Official Protocol Title:	A Phase 3 Study of Pembrolizumab in Combination with Pemetrexed/Platinum (Carboplatin or Cisplatin) Followed by Pembrolizumab and Maintenance Olaparib vs Maintenance Pemetrexed in the First-Line Treatment of Participants with Metastatic Non-squamous Non-Small-Cell Lung Cancer (NSCLC)
NCT number:	NCT03976323
Document Date:	17-OCT-2024

TITLE PAGE

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Protocol Title: A Phase 3 Study of Pembrolizumab in Combination with Pemetrexed/Platinum (Carboplatin or Cisplatin) Followed by Pembrolizumab and Maintenance Olaparib vs Maintenance Pemetrexed in the First-Line Treatment of Participants with Metastatic Nonsquamous Non-Small-Cell Lung Cancer (NSCLC)

Protocol Number: 006-08

Compound Number: MK-7339

Sponsor Name: Merck Sharp & Dohme LLC (hereafter called the Sponsor or MSD)

Legal Registered Address:

126 East Lincoln Avenue
P.O. Box 2000
Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

NCT	3976323
EU CT	2023-509774-40
EudraCT	2018-004720-11
JRCT	Not Applicable
WHO/UTN	U1111-1300-7107
IND	140819

Approval Date: 17 October 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 08	17-OCT-2024	To rectify the incorrect standard text mistakenly added in last amendment.
Protocol Amendment 07	27-MAY-2024	At the final analysis, the pembrolizumab plus olaparib arm did not meet the primary endpoint of OS. In addition, at the protocol prespecified final PFS analysis at Interim Analysis 2 that occurred on PFS was not statistically significant compared with the control arm. The study will remain open so ongoing participants will have continued access to olaparib, pemetrexed and pembrolizumab if they qualify per protocol or until transferred to an extension study, if applicable.
Protocol Amendment 06	07-OCT-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	23-DEC-2021	The protocol was amended to update the assumptions and timing of the analyses in the SAP to allow reasonable intervals between IAs and FA, and sufficient duration of follow-up based on updated enrollment period and the long-term survival data from the reference study KEYNOTE-189.
Protocol Amendment 04	10-MAR-2021	Add back the clarification sentence for inclusion criteria applicable only to maintenance phase, update Section 6.6.3 to align with pembrolizumab USPI, and correct reference in Table 13 to link DL header with Table 11 instead of Table 10.
Protocol Amendment 03	04-DEC-2020	Updated the RECIST and iRECIST language to make the study intervention decision process following disease progression consistent throughout the protocol, updated language to improve clarity and decrease redundancy throughout the protocol.

Document	Date of Issue	Overall Rationale
Protocol Amendment 02	29-AUG-2019	Further defined inclusion criteria #5 to ensure adequate tissue collection prior to patient enrollment, changing collection times of plasma and serum biomarkers, and clarifying 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: 08

Overall Rationale for the Amendment:

To rectify the incorrect standard text mistakenly added in last amendment.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
Section 4.2.2 Rationale for the Use of an Active Comparator	Removed text on using the C-SSRS.	To rectify the incorrect standard text mistakenly added in last amendment.

Section Number and Name	Description of Change	Brief Rationale
Additional Changes		
Throughout document	Minor administrative, formatting, grammatical, and/or typographical changes were made throughout the document.	To ensure clarity and accurate interpretation of the intent of the protocol.
Title Page	Added study NCT number.	To provide additional study identification number.
Section 1.3.2, Maintenance Phase - Schedule of Assessments	Added information regarding biomarker collection through EOT visit.	To provide information regarding last required biomarker collection.
Section 1.3.3, End-of-Treatment and Long-term Follow-up - Schedule of Assessments	Notes column text added to highlight that ePRO and efficacy assessments are no longer required per Amendment 07.	To ensure assessment changes are noted.
	Added that participants in follow-up not eligible for second course treatment are to be discontinued.	To provide guidance on participants to be discontinued.
	Removed collection of prior/concomitant medications in Long-term Follow-up.	To remove unnecessary collection.
	Added note that survival status assessments will not be collected past EOT.	To instruct that survival status assessments are not to be done after EOT.
	Shortened arrow in survival status row to only include EOT.	See rationale for survival status above.
	Added note that efficacy assessments will not be collected past EOT.	To instruct that efficacy assessments are not to be done after EOT.
	Removed ePRO assessments will not be collected past EOT and added note on this.	To instruct that ePRO assessments are not to be done after EOT.
	Removed biomarker collection after EOT.	To stop unneeded biomarker collections.
	Footnotes updated to reflect collections that are not needed past EOT.	To align with SoA.

Section Number and Name	Description of Change	Brief Rationale
Section 1.3.4, Second Course Phase	Removed collection of new anticancer treatment at imaging and survival follow-ups.	To instruct that these assessments are not to be done after EOT.
	Added note that vital status assessments will not be collected past EOT.	See rationale for Section 1.3.3 for vital status.
	Added note that efficacy assessments will not be collected past EOT.	See rationale for Section 1.3.3 for efficacy assessments.
	Footnote for imaging updated to reflect collections that are not needed past EOT.	To align with SoA.
Section 4.2.1.6.1, Planned Genetic Analysis	Section deleted.	This text is not needed since there is no requirement for any other genetic analyses than the one explained in Section 4.2.1.6.
Section 4.2.2, Rationale for the Use of an Active Comparator	Removed text on suicidal ideation.	See rationale for primary amendment.
Section 5.2, Exclusion Criteria	Deleted exclusion criterion #16.	This was added in error in the last amendment but was deleted in this amendment as it is redundant to existing criteria.
	Added reference to Section 6.5 to exclusion criterion #21.	To provide reference for information on COVID-19 vaccinations.
	Deleted exclusion criterion #27.	See rationale for Sec 5.2, deletion of exclusion criterion #16.
	Deleted exclusion criterion #28.	See rationale for Sec 5.2, deletion of exclusion criterion #16.
	Deleted exclusion criterion #29.	See rationale for Sec 5.2, deletion of exclusion criterion #16.
	Deleted exclusion criterion # 31.	See rationale for Sec 5.2, deletion of exclusion criterion #16.
	Deleted exclusion criterion #33.	See rationale for Sec 5.2, deletion of exclusion criterion #16.
	Deleted exclusion criterion #34.	See rationale for Sec 5.2, deletion of exclusion criterion #16.
	Deleted exclusion criterion #35.	See rationale for Sec 5.2, deletion of exclusion criterion #16.
	Deleted exclusion criterion #36.	See rationale for Sec 5.2, deletion of exclusion criterion #16.
	Deleted exclusion criterion #37.	See rationale for Sec 5.2, deletion of exclusion criterion #16.
	Deleted exclusion criterion #38.	See rationale for Sec 5.2, deletion of exclusion criterion #16.
	Deleted exclusion criterion #39.	See rationale for Sec 5.2, deletion of exclusion criterion #16.
	Deleted exclusion criterion #40.	See rationale for Sec 5.2, deletion of exclusion criterion #16.
	Deleted exclusion criterion #41.	See rationale for Sec 5.2, deletion of exclusion criterion #16.

Section Number and Name	Description of Change	Brief Rationale
	Deleted exclusion criterion #48.	See rationale for Sec 5.2, deletion of exclusion criterion #16.
	Deleted exclusion criterion #49.	See rationale for Sec 5.2, deletion of exclusion criterion #16.
Section 8.1.1, Informed Consent	Moved and revised text regarding obtaining and documenting informed consent from Section 8.1.1.1.	To ensure information in this section is applicable for all informed consents.
Section 8.1.1.1, General Informed Consent	Moved text regarding obtaining and documenting informed consent from Section 8.1.1.1.	See rationale for Section 8.1.1.
Section 8.2.1.3, End-of-treatment and Follow-up Tumor Imaging	Added that participants should continue with imaging per local standard of care after the EOT Visit.	To align with SoA.
Section 8.3.4.1, Bone Marrow or Blood Cytogenic Samples	Removed text regarding collection of blood samples.	See rationale for primary amendment item.
Section 8.4.3, Follow-up of AE, SAE, and Other Reportable Safety Event Information	Removed reporting for nonserious AEs.	To be consistent with regulatory reporting requirements as reporting on nonserious AEs is not required.
Section 8.4.7, Events of Clinical Interest	Reverted to original text.	See rationale for primary amendment item.
Section 8.8.1, Planned Genetic Analysis Sample Collection	Deleted redundant text.	See rationale for Section 8.1.1.1.
Section 8.11.6.3, Survival Follow-up Contacts	Removed text requiring participants to return for a Day 14 poststudy visit.	See rationale for primary amendment item.
Section 10.1.1, Code of Conduct for Clinical Trials	Reverted to original text.	See rationale for primary amendment item.
Section 10.1.7, Compliance with Law, Audit, and Debarment	Reverted to original text.	See rationale for primary amendment item.
Section 10.1.8, Data Quality Assurance	Added example of EU CTR retention period.	To address HA requirement.
Section 10.1.10, Study and Site Closure	Added that participants in survival follow-up will be discontinued from the study.	To clarify that participants in survival follow-up will be discontinued from the study.
	Added that participants in follow-up not eligible for second course treatment are to be discontinued.	See rationale for Section 1.3.3, End of Treatment and Long-term Follow-up - Schedule of Assessments for second course treatment discontinuation.
Section 10.4, Appendix 4: Medical Device and Drug–Device Combination Products: Product Quality Complaints/Malfunctions: Definitions, Recording, and Follow-up	Removed text in this section and updated it as not applicable.	See rationale for primary amendment item...

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3 Study of Pembrolizumab in Combination with Pemetrexed/Platinum (Carboplatin or Cisplatin) Followed by Pembrolizumab and Maintenance Olaparib vs Maintenance Pemetrexed in the First-Line Treatment of Participants with Metastatic Nonsquamous Non-Small-Cell Lung Cancer (NSCLC)

Short Title: Phase 3 Study of Pembrolizumab with Maintenance Olaparib or Maintenance Pemetrexed in 1L Metastatic Nonsquamous NSCLC

Acronym: Not applicable

Hypotheses, Objectives, and Endpoints:

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

In male and female participants with Stage IV nonsquamous non–small-cell lung cancer (NSCLC) with stable disease (SD), partial response (PR), or complete response (CR) following induction treatment with pembrolizumab combined with pemetrexed and platinum (carboplatin or cisplatin):

Primary Objective	Primary Endpoint
• Objective: To compare pembrolizumab plus maintenance olaparib with pembrolizumab plus maintenance pemetrexed with respect to progression-free survival (PFS) assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 by blinded independent central review (BICR). • Hypothesis (H1): Pembrolizumab plus maintenance olaparib is superior to pembrolizumab plus maintenance pemetrexed 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 maintenance pemetrexed with respect to overall survival (OS). • Hypothesis (H2): Pembrolizumab plus maintenance olaparib is superior to pembrolizumab plus maintenance pemetrexed 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 maintenance pemetrexed.	• 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 with pembrolizumab plus pemetrexed.	• Change from baseline (at randomization) and the 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 (Core 30 [C30]/Items 29 and 30) Cough (LC13/Item 1) Chest pain (LC13/Item 10) Dyspnea (C30/Item 8) Physical functioning (C30/Items 1 through 5)

Overall Design:

Study Phase	Phase 3
Primary Purpose	Treatment
Indication	Non-small cell lung cancer
Population	Adult participants with treatment-naïve, Stage IV nonsquamous NSCLC
Study Type	Interventional
Intervention Model	Parallel This is a multi site study.
Type of Control	Active Control Without Placebo
Study Blinding	Unblinded open-label
Blinding Roles	No blinding
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 1005 participants were enrolled into the Induction Phase, with approximately 672 participants required for randomization into the Maintenance Phase, as described in Section 9.9.

Intervention Groups and Duration:

Induction Phase (4 Cycles)

All participants will receive the study intervention (pembrolizumab plus pemetrexed/platinum) in a nonrandomized Induction Phase:

- Pembrolizumab 200 mg intravenous (IV) every 3 weeks (Q3W) on Day 1 (Cycles 1 through 4)
- Pemetrexed 500 mg/m^2 IV Q3W on Day 1 (Cycles 1 through 4)
- Platinum chemotherapy, investigator's choice: carboplatin or cisplatin
    - Carboplatin titrated to an area under the plasma drug concentration-time curve of 5 mg/mL/min IV Q3W on Day 1 (Cycles 1 through 4)

      OR

- Cisplatin 75 mg/m2 IV Q3W on Day 1 (Cycles 1 through 4)

Maintenance Phase (Up to 31 Cycles of Pembrolizumab Intervention)

Participants with a PR or CR or with SD who meet the eligibility criteria after the fourth cycle of the Induction Phase will be randomly assigned to pembrolizumab plus maintenance olaparib or pembrolizumab plus maintenance pemetrexed.

- Pembrolizumab 200 mg IV Q3W will continue for a maximum of 31 cycles, or until specific discontinuation criteria are met (Section 7.1).
- Olaparib 300 mg twice daily will continue, until specific discontinuation criteria are met (Section 7.1).
- Pemetrexed 500 mg/m^2 IV Q3W 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 maintenance olaparib or pemetrexed until specific discontinuation criteria are met (Section 7.1). If maintenance olaparib or pemetrexed 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.

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 60 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	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use
Pembrolizumab	Active	25 mg/mL	200 mg	IV Infusion	Q3W/Induction and Maintenance Phases for a maximum of 35 cycles	Test Product
Carboplatin	Chemo -therapy	10 mg/mL[a]	AUC 5 mg/mL/min	IV Infusion	Q3W/Induction Phase (4 cycles)	Background Treatment
Cisplatin	Chemo -therapy	1 mg/mL	75 mg/m^2	IV Infusion	Q3W/Induction Phase (4 cycles)	Background Treatment
Pemetrexed	Chemo -therapy	500 mg[b]	500 mg/m^2	IV Infusion	Q3W/Induction and Maintenance Phases	Background Treatment
Olaparib	Active	150 mg, 100 mg[c]	300 mg BID	Oral	BID/ Maintenance Phase	Test Product

Abbreviations: BID = twice daily; IM = intramuscular; IV = intravenous(ly); MASCC = Multinational Association of Supportive Care in Cancer; Q3W = every 3 weeks.

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

b All participants taking pemetrexed should receive the appropriate supplementation of vitamin B12, folic acid, and corticosteroid prophylaxis, as listed below (or as per local label):

- Folic acid 350-1000 µg PO: at least 5 doses of folic acid must be taken during the 7 days preceding the first dose of pemetrexed, and folic acid dosing must continue during the full course of therapy and for 21 days after the last dose of pemetrexed.
- Vitamin B12 1000 µg IM injection in the week preceding the first dose of pemetrexed and once every 3 cycles thereafter. Subsequent vitamin B12 injections may be given on the same day as pemetrexed administration.
- Dexamethasone prophylaxis 4 mg, PO BID (or equivalent). Taken the day before, day of, and day after pemetrexed administration. Higher or additional doses are permitted for antiemetic prophylaxis during Cycles 1 through 4, but not to exceed the doses in the MASCC guidelines (Section 8.1.8.1.6).

c 300-mg dose will be made up of 2 × 150 mg tablets; 100 mg tablets are provided for dose reductions, as outlined in Section 6.6.2.

Total Number of Intervention Groups/Arms	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-specific contact. Induction Phase: After the Screening Phase , participants will enter the nonrandomized Induction Phase and will receive 4 cycles of assigned study intervention for approximately 3 months: pembrolizumab in combination with pemetrexed and either carboplatin or cisplatin. Maintenance Phase: Only participants who have received 4 cycles of study intervention during the Induction Phase, have at least 1 evaluable imaging time point during the Induction Phase, have no imaging visit with an overall response of progressive disease (as verified by BICR), are clinically stable, and meet eligibility criteria to participate in the Maintenance Phase will be randomized to receive pembrolizumab with maintenance olaparib, or pembrolizumab with maintenance pemetrexed. Participants entering the Maintenance Phase will receive randomly assigned study intervention until centrally verified disease progression is radiographically documented per RECIST 1.1 (verified by BICR) and, when clinically appropriate, confirmed by the site per modified RECIST 1.1, for immune-related therapeutics, 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 study intervention. 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 or pemetrexed until specific discontinuation criteria are met (Section 7.1). If maintenance olaparib or pemetrexed 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, 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 centrally verified disease progression is documented radiographically per RECIST 1.1, initiating a nonstudy cancer treatment, withdrawing consent, becoming lost to follow-up, or EOS. All randomized participants will be followed by telephone call every 3 months for OS until death, withdrawal of consent, or the EOS. Each randomized participant is 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).

Study Governance Committees:

Executive Oversight Committee	Yes
Data Monitoring Committee	Yes
Clinical Adjudication Committee	No
Steering Committee	Yes

Study governance considerations are outlined in the protocol Appendix 1.

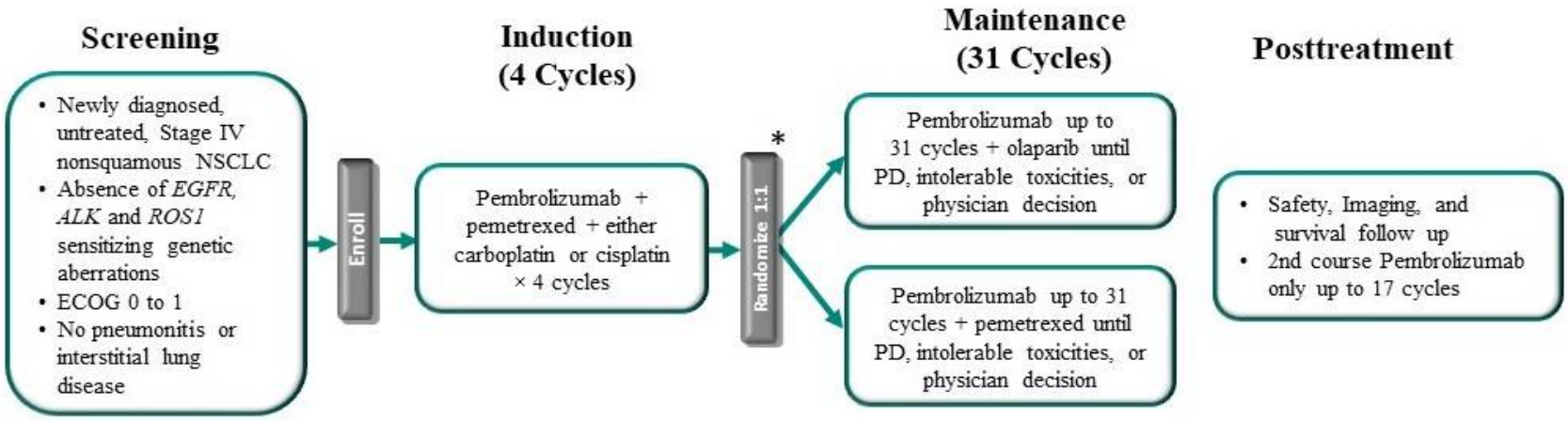
Study Accepts Healthy Participants: No

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

1.2 Schema

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

Figure 1 Study Design Overview



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

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

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 pemetrexed, until specific discontinuation criteria are met (Section 7.1). If maintenance olaparib or maintenance pemetrexed 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).

Imaging should be performed within 28 days of entering Maintenance Phase.

In the Posttreatment Phase, participants who discontinue study intervention for reasons other than PD will move into the follow-up phase (Section 8.12.6). All participants may be eligible for up to 1 additional year (17 cycles) of pembrolizumab treatment if they progress after having received 35 cycles of pembrolizumab and with SD, PR, or CR in either arm (Section 8.11.5). The second course of pembrolizumab is optional.

