platinum drugs. Proc Natl Acad Sci U S A. 2008 Nov 4;105(44):17079-84.	[04XXWS]
[Sandler, A., et al 2006]	Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 2006;355(24):2542-50.	[03QCL5]
[Scagliotti, G. V., et al 2008]	Scagliotti GV, Parikh P, von Pawel J, Biesma B, Vansteenkiste J, Manegold C, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol 2008;26(21):3543-51.	[00VSVP]
[Scagliotti, G., et al 2009]	Scagliotti G, Hanna N, Fossella F, Sugarman K, Blatter J, Peterson P, et al. The differential efficacy of pemetrexed according to NSCLC histology: a review of two Phase III studies. Oncologist. 2009 Mar;14(3):253-63.	[04QN4F]
[Schiller, J. H., et al 2002]	Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 2002;346:92-8.	[00VSVV]
[Seymour, L., et al 2017]	Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekar S, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol. 2017 Mar;18(3):e143-52.	[04P9RV]

[Sheppard, K-A, et al 2004]	Sheppard K-A, Fitz LJ, Lee JM, Benander C, George JA, Wooters J, et al. PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3zeta signalosome and downstream signaling to PKCtheta. FEBS Lett. 2004;574:37-41.	[00VMQC]
[Smith, T. J., et al 2015]	Smith TJ, Bohlke K, Lyman GH, Carson KR, Crawford J, Cross SJ, et al. Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol. 2015 Oct 1;33(28):3199-212.	[04KHR8]
[Socinski, Mark A., et al 2012]	Socinski MA, Bondarenko I, Karaseva NA, Makhson AM, Vynnychenko I, Okamoto I, et al. Weekly nab-Paclitaxel in Combination With Carboplatin Versus Solvent-Based Paclitaxel Plus Carboplatin as First-Line Therapy in Patients With Advanced Non-Small-Cell Lung Cancer: Final Results of a Phase III Trial. J Clin Oncol 2012;30:2055-62.	[03NGVX]
[Thatcher, N., et al 2015]	Thatcher N, Hirsch FR, Luft AV, Szczesna A, Ciuleanu TE, Dediu M, et al. Necitumumab plus gemcitabine and cisplatin versus gemcitabine and cisplatin alone as first-line therapy in patients with stage IV squamous non-small-cell lung cancer (SQUIRE): an open-label, randomised, controlled phase 3 trial. Lancet Oncol. 2015 Jul;16(7):763-74.	[04C5NH]
[Tutt, A., et al 2010]	Tutt A, Robson M, Garber JE, Domchek SM, Audeh MW, Weitzel JN, et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: a proof-of-concept trial. Lancet. 2010 Jul 24;376:235-44.	[04Y07D]

[Watkins, J. A., et al 2014]	Watkins JA, Irshad S, Grigoriadis A, Tutt ANJ. Genomic scars as biomarkers of homologous recombination deficiency and drug response in breast and ovarian cancers. Breast Cancer Res. 2014 Jun 3;16:211.	[04XVNB]
[Wolchok, J. D., et al 2009]	Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, LebbéC, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 2009;15(23):7412-20.	[00VMNZ]
[Zhang, X., et al 2004]	Zhang X, Schwartz J-CD, Guo X, Bhatia S, Cao E, Chen L, et al. Structural and functional analysis of the costimulatory receptor programmed death-1. Immunity 2004;20:337-47.	[00VMQJ]