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 No.		**1**	**2**	**3**	**4**	
Day (in Cycle)		**1**	**1**	**1**	**1**	
Visit Number/Title	**1**	**2**	**3**	**4**	**5**	
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 FBR ICF.
Inclusion/Exclusion Criteria	X					
Participant Identification Card	X	X				At the time of Visit 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	X	X	X	X	Include blood transfusions during review of concomitant medications
NSCLC Disease Details	X					
TEA	X					The investigator must complete this form in eCRF and provide rationale to document the choice of platinum chemotherapy (carboplatin or cisplatin) prior to randomization
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.
Administration of Study Intervention						
Pembrolizumab		X	X	X	X	200 mg Q3W
Pemetrexed		X	X	X	X	500 mg/m^2 Q3W; see Section 4.3.3.3 regarding B12, folate, and dexamethasone supplementation with pemetrexed administration.
Carboplatin or Cisplatin		X	X	X	X	Carboplatin: AUC 5 mg/ml/min IV Q3W or Cisplatin: 75 mg/m^2 IV Q3W.

Study Period	**Screening Phase**	**Induction Phase (3-week Cycles)[a]**				**Notes**
Cycle No.		**1**	**2**	**3**	**4**	
Day (in Cycle)		**1**	**1**	**1**	**1**	
Visit Number/Title	**1**	**2**	**3**	**4**	**5**	
Scheduling Window (Days):	**-28 to -1**	**+ 3**	**± 3**	**± 3**	**± 3**	
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.
Efficacy Procedures[b]						
CT/MRI Imaging of Chest, Abdomen, and Pelvis	X		X		X[d]	Screening images are to be captured within 28 days of first dose. The first on study imaging visit has a window of +7 days. All other imaging visits have a visit window of ±7 days. During Induction Phase, images will be captured Q6W from date of 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[c]	X		X		X	
Safety Procedures						
AE Monitoring	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 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.
Complete Physical Examination (Including Height)	X					Height at screening only
Directed Physical Examination		X	X	X	X	Directed physical examination performed as clinically indicated prior to intervention administration.
Weight	X	X	X	X	X	
Vital Signs (heart rate, DBP, SBP, RR, temperature)	X	X	X	X	X	Assessments performed prior to intervention administration.
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 No.		**1**	**2**	**3**	**4**	
Day (in Cycle)		**1**	**1**	**1**	**1**	
Visit Number/Title	**1**	**2**	**3**	**4**	**5**	
Scheduling Window (Days):	**-28 to -1**	**+ 3**	**± 3**	**± 3**	**± 3**	
Hematology	X	X	X	X	X	Screening samples to be collected within 10 days prior to the first dose of study intervention. On treatment samples to be collected prior to administration of study intervention, which can be conducted 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		Tests performed every other cycle. Participants may be dosed while thyroid function tests are pending.
HBV, HCV, and HIV Testing	X					Testing at screening only required if mandated by local health authority or institutional guidelines. Refer 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 first dose of study intervention. Testing during Induction Phase must be conducted as clinically indicated and per local regulations where applicable. Serum test is only required if urine test is positive or not evaluable. More frequent pregnancy testing may be indicated, as dictated by local regulations.
PT or INR and aPTT	X					Screening samples collected within 10 days of intervention initiation. PT or INR and aPTT should be monitored more closely in participants receiving anticoagulant therapy during intervention and safety Follow-up Phase.
CrCl Calculation	X	X	X	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.
ECOG Performance Status	X	X	X	X	X	Screening assessment is to be performed within 7 days prior to administration of study intervention.
Biomarkers						
Blood for Genetic Analysis		X				To be collected prior to administration of study intervention.
Blood for RNA Analysis		X		X		To be collected prior to administration of study intervention. These collections are to correspond to the imaging time points.
Blood for Plasma Biomarker Analysis		X		X		To be collected prior to administration of study intervention. These collections are to correspond to the imaging time points.
Blood for Serum Biomarker Analysis		X		X		To be collected prior to administration of study intervention. These collections are to correspond to the imaging time points.
Blood for ctDNA		X		X		To be collected prior to administration of study intervention. These collections are to correspond to the imaging time points.

Study Period	**Screening Phase**	**Induction Phase (3-week Cycles)[a]**				**Notes**
Cycle No.		**1**	**2**	**3**	**4**	
Day (in Cycle)		**1**	**1**	**1**	**1**	
Visit Number/Title	**1**	**2**	**3**	**4**	**5**	
Scheduling Window (Days):	**-28 to -1**	**+ 3**	**± 3**	**± 3**	**± 3**	

Abbreviations: AE = adverse event; aPTT = activated partial thromboplastin time; AUC = area under the concentration-time curve; CrCl = creatinine clearance; ctDNA = circulating tumor DNA; DBP = diastolic blood pressure; DC = discontinue/discontinuation; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end-of-treatment; FBR = Future Biomedical Research; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; 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; PT = prothrombin time; Q3W = every 3 weeks; Q6W = every 6 weeks; RR = respiratory rate; SAE = serious adverse event; SBP = systolic blood pressure; TEA = Treatment Eligibility Assessment; 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 Visit; refer to Section 1.3.3.

b Imaging should continue to be performed until PD is centrally verified, the start of new anticancer treatment, withdrawal of consent, pregnancy, or death, whichever occurs first.

c 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.

d Imaging must occur at Week 12. Imaging should be performed within 28 days of entering the Maintenance Phase.

Note: For country-specific requirements see Appendix 7.

1.3.2 Maintenance Phase

Study Period	Post-induction/ Pre-randomization Visit[a]	Maintenance Phase (3-week Cycles)[b]	Notes
Cycle	**-**	**1+**	As of Amendment 07, tumor imaging will be assessed locally based on the site's standard of care imaging schedule. Biomarkers will only be collected through the EOT visit (see Section 1.3.3). Also, participants who are still on study treatment will no longer require ePRO assessments.
Day (in Cycle)	**-**	**1**	
Visit Number/Title	**6**	**7+**	
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 the Sponsor. Participants with PD must be excluded from the Maintenance Phase and should enter 30-day 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
Administration of Study Intervention			
Olaparib		X	To initiate maintenance olaparib, creatinine clearance (CrCl) must be ≥51 mL/min. Only for participants randomized to olaparib. 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.
Olaparib Container Return		X	Only for participants randomized to olaparib.
Pembrolizumab		X	Participants will need to return to the site Q3W for dosing at 200mg 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.
Pemetrexed		X	Only for participants randomized to pemetrexed. 500 mg/m^2; participants will need to return to the site Q3W for dosing until progression of disease, intolerable toxicities, or physician decision. Maintenance pemetrexed to start at least 4 weeks and no later than 6 weeks from Cycle 4, Day 1 of study medication in the Induction Phase. See Section 4.3.3.3 regarding B12, folate, and dexamethasone supplementation with pemetrexed administration.

Study Period	**Post-induction/ Pre-randomization Visit[a]**	**Maintenance Phase (3-week Cycles)[b]**	**Notes**
Cycle	**-**	**1+**	As of Amendment 07, tumor imaging will be assessed locally based on the site's standard of care imaging schedule. Biomarkers will only be collected through the EOT visit (see Section 1.3.3). Also, participants who are still on study treatment will no longer require ePRO assessments.
Day (in Cycle)	**-**	**1**	
Visit Number/Title	**6**	**7+**	
Scheduling Window (Days):	**± 3**	**± 3**	
Efficacy Procedures			Imaging should continue to be performed until PD is centrally 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 centrally 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 Maintenance Phase, images will be captured Q6W for the first 60 weeks from the date of randomization, followed by Q9W thereafter until centrally verified 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 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 occurs first. New diagnosis of MDS or AML should be reported throughout the study including the follow-up phase.
Directed Physical Examination	X	X	Directed physical examination performed as clinically indicated prior to study intervention administration.
Weight	X	X	
Vital Signs (heart rate, DBP, SBP, RR, Temperature)	X	X	Assessments performed prior to study intervention administration.
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. Thyroid function tests at Cycle 1 followed by every other cycle through Cycle 31. Participants may be dosed while thyroid function tests are pending.
Chemistry	X	X	
Thyroid Function Tests (Total T3 or Free T3, FT4, TSH)		X	

Study Period	**Post-induction/ Pre-randomization Visit[a]**	**Maintenance Phase (3-week Cycles)[b]**	**Notes**
Cycle	**-**	**1+**	As of Amendment 07, tumor imaging will be assessed locally based on the site's standard of care imaging schedule. Biomarkers will only be collected through the EOT visit (see Section 1.3.3). Also, participants who are still on study treatment will no longer require ePRO assessments.
Day (in Cycle)	**-**	**1**	
Visit Number/Title	**6**	**7+**	
Scheduling Window (Days):	**± 3**	**± 3**	
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.
CrCl Calculation	X	X	CrCl is calculated using the Cockcroft-Gault formula (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. To initiate maintenance pemetrexed arm, CrCl must be ≥45 mL/min.
ECOG Performance Status	X	X	ECOG performance status will be evaluated prior to first administration of study intervention (within 7 days) and before administration of study intervention in each cycle.
Patient-Reported Outcomes			
EORTC QLQ-C30		CCI [redacted]	
EORTC QLQ-LC13			
EQ-5D-5L			
Biomarkers			
Blood for ctDNA	X	X	ctDNA will be collected at the Post-induction/Pre-Randomization Visit, Cycle 1, Day 1, and Q6W for the first 60 weeks from the date of randomization, followed by Q9W thereafter, until disease progression, or the start of new anticancer treatment. These collections are to correspond to the imaging time points.
Blood for RNA analysis	X	X	To be collected at Post-induction/Pre-Randomization Visit, Cycle 1, Day 1 and Q6W for the first 60 weeks from the date of randomization, followed by Q9W thereafter, until centrally verified disease progression, or the start of new anticancer treatment. These collections are to correspond to the imaging time points.
Blood for plasma biomarker analysis	X	X	To be collected at Post-induction/Pre-Randomization Visit, Cycle 1, Day 1 and Q6W for the first 60 weeks from the date of randomization, followed by Q9W thereafter, until centrally verified disease progression, or the start of new anticancer treatment. These collections are to correspond to the imaging time points.
Blood for serum biomarker analysis	X	X	To be collected at Post-induction/Pre-Randomization Visit, Cycle 1, Day 1 and Q6W for the first 60 weeks from the date of randomization, followed by Q9W thereafter, until centrally verified disease progression, or the start of new anticancer treatment. These collections are to correspond to the imaging time points.

Study Period	Post-induction/ Pre-randomization Visit[a]	Maintenance Phase (3-week Cycles)[b]	Notes
Cycle	**-**	**1+**	As of Amendment 07, tumor imaging will be assessed locally based on the site's standard of care imaging schedule. Biomarkers will only be collected through the EOT visit (see Section 1.3.3). Also, participants who are still on study treatment will no longer require ePRO assessments.
Day (in Cycle)	**-**	**1**	
Visit Number/Title	**6**	**7+**	
Scheduling Window (Days):	**± 3**	**± 3**	

Abbreviations: AE = adverse event; AUC = area under the curve; BID = twice daily; CrCl = creatinine clearance; DBP = diastolic blood pressure; DC = discontinue/discontinuation; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Core 30; EORTC QLQ-LC13 = European Organisation for Research and Treatment of Cancer Quality of Life Cancer Quality of Life Questionnaire Lung Cancer 13; EOT = end-of-treatment; ePRO = electronic patient-reported outcome; EQ-5D-5L = European Quality of Life Five-dimension Five-level Scale Questionnaire; PD = progressive disease; PRO = patient-reported outcome; Q3W = every 3 weeks; Q6W = every 6 weeks; Q9W = every 9 weeks; Q12W = every 12 weeks; RNA = ribonucleic acid; RR = respiratory rate; SAE = serious adverse event; SBP = systolic blood pressure; 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 intervention 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**
Study Period	**Safety Follow-up**	**EOT**	**Long-Term Follow-up**			**Effective with Amendment 7, ePROs and all efficacy follow-up will continue to be collected at the EOT visits but will not be collected during long-term follow-up.**
Visit Number/Title	**Safety**	**DC**	**Safety[a]**	**Follow-Up[a,b]**	**Survival Follow-up[c]**	**Effective with Amendment 08, participants who are in follow-up and did not receive 35 doses of pembrolizumab during the initial treatment period and/or are not eligible for second course treatment should be discontinued.**
Scheduling Window (Days):	**30 Days After Last Dose (+ 7 days)**	**At Time of DC (± 3 days)**	**30 Days After Last Dose (+ 7 days)**	**Q6W up to 60 weeks Post-randomization, thereafter Q9W (± 7 days)**	**Q12W (± 14 days)**	
Administrative Procedures						
Prior/concomitant medication review	X	X	X			Include blood transfusions during review of concomitant medication.
Survival status		◄——►				Continued after centrally verified PD or start of new anticancer treatment through the EOT Visit. In addition, upon Sponsor request, participants may be contacted for survival status at any time during the study.
Efficacy Procedures						Imaging should continue to be performed until PD is centrally verified, the start of new anticancer treatment, withdrawal of consent, pregnancy, or death, whichever occurs first, through the EOT Visit.

	Participants Who Receive Induction Phase Treatment and are Not Randomized	**Participants Randomized to Maintenance Phase**				**Notes** **Effective with Amendment 7, ePROs and all efficacy follow-up will continue to be collected at the EOT visits but will not be collected during long-term follow-up.** **Effective with Amendment 08, participants who are in follow-up and did not receive 35 doses of pembrolizumab during the initial treatment period and/or are not eligible for second course treatment should be discontinued.**
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 up to 60 weeks Post-randomization, thereafter Q9W (± 7 days)**	**Q12W (± 14 days)**	
CT/MRI imaging of chest, abdomen, and pelvis	X[d]	X[d]				All imaging visits have a visit window of ±7 days. Imaging will be captured Q6W for the first 60 weeks from the date of randomization, followed by Q9W thereafter until centrally 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.
MRI of brain[e]	X[d]	X[d]		X		
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 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 occurs first. New diagnosis of MDS or AML should be reported throughout the study including the follow-up phase.

	Participants Who Receive Induction Phase Treatment and are Not Randomized	**Participants Randomized to Maintenance Phase**				**Notes** **Effective with Amendment 7, ePROs and all efficacy follow-up will continue to be collected at the EOT visits but will not be collected during long-term follow-up.** **Effective with Amendment 08, participants who are in follow-up and did not receive 35 doses of pembrolizumab during the initial treatment period and/or are not eligible for second course treatment should be discontinued.**
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 up to 60 weeks Post-randomization, thereafter Q9W (± 7 days)**	**Q12W (± 14 days)**	
Complete physical examination	X	X				
Directed physical examination			X			
Weight	X	X	X			
Vital signs (heart rate, DBP, SBP, RR, temperature)	X	X	X			
12-lead ECG		X				12-lead ECG is to be performed using local standard procedures. Additional ECGs are to be performed, as clinically indicated.
Hematology	X	X	X			
Urinalysis	X		X			
Chemistry	X	X	X			
Thyroid function tests (total T3 or free T3, FT4, TSH)	X	X	X			
Urine pregnancy test (WOCBP only)	X	X	X			Testing during EOT and Long-term Follow-up Phase must be conducted as clinically indicated and per local regulations, where applicable. Serum test is only required if urine test is positive, or not evaluable.

	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**			**Effective with Amendment 7, ePROs and all efficacy follow-up will continue to be collected at the EOT visits but will not be collected during long-term follow-up.** **Effective with Amendment 08, participants who are in follow-up and did not receive 35 doses of pembrolizumab during the initial treatment period and/or are not eligible for second course treatment should be discontinued.**
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 up to 60 weeks Post-randomization, thereafter Q9W (± 7 days)**	**Q12W (± 14 days)**	
CrCl calculation	X	X	X			CrCl is calculated using the Cockcroft-Gault formula (Table 3). As an alternative, CrCl can be determined from a 24-hour urine collection.
ECOG Performance Status	X	X	X			
Patient-Reported Outcomes						
EORTC QLQ-C30		X				Perform ePROs in the order listed in the SoA (ie, EORTC QLQ-C30 first). Effective with Amendment 7, ePROs will continue to be collected at the EOT visit but will not be collected during long-term follow-up.
EORTC QLQ-LC13		X				
EQ-5D-5L		X				
Biomarkers						
Blood for RNA analysis		X				Biomarkers will continue to be collected at the EOT visit but will not be collected during long-term follow-up. Once centrally verified PD occurs, the final biomarker samples are collected. If participant discontinues due to PD, biomarker samples will be collected at EOT visit.
Blood for plasma biomarker analysis		X				
Blood for serum biomarker analysis		X				
Blood for ctDNA		X				

	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**			**Effective with Amendment 7, ePROs and all efficacy follow-up will continue to be collected at the EOT visits but will not be collected during long-term follow-up.** **Effective with Amendment 08, participants who are in follow-up and did not receive 35 doses of pembrolizumab during the initial treatment period and/or are not eligible for second course treatment should be discontinued.**
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 up to 60 weeks Post-randomization, thereafter Q9W (± 7 days)**	**Q12W (± 14 days)**	

Abbreviations: AE = adverse event; DBP = diastolic blood pressure; DC = discontinue/discontinuation; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Core 30; EORTC QLQ-LC13 = European Organisation for Research and Treatment of Cancer Quality of Life; EOS = end of study; EOT = end-of-treatment; EQ-5D-5L = European Quality of Life Five-dimension Five-level Scale Questionnaire; PD = progressive disease; PRO = patient reported outcome; Q9W = every 9 weeks; Q12W = every 12 weeks; RR = respiratory rate; SAE = serious adverse event; SBP = systolic blood pressure; 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 the Long-term Follow-up Phase imaging. For participants who DC for reasons other than centrally verified PD, imaging continues until centrally verified PD or initiation of a new antineoplastic therapy through the EOT Visit.

c Participants who either DC for centrally verified PD or start a new anticancer therapy will enter the Survival Follow-up Phase and will be monitored approximately every 12 weeks (84 ± 14 days) by telephone call to assess for survival status until death, withdrawal of consent, or the EOS, whichever occurs earlier. Effective with Amendment 7, Survival Follow-up ends after the EOT Visit.

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 lesions 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.

Note: For country-specific requirements see Appendix 7.

1.3.4 Second Course Phase

Study Period	Second Course Treatment						EOT	Posttreatment			Notes
Treatment Cycle	C1	C2	C3	C4	C5	C6+	At Time of DC	Safety Follow-up[a]	Imaging Follow-up[b]	Survival Follow-up	Effective with Amendment 7, all efficacy follow-up will continue to be collected at the EOT visits but will not be collected during posttreatment follow-up.
Cycle Day	1	1	1	1	1	1		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			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 by phone or email.
Vital Status	←----------									----------→	All participants may be contacted for vital status at any time during the study through the EOT Visit.
Clinical Assessments or Procedures											
Review Adverse Events	X	X	X	X	X	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 diagnosis of MDS or AML should be reported throughout the study including the follow-up phase.
Full Physical Examination	X						X				
Directed Physical Examination		X	X	X	X	X		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**						**EOT**	**Posttreatment**			**Notes**
Treatment Cycle	**C1**	**C2**	**C3**	**C4**	**C5**	**C6+**	**At Time of DC**	**Safety Follow-up[a,]**	**Imaging Follow-up[b]**	**Survival Follow-up**	**Effective with Amendment 7, all efficacy follow-up will continue to be collected at the EOT visits but will not be collected during posttreatment follow-up.**
Cycle Day	**1**	**1**	**1**	**1**	**1**	**1**		**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 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 study intervention. Testing during Second Course must be conducted as clinically indicated and per local regulations where applicable. Serum test is only required if urine test is positive or not evaluable. 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 coumadin-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.
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 (eg, C3, C5, C7, etc.).
Efficacy Measurements											
CT/MRI Imaging of Chest, Abdomen, and Pelvis	X			X		X	X				Perform within 28 days prior to Second Course Cycle 1. Q12W from Second Course Cycle 1 onward or more frequently, as clinically indicated. If imaging was obtained within 28 days prior to DC, an additional scan is not needed at DC. Effective with Amendment 7, no further imaging is to be performed after the EOT Visit.

Study Period	**Second Course Treatment**						**EOT**	**Posttreatment**			**Notes**
Treatment Cycle	**C1**	**C2**	**C3**	**C4**	**C5**	**C6+**	**At Time of DC**	**Safety Follow-up[a]**	**Imaging Follow-up[b]**	**Survival Follow-up**	**Effective with Amendment 7, all efficacy follow-up will continue to be collected at the EOT visits but will not be collected during posttreatment follow-up.**
Cycle Day	**1**	**1**	**1**	**1**	**1**	**1**		**30 Days from Last Dose (+ 7)**	**Q12W (± 7)**	**Q12W (± 7)**	
Scheduled Days		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**					
MRI of Brain	X			X		X	X				Perform within 28 days prior to Second Course Cycle 1 for participants who are known to be positive for brain metastases or are clinically symptomatic. If positive for brain metastases at start of Second Course, continue imaging Q12W from Second Course Cycle 1 onward or more frequently, as clinically indicated. If imaging was obtained within 28 days prior to DC, an additional scan is not needed at DC. Effective with Amendment 7, no further imaging is to be performed after the EOT Visit.
Dispensing and Administration of Study Intervention											
Pembrolizumab	X	X	X	X	X	X					200 mg IV Q3W

Abbreviations: AE = adverse event; HCG = human chorionic gonadotropin; BP = blood pressure; C1 = Cycle 1; C2 = Cycle 2; CR = complete response; CT = computed tomography; DC = discontinued/discontinuation; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end-of-treatment; FT4 = free thyroxine; MRI = magnetic resonance imaging; Q3W = every 3 weeks; 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 are 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 centrally verified 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. Effective with Amendment 7, no further imaging is to be performed after the EOT Visit.

Note: For country-specific requirements see Appendix 7.

2 INTRODUCTION

This clinical study will evaluate the polyadenosine 5′-diphosphoribose polymerization (PARP) inhibitor, olaparib, in combination with pembrolizumab for the treatment and maintenance of nonsquamous non–small-cell lung cancer (NSCLC).

2.1 Study Rationale

Nonsquamous NSCLC accounts for approximately 65% to 70% of all NSCLC, with the majority of patients having advanced disease at diagnosis that is not amenable to surgical resection, as such additional treatment options are needed.

Pembrolizumab monotherapy has changed 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 programmed cell death ligand 1 (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 nonsquamous 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; HR: 0.81) and TPS ≥20% (17.7 months vs. 13.0 months; HR: 0.77), compared with chemotherapy alone, while continuing to show 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. Yet, despite these encouraging data, there is still substantial room for improvement of the treatment options available to these patients.

To expand on the efficacy of pembrolizumab, KEYNOTE-21 Cohort G and KEYNOTE-189 were designed to combine the agent with pemetrexed and a platinum in patients with metastatic nonsquamous NSCLC, as chemotherapy has been shown to augment the antitumor immune response. KEYNOTE-21G is a Phase 2 study that randomized 123 patients to pembrolizumab with pemetrexed and carboplatin versus pemetrexed with carboplatin in patients with metastatic nonsquamous NSCLC in whom there were no *EGFR* or *ALK* genomic tumor aberrations who had not previously received systemic therapy for their advanced disease. The study met its primary endpoint of improvement in objective response rate (ORR), as well as the key secondary endpoint of PFS, leading to Food and Drug Administration (FDA) accelerated approval of pembrolizumab in combination with pemetrexed/carboplatin. In an updated analysis, the following were noted: improvement in ORR was 24.8% (95% confidence interval [CI]: 7.2 to 40.9) with 56.7% for the pembrolizumab with chemotherapy arm and 31.7% for the control; PFS HR 0.54 (95% CI: 0.33 to 0.88) with median PFS 19.0 versus 8.9 months, for the pembrolizumab with chemotherapy arm compared with the control, respectively; and OS HR 0.59 (95% CI: 0.34

to 1.05) with median OS not reached in the pembrolizumab combination arm and 20.9 months in the control [Borghaei, H., et al 2017].

KEYNOTE-189 is a global, multicenter, placebo-controlled trial that randomized 616 participants with untreated Stage IV nonsquamous NSCLC in a 2:1 fashion to receive pemetrexed and investigator's choice of either carboplatin or cisplatin in combination with pembrolizumab or saline placebo for 4 cycles, followed by pembrolizumab or saline for a total of 35 cycles, plus pemetrexed maintenance therapy. 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. The study showed a clinically meaningful and statistically significant improvement in OS with an HR of 0.49 (95% CI: 0.38 to 0.64, $p<0.00001$) and a median OS of not reached in the pembrolizumab combination arm compared with 11.3 months in the chemotherapy alone arm. Similarly, there was significant PFS benefit with an HR of 0.52 (95% CI: 0.43 to 0.64, $p<0.0001$) with a median PFS of 8.8 months and 4.9 months in the pembrolizumab combination arm vs. chemotherapy alone arm, respectively. ORR also was significantly improved in the pembrolizumab combination arm (47.6%) compared with chemotherapy alone (18.9%), $p<0.00001$. Importantly, all subgroups benefited from pembrolizumab in combination with pemetrexed and carboplatin or cisplatin, 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 do continue to progress and succumb to this disease and as such, there can be further improvement on the available therapeutic options. 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. NSCLC also is a prime candidate for olaparib use as homologous recombination deficiency loss of heterozygosity (HRD-LOH) scores are as high as in breast and ovarian cancers, as per The Cancer Genome Atlas. Further, preclinical data suggest that olaparib and anti-PD(L)-1 inhibitors show synergistic therapeutic benefit. Therefore, adding olaparib as maintenance therapy to pembrolizumab in the treatment of patients with platinum-sensitive lung cancers has the potential for further treatment benefit, which is clearly necessary.

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 an oral anticancer therapy, as monotherapy (including maintenance) and in combination with chemotherapy and other anticancer agents.

PARP inhibition is a novel approach to targeting tumors with deficiencies in DNA repair mechanisms. The PARP enzymes are essential for repairing DNA single-strand breaks (SSBs). Inhibiting PARPs leads to the persistence of SSBs, which are then converted to the more serious DNA double-strand breaks (DSBs) during DNA replication. During cell division, DSBs can be efficiently repaired in normal cells by homologous recombination

repair (HRR). Tumors with homologous recombination deficiency (HRD), such as ovarian cancers in patients with the 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, thus preventing their repair [Helleday, T. 2011] [Murai, J., et al 2012]. Olaparib has shown efficacy in ovarian, prostate, and pancreatic tumors with BRCA1 and BRCA2 mutations and 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 IgG4 mAb with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and PD-L2. Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an IV immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across several indications. For more details on specific indications refer to the IB.

2.2.3 Non–small-Cell Lung Cancer

Lung cancer is the most common malignancy in the world, with an estimated incidence in 2012 of 2.1 million and an associated 1.8 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]. Mortality from lung cancer is the leading cause of cancer death in men and the second leading cause in women [Torre, L. A., et al 2015]. In the United States (US) in early 2018, there were an estimated 234,000 new cases and 154,000 deaths from lung cancer [Siegel, R. L., et al 2018].

Non–small-cell lung cancer represents approximately 80% to 85% of all lung cancers [National Cancer Institute 2016] and consists of 2 major types: nonsquamous carcinoma (~65% to 70% of cases) and squamous carcinoma (~30% to 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 nonsquamous NSCLC.

Importantly, in nonsquamous NSCLC, molecular profiling and availability of targeted therapy have helped change the treatment approach for a subset of patients. The EGFR tyrosine kinase inhibitors gefitinib, erlotinib, and afatinib have showed marked superiority over chemotherapy in patients with activating *EGFR* mutations; and osimertinib in front line has shown improved outcomes over earlier generations of EGFR tyrosine kinase inhibitors. Similarly, multiple ALK inhibitors, including crizotinib, ceritinib, alectinib, and brigantinib have shown significant activity in *ALK*-rearranged NSCLC and have received regulatory approval for use. Interestingly, the ALK inhibitors are also active in a rare subgroup of *ROS-1*-rearranged NSCLC patients. Data have shown poorer outcomes in patients with tumors harboring a targetable mutation that are not treated with a tyrosine kinase inhibitor [Kris, M. G., et al 2014].

Prior to the use and availability of pembrolizumab, platinum-based chemotherapy, with or without maintenance therapy, was the standard first-line (1L) therapy for patients with advanced/metastatic NSCLC with good Eastern Cooperative Oncology Group (ECOG) performance status scores (0 or 1), without *EGFR* or *ALK* genomic tumor aberrations [Oken, M. M., et al 1982]. Chemotherapy regimens used in the 1L treatment of metastatic NSCLC include cisplatin or carboplatin in combination with paclitaxel, nab-paclitaxel, gemcitabine, pemetrexed, or docetaxel [Peters, S., et al 2012] [Peters, S., et al 2012]. Multiple Phase 3 studies have showed similar efficacy for most platinum-based chemotherapy in participants with NSCLC; response rates have ranged from 15% to 33%, with median PFS values of approximately 4.5 to 6.3 months and median OS values of 10.3 to 12.6 months [Socinski, Mark A., et al 2012] [Sandler, A., et al 2006] [Scagliotti, G. V., et al 2008] [Thatcher, N., et al 2015] A meta-analysis of randomized, controlled clinical studies compared chemotherapy regimens containing cisplatin or carboplatin in combination with third-generation antineoplastic agents, including docetaxel, paclitaxel, and gemcitabine. No clinically meaningful difference in the safety and efficacy of carboplatin versus cisplatin-containing regimens was found [Ardizzoni, A., et al 2007], with a median OS of 8.4 months compared with 9.1 months, and 1-year survival rates of 34% versus 37%, for carboplatin and cisplatin, respectively. These data support the interchangeable use of carboplatin and cisplatin in combination with standard-of-care (SOC) antineoplastic agents, which also is reflected in clinical utilization data and supported by National Comprehensive Cancer Network (NCCN) recommendations [National Comprehensive Cancer Network 2016] and The European Society for Medical Oncology (ESMO) Guidelines [Novello, S., et al 2016]. Studies have assessed differences in outcomes if 6 or fewer cycles of platinum-doublet-containing regimens are administered [Park, J. O., et al 2007] [Rossi, A., et al 2014]. Although PFS is longer with 6 cycles of chemotherapy compared with 3 or 4, increased toxicities are seen without a statistically significantly improved OS [Park, J. O., et al 2007] [Rossi, A., et al 2014]. Therefore, the ESMO Guidelines specifically state that patients should receive 4

cycles of platinum-based doublets followed by maintenance therapy, or a maximum of 6 cycles if maintenance intervention is not appropriate [Novello, S., et al 2016].

The results of a landmark Phase 3 study evaluating cisplatin and pemetrexed compared with cisplatin and gemcitabine underscored that knowledge of histologic subtypes are important to determine the appropriate treatment choice in NSCLC [Scagliotti, G. V., et al 2008]. The study had a noninferiority design and enrolled 1725 patients with previously untreated NSCLC. Although OS was noninferior with cisplatin and pemetrexed compared with cisplatin and gemcitabine (median survival 10.3 months versus 10.3 months; HR 0.94; 95% CI 0.84 to 1.05%), planned subgroup analyses showed that cisplatin and pemetrexed was superior in patients with nonsquamous NSCLC (n=1000; HR 0.81; 95% CI: 0.7 to 0.94; *p*=0.005), and cisplatin and gemcitabine led to improved survival in patients with squamous cell histology (n=473; 10.8 months versus 9.4 months, respectively, *p*=0.05) [Scagliotti, G. V., et al 2008]. Pemetrexed and platinum therapy has become a significant treatment of choice for metastatic nonsquamous NSCLC.

The PARAMOUNT study showed that continuation of pemetrexed after achieving stable disease or response with the initial 4 cycles of pemetrexed/cisplatin in participants with advanced nonsquamous NSCLC confers a significant survival benefit compared with placebo (median OS 13.9 months versus 11.0 months from randomization at the initiation of maintenance therapy [Paz-Ares, L., et al 2012] [Paz-Ares, L. G., et al 2013]). Subsequently, maintenance therapy with pemetrexed became the SOC in patients with nonsquamous NSCLC who had not progressed during pemetrexed/cisplatin induction therapy.

While the addition of bevacizumab to carboplatin/paclitaxel followed by bevacizumab maintenance therapy in eligible patients with NSCLC showed improved OS (HR: 0.79) [Sandler, A., et al 2006], the combination of bevacizumab to cisplatin/gemcitabine revealed no survival benefit (HR: 0.93 and 1.03 for low- and high-dose bevacizumab regimens, respectively) [Reck, M., et al 2010]. Additionally, given the safety profile of bevacizumab, use of the drug has been variable worldwide. In summary, observed results for these modern chemotherapy regimens, with or without maintenance therapy, have shown only modest improvements in survival and indicate that effective and tolerable treatment options are needed for patients with advanced nonsquamous NSCLC without actionable genetic aberrations.

Pembrolizumab has led to a paradigm shift from standard platinum-based doublets for NSCLC. KEYNOTE-21 Cohort G and KEYNOTE-189 have further re-defined the standard of care for patients with nonsquamous NSCLC. Cohort G of KEYNOTE-21 evaluated pembrolizumab combined with pemetrexed/carboplatin versus pemetrexed/carboplatin alone in previously untreated patients with nonsquamous NSCLC in the setting of a Phase 2 study. The prespecified analysis of KEYNOTE-21 Cohort G showed a statistically significant and clinically meaningful benefit in ORR and PFS, which was the basis for FDA accelerated approval of pembrolizumab in combination with pemetrexed/carboplatin for the 1L treatment of patients with metastatic nonsquamous NSCLC irrespective of PD-L1 tumor expression [Langer, C. J., et al 2016].

KEYNOTE-189 was the confirmatory Phase 3 study intended to enforce and expand upon the results of KEYNOTE-21 Cohort G. In KEYNOTE-189, treatment with pembrolizumab in combination with pemetrexed/platinum chemotherapy (cisplatin or carboplatin) provided a clinically meaningful and significant improvement in OS (HR: 0.49; $p<0.00001$; median OS not reached vs. 11.3 months), PFS (HR: 0.52; $p<0.00001$; median PFS 8.8 months vs. 4.9 months), and objective response rate (ORR; 47.6% vs. 18.9%; $p<0.001$) for previously untreated patients with metastatic nonsquamous NSCLC. Importantly, in KEYNOTE-189, all subgroups benefited from pembrolizumab in combination with chemotherapy, including patients whose tumors did not express PD-L1; therefore, extending the benefit of pembrolizumab to those with PD-L1 negative tumors. The magnitude of benefit observed in this study is unprecedented in NSCLC clinical trials, and regulatory agencies have begun to approve pembrolizumab in combination with pemetrexed and platinum for this indication. Median OS was 22.0 (19.5 to 25.2) months in the pembrolizumab-combination group versus 10.7 (8.7 to 13.6) months in the placebo-combination group (hazard ratio [HR], 0.56; 95% CI, 0.45 to 0.70]). Median PFS was 9.0 (8.1 to 9.9) months and 4.9 (4.7 to 5.5) months, respectively (HR, 0.48; 95% CI, 0.40 to 0.58) [Gadgeel, S., et al 2020].

More recently, results have been reported for a 3-arm, randomized study of the anti-PD-L1 inhibitor atezolizumab combined with carboplatin/paclitaxel chemotherapy and bevacizumab in patients with nonsquamous NSCLC. The comparison of atezolizumab combined with chemotherapy and bevacizumab to chemotherapy and bevacizumab alone showed a 38% improvement in PFS (8.3 vs. 6.8 months; HR 0.62 (95% CI: 0.52 to 0.74): $p<0.001$) and OS (19.2 vs. 14.7 months; HR 0.78 (95% CI: 0.64 to 0.96); $p=0.02$) favoring the atezolizumab-containing arm, with a comparable safety profile in both treatment groups [Socinski, M. A., et al 2018]. These results provided further evidence that the combination of standard chemotherapy with immunotherapy, which is a well-understood and broadly used treatment in NSCLC, is a clinically meaningful approach.

Despite these impressive results, for patients with advanced nonsquamous NSCLC there is a 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 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 error rate compared with other forms of DNA repair [Prakash, R., et al 2015]. During DNA replication (S phase), pre-existing or chemotherapy-induced SSBs are converted to DSBs if not adequately repaired by intracellular mechanisms [Fong, Peter C., et al 2009], such as HRR. Cells unable to perform HRR (eg, due to inactivation of genes required for homologous recombination, such as *BRCA1* or *BRCA2*) are more likely to use the error-prone nonhomologous end-joining (NHEJ) or alternative (alt)-NHEJ pathways to repair these DSBs and risk accumulating multiple lesions or loss of heterozygosity (LOH) due to an increase in deletions and accompanying genomic instability. Over time, 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.

Thus, 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 cyclic guanosine monophosphate-adenosine monophosphate synthase-stimulator of interferon genes 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 show improved therapeutic benefit than each alone, likely being synergistic. Therefore, there is 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 in controlling outgrowth of neoplastic transformation has been known for decades [Disis, M. L. 2010]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies [Dong, H., et al 2002] [Hino, R., et al 2010] [Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC. 2012] [Patnaik, A., et al 2012] [Hodi, F. S., et al 2010] [Chapman, P. B., et al 2011] [Robert, C., et al 2011]. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells to FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in solid malignancies, including ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma (HCC); malignant melanoma; and renal cell carcinoma (RCC). TILs can be expanded ex vivo and re-infused, inducing durable objective tumor responses in cancers such as melanoma [Sasaki, A., et al 2008] [Shen, Z., et al 2010].

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 downmodulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene *Pdcd1*) is an Ig superfamily member related to CD28 and CTLA-4, which has been shown to negatively

regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [Talmadge, J. E., et al 2007] [Usubütün, A., et al 1998]. The mechanism by which PD-1 downmodulates T-cell responses is similar to, but distinct from, that of CTLA-4, as both molecules regulate an overlapping set of signaling proteins [Nobili, C., et al 2008] [Hiraoka, N. 2010]. PD-1 was shown to be expressed on activated lymphocytes, including peripheral CD4+ and CD8+ T-cells, B cells, T regs, and natural killer cells [Hodi, F. S. and Dranoff, G. 2010] [Kloor, M. 2009]. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including nonhematopoietic tissues and various tumors. Both ligands are type I transmembrane receptors, containing IgV- and IgC-like domains in the extracellular region and short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various nonhematopoietic tissues, most notably on vascular endothelium, whereas the PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues [Lee, H. E., et al 2008]. Although healthy organs express little (if any) PD-L1, a variety of cancers were shown to express abundant levels of this T-cell inhibitor. High expression of PD-L1 on tumor cells (and to a lesser extent of PD-L2) has been found to correlate with poor prognosis and survival in various cancer types, including RCC 17 [Liotta, F., et al 2011], pancreatic carcinoma [Suzuki, H., et al 2010], HCC [Chew, V., et al 2010], and ovarian carcinoma. [Pölcher, M., et al 2010]. Further, PD-1 has been suggested to regulate tumor-specific T-cell expansion in participants with melanoma [Oble, D. A., et al 2009].

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, 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. 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 Network data [Cerami, E., et al 2012] [Gao, J., et al 2013].

2.2.6 Preclinical and Clinical Studies

A summary of preclinical and clinical study data for pembrolizumab and olaparib is provided in their respective IBs.

2.2.7 Ongoing Clinical Studies

A summary of ongoing clinical study data for pembrolizumab and olaparib is provided in their respective IBs.

2.2.8 Other Study-related Therapies

A platinum doublet with pemetrexed is the most frequently used 1L chemotherapy for chemotherapy-naïve metastatic nonsquamous NSCLC patients. Pembrolizumab in combination with pemetrexed and cisplatin or carboplatin is also being evaluated in a randomized Phase 3 study, KN189, and those 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 utilize pembrolizumab in combination with pemetrexed and cisplatin or carboplatin.

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

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

In male and female participants with Stage IV nonsquamous non–small-cell lung cancer (NSCLC) with stable disease (SD), partial response (PR), or complete response (CR) following induction treatment with pembrolizumab combined with pemetrexed and platinum (carboplatin or cisplatin):

Primary Objective	**Primary Endpoint**
• Objective: To compare pembrolizumab plus maintenance olaparib with pembrolizumab plus maintenance pemetrexed with respect to progression-free survival (PFS) assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 by blinded independent central review (BICR). • Hypothesis (H1): Pembrolizumab plus maintenance olaparib is superior to pembrolizumab plus maintenance pemetrexed 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 maintenance pemetrexed with respect to overall survival (OS). • Hypothesis (H2): Pembrolizumab plus maintenance olaparib is superior to pembrolizumab plus maintenance pemetrexed with respect to OS.	• OS, the time from the date of randomization to death due to any cause.
At the final analysis, the pembrolizumab plus olaparib arm did not meet the primary endpoint of OS. PFS was not statistically significant compared with the control arm.	

Secondary Objectives	Secondary Endpoints
• Objective: To evaluate the safety and tolerability of pembrolizumab plus maintenance olaparib compared to pembrolizumab plus maintenance pemetrexed.	• 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 with pembrolizumab plus pemetrexed.	• Change from baseline (at randomization) and the 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 (Core 30 [C30]/Items 29 and 30) Cough (LC13/Item 1) Chest pain (LC13/Item 10) Dyspnea (C30/Item 8) Physical functioning (C30/Items 1 through 5)
Tertiary/Exploratory Objectives	**Tertiary/Exploratory Endpoints**
• Objective: To evaluate pembrolizumab plus maintenance olaparib compared to pembrolizumab plus maintenance pemetrexed with respect to objective response rate (ORR) and duration of response (DOR) assessed according to RECIST 1.1 (Section 4.2.1.1) by BICR.	• Objective response (OR), complete response (CR) or partial response (PR) after the date of randomization. • DOR, the time from first documented evidence of CR or PR after the date of randomization until either documented disease progression or death due to any cause, whichever occurs first.

• Objective: To evaluate the effect of PD-L1 expression levels on the efficacy endpoints of OS and PFS assessed according to RECIST 1.1 (Section 4.2.1.1) by BICR.	• PFS • OS
• Objective: To evaluate pembrolizumab plus maintenance olaparib compared to pembrolizumab plus maintenance pemetrexed with respect to new anticancer therapy (PFS2), as assessed by the investigator using RECIST 1.1.	• PFS2, the time from randomization to subsequent disease progression after initiation of new anticancer therapy, or death from any cause, whichever occurs first.
• Objective: To evaluate pembrolizumab plus maintenance olaparib compared to pembrolizumab plus pemetrexed with respect to the time to first subsequent anticancer therapy (TFST) and the time to second subsequent anticancer treatment (TSST)	• TFST, the time from the date of randomization to initiation of first subsequent anticancer treatment or death due to any cause, whichever occurs first • TSST, the time from the date of randomization to initiation of second subsequent anticancer treatment or death due to any cause, whichever occurs first
• Objective: To characterize health utilities using the 5-level version of the European Quality of Life 5-dimension Questionnaire (EQ-5D-5L) to generate utility scores for use in economic models.	Health utilities using the EQ-5D-5L.
• Objective: To identify molecular (genomic, metabolic, and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of pembrolizumab in combination with maintenance olaparib.	• Germline genetic variation, genetic (DNA) mutations from tumor, tumor and blood RNA variation, proteomics and immunohistochemistry, and other blood-derived biomarkers.

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 3, randomized, active-controlled, parallel-group, multisite, unblinded study of the combination of pembrolizumab plus pemetrexed plus platinum (carboplatin or cisplatin) followed by continued pembrolizumab and maintenance olaparib compared with continued pembrolizumab and maintenance pemetrexed in participants with metastatic nonsquamous NSCLC maintenance in need of 1L intervention.

This study will be conducted in 4 phases: Screening, an Induction Phase, a Maintenance Phase, and a 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 was an open-label 12-week period, during which approximately 1005 eligible participants were enrolled to receive 4 cycles of pembrolizumab 200 mg IV every 3 weeks (Q3W) in combination with pemetrexed and carboplatin or cisplatin; refer to Table 2 for dosing information. During the Induction Phase, participants had study visits every 3 weeks for assessments. Tumor response during the Induction Phase was evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, with radiographic imaging at enrollment and 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 response 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, unblinded period, during which approximately 672 participants were eligible for randomization to pembrolizumab combined with maintenance olaparib, or pembrolizumab combined with maintenance pemetrexed (Table 2), if they met all of the following key requirements:

- Received 4 cycles of study intervention during the Induction Phase with at least 1 evaluable scan and no overall responses of PD by RECIST 1.1, as determined by central imaging review (Consultation with the Sponsor is required if a participant receives fewer than 4 cycles of study intervention during the Induction Phase without PD, and the investigator would like to randomize the participant to the Maintenance Phase)
- Have an ECOG performance status score of 0 or 1 at Pre-randomization Visit
- All adverse events (AEs; except alopecia, Grade 2 fatigue, and endocrine-related AEs Grade ≤2 requiring treatment or hormone replacement) have resolved to Grade ≤1 or baseline following Induction Phase Treatment
- Have adequate organ function, as indicated by the laboratory values in Table 3
- Are taking no medications or vaccinations specifically prohibited in the exclusion criteria (Section 5.2).

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

Randomization will be stratified by ECOG performance status score (0 or 1) at Pre-randomization Visit, PD-L1 expression (TPS <50% vs. ≥50%), and response at 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 31 cycles during the Maintenance Phase, the participant may continue with maintenance olaparib or pemetrexed until specific discontinuation criteria are met (Section 7.1). If maintenance olaparib or pemetrexed 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 through 4)	**Maintenance Phase (Up to 31 Cycles)**

• Pembrolizumab 200 mg IV Q3W on Day 1
• Pemetrexed 500 mg/m^2 IV Q3W on Day 1
• Platinum, investigator's choice (carboplatin or cisplatin)
  • Carboplatin titrated to an AUC of 5 mg/mL/min IV Q3W on Day 1
OR
  • Cisplatin 75 mg/m^2 IV Q3W on Day 1
	• 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 PO BID daily to 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, will continue until specific discontinuation criteria are met (Section 7.1)
	• Pemetrexed 500 mg/m^2 IV Q3W on Day 1, will continue until specific discontinuation criteria are met (Section 7.1)

Abbreviations: AUC = area under the concentration-time curve; BID = twice daily; IV = intravenous(ly); PO = oral(ly); Q3W = every 3 weeks.	

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

Participants randomized into the Maintenance Phase will be evaluated with radiographic imaging to assess response to study intervention at regular intervals throughout the study, as described in Section 8.2.1. The images obtained 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 will be submitted to the central imaging vendor, 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 determination of ORR (Section 8.2). Initial tumor imaging showing site-assessed PD should be immediately submitted for verification by BICR prior to study intervention discontinuation.

Participants in the Maintenance Phase will receive randomly assigned study intervention until centrally verified disease progression is radiographically documented and, when clinically appropriate, confirmed by the site per modified RECIST 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 study intervention. Pembrolizumab will continue for a maximum of 31 cycles, or until specific discontinuation criteria are met (Section 7.1). Olaparib and pemetrexed will continue until specific discontinuation criteria are met (Section 7.1).

Participants treated with pembrolizumab who complete a total of 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 17 additional cycles (approximately 1 year) of pembrolizumab if they experience radiographic disease progression after stopping treatment in the Maintenance Phase. This retreatment is termed the Second Course Phase and is only available if the study remains open and the participant meets the criteria listed in Section 7.1. Responses or events of progression occurring during Second Course Phase will not be counted toward the ORR and PFS endpoints.

Adverse event monitoring will be ongoing during the study and graded in severity according to the guidelines in the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v 4.0 (Section 8.4). Adverse events will be reported by the investigator or delegate from the start of induction treatment through 30 days following cessation of study intervention. Serious AEs (SAEs) will be reported by the investigator or delegate from the start of study intervention 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. Patient-reported outcomes (PROs) will be used to assess symptomatic improvement and participants will provide information regarding their health-related quality of life (HRQoL). Participants will be evaluated for time to true deterioration (TTD) in global health status/QoL, cough, chest pain, dyspnea, and physical functioning.

Note: As of Amendment 07, ePRO assessments will no longer be collected.

In addition, blood for identification of molecular biomarkers (eg, genomic, metabolic, and/or proteomic) that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of olaparib will be collected at regular intervals (see Section 4.2.1.4).

Participants who discontinue study intervention for reasons other than centrally verified PD will have Long-term Follow-up for disease status (including imaging), until PD, initiating a new anticancer therapy, withdrawing informed 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 (EOC) of the Sponsor (Section 10.1.4). The eDMC responsibilities and review schedules will be outlined in the eDMC charter.

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

KEYLYNK-006 was designed to evaluate the efficacy and safety of pembrolizumab plus maintenance olaparib compared with pembrolizumab plus maintenance pemetrexed after induction therapy with pembrolizumab and chemotherapy with the dual primary endpoints of PFS by BICR and OS.

At the final analysis, the pembrolizumab plus olaparib arm did not meet the primary endpoint of OS. PFS was not statistically significant compared with the control arm. No new safety signals were observed in any of the treatment arms. Note: All study participants still receiving study treatment will discuss next steps with the investigator. If continuing to receive therapy on study the participant should follow the modified study procedures. Participants currently on study treatment will have continued access to olaparib, pemetrexed, and pembrolizumab if they qualify per protocol. There will be no further analyses for efficacy and ePRO endpoints.

4.2 Scientific Rationale for Study Design

Further improvements can be made on the therapeutic options available for patients with previously untreated metastatic nonsquamous NSCLC, notwithstanding the progress made with the use of molecularly targeted agents in patients with actionable mutations and with the use of the use of the anti-PD1/anti-PD-L1 antibodies to inhibit suppression of the immune system, which have begun to change outcomes in this patient population.

A potential opportunity to improve upon the current therapeutic strategy in nonsquamous NSCLC 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 nonsquamous NSCLC. Notably, in the MEDIOLA trial, a Phase 2 basket study that included patients with small-cell

lung cancer, 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 and the combination has been generally well tolerated, with no new safety signals identified for either compound.

This open-label, active-controlled Phase 3 study will build on the current SOC in the front-line treatment of patients with Stage IV NSCLC established by the results of KEYNOTE-189 utilizing 4 cycles of pembrolizumab combined with pemetrexed and platinum followed by pembrolizumab for up to a total of 35 cycles plus pemetrexed maintenance. However, this study design will utilize a novel strategy to prevent progression of disease by replacing pemetrexed with olaparib. Participants with platinum-sensitive disease (SD, CR, or PR) to 4 cycles of pembrolizumab, pemetrexed, and platinum will be randomized to pembrolizumab and maintenance olaparib or pembrolizumab and maintenance pemetrexed. By using a different mechanism of action and continuing to induce DNA damage and to upregulate PD-L1, the combination of pembrolizumab and maintenance olaparib will lead to improved tumor control compared with pembrolizumab and maintenance pemetrexed.

Replacing pemetrexed with olaparib may decrease toxicity, eliminate the need for pre-medication, and provide a more convenient route of drug administration. 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 continued pembrolizumab and maintenance pemetrexed.

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 read by a central imaging vendor blinded to treatment assignment to minimize bias in the response assessments. The final determination of radiologic progression will be based on the central assessment of progression, rather than a local site investigator/radiology assessment. Real-time verification of site-detected radiologic progression by central review will be communicated to the site.

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 8.2.1.4). 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 8.2.1.4.1). 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 study 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 OS 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 takes into account 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 (ie, 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 FDA and the European Medicines Agency (EMA) [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 frequently used for evaluating investigational-systemic anticancer treatments are included as safety endpoints including, but not limited to, the incidence of, causality, and outcome of AEs/SAEs, and changes in vital signs and laboratory values. AEs will be assessed as defined by CTCAE, Version v 4.0.

4.2.1.3 Patient-reported Outcomes

Note: As of Amendment 07, participants who are still on study treatment will no longer require ePRO assessments.

Symptomatic improvement is considered a clinical benefit and accepted by health authorities as additional evidence of risk-benefit profile of any new study intervention. As part of the analyses for this study, health-related quality of life (HRQoL) and disease-related symptoms will be investigated among all participants using the following assessment questionnaires: European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) Core 30 (C30), EORTC QLQ Lung Cancer Module 13 (LC13), and European Quality of Life Five-dimension Five-level Scale Questionnaire (EQ-5D-5L). Patient-reported outcomes are not pure efficacy or safety endpoints because they are affected by disease progression and treatment tolerability.

4.2.1.4 EORTC QLQ-C30 and QLQ-LC13

The EORTC QLQ C30 is a psychometrically and clinically validated instrument appropriate for assessing QoL in oncology studies [Aaronson, N. K., et al 1993]. EORTC QLQ-C30 is the most widely used, cancer-specific, HRQoL instrument. It contains 30 items and measures 5 functional dimensions (physical, role, emotional, cognitive, and social); 3 symptom items (fatigue, nausea/vomiting, and pain); 6 single items (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact); and a global health and QoL scale [Aaronson, N. K., et al 1993]. For the global health status or QoL and function scales, a higher value indicates a better level of function; for symptom scales and items, a higher value indicates increased severity of symptoms. TTD and mean change from baseline in global health status or QoL scale of the EORTC QLQ-C30, will be evaluated as secondary objectives.

The EORTC QLQ-LC13, a supplemental lung cancer-specific module used in combination with QLQ-C30, is comprised of multi- and single-item measures of lung cancer-associated symptoms (cough, hemoptysis, dyspnea, and site-specific pain) and treatment-related symptoms (sore mouth, dysphagia, peripheral neuropathy, and alopecia) [Bergman, B., et al 1994]. It is scored on a 4-point scale (1 = not at all, 2 = a little, 3 = quite a bit, and 4 = very much) and has been translated and validated into more than 60 languages.

The EORTC QLQ-C30 and QLQ-LC13 are the most frequently used and reported PRO measures in lung cancer clinical studies. The reliability, validity, and practicality of these instruments have been reported [Bergman, B., et al 1994] [Aaronson, N. K., et al 1993].

4.2.1.5 EQ-5D-5L

The EQ-5D-5L is a standardized instrument for use as a measure of health outcome and will provide data to develop health utilities for use in health economic analyses [Rabin, R. and de Charro, F. 2001]. The 5 health state dimensions in the EQ-5D-5L include the following: Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression. Each dimension is rated on a 5-point scale from 1 (no problem) to 5 (unable to/extreme problems). The EQ-5D-5L also includes a graded (0 to 100) vertical visual analog scale on which the

participant rates his or her general state of health at the time of the assessment. This instrument has been used extensively in cancer studies and published results from these studies support its validity and reliability [Pickard, A. S., et al 2007].

4.2.1.6 Planned Exploratory Biomarker Research

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

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

This research may evaluate whether genetic variation within a clinical study population correlates with response to the treatment(s) under evaluation. If genetic variation is found to predict efficacy or AEs, the data might inform optimal use of therapies in the patient population. Furthermore, it is important to evaluate germline DNA variation across the genome to interpret tumor-specific DNA mutations. In addition to studying variation across the human genome, mutations in DNA damage repair genes including, but not limited to *BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D,* and *RAD54L*, as well as genome scars, including LOH, may be investigated. Based on data from participants in several olaparib studies in multiple cancer types, known or suspected deleterious mutations in these genes and LOH may be predictive of a response to the combination of olaparib and pembrolizumab. Finally, MSI may be evaluated as this is an important biomarker for some cancers (ie, colorectal cancer).

Genetic (DNA) analyses from tumor

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

important biomarker for some cancers (ie, colorectal cancer). Circulating tumor DNA and/or RNA may also be evaluated from blood samples.

Tumor and/or blood RNA analyses

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

Proteomics and immunohistochemistry (IHC) using blood or tumor

Tumor, tissue, and blood samples from this study may undergo proteomic analyses (eg, PD-L1 IHC). PD-L1 protein level in tumor sections, assessed by IHC, has been shown to correlate with response to pembrolizumab in patients with NSCLC, and an in vitro diagnostic (IVD) device has been developed for use with pembrolizumab in NSCLC. Preliminary data indicates that this association may also be true in additional cancer types (ie, triple negative breast cancer, head and neck, and gastric). Additional tumor or blood-derived proteins may also correlate with response to olaparib and pembrolizumab. Therefore, tumor tissue may be subjected to proteomic analyses using a variety of platforms that could include but are not limited to immunoassays and liquid chromatography/mass spectrometry. This approach could identify novel protein biomarkers that could aid in patient selection for olaparib (MK-7339) and pembrolizumab (MK-3475) therapy.

Other biomarkers

In addition to expression on the tumor tissue, other tumor derived cells, proteins and DNA/RNA can be shed from tumor and released into the blood. Assays such as enzyme-linked immunoassay (ELISA) that measure proteins and assays that measure cell-free DNA/RNA (cfDNA/cfRNA) may also be evaluated from blood samples. Correlation of these biomarkers with response to treatments may identify new approaches for predictive biomarkers in blood, representing a major advance from today's reliance on assessing tumor biomarkers. This research would serve to develop such assays for future clinical use.

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

4.2.1.7 Future Biomedical Research

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

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

4.2.2 Rationale for the Use of an Active Comparator

The use of the active comparator combination of pembrolizumab with pemetrexed in the Maintenance Phase ensures that participants receive the current SOC. In this study, pembrolizumab plus maintenance olaparib following the Induction Phase with pembrolizumab combined with pemetrexed and platinum in those participants with SD, PR, or CR, will be evaluated to show superiority to pembrolizumab plus maintenance pemetrexed with regard to PFS and OS.

4.3 Justification for Dose

4.3.1 Starting Dose for Olaparib

The safety and efficacy of olaparib have been showed in the clinical programs using predominantly the capsule formulation (400 mg [8 capsules] twice daily [BID]). However, an improved tablet formulation (2 tablets BID) has been developed and will be used in this study. The recommended tablet formulation of olaparib as monotherapy is 300 mg BID, which is considered similar in terms of efficacy and safety to the capsule 400 mg BID dose. However, the capsule and the tablet formulations are not bioequivalent, as observed in Study 24, in which 300 mg BID tablet dose matched or exceeded the exposure of the 400 mg capsule in terms of area under concentration-time curve (AUC), maximum concentration (C_{max}), and minimum concentration (C_{min}). 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. Tablet formulation is used across the olaparib Phase 3 program. Olaparib, when given in the tablet formulation has a time to maximum plasma concentration (t_{max}) typically of 0.5 to 2 hours and a mean terminal half-life ($t_{1/2}$) of approximately 12 to 15 hours. Based on the average single-dose $t_{1/2}$, 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 IB.

4.3.2 Starting Dose for Pembrolizumab

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

- Clinical data from 8 randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg 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 these studies showed flat dose- and exposure-response relationships across the studied doses, 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 by direct binding to cancer cells.

Additionally, pharmacology data clearly showed target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively showed 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 Starting Dose for Chemotherapy

The doublet chemotherapy treatment (pemetrexed and carboplatin or cisplatin) used in this study is a well-established regimen for nonsquamous NSCLC. See Section 6.1 for information on the order in which study interventions should be administered.

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.

4.3.3.3 Pemetrexed

Pemetrexed 500 mg/m^2 will be administered as an IV infusion over 10 minutes Q3W according to local practice and labels until progression or unacceptable toxicity. All participants should receive the appropriate supplementation of vitamin B12, folic acid, and corticosteroid prophylaxis, as listed below (or as per local label):

- Folic acid 350 to 1000 µg orally (PO): at least 5 doses of folic acid must be taken during the 7 days preceding the first dose of pemetrexed, and folic acid dosing must continue during the full course of therapy and for 3 weeks after the last dose of pemetrexed.
- Vitamin B12 1000 µg intramuscular (IM) injection in the week preceding the first dose of pemetrexed and once every 3 cycles thereafter. Subsequent vitamin B12 injections may be given the same day as pemetrexed administration.
- Dexamethasone prophylaxis 4 mg PO BID (or equivalent). Taken the day before, day of, and day after pemetrexed administration. Higher or additional doses are permitted for antiemetic prophylaxis during Cycles 1 through 4, but not to exceed the doses in the Multinational Association of Supportive Care in Cancer (MASCC) guidelines (Section 8.1.8.1.6).

4.3.3.4 Cisplatin

Cisplatin 75 mg/m^2 should be infused after the pemetrexed infusion for the first 4 cycles and should be immediately preceded and followed by hydration procedures and administered according to local practice and labels.

4.3.3.5 Carboplatin

Carboplatin AUC 5 mg/mL/min will be administered as an IV infusion over 15 to 60 minutes Q3W for 4 cycles immediately after maintenance pemetrexed, according to local practice and labels.

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 (Section 7.3), or the last participant on active treatment is consented in the extension study. For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory test result or at the time of final contact with the last participant, whichever comes last.

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

4.4.1 Clinical Criteria for Early Study Termination

The clinical study may be terminated early if the extent (incidence and/or severity) of emerging effects is such that the risk/benefit ratio to the study population as a whole is unacceptable. In addition, further recruitment in the study or at (a) particular study site(s) may be stopped as described in Appendix 1.10.

5 STUDY POPULATION

As stated in the Code of Conduct for Clinical Trials (Appendix 1.1), this study includes participants of varying age (as applicable), race, ethnicity, and sex (as applicable). The collection and use of these demographic data will follow all local laws and participant confidentiality guidelines while supporting the study of the disease, its related factors, and the IMP under investigation.

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

5.1 Inclusion Criteria

An individual is eligible for inclusion in the study if the individual meets all of the following criteria:

Type of Participant and Disease Characteristics

1. Have a histologically confirmed or cytologically confirmed diagnosis of nonsquamous NSCLC.
2. Have Stage IV (T any, N any, M1a, M1b, or M1c - American Joint Committee on Cancer (AJCC) 8th Edition) nonsquamous NSCLC.
3. Have confirmation that EGFR, ALK, or ROS1-directed therapy is not indicated (documentation of absence of tumor-activating *EGFR* mutations AND absence of *ALK* and *ROS1* gene rearrangements, OR presence of a *K-Ras* mutation).
4. Have measurable disease, based on RECIST 1.1, as determined by the local site investigator/radiology assessment. Lesions that appear measurable, but are situated in a previously irradiated area, can be considered measurable (eligible for selection as target lesions) if they have shown documented growth since the completion of radiation.
5. Have provided archival tumor tissue sample or newly obtained core or excisional 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 life expectancy of at least 3 months.
7. Have an ECOG performance score of 0 or 1 assessed within 7 days prior to the administration of study intervention.

8. 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.
9. Have adequate organ function, as indicated by the following laboratory values (Table 3). All screening laboratory tests should be performed within 10 days prior to the first dose of study intervention.

Table 3 Adequate Organ Function Laboratory Values

Systems	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500 cells/µL
Platelets	≥100 000 cells/µL
Hemoglobin	≥9.0 g/dL, or ≥5.6 mmol/L[1]
Renal	
Estimated CrCl using the Cockcroft-Gault equation[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); AST (SGOT) = aspartate aminotransferase (serum glutamic oxaloacetic transaminase); CrCl = creatinine clearance; 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 CrCl using Cockcroft-Gault:

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

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

As an alternative, CrCl 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

10. Be at least 18 years of age at the time of signing the informed consent.

Male Participants

11. Male participants are eligible to participate if they agree to the following during the intervention period and 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 a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a woman of childbearing potential (WOCBP) who is not currently pregnant. Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile-vaginal penetration.

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

12. A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:
    a. Is not a WOCBP

    OR

b. Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate <1% per year), or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5 during the intervention period and for at least 180 days after the last dose of study intervention and agrees not to donate eggs (1ova, 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

13. Have (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 study without participating in future biomedical research.

Additional Criteria Applicable to Maintenance Phase Only, Prior to Randomization

14. Have a CR/PR or SD of their NSCLC after completion of the study-specified Induction Phase, as determined by central imaging review.
15. Have an ECOG performance status score at randomization of 0 or 1 as assessed at Pre-randomization Visit (most recent assessment within the visit).
16. 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.
17. Have adequate organ function, as indicated by the laboratory values in Table 3 above.
18. Are not taking medications or vaccinations specifically prohibited in the exclusion criteria (Section 5.2).

19. 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.
20. Have not withdrawn consent to continue treatment.
21. 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 meets any of the following criteria:

Medical Conditions

1. Has predominantly squamous cell histology NSCLC. Mixed tumors will be categorized by the predominant cell type; if small cell elements are present, the participant is ineligible.
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 severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients.
5. Participant has a known hypersensitivity to any components or excipients of cisplatin, carboplatin, pemetrexed, or olaparib.
6. Has 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) is not considered a form of systemic treatment and is allowed.
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 (noninfectious) pneumonitis that required steroids or has current pneumonitis.

9. Has an active infection requiring systemic therapy.
10. Has a 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 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. Has a known history of active tuberculosis (TB; *Mycobacterium tuberculosis*).
13. Has symptomatic ascites or pleural effusion. A participant who is clinically stable following treatment for these conditions (including therapeutic thoraco- or paracentesis) is eligible.
14. Has a known history of interstitial lung disease. Lymphangitic spread of the NSCLC is not exclusionary.
15. Has myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) or with features suggestive of MDS/AML.

Prior/Concomitant Therapy

16. Before the first dose of study intervention:
    a. Has received prior systemic cytotoxic chemotherapy for metastatic disease.
    b. Has received antineoplastic biological 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.
17. Has received prior therapy with olaparib or with any other PARP inhibitor.
18. Has received radiation therapy to the lung that is >30 Gy within 6 months of the first dose of study intervention.
19. Is expected to require any other form of antineoplastic therapy while on study.
20. 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).
21. Received a live or live-attenuated vaccine within 30 days before the first dose of study intervention. Administration of killed vaccines are allowed.
    Refer to Section 6.5 for information on COVID-19 vaccines.
22. Is unable to interrupt aspirin or other nonsteroidal anti-inflammatory drugs, other than an aspirin dose ≤1.3 g per day, for a 5-day period (an 8-day period for long-acting agents, such as piroxicam).
23. Is unable or unwilling to take folic acid or vitamin B12 supplementation.
24. Received colony-stimulating factors (eg, granulocyte colony-stimulating factor [G-CSF], granulocyte-macrophage colony-stimulating factor 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.

25. 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
26. Is currently receiving either strong (eg, 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 (21 days) 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

27. 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 treatment.
    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

28. 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

29. Is considered a poor medical risk, in the opinion of the treating investigator, due to a serious, uncontrolled medical disorder or nonmalignant 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.
30. Has a known psychiatric or substance abuse disorder that would interfere with cooperation with the requirements of the study.

31. 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.
32. Is unable to swallow orally administered medication, or has a gastrointestinal disorder affecting absorption (eg, gastrectomy, partial bowel obstruction, or malabsorption).
33. Has had an allogeneic-tissue/solid-organ transplant.
34. Completed palliative radiotherapy within 7 days of the first dose. Participants must have recovered from all radiation-related toxicities and not require corticosteroids.

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 an AE 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 study. In order to participate in the study, 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 study 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.

5.3.4 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.

No restrictions are required.

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 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 the study intervention OR withdraws from the study will not be replaced.

6 STUDY INTERVENTION

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

Clinical supplies will be packaged to support enrollment. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

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; pemetrexed and platinum should be given as per SOC.

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

Note: At the final analysis, the pembrolizumab plus olaparib arm did not meet the primary endpoint of OS. PFS was not statistically significant compared to the control arm. Participants taking olaparib or pemetrexed 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. 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 or NIMP/ AxMP	Sourcing
Pembrolizumab	Experimental	Active	Drug	Solution	25 mg/mL	200 mg	IV Infusion	Q3W/Induction and Maintenance Phases for a maximum of 35 cycles	Test Product	IMP	Centrally
Carboplatin	Other	Chemo -therapy	Drug	Solution	10 mg/mL[a]	AUC 5 mg/mL/min	IV Infusion	Q3W/Induction Phase (4 cycles)	Background Treatment	NIMP/AxMP	Centrally or locally
Cisplatin	Other	Chemo -therapy	Drug	Solution	1 mg/mL	75 mg/m^2	IV Infusion	Q3W/Induction Phase (4 cycles)	Background Treatment	NIMP/AxMP	Centrally or locally
Pemetrexed	Other	Chemo -therapy	Drug	Injection, Powder, Lyophilized, For Solution	500 mg[b]	500 mg/m^2	IV Infusion	Q3W/Induction and Maintenance Phases	Background Treatment	IMP	Centrally or locally
Olaparib	Experimental	Active	Drug	Tablet	150 mg, 100 mg[c]	300 mg BID	Oral	BID/ Maintenance Phase	Test Product	IMP	Centrally

Abbreviations: AUC = area under the plasma drug concentration time curve; BID = twice daily; D1 = Day 1; IM = intramuscular; IMP = investigational medicinal product; IV = intravenous(ly); MASCC = Multinational Association of Supportive Care in Cancer; N/A = not applicable; NIMP = non-investigational medicinal product; Q3W = every 3 weeks; SOC = standard of care.

Definitions of IMP and NIMP are based on guidance issued by the European Commission. Regional and/or country differences of the definition of IMP/NIMP may exist. In these circumstances, local legislation is followed.

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

b All participants taking pemetrexed should receive the appropriate supplementation of vitamin B12, folic acid, and corticosteroid prophylaxis, as listed below (or as per local label):

- Folic acid 350-1000 µg PO: at least 5 doses of folic acid must be taken during the 7 days preceding the first dose of pemetrexed, and folic acid dosing must continue during the full course of therapy and for 21 days after the last dose of pemetrexed.
- Vitamin B12 1000 µg IM injection in the week preceding the first dose of pemetrexed and once every 3 cycles thereafter. Subsequent vitamin B12 injections may be given on the same day as pemetrexed administration.

- Dexamethasone prophylaxis 4 mg, PO BID (or equivalent). Taken the day before, day of, and day after pemetrexed administration. Higher or additional doses are permitted for antiemetic prophylaxis during Cycles 1 through 4, but not to exceed the doses in the MASCC guidelines (Section 8.1.8.1.6).

c 300-mg dose will be made up of 2 × 150 mg tablets; 100 mg tablets are provided for dose reductions, as outlined in Section 6.6.2.

All study interventions will be administered on an outpatient basis.

All products indicated in Table 4 will be provided centrally by the Sponsor or locally by the study site, subsidiary, or designee, depending on local country operational or regulatory requirements.

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

Refer to Section 6.1 for details regarding administration of the study intervention.

6.1.1 Treatment

The initial treatment or first course of pembrolizumab consists of 35 treatments. Note: The number of treatments is calculated starting with the first dose.

These participants may be eligible for Second Course described in Section 8.11.5.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

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

Olaparib is a tablet for oral administration; no preparation is required. Refer to the olaparib Pharmacy Manual for further instructions. Olaparib will be provided in high-density polyethylene bottles with child-resistant closures. Each bottle will be labeled in accordance with Good Manufacturing Practice Annex 13 and per country regulatory requirement.

Pemetrexed and carboplatin/cisplatin 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 start of the study.

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 performed via the IRT system.

6.3.2 Stratification

Intervention allocation/randomization will be stratified according to the following factors:

- Most recent ECOG at Pre-randomization Visit (0 vs. 1)
- PD-L1 expression (TPS <50% vs. ≥50%)
  - PD-L1 nonevaluable subjects will be grouped with the TPS <50% group.
- Response at randomization (CR/PR vs. SD)
  - Confirmed and unconfirmed CR/PR will be stratified together. That is, initial CR or PR in response to induction therapy does not need to be confirmed by imaging at least 4 weeks later. All responses will need to be centrally assessed (ie, BICR). See Section 8.2.1.2 for stratification guidelines for non-evaluable imaging.

6.3.3 Blinding

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

6.4 Study Intervention Compliance

6.4.1 Olaparib Compliance

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

Site staff will perform 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 the study monitor completes reconciliation. Olaparib 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 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 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, Carboplatin/Cisplatin, and Pemetrexed Compliance

Pembrolizumab and chemotherapy will be administered on an outpatient basis.

Interruptions from the protocol-specified pembrolizumab, carboplatin/cisplatin, or pemetrexed intervention plan require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management (Section 7.1).

Pembrolizumab may be interrupted for a maximum of 12 weeks from last dose; chemotherapy may be interrupted for a maximum of 6 weeks from last dose.

If there are interruptions in the study intervention schedule or infusion/injection was stopped, the details of and reason for any interruption or infusion/injection 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 Guidelines for irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations and for other allowed dose interruptions.

6.5 Concomitant Therapy

If there is a clinical indication for any medications or vaccinations prohibited, the investigator must discuss any questions regarding this with the Sponsor's Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator and the Sponsor.

The following medications and vaccinations are prohibited during the study:

- Live or live-attenuated vaccines within 30 days before the first dose of study intervention and while participating in the study, and for 30 days after 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, replication-incompetent adenoviral vaccines, or inactivated vaccines. These vaccines will be treated just as any other concomitant therapy.

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

- 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.

- 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.
- 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 COPD
- Phenytoin during therapy with cisplatin/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.

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

If the investigator determines that a participant requires any of the following prohibited medications and vaccinations for any reason during the study, study intervention must be discontinued:

- Systemic antineoplastic chemotherapy, immunotherapy, or biological therapy not specified in this protocol
- Investigational agents other than those specified in this protocol
- 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.

  Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.
- Surgery for tumor control.

Based on in vitro data, olaparib may increase the exposure to substrates of CYP3A4, organic-anion-transporting polypeptide 1B1, organic cation transporter 1/2/3, and multidrug and toxic compound extrusion 1/2 and reduce exposure to substrates of CYP2B6. Caution should be observed if substrates of these isoenzymes or transporter proteins are co-administered. 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 medications will be recorded on the eCRF including all prescriptions, OTC products, herbal supplements, and IV medications, and fluids. If changes occur during the study period, documentation of drug dosage, frequency, route, and date should also be included on the eCRF.

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

6.5.1 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 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 for guidelines regarding dose modification and supportive care.

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

6.6 Dose Modification (Escalation/Titration/Other)

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 must be withheld. Olaparib 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 Dosing 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, pemetrexed 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 judgement 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 maintenance 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 maintenance 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; 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 maintenance olaparib, for a maximum of 3 weeks (21 days), until event recovers to ≤Grade 1. • Repeated incidence: reduce the dose of maintenance olaparib to 250 mg BID. A second dose reduction to 200 mg BID may be considered if additional Grade 3 or 4 events occur.

Abbreviations: AE = adverse event; BID = twice daily; G-CSF = granulocyte-colony stimulating factor; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

- AEs of neutropenia and leukopenia should be managed as deemed appropriate by the investigator with close follow-up and interruption of study intervention if CTCAE Grade 3 or worse neutropenia occurs.
- Primary prophylaxis with G-CSF is not recommended; however, if a participant develops febrile neutropenia, study intervention should be stopped and appropriate management, including G-CSF, should be given according to local hospital guidelines. 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 given 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.

Maintenance olaparib 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, which outlines the Toxicity Management Guidelines for pembrolizumab as it can also 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 anti-emetic 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 or antihistamines).

6.6.2.3.3 Management of Renal Impairment

To initiate maintenance olaparib, creatinine clearance (CrCl) must be ≥51 mL/min. As an alternative, CrCl can be determined from a 24-hour urine collection.

If subsequent to study entry and/or while still on study therapy, a participant's estimated 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 with the Cockcroft-Gault formula, 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; CrCl = creatinine clearance.

a. CrCl of 31 to 50 mL/min, as calculated with the Cockcroft-Gault formula. As an alternative, CrCl 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.

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

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 Nontoxicity-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 maintenance 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 maintenance 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 maintenance 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 maintenance 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.

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		

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other therapies	Monitoring and Follow-up
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Recurrent Grade 3 or Grade 4	Permanently discontinue		
AST / ALT Elevation or Increased Bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5-1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [a]	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes

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

Pembrolizumab monotherapy, coformulations, or IO combinations 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 monotherapy, coformulations, or IO combinations associated infusion reactions are provided in Table 10.

Table 10 Pembrolizumab Monotherapy, Coformulations, or IO Combinations 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/h to 50 mL/h). 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 intervention.	Participant may be premedicated 1.5 h (±30 min) prior to infusion of study intervention with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500 to 1000 mg po (or equivalent dose of analgesic).

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms after initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study intervention.	No subsequent dosing

CTCAE=Common Terminology Criteria for Adverse Events; h=hour; IV=intravenous; NCI=National Cancer Institute; NSAIDs=nonsteroidal anti-inflammatory drugs.
Note: 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 CTCAE v4.0 at http://ctep.cancer.gov

Other Allowed Dose Interruption for Pembrolizumab Monotherapy, Coformulations, or IO Combinations

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

6.6.4 Chemotherapeutic (Pemetrexed/Platinum) Dose Modifications

If a participant experiences a ≥10% weight change during Cycles 1 through 4, the doses of pemetrexed, cisplatin, or carboplatin 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 cisplatin/carboplatin, pemetrexed, or pembrolizumab alone, or to the combination, and use a stepwise dose modification (Table 5 through Table 13).

Dose modifications must be based on the maximum toxicity experienced during an intervention administration 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 recommended dose adjustment should be followed (ie, the dose reduction appropriate to the most severe toxicity). Participants who require a third dose modification to any particular component will have that intervention discontinued. 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 agents 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, the participant cannot proceed to the Maintenance Phase. If pembrolizumab and/or pemetrexed are discontinued during 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 <1,500/mm^3
- Platelet count <100,000/mm^3
- Hemoglobin level <9 g/dL
- Total bilirubin level >1.5 × upper limit of normal (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 on the Cockcroft-Gault formula; alternatively, CrCl can be determined from a 24-hour urine collection)

During Induction Phase Cycles 1 through 4 of pemetrexed plus cisplatin/carboplatin:

- If pemetrexed dosing is delayed or interrupted on Day 1, the platinum agent and pembrolizumab should also be delayed/interrupted. If pemetrexed plus cisplatin/carboplatin is delayed or interrupted during Cycles 1 through 4, participants should be seen weekly until toxicity resolves.
- If platinum dosing is delayed or interrupted on Day 1, pembrolizumab and pemetrexed should also be delayed/interrupted. If pemetrexed plus cisplatin/carboplatin is delayed or interrupted during Cycles 1 through 4, participants should be seen weekly until toxicity resolves.
- If pembrolizumab dosing is delayed or interrupted, pemetrexed plus cisplatin/carboplatin 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 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 reason for the dose interruption or reduction should be captured on the appropriate eCRF. The chemotherapy guidance for pembrolizumab/pemetrexed arm should be followed during Maintenance Phase.

The NCI 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 13. These serve as a guide and do not replace investigator judgment and applicable local label recommendations, if more stringent. A participant is allowed to switch from cisplatin to carboplatin if the participant develops unexpected toxicities with the use of cisplatin (including hearing loss), becomes ineligible for further cisplatin therapy, and/or the investigator considers switching to carboplatin to be in the best interest of the participant.

Table 11 Dose Modifications for Chemotherapeutic Agents

Drug	Dose Level 0	Dose Level -1	Dose Level -2	Dose Level -3
Cisplatin	75 mg/m^2	56 mg/ m^2	38 mg/ m^2	Discontinue
Carboplatin	AUC 5 mg/mL/min Maximum dose 750 mg	AUC 3.75 mg/mL/min Maximum dose 562.5 mg	AUC 2.5 mg/mL/min Maximum dose 375 mg	Discontinue
Pemetrexed	500 mg/m^2	375 mg/m^2	250 mg/m^2	Discontinue
Abbreviations: AUC = area under the concentration-time curve; BID = twice daily. For olaparib, follow dose medications as outlined in Section 6.6.2 (and all of its subsections). For pembrolizumab, follow dose modifications as outlined in Section 6.6.3 (and all of its subsections).				

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	Pemetrexed	Cisplatin/Carboplatin
		Dose Level (DL) from Table 11	
≥50,000/mcL AND	≥ 500/mcL	DL 0	DL 0
≥50,000/mcL AND	< 500/mcL	DL -1	DL -1
<50,000/mcL without Bleeding AND	ANY	DL -1	DL -1
<50,000/mcL with Grade ≥2 Bleeding AND	ANY	DL -2	DL -2
ANY AND	< 1,000/mcL + fever ≥ 38.5°C (101°F)	DL -1	DL -1
Abbreviations: ANC = absolute neutrophil counts; DL = dose level; mcL = microliter(s).			

Table 13 Recommended Dose Modifications for Chemotherapy Non-Hematological Toxicity

Event	CTCAE Grade	Pemetrexed	Cisplatin	Carboplatin
		Dose Level (DL) from Table 11		
Nausea or Vomiting	Grade 3 or 4	DL 0	DL 0	DL 0
Diarrhea	Grade 3 or 4	DL -1	DL -1	DL 0
Mucositis	Grade 3 or 4	DL -2	DL 0	DL 0
Neurotoxicity	Grade 2	DL 0	DL -2	DL 0
	Grade 3 or 4	DL -1	Discontinue	DL -1
Transaminase Elevation	Grade 3	DL -1	DL -1	DL -1
	Grade 4	Discontinue	Discontinue	Discontinue
Other Nonhematological Toxicity	Grade 3 or 4	DL -1	DL -1	DL -1

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

6.6.4.1 Creatinine Clearance

Creatinine clearance will be calculated using the original weight-based Cockcroft and Gault formula. As an alternative, CrCl can be determined from a 24-hour urine collection.

- During the Induction Phase, the CrCl must be ≥51 mL/min prior to the administration of chemotherapy.
- During the Maintenance Phase, for those participants in the pembrolizumab and maintenance pemetrexed arm, the CrCl must be ≥45 mL/min prior to the administration of chemotherapy.
  Note: Maintenance pemetrexed may be delayed for up to 42 days to allow the participant time to recover from the toxicity. If a participant's CrCl value has not returned to ≥45 mL/min within 42 days after the previous dose, maintenance pemetrexed must be discontinued and pembrolizumab can continue.

6.7 Intervention After the End of the Study

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

6.8 Clinical Supplies Disclosure

This study is open-label; therefore, the participant, the study site personnel, the Sponsor, and/or designee are not blinded. Study intervention (pembrolizumab [25 mg/mL] and olaparib [150 or 100 mg]) is included in the label text; random code/disclosure envelopes or lists are not provided.

6.9 Standard Policies

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 before completion of the protocol-specified treatment period will still continue to be monitored in this study and participate in the study visits and procedures as specified in Section 1.3 and Section 8.12.4 unless the participant has withdrawn from the study Section 7.2.

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.

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.
- 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.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive serum pregnancy test.
- Radiographic disease progression outlined in Section 8.2 (after obtaining informed consent addendum and Sponsor communication, the investigator may elect to continue treatment beyond iRECIST disease progression).
- Any progression or recurrence of malignancy, or any occurrence of another malignancy that requires active treatment.
- 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 (e.g. recurrent Grade 2 pneumonitis, recurrent Grade 3 colitis, recurrent Grade 3 diarrhea).

- Unacceptable AEs or toxicities (Section 6.6.1).
- Bone marrow findings consistent with MDS or AML.
- 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.
- Interruption of pemetrexed, carboplatin, or cisplatin for more than 6 weeks without Sponsor consultation.
- Interruption of pembrolizumab administration for >12 consecutive weeks for an AE/toxicity or for >3 weeks (>21 days) for administrative reasons without Sponsor consultation.
- Interruption of administration of olaparib for >21 consecutive days without Sponsor consultation.
- Intercurrent illness other than another malignancy as noted above that prevents further administration of treatment.
- Prohibited medication or vaccination required, and agreement between Sponsor, investigator, and participant to discontinue (Section 6.5.1).

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.

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).

7.2 Participant Withdrawal From the Study

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

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

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from FBR, are outlined in Section 8.1.8.2 and Section 8.1.8.3. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

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

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.
- Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study-site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All study-related medical decisions must be made by an investigator who is a qualified physician.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before providing documented informed consent may be used for screening or baseline purposes provided the procedures meet 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

Informed consent will adhere to IRB/IEC requirements, applicable laws and regulations, and Sponsor requirements. The ICF, any subsequent revised ICF, and any written information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use.

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 their legally acceptable representative) and of the person conducting the consent discussion.

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

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

8.1.1.1 General Informed Consent

Specifics about the study and the study population are to be included in the ICF.

The participant (or their legally acceptable representative) should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's or the participant's legally acceptable representative's dated signature.

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

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or medically qualified designee will explain the FBR consent to the participant, or the participant's legally acceptable representative, answer all of his/her questions, and obtain documented informed consent before performing any procedure related to FBR. A copy of the informed consent will be given to the participant before performing any procedure related to FBR.

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 ID 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. Details regarding the disease for which the participant has enrolled in this study will be recorded separately and not listed as medical history.

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

8.1.4.1 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 starting the study. Treatment for the disease for which the participant has enrolled in this study will be recorded separately and not listed as a prior medication.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study through the Safety Follow-up Visit. In addition, new medications started during the Second Course through the Second Course Safety Follow-up Visit should be recorded.

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 before intervention allocation. Each participant will be assigned only 1 screening number. Screening numbers must not be reused for different participants.

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

8.1.6.1 Treatment Eligibility Assessment (TEA) Form

- A TEA form located in the eCRF is included in this study to document the choice of platinum chemotherapy (carboplatin or cisplatin) and the rationale. These data may be required to support reimbursement efforts for pembrolizumab and maintenance olaparib following pembrolizumab in combination with pemetrexed/platinum (carboplatin or cisplatin).
- The investigator must complete this form and provide rationale to document the choice of platinum chemotherapy (carboplatin or cisplatin) prior to induction.

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 who 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, pemetrexed, carboplatin, and cisplatin during the Induction Phase will be monitored by the investigator and/or study staff.

During the Maintenance Phase, administration of pembrolizumab and either olaparib or pemetrexed 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 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, respectively.

Note: Participants taking olaparib or pemetrexed 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.

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 within ±3 days of the targeted Day 1 for each cycle.

Cycles 1-4 (Induction Phase)

Participants will receive pembrolizumab 200 mg (Day 1) with pemetrexed 500 mg/m^2 and the investigator's choice of carboplatin AUC 5 mg/mL/min or cisplatin 75 mg/m^2 for 4 cycles.

Cycles 1-31 (Maintenance Phase)

Participants will continue pembrolizumab 200 mg and begin maintenance therapy with either olaparib 300 mg BID or pemetrexed 500 mg/m^2 Q3W.

8.1.8.1.1 Pembrolizumab

Pembrolizumab will be administered as a 30-minute IV infusion Q3W, and it 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 Pemetrexed

Pemetrexed 500 mg/m^2 will be administered as an IV infusion over 10 minutes Q3W as per local practice and labels. All participants should receive the appropriate supplementation of vitamin B12 and folic acid and corticosteroid prophylaxis as listed below (or as per local label):

- Folic acid 350 to 1000 µg PO: at least 5 doses of folic acid must be taken during the 7 days preceding the first dose of pemetrexed, and folic acid dosing must continue during the full course of therapy and for 21 days after the last dose of pemetrexed.
- Vitamin B12 1000 µg IM injection in the week preceding the first dose of pemetrexed and once every 3 cycles thereafter. Subsequent vitamin B12 injections may be given the same day as pemetrexed administration.
- Dexamethasone prophylaxis 4 mg PO BID (or equivalent). Taken the day before, day of, and day after pemetrexed administration. Higher or additional doses are permitted for antiemetic prophylaxis during Cycles 1 to 4 but not to exceed doses in MASCC guidelines (Section 8.1.8.1.6).

8.1.8.1.3 Platinum-based Chemotherapy

8.1.8.1.3.1 Carboplatin

Carboplatin (AUC 5 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 pembrolizumab as per local practice and labels. The carboplatin dose should be calculated using the Calvert formula (see below) and should not to exceed 750 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 5 × (125 + 25)
  = 5 × 150
  = 750 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)]

Alternatively, CrCl can be determined from a 24-hour urine collection.

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.

8.1.8.1.3.2 Cisplatin

Cisplatin (75 mg/m^2) will be administered as an IV infusion over 30 to 180 minutes Q3W on Day 1 for up to 4 cycles (Induction Phase) and after pembrolizumab as per local practice and labels.

Participants are allowed to switch from cisplatin to carboplatin if the participant becomes ineligible for further cisplatin therapy according to local guidelines and the investigator considers switching to carboplatin to be in the best interest of the participant.

8.1.8.1.4 Olaparib

Participants must have at least one evaluable scan and no overall response of PD prior to starting either olaparib or pemetrexed in the Maintenance Phase. During the Maintenance Phase, olaparib administration will be witnessed by the investigator and/or study staff on Day 1 of the first cycle, and participants will then self-administer olaparib PO for the remainder of the 21-day treatment cycle. Participants will be instructed to self-administer olaparib at approximately the same time of day. If vomiting occurs within 2 hours after the olaparib 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 more 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.

8.1.8.1.5 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 patient population, especially as many participants have multiple comorbidities and advanced disease. Granulocyte-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].

8.1.8.1.6 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].

8.1.9 Discontinuation and Withdrawal

Participants who discontinue study intervention before completion of the treatment period should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA and Section 8.11.3.

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the final study visit at the time of withdrawal. Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.9.1 Withdrawal From Future Biomedical Research

Participants may withdraw their consent for FBR. Participants may withdraw consent at any time by contacting the study investigator. If medical records for the 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 FBR 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 before 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.

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

8.1.10 Participant Blinding/Unblinding

This is an open-label, unblinded study.

8.1.11 Calibration of Equipment

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

8.1.12 Tissue Collection

8.1.12.1 Tumor Tissue for Biomarker Status

During the Screening Phase, participants are required to have provided a newly obtained core or incisional biopsy of a tumor lesion not previously irradiated or, if not available, an archival tumor tissue sample. FFPE tissue blocks are preferred to slides. Newly obtained biopsies are preferred to archived tissue. Note: details pertaining to tumor tissue submission are in the Procedures Manual). Tissue is needed for central determination of PD-L1, HRRm, HRD-LOH, tumor mutation burden, and microsatellite instability-high status.

8.2 Efficacy Assessments

Immunogenicity assessments will not be performed in this study.

8.2.1 Tumor Imaging and Assessment of Disease

Throughout this section, the term 'scan' refers to any medical imaging data used to assess tumor burden and may include cross-sectional imaging (such as CT or MRI), medical photography, or other methods as specified in this protocol.

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. Tumor imaging is strongly preferred, as follows:

- CT with IV and oral contrast (preferred) of the chest, abdomen, and pelvis for all participants, or noncontrast 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, and 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. Treatment should continue until PD has been 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.

8.2.1.2 Tumor Imaging During the Study

During the Induction Phase, the first on-study imaging assessment should be performed at 6 weeks (42 days + 7 days) from the date of first dose. The second on-study imaging assessment should be performed at 12 weeks (84 days ± 7 days) from the date of first dose. All imaging must be submitted to the central imaging vendor for expedited BICR to determine lack of progression during the Induction Phase, which is required to be eligible for randomization.

For stratification purposes, confirmed and unconfirmed CR/PR will be stratified together. Nonevaluable imaging at Week 12 (84 days ± 7 days) will use the response obtained at the latest evaluable scan obtained at pre-randomization (Week 6 [42 days ± 7 days]) for stratification. Those patients with 2 nonevaluable scans during induction at Weeks 6 and 12 will not be randomized into the Maintenance Phase.

All imaging prior to initiating the Maintenance Phase should have been performed within 28 days of the date of randomization, and these imaging studies will serve as the new baseline. For participants randomized into the Maintenance Phase, imaging will be performed at 6 weeks (42 days + 7 days) after randomization, then every 6 weeks (Q6W; 42 days ± 7 days) for the first 60 weeks from the date of randomization, after which imaging will increase to every 9 weeks (Q9W; 63 ± 7 days). Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until centrally verified disease progression per RECIST 1.1 is identified by the investigator and verified by BICR (unless the investigator elects to continue treatment and follow iRECIST), the start of new anticancer treatment, withdrawal of consent, or death,

whichever occurs first. All supplemental imaging must be submitted to the central imaging vendor.

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

For participants who enter the Maintenance Phase and discontinue study intervention without centrally verified disease progression, every effort should be made to continue monitoring disease status by tumor imaging using the same imaging schedule used while on treatment (every 6 weeks (42 days ±7 days) for the first 60 weeks from the date of randomization) and then increase to Q9W (63 ±7 days) thereafter until the start of a new anticancer treatment, disease progression, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first.

Participants should continue with imaging per local standard of care after the EOT Visit.

8.2.1.4 Second Course Phase (Retreatment) Tumor Imaging

Tumor scans must be performed within 28 days prior to restarting treatment with pembrolizumab. Central reading will be used to determine eligibility.

The first on-study imaging assessment should be performed at 12 weeks (84 days ± 7 days) after the restart of treatment. Subsequent tumor imaging should be performed every 12 weeks (84 days ± 7 days) or more frequently, if clinically indicated. Participants who remain on treatment will have imaging performed as determined by the treating physician per the local standard of care, but not less frequently than every 12 weeks (84 days ± 7 days).

Per iRECIST (Section 8.2.1.6), if tumor imaging shows initial PD, tumor assessment should be repeated 4 to 8 weeks later in order 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 <4 weeks later and may wait until the next scheduled imaging time point, if the participant is 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.

For participants who discontinue Second Course Phase 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 Second Course Phase study intervention without locally verified disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging Q12W (84 days ± 7 days) from Second Course Phase Cycle 1, or more frequently, as clinically indicated thereafter, until the start of a new anticancer treatment, disease progression, death, withdrawal of consent, or the end of study, whichever occurs first.

8.2.1.4.1 Brain Imaging During Second Course Phase

A brain scan within 28 days of restarting pembrolizumab will only be performed in participants who have a history of protocol-eligible brain metastases or are clinically symptomatic. Subsequent brain scans in these participants will be performed Q12W (± 7 days), or as clinically indicated, after restarting pembrolizumab.

8.2.1.5 RECIST 1.1 Assessment of Disease

RECIST 1.1 will be used as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (eg, discontinuation of study intervention). Although RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, this protocol allows a maximum of 10 target lesions in total and 5 per organ, if clinically relevant to enable a broader sampling of tumor burden.

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
  - Resume imaging per protocol schedule (≥4 weeks to next scan)
  - 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:

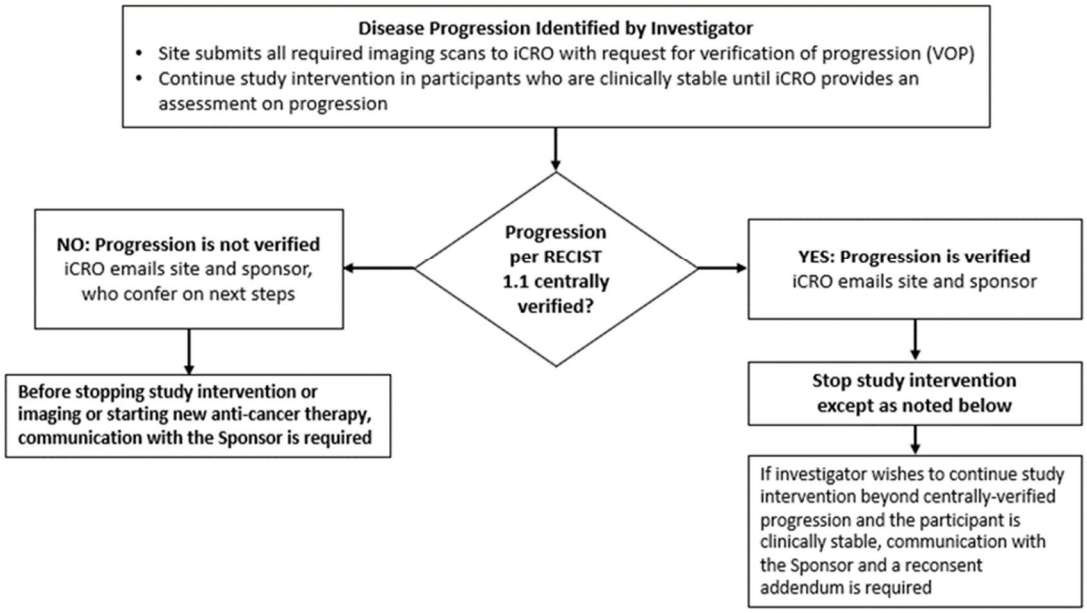
- Investigator judgement will determine action
- If participant is clinically stable and study intervention is to continue, communication with the Sponsor is required and a reconsent addendum must be signed
- Obtain scan(s) locally per original protocol schedule
- Do not send scan(s) to iCRO

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 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

8.2.2 Patient-reported Outcomes

Note: As of Amendment 07, participants who are still on study treatment will no longer require ePRO assessments. Original protocol text has been retained for reference.

CCI

[redacted]

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. The total amount of blood/tissue to be drawn/collected over the course of the study (from prestudy to poststudy visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant, can be found in Section 8.

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

8.3.1 Physical Examinations

A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) 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 study intervention administration and at other times according to the SoA (Section 1.3). 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

Temperature, pulse rate, respiratory rate, and blood pressure will be assessed.

8.3.3 Electrocardiograms

A standard 12-lead ECG will be performed using local standard procedures. The timing of the ECG is specified in the SoA (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 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 6.6.2.2.

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 perform the tests on a blood sample.

8.3.5 Performance Assessments: 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 the participant's ECOG status at Screening Phase, prior to administration of each dose of study intervention, and during the follow-up phase, as specified in the SoA (Section 1.3).

8.4 Adverse Events, Serious Adverse Events, 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 need to document if an SAE was associated with a medication error, misuse, or abuse.

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 informed consent, but before intervention allocation/randomization, must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event 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 after 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 after cessation of study intervention or 30 days after cessation of study intervention if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator.
- All pregnancies and exposure during breastfeeding, from the time of intervention allocation/randomization through the time required to eliminate systemic exposure after cessation of study intervention as described in Section 5.1, or 30 days after 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 the time 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 the investigator 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.

Table 14 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Period:** Consent to Randomization/ Allocation	**Reporting Period:** Randomization/ Allocation Through Protocol-specified Follow-up Period	**Reporting Period:** After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor
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
SAE, including Cancer and Overdose	Report if: – due to protocol-specified intervention – causes exclusion – participant is receiving placebo run-in or other run-in treatment	Report all	Report if: – drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/Lactation Exposure	Report if: – due to intervention – causes exclusion	Report all	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event
ECI (requiring regulatory reporting)	Report if: – due to intervention – causes exclusion	Report – potential DILI – requiring regulatory reporting	Not required	Within 24 hours of learning of event
ECI (does 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 (unless an SAE)

DILI=drug-induced liver injury; ECI=event of clinical interest; NSAE=nonserious adverse event; SAE=serious adverse 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. SAEs and other reportable safety events, including pregnancy and exposure during breastfeeding, 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). The investigator will also make every attempt to follow 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 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 SAEs) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Note: To meet EU CTR requirements, the Sponsor will report SUSARs to the Eudravigilance database via E2B(R3) electronic ICSR form in compliance with CTR 536/2014.

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 (spontaneously reported to the investigator or their designee) that occurs in a participant 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

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

Events of clinical interest for this study include:

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

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

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

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

8.5 Treatment of Overdose

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.

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

8.6 Pharmacokinetics

Pharmacokinetic parameters will not be evaluated in this study.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Biomarkers

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

- Archival or newly obtained tumor tissue
- Blood for genetic analysis
- Blood for RNA analyses
- Blood for circulating tumor DNA
- Blood for serum and plasma biomarker analyses

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

8.8.1 Planned Genetic Analysis Sample Collection

The genetic analysis specimen should be collected for the analysis of the association between genetic variants in DNA and drug response. This specimen will not be collected at the site if the IRB/IEC does not approve the collection based on a local law or regulation. If the specimen is collected, leftover extracted DNA will be stored for FBR if the participant provides documented informed consent for this research.

The genetic analysis specimen should be obtained pre-dose on Day 1 but may be collected at the next scheduled visit, if needed. Specimen collection, storage, and shipment instructions for genetic analysis specimens will be in the Central Laboratory Manual.

8.9 Future Biomedical Research Sample Collection

All specimen collections for study-specific assessments shown in the SoA are described within the full Informed Consent.

If the participant has provided documented informed consent for FBR, leftover specimens will be used for FBR. The following specimens will be included for FBR:

- Leftover specimens listed in Sections 8.8.

8.10 Health Economics Medical Resource Utilization and Health Economics

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

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

All-cause hospitalizations and emergency department visits must be reported in the eCRF. See Section 8.4.1 for reporting requirements.

8.11 Visit Requirements

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

8.11.1 Screening

Approximately 28 days before intervention allocation/randomization, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5. Screening procedures are to be completed within 28 days before the first dose of study intervention.

A test performed, as part of routine clinical management prior to the participant signing consent, is not to be repeated if performed within the specified time frame and the results are acceptable.

Screening procedures may be repeated after consultation with the Sponsor. If a study assessment needs to be repeated, the investigator may perform a retest of screening procedures to assess the eligibility of a participant as noted in Sections 5.1 and 5.2. Participants who are retested will retain their original screening number.

8.11.2 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 the

inclusion/exclusion criteria to ensure eligibility. A checklist will be completed and must be reviewed and approved by the Sponsor.

Participants with PD must be excluded from the Maintenance Phase and should enter EOT (refer to Section 1.3.3).

8.11.3 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.

8.11.4 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).

8.11.5 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 1 additional year (17 cycles) of treatment with pembrolizumab if they progress after stopping study treatment from the Maintenance Phase. This retreatment is termed the Second Course Phase, and it 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
- No new anticancer treatment was administered after the last dose of study intervention
- The participant meets all of the safety parameters listed in the inclusion criteria and none of the safety parameters listed in the exclusion criteria
- The study is ongoing
- 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.

8.11.6 Posttreatment Visit

8.11.6.1 Safety Follow-up Visit

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

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

8.11.6.2 Efficacy Follow-up Visits

Participants who complete the protocol-required cycles of study intervention or who discontinue study intervention for a reason other than disease progression will begin Efficacy Follow-up and should be assessed Q6W (42 days ± 7 days) during the 60 weeks following randomization and thereafter approximately Q9W (63 days ± 7 days) to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anticancer therapy, disease progression, death, end of study. or withdrawal of consent, whichever occurs first. Information regarding poststudy anticancer treatment will be collected if new treatment is initiated. Participants who completed all efficacy assessments and/or will not have further efficacy assessments must enter Survival Follow-up.

8.11.6.3 Survival Follow-up Contacts

Participant survival 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:

- For participants who discontinue treatment intervention and who will not enter Efficacy Follow-up, the first survival follow-up contact will be scheduled 12 weeks after the Discontinuation Visit and/or Safety Follow-up Visit (whichever is last).
- For participants who complete assessments in Efficacy Follow-up, the first survival follow-up contact will be scheduled 12 weeks after the last efficacy assessment follow-up visit has been performed.

8.11.7 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 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 participants who do not/will not have a scheduled study visit or study contact during the Sponsor-defined period will be contacted for their vital status.

If a participant withdraws consent or is lost to follow-up, vital status (survival information) can be conducted by review of medical records or public records when vital status is in question in accordance with local regulations, unless the participant has specifically withdrawn consent for collection of vital status data.

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If changes are made to primary and/or key secondary hypotheses or the statistical methods related to those hypotheses after the study has begun, but prior to any unblinding/final database lock, then the protocol will be amended (consistent with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [ICH] Guideline E9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to unblinding/final database lock, will be documented in a 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) will be developed to detail biomarker analyses. The PRO analysis plan will be included in the sSAP.

9.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below. The comprehensive plan is provided in Section 9.2 through Section 9.12.

Study Design Overview	A Phase 3 Study of Pembrolizumab in Combination with Pemetrexed/Platinum (Carboplatin or Cisplatin) Followed by Pembrolizumab and Maintenance Olaparib vs Maintenance Pemetrexed in the First-Line Treatment of Participants with Metastatic Nonsquamous Non-Small-Cell Lung Cancer
Treatment Assignment	After the Induction Phase treatment with pembrolizumab in combination with pemetrexed and platinum, approximately 672 eligible participants will be randomized in a 1:1 ratio to one of 2 treatment arms: 1. Pembrolizumab + olaparib 2. Pembrolizumab + pemetrexed Stratification factors are as follows: • ECOG PS of 0 vs. 1 • PD-L1 TPS: <50% vs. ≥50% • CR/PR vs. SD at Randomization
Analysis Populations	Efficacy: Intent-to-Treat (ITT) Safety: All Participants as Treated (APaT) PROs: Full Analysis Set (FAS)
Primary Endpoints	• PFS per RECIST 1.1 (Section 4.2.1.1) by BICR • OS
Secondary Endpoints	• Safety and tolerability • PROs

Statistical Methods for Key Efficacy Analyses	The dual primary hypotheses of PFS and OS will be evaluated by comparing pembrolizumab plus maintenance olaparib to pembrolizumab plus maintenance pemetrexed using a stratified log-rank test. The hazard ratio (HR) will be estimated using a stratified Cox regression model. Event rates over time will be estimated within each treatment arm using the Kaplan-Meier method.
Statistical Methods for Key Safety Analyses	The analysis of safety results in APaT will follow a tiered approach. The tiers differ with respect to the analyses that will be performed. There are no events of interest that warrant elevation to Tier 1 events in this study. Tier 2 safety parameters will be assessed via point estimates with 95% confidence intervals (CIs) provided for between-treatment comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters. The 95% CIs for the between-treatment differences in percentages will be provided using the Miettinen and Nurminen method.
Interim Analyses	CCI [redacted]
Multiplicity	The overall Type I error rate over the multiple endpoints will be strongly controlled at 2.5% (one-sided). CCI [redacted]

Sample Size and Power	Assumes that approximately 33% of patients progress or drop out during the Induction Phase, approximately 1005 participants will need to be enrolled into Induction Phase. The randomized sample size is approximately 672 participants. 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.

Although the study is open-label, analyses or summaries generated by randomized treatment assignment, and/or actual treatment received will be limited and documented. In addition, the independent radiologist(s) will perform the central imaging review without knowledge of treatment group assignment.

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

Planned interim analyses are described in Section 9.7.

The members of the Data Monitoring Committee (DMC) must not be involved with the study in any other way (eg, they cannot be study investigators) and must have no competing interests that could affect their roles with respect to the study.

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

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

In addition, an unblinding plan will be developed to maintain information about unblinding of Sponsor personnel prior to full unblinding at Sponsor. The personnel who have access to allocation schedules at what times will be documented in Appendix 4 (Interim Analysis Data Sources Memo) in the DMC Charter.

9.3 Hypotheses/Estimation

Objectives and hypotheses of the study are provided 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

Progression-free survival is defined as the time from randomization to the first documented disease progression per RECIST 1.1 (Section 4.2.1.1) based on BICR or death due to any cause, whichever occurs first.

Overall Survival

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

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[redacted]

9.4.2 Safety Endpoints

Safety measurements are described in Section 4.2.1.1.1, Section 8.3, and Section 8.4.

9.4.3 Patient-reported Outcome Endpoints

The following secondary PRO endpoints will be evaluated as described in Section 4.2.1.3:

- Global Health Status/QoL scale (EORTC QLQ-C30 Items 29 and 30)
- Single-item symptom scales: cough (EORTC QLQ-LC13 Item 1), chest pain (EORTC QLQ-LC13 Item 10), and dyspnea (EORTC QLQ-C30 Item 8)
- Composite-symptom endpoints: cough (QLQ-LC13 Item 1), chest pain (QLQ-LC13 Item 10), and dyspnea (QLQ-C30 Item 8)
- Physical functioning scale (EORTC QLQ-C30 Items 1 through 5)

Exploratory PRO endpoints include:

- EQ-5D-5L health-state dimensions (Items 1 through 5)
- EQ-5D-5L VAS (Item 6)

9.5 Analysis Populations

9.5.1 Efficacy Analysis Populations

The intent-to-treat (ITT) population will serve as the population for primary efficacy analysis. All randomized participants will be included in this population. Participants will be included in the treatment group to which they are randomized.

Details on the approach to handling missing data are provided in Section 9.6.

9.5.1.1 Safety Analysis Populations

The All Participants as Treated (APaT) population will be used for the analysis of safety data in this study. The APaT population consists of all randomized participants who received at least 1 dose of study intervention. Participants will be included in the treatment group corresponding to the study intervention they actually received for the analysis of safety data using the APaT population. For most participants, this will be the intervention group to which they are randomized. Participants who take incorrect study intervention for the entire treatment period will be included in the intervention group corresponding to the study intervention actually received. Any participant who receives the incorrect study intervention for 1 cycle, but receives the correct intervention for all other cycles, will be analyzed according to the correct intervention group, and a narrative will be provided for any events that occur during the cycle for which the participant is incorrectly dosed.

At least 1 laboratory or vital sign measurement obtained subsequent to at least 1 dose of study intervention is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required. The baseline value is defined as the last available measurement on or before the participant's first study intervention during Maintenance Phase.

Details on the approach to handling safety analyses are provided in Section 9.6.

9.5.2 Patient-reported Outcomes Analysis Population

The PRO analyses are based on the PRO Full Analysis Set population, defined as randomized participants who have at least 1 PRO assessment available and have received at least 1 dose of study intervention.

9.6 Statistical Methods

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

9.6.1 Statistical Methods for Efficacy Analyses

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 these values 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 endpoint in this study.

9.6.1.1 Progression-free Survival

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

Since PD is assessed periodically, PD can occur any time in the time interval between the last assessment when PD was not documented and the assessment when PD is documented. The true date of PD will be approximated by the date of the first assessment when PD is objectively documented per RECIST 1.1 by BICR. Death is always considered 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 the investigator's assessment.

In order to evaluate the robustness of the PFS endpoint per RECIST 1.1 by BICR, 1 primary and 2 sensitivity analyses with a different set of censoring rules will be performed. For the primary analysis, if the events (PD or death) are immediately after more than one missed disease assessment, the data are censored at the last disease assessment prior to missing visits. Also, data after new anticancer therapy are censored at the last disease assessment prior to the initiation of new anticancer therapy. The first sensitivity analysis follows the intent-to-treat principle. That is, PDs/deaths are counted as events, regardless of missed study visits or initiation of new anticancer therapy. The second sensitivity analysis considers

initiation of new anticancer treatment or discontinuation of treatment due to reasons other than complete response to be a PD event for participants without documented PD or death. If a participant meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied.

The censoring rules for primary and sensitivity analyses are summarized in Table 15.

Table 15 Censoring Rules for Primary and Secondary Analyses of PFS

Situation	Primary Analysis	Sensitivity Analysis 1	Sensitivity Analysis 2
PD or death documented after ≤1 missed disease assessment, and before new anticancer intervention, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death	Progressed at date of documented PD or death
PD or death documented immediately after ≥2 consecutive missed disease assessments or after new anticancer intervention, if any	Censored at last disease assessment prior to the earlier date of ≥2 consecutive missed disease assessment and new anticancer intervention, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death
No PD and no death; new anticancer intervention is not initiated	Censored at last disease assessment	Censored at last disease assessment	Progressed at treatment discontinuation due to reasons other than complete response; otherwise censored at last disease assessment if still on study intervention or completed study intervention.
No PD and no death; new anticancer intervention is initiated	Censored at last disease assessment before new anticancer intervention	Censored at last disease assessment	Progressed at date of new anticancer intervention

Abbreviations: PD = progressive disease; PFS = progression-free survival.

In case the proportional hazards assumption is not valid, supportive analyses using the restricted mean survival time (RMST) method may be conducted for PFS to account for the possible non-proportional hazards effect.

CCI [redacted]

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

9.6.1.2 Overall Survival (OS)

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

In case the proportional hazards assumption is not valid, the RMST method may be conducted for OS to account for the possible nonproportional hazards effect as a sensitivity analysis.

9.6.1.3 Analysis Strategy for Key Efficacy Endpoints

A summary of the primary analysis strategy for the key efficacy endpoints is provided in Table 16.

Table 16 Efficacy Analysis Methods for Key Efficacy Endpoints

Endpoint/ Variable	Statistical Method	Analysis Population	Missing Data Approach
Primary Analyses:			
PFS (RECIST 1.1) by BICR	Testing: Stratified log-rank test To assess treatment difference Estimation: Stratified Cox model with Efron's tie handling method to assess the magnitude of treatment difference	ITT	1. Primary censoring rule 2. Sensitivity analysis 1 3. Sensitivity analysis 2 More details are in Table 14
OS	Testing: Stratified log-rank test To assess treatment difference Estimation: Stratified Cox model with Efron's tie handling method to assess the magnitude of treatment difference	ITT	Censored at last known alive date
Abbreviations: BICR = blinded independent central review; ITT = intention to treat; OS = overall survival; PFS = progression-free survival; RECIST 1.1 = response evaluation criteria in solid tumors version 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).

Table 17 Analysis Strategy for Safety Parameters

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

Abbreviations: AE = adverse event; ECG = electrocardiogram; PDLC = pre-defined 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.

The tiers differ with respect to the analyses that will be performed. Adverse events (specific terms and system organ class terms) and events that meet predefined limits of change in laboratory, vital signs, and ECG parameters are either prespecified as Tier 1 endpoints, or they will be classified as belonging to Tier 2 or Tier 3, based on the number of observed events.

Tier 1 Events

Safety parameters or adverse events of special interest (AEOSIs) that are identified a priori constitute Tier 1 safety endpoints that will be subject to inferential testing for statistical significance with p-values and 95% CIs provided for between-group 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% CIs provided for 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 show the event. The threshold of at least 10% of participants was chosen for Tier 2 events, because the population enrolled in this study is in critical condition and usually experiences various AEs of similar types, regardless of treatment; events reported less frequently 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 AEs (≥5% of participants in one of the intervention groups) and SAEs (≥5% of participants in one of the intervention groups) will be considered Tier 2 endpoints. Because many 95% CIs may be provided without adjustment for multiplicity, the CIs should be regarded as a helpful descriptive measure to be used in safety review, not a formal method for assessing the statistical significance of the between-group differences.

Tier 3 Events

Safety parameters 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

Continuous measures, such as changes from baseline (ie, the last available measurement on or before the first study intervention during Maintenance Phase) in laboratory, vital signs, and ECG parameters that are not pre-specified 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 intervention group in tabular format.

9.6.3 Statistical Methods for PRO Analyses

Changes from baseline (at randomization) in the following secondary PRO endpoints from the EORTC QLQ-C30 and QLQ-LC13 questionnaires will be assessed:

- Global health status/QoL score (QLQ-C30 Items 29 and 30)
- Cough score (QLQ-LC13 Item 1)
- Chest pain score (QLQ-LC13 Item 10)
- Dyspnea score (QLQ-LC13 Item 8)
- Physical functioning score (QLQ-C30 Items 1 through 5)

A constrained longitudinal data analysis model will be applied for each endpoint, with the PRO score as the response variable, and treatment, time, treatment by time interaction, and clinical study stratification factors as covariates. Least-square mean change from baseline (at randomization) will be summarized for each outcome. Treatment effect on PRO score change from baseline will primarily be evaluated at Week 18 post-randomization. If the overall PRO completion or compliance rates at Week 18 are less than 60% or 80%, respectively, then the primary analysis time point will be moved to the next earliest time point in which the rates are at least 60% for completion and at least 80% for compliance. The difference in the least-square mean change from baseline will be reported at the primary analysis time point.

Descriptive analyses will assess the empirical mean change (with 95% CIs) from baseline across all time points for each endpoint.

TTD is defined as the time from baseline (at randomization) to the first onset of a ≥10-point decrease in PRO score with confirmation by the subsequent visit of a ≥10-point deterioration from randomization. The Kaplan-Meier method will be used to estimate the TTD survival curves for global health status/QoL (QLQ-C30 Items 29 and 30), cough (QLQ-LC13 Item 1), chest pain (QLQ-LC13 Item 10), dyspnea (QLQ-C30 Item 8), and physical functioning (QLQ-C30 Items 1 through 5), separately, in each intervention arm. In addition, TTD survival curves will be estimated for the composite endpoint of cough, chest pain, or dyspnea by intervention arm. Stratified Cox proportional hazards models with Efron's method of tie handling will be used to assess the magnitude of the intervention difference for pembrolizumab plus olaparib compared with pembrolizumab plus pemetrexed. Stratification factors used for randomization will be used in the stratified Cox proportional hazards models. The hazard ratio, 95% CI, and nominal p-value will be reported.

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

9.6.4 Summaries of Baseline Characteristics and Demographics

The comparability of the 2 intervention arms for each relevant demographic and baseline characteristic will be assessed by the use of 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 randomized, and the primary reason for screening failure and discontinuation will be displayed. Demographic variables (such as age, gender), baseline characteristics will be summarized by intervention either by descriptive statistics or categorical tables. The reasons for exclusion from the ITT population (if any) will be summarized.

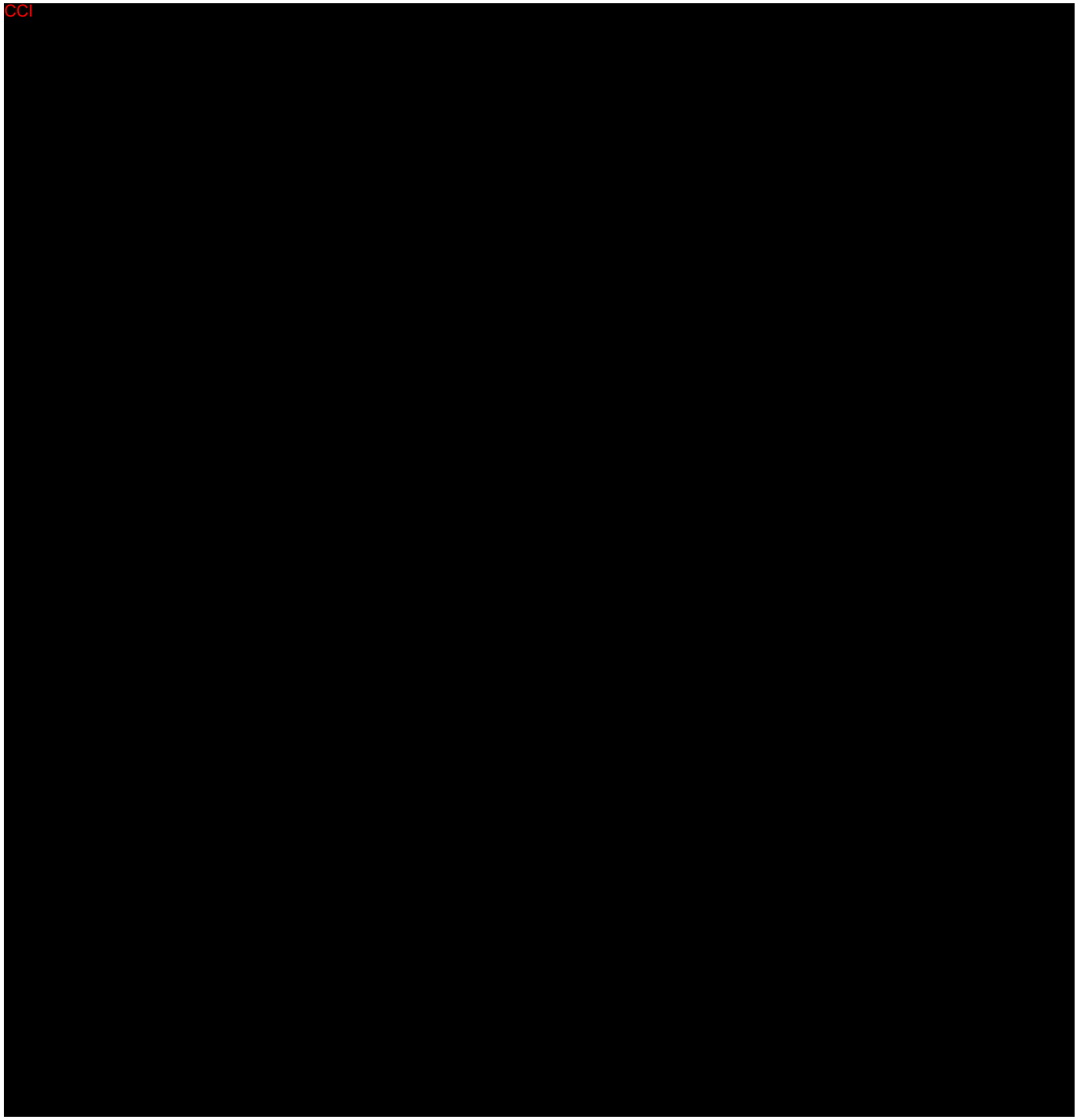
9.7 Interim Analyses

An eDMC will serve as the primary reviewer of the results of the interim analysis (analyses) of the study and will make recommendations for discontinuation of the study or protocol modifications to the EOC of the Sponsor (Appendix 1). If the DMC recommends modifications to the protocol design or study discontinuation, this executive committee (and potentially other limited Sponsor personnel) may be unblinded to results at the treatment level in order to act on these recommendations. The extent to which individuals are unblinded with respect to results of interim analyses will be documented. Additional logistical details will be provided in the DMC Charter.

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

9.7.1 CCI [redacted]

CCI [redacted]



9.7.2 CCI [redacted]

CCI [redacted]

9.8 Multiplicity

The overall Type I error rate is strongly controlled at a 0.025 (one-sided) α level. The study uses the graphical method of Maurer and Bretz [Anderson, K. M., et al 2017] to provide strong multiplicity control for multiple hypotheses as well as interim efficacy analyses; this method specifically extends previous graphical multiplicity methods to cases where individual hypotheses are tested in a group sequential fashion using an error spending approach. CCI

CCI

9.8.1 CCI

CCI

CCI [redacted]

9.8.2 CCI [redacted]

[redacted]

CCI

[redacted]

CCI

9.8.3 Safety Analyses

The DMC has responsibility for assessment of the overall risk:benefit. When prompted by safety concerns, the DMC can request corresponding efficacy data. 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 DMC review of unplanned efficacy data prompted by safety concerns, a sensitivity analysis for PFS and OS adopting a conservative multiplicity adjustment may be prespecified in the sSAP. This analysis will be performed if requested by the DMC.

9.9 Sample Size and Power Calculations

The study randomized approximately 672 participants in a 1:1 ratio into the 2 study interventions, pembrolizumab combined with maintenance olaparib and pembrolizumab combined with maintenance pemetrexed. PFS and OS are dual primary endpoints for the study.

9.10 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 for a participant is defined as the number of cycles in which the participant received study intervention. 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 Interventional Clinical Trials

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

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical

trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

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

III. Participant Protection

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

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, frequently 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

The Sponsor will conduct this study in compliance with all applicable data protection regulations. 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 their 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 their 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. The Sponsor has EU-approved Binding Corporate Rules since 2017, covering all aspects of its Global Privacy Program (Corporate Policy 20), and is self-certified pursuant to the EU-US Data Privacy Framework.

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 before 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 Steering Committee

This study will be conducted in consultation with a Steering Committee. The Steering Committee may be comprised of:

- Sponsor personnel,
- Investigators participating in the study, and
- Consulting therapeutic-area experts and clinical trialists.

The Steering Committee will provide guidance on the operational aspects of the study, evaluate recommendations from the DMC, and make recommendations to the EOC.

Specific details regarding responsibilities and governance of the Steering Committee will be described in a separate charter.

10.1.4.2 Executive Oversight Committee

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

10.1.4.3 External Data Monitoring Committee

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

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

study results, consider the overall risk and benefit to study participants (Section 9.7) 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 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 ICMJE authorship requirements.

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical trials Regulation 536/2014, 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, https://euclinicaltrials.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 trials Regulation 536/2014 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 Regulation 536/2014, 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, ICH 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 Trials.

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

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

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

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

10.1.8 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF. Detailed information regarding Data Management procedures for this protocol will be provided separately. The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF. The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents. Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the study site upon request for inspection, copying, review, and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor or any regulatory authorities as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/CRFs. The Sponsor or designee is responsible for the data management of this study including quality checking of the data. Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements. Records and

documents, including participants' documented informed consent, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period (eg, EU CTR: 25 years after the end of the study). 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 or designee will promptly notify that study site's IRB/IEC as specified by applicable regulatory requirement(s).

As of Amendment 07, at the final analysis, the pembrolizumab plus olaparib arm did not meet the primary endpoint of OS. In addition, at the protocol prespecified final PFS analysis at Interim Analysis 2 that occurred on PFS was not statistically significant compared with the control arm. The study will remain open so ongoing participants will have continued access to olaparib, pemetrexed and pembrolizumab if they qualify per protocol or until transferred to an extension study, if applicable. Given that the study did not meet primary endpoints, central imaging verification, ePRO data, and survival follow-up will no longer be collected. Participants in survival follow-up will be discontinued from the study. Effective with Amendment 08, participants who are in follow-up and did not receive 35 doses of pembrolizumab during the initial treatment period and/or are not eligible for second course treatment should be discontinued.

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 Sections 5.1 and 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	Platelet count RBC count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Chemistry	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 (as needed in WOCBP only) • Serum or urine human chorionic gonadotropin (hCG) pregnancy test (as needed for WOCBP). • Serology (HIV antibody, hepatitis B surface antigen, 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)			
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			

Laboratory Assessments	Parameters
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; WOCBP = woman/women of childbearing potential. 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 Definitions of Medication Error, Misuse, and Abuse

Medication Error

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

Misuse

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

Abuse

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

10.3.2 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.
- Note: For purposes of AE definition, study intervention includes any pharmaceutical product, biological product, vaccine, diagnostic agent, medical device, combination product, 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 preexisting 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 preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgical procedure(s) planned prior to informed consent to treat a preexisting condition that has not worsened.
- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.3 Definition of SAE

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

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

a. Results in death
b. Is life-threatening
   - The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization
   - Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a preexisting condition that has not worsened is not an SAE.) A preexisting condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant's medical history.

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

e. Is a congenital anomaly/birth defect
   - In offspring of participant taking the product regardless of time to diagnosis.

f. Other important medical events
   - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.
   - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.4 Additional Events Reported in the Same Manner as SAE

Additional events that require reporting in the same manner as SAE

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

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

10.3.5 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.

- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity/toxicity

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

- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI CTCAE, version 4.0. Any AE that changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.
  - Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
  - Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
  - Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
  - Grade 4: Life-threatening consequences; urgent intervention indicated.
  - Grade 5: Death related to AE.

  Note: A semi-colon indicates 'or' within the description of the grade.

Assessment of causality

- Did the study intervention cause the AE?
- The determination of the likelihood that the study intervention 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 study intervention and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the study intervention caused the AE:**
  - **Exposure:** Is there evidence that the participant was actually exposed to the study intervention 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 study intervention? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with IMP)?
  - **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 study intervention 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 study intervention; (3) the study is a single-dose drug study; or (4) study intervention (s) is/are only used 1 time.)
  - **Rechallenge:** Was the participant reexposed to the study intervention 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) study intervention (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 STUDY INTERVENTION, OR IF REEXPOSURE TO THE STUDY INTERVENTION 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 study intervention 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 their 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 study intervention relationship).
  - Yes, there is a reasonable possibility of study intervention relationship:
    - There is evidence of exposure to the study intervention. The temporal sequence of the AE onset relative to the administration of the study intervention is reasonable. The AE is more likely explained by the study intervention than by another cause.
  - No, there is not a reasonable possibility of study intervention relationship:
    - Participant did not receive the study intervention OR temporal sequence of the AE onset relative to administration of the study intervention is not reasonable OR the AE is more likely explained by another cause than the study intervention. (Also entered for a participant with overdose without an associated AE.)
- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes.
- 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 their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.
- For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each AE causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (ie, to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the investigator's opinion, there is sufficient data to support full attribution of the AE to the single agent.

Follow-up of AE and SAE

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

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

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

- The primary mechanism for reporting to the Sponsor will be the 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: Medical Device and Drug–Device Combination Products: Product Quality Complaints/Malfunctions: Definitions, Recording, and Follow-up

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 nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraceptive 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, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea 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 at monthly intervals during intervention.
- Pregnancy testing ([urine or serum] as required by local regulations) should be conducted 30 days after the last dose of study intervention.
- 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.

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

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]
b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]
c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]
d. DNA: Deoxyribonucleic acid.
e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research3, 4

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

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

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

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

3. Summary of Procedures for Future Biomedical Research3, 4

a. Participants for Enrollment
All participants enrolled in the clinical study will be considered for enrollment in future biomedical research.

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

the participant will be kept at the clinical study site under secure storage for regulatory reasons.

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

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

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

4. Confidential Participant Information for Future Biomedical Research[3, 4]

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

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

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

5. Biorepository Specimen Usage[3, 4]

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

6. Withdrawal From Future Biomedical Research[3, 4]

Participants may withdraw their consent for FBR and ask that their biospecimens not be used for FBR. Participants may withdraw consent at any time by contacting the study investigator. If medical records for the study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to study use only. If specimens were collected from study participants specifically for FBR, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed before 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.

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

7. Retention of Specimens[3, 4]

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

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

8. Data Security[3, 4]

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

9. Reporting of Future Biomedical Research Data to Participants[3, 4]

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

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

10. Future Biomedical Research Study Population[3, 4]

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

11. Risks Versus Benefits of Future Biomedical Research[3, 4]

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

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

12. Questions

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

13. References

1. National Cancer Institute [Internet]: Available from https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45618
2. International Council on Harmonisation [Internet]: E15: Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. Available from http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html
3. Industry Pharmacogenomics Working Group [Internet]: Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

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

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

Confidential Participant Information for Biomarker Research [1]

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

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

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

Biorepository Specimen Usage

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

Retention of Specimens

Biomarker and other specimens will be stored in the biorepository for potential analysis for up to 15 years from the end of the study. If there are regulatory or governmental authority questions that are being answered, specimens may be stored for longer. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

The specimens will be stored in a limited access facility that operates to assure the integrity of the specimens and under strict supervision. Specimens will be destroyed according to

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

Data Security

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

Reporting of Exploratory Research Data to Participants

Results obtained from genetic and biomarker research will not be given to study participants or the trial doctor.

If important research findings are discovered, the Sponsor may share this information by:

- publishing the results in peer-reviewed journals
- presenting the results at national meetings
- providing the results on a publicly accessible website that would be available to doctors and participants

Participants will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

Questions

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

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10.7 Appendix 7: Country-specific Requirements

10.7.1 France Country-specific Requirements

1. Section 1.3.1: Schedule of Activities for Screening and Induction Phases
   Pregnancy testing is required at each cycle during treatment as well as at the end of study treatment.

2. Section 1.3.2: Schedule of Activities for Maintenance Phase
   Pregnancy testing is required at each cycle during treatment as well as at the end of study treatment.

3. Section 1.3.4: Schedule of Activities for Second Course Phase
   Pregnancy testing is required at each cycle during treatment as well as at the end of study treatment.

4. Section 10.5 Appendix 3: Contraceptive Guidance and Pregnancy Testing
   Pregnancy testing is required at each cycle during treatment as well as at the end of study treatment.

10.7.2 Germany Country-specific Requirements

1. Section 5.2 Exclusion Criteria

- Exclusion Criterion 10: HIV testing is required for participants who are residents of Germany.
- Exclusion Criterion 11: Hepatitis B and C testing is required for participants who are residents of Germany.
- Exclusion Criterion 12: TB testing is required for participants who are residents of Germany.

2. 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.
3. 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.
4. Section 1.3.4: Schedule of Activities for Second Course Phase
   Pregnancy testing is required at each cycle during treatment as well as at the end of study treatment.
5. Section 6.5.1 (Prohibited Concomitant Medications): Live vaccines must not be administered for 90 days after the last dose of study intervention.

6. Section 4.4: Legally Acceptable Representative
   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.
7. Section 10.5 Appendix 3: 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 Country-specific Requirements

For the assistance to early diagnosis of pneumonitis/interstitial lung disease (ILD) in study participants, the following items, such as pulse oximetry monitoring (peripheral capillary oxygen saturation [SpO_2]), C-reactive protein (CRP), Krebs von den Lungen-6 (KL-6), and surfactant protein-D (SP-D), will be measured in this study. These items should be measured as follows:

- SpO_2 at the timing of vital sign assessment.
- CRP, KL-6, and SP-D at screening*, predose on Day 1 of every cycle, end-of-treatment, and the Safety Follow-up Visit (30 days after last dose).

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

If pneumonitis/ILD occurs regardless of causality with study intervention, 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 Country-specific Requirements

1. 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.
2. Males are to be advised to seek counseling on sperm storage before starting pemetrexed and platinum-based therapy as per respective SmPCs.
3. 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.
4. 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.

5. Section 1.3.4: Schedule of Activities for Second Course Phase

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

6. Section 10.5 Appendix 3: 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 disease progression by RECIST 1.1, the investigator will decide whether to continue a participant on study intervention until repeat scans 4 to 8 weeks later are 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 with any prior iUPD time point
  - For nontarget lesions, worsening is any significant growth in lesions overall, compared with 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 disease progression 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 disease progression 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 pseudoprogression, 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 Pseudoprogression Resolves

After resolution of pseudoprogression (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 disease progression threshold (≥20% and ≥5 mm increase from nadir) either for the first time, or after resolution of previous pseudoprogression. The nadir is always the smallest sum of diameters seen during the entire study, either before or after an instance of pseudoprogression.
- 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 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
ANC	absolute neutrophil count
APaT	all participants as treated
AST	aspartate aminotransferase
ATM	ataxia-telangiectasia mutated
AUC	area under concentration-time curve
BCG	Bacillus Calmette–Guérin
BICR	blinded independent central review
BID	twice daily
BRCA1/2	breast cancer susceptibility gene 1/2
BRCAm	breast cancer susceptibility gene mutation
C30	Core 30
CI	confidence interval
C_{max}	maximum plasma concentration
CONSORT	Consolidated Standards of Reporting Trials
COPD	chronic obstructive pulmonary disease
CR	complete response
CrCl	creatinine clearance
CRF	Case Report Form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trials Facilitation and Coordination Group
CTR	clinical trial regulation
CYP	cytochrome P450

Abbreviation	Expanded Term
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
EEA	European economic area
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EOC	Executive Oversight Committee
EORTC	European Organization for Research and Treatment of Cancer
EOS	end of study
EOT	end-of-treatment
ePRO	electronic patient-reported outcomes
EQ-5D-5L	European Quality of Life Five-dimension Five-level Scale Questionnaire
ESMO	European Society for Medical Oncology
EU	European Union
FAS	full analysis set
FBR	future biomedical research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FSH	follicle-stimulating hormone
FSR	first site ready
FT4	free thyroxine
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor

Abbreviation	Expanded Term
GFR	glomerular filtration rate
GM-CSF	granulocyte-macrophage colony-stimulating factor
GMP	Good Manufacturing Practice
Hb	hemoglobin
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate
HRD	homologous recombination deficiency
HRD-LOH	homologous recombination deficiency loss of heterozygosity
HRQoL	health-related quality of life
HRR	homologous recombination repair
HRRm	homologous recombination repair mutations
HRT	hormone replacement therapy
IB	investigator 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
ICSR	Individual case study report
IEC	Independent Ethics Committee
Ig	immunoglobulin
IHC	immunohistochemistry
ILD	interstitial lung disease
IM	intramuscular
IND	Investigational New Drug
IO	immuno-oncology
iPR	iRECIST partial response
irAE	immune-related adverse event

Abbreviation	Expanded Term
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
ITT	intent-to-treat
IUD	intrauterine device
iUPD	iRECIST unconfirmed progressive disease
IV	intravenous
LC13	Lung Cancer Module 13
LOH	loss of heterozygosity
MASCC	Multinational Association of Supportive Care in Cancer
MDS	myelodysplastic syndrome
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCT	National Clinical Trial
NHEJ	nonhomologous end-joining
NSCLC	non–small-cell lung cancer
ORR	objective response rate
OS	overall survival
PARP	polyadenosine 5′ diphosphoribose 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
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PRO	patient reported outcome

Abbreviation	Expanded Term
PT	prothrombin time
Q12W	every 12 weeks
Q2W	every 2 weeks
Q3W	every 3 weeks
Q6W	every 6 weeks
Q9W	every 9 weeks
QLQ	Quality of Life Questionnaire
QoL	quality of life
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RMST	restricted mean survival time
RNA	ribonucleic acid
SAE	serious adverse event
SD	stable disease
SoA	schedule of activities
SOC	standard of care
SpO_2	pulse oximetry monitoring
sSAP	supplemental statistical analysis plan
SSB	single strand break
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	terminal half-life
TIL	tumor-infiltrating lymphocytes
T_{max}	time to maximum plasma concentration
TPS	tumor proportion score
ULN	upper limit of normal
USPI	United States prescribing information
VOP	verification of progression
WOCBP	woman/women of childbearing potential

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