Official Protocol Title:	Protocol/Amendment No.: 001-05 A Randomized Phase 3, Double-Blind Study of Chemotherapy With or Without Pembrolizumab Followed by Maintenance With Olaparib or Placebo for the First-Line Treatment of BRCA non-mutated Advanced Epithelial Ovarian
NCT number:	NCT03740165
Document Date:	19-Aug-2025

Title Page

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Protocol Title: A Randomized Phase 3, Double-Blind Study of Chemotherapy With or Without Pembrolizumab Followed by Maintenance With Olaparib or Placebo for the First-Line Treatment of BRCA non-mutated Advanced Epithelial Ovarian Cancer (EOC) (KEYLYNK-001 / ENGOT-ov43 / GOG-3036)

Protocol Number: 001-05/ENGOT-ov43/GOG-3036

Compound Number: MK-7339

Sponsor Name and Legal Registered Address:

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

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P.O. Box 2000
Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

NCT: NCT03740165

IND NUMBER: 139,020

EU CT: 2022-502124-52

EudraCT NUMBER: 2018-001973-25

WHO/UTN: U1111-1283-3793

Approval Date: 19 August 2025

Sponsor Signatory

Typed Name: Date
Title:

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

Investigator Signatory

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

Typed Name: Date
Title:

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 05	19-AUG-2025	To add the option of an extension study and discontinue all blood collections for ctDNA analysis and all PRO collections.
Amendment 04	07-NOV-2022	Recent data from studies using olaparib as front-line maintenance treatment for patients with HRD negative ovarian cancer have suggested a limited overall survival benefit (ie, PAOLA-1), which represents about 70% of all *BRCA*wt population. Pembrolizumab, in addition to chemotherapy (Arm 2), could provide added benefit over standard-of-care chemotherapy (Arm 3) in the HRD negative subgroup (where PARP inhibitors have shown limited efficacy), in particular in the CPS ≥10 population. Therefore, the multiplicity strategy was amended to prioritize the PFS hypothesis for the pembrolizumab arm in the CPS ≥10 population and to add an OS hypothesis for the pembrolizumab arm in the CPS ≥10 population.
Amendment 03	12-MAR-2021	Data from external studies in ovarian cancer have suggested an enriched treatment effect for programmed cell death 1 ligand 1 (PD-L1) inhibitors with increasing PD-L1 expression. The cutoff of combined positive score (CPS) ≥10 has been included to identify a population of participants that could potentially benefit more from chemotherapy with or without pembrolizumab (±bevacizumab) followed by maintenance with olaparib (±pembrolizumab) or placebo for the first-line treatment of *BRCA1/2* non-mutated advanced epithelial ovarian cancer (EOC).
Amendment 02	20-AUG-2020	To clarify study-related procedures and assessments, to add ctDNA collections, and to allow docetaxel for participants who cannot tolerate paclitaxel following Sponsor consultation.

Document	Date of Issue	Overall Rationale
Amendment 01	02-MAY-2019	Multiple updates were incorporated, including: Extending period from primary debulking surgery to start of lead-in chemotherapy; extending the Screening Period to better reflect the standard of care across many countries; allowing additional time for recovery from toxicities associated with lead-in chemotherapy following Sponsor consultation; allowing participants to start maintenance earlier if they cannot tolerate 6 cycles of treatment following Sponsor consultation; revision of hemoglobin levels required for study entry; and clarification of discontinuation criteria based on clinical progression as determined by CA-125 and concurrent malignant bowel obstruction.
Original protocol	28-AUG-2018	N/A

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 05

Overall Rationale for the Amendment:

To add the option of an extension study and discontinue all blood collections for ctDNA analysis and all PRO collections.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
Section 6.7, Treatment After the End of the Study	Duration of Participation: Added the possibility of an extension study.	To address a change in strategy by providing the option of an extension study.

Section Number and Name	Description of Change	Brief Rationale
Additional Changes		
Title Page	Added NCT, EU CT, and WHO/UTN numbers.	To include current trial registry information.
Section 1.1, Synopsis	Overall Design: Updated the estimated duration of the study from 6 years to 7 years.	To align with the current estimated duration between first patient enrolled and last patient, last visit.
	Duration of Participation: Noted that all blood collections for ctDNA analysis and all PRO collections will be discontinued.	To discontinue nonessential assessments.
Section 1.3.1, SoA – Adjuvant Treatment Period With Primary Debulking Followed by Maintenance	Discontinued all PRO collections.	See Section 1.1 rationale, nonessential assessments.
	Discontinued all blood collections for ctDNA analysis.	See Section 1.1 rationale, nonessential assessments.
Section 1.3.2, SoA – Neoadjuvant/Adjuvant Treatment Period With Interval Debulking Followed by Maintenance	Discontinued all PRO collections.	See Section 1.1 rationale, nonessential assessments.
	Discontinued all blood collections for ctDNA analysis.	See Section 1.1 rationale, nonessential assessments.
Section 4.1, Overall Design	Noted that all blood collections for ctDNA analysis and all PRO collections will be discontinued.	See Section 1.1 rationale, nonessential assessments.
	Added the option of an extension study.	See rationale for Section 1.1, Duration of Participation - strategy, extension study.

Section Number and Name	Description of Change	Brief Rationale
Section 4.2.1.3, Patient-reported Outcomes	Noted that all PRO collections will be discontinued.	See Section 1.1 rationale, nonessential assessments.
Section 4.4, Beginning and End of Study Definition	Refined the definitions of start and end of study.	To align with the EU CTR.
	Added text regarding the estimated maximum duration of the study to attain final assessment.	See above rationale pertaining to the EU CTR.
Section 6.7, Treatment After the End of the Study	Added extension study language for intervention after the end of the current study.	See rationale for Section 1.1, Duration of Participation - strategy, extension study.
Section 8, Study Assessments and Procedures	Added a statement to specify that the Sponsor will provide ample notification to investigators should additional procedures/assessments be discontinued in the future.	To allow the Sponsor the option of discontinuing future procedures/assessments if needed.
Section 8.2.4, Quality-of-Life Assessment	Noted that all PRO collections will be discontinued.	See Section 1.1 rationale, nonessential assessments.
Section 8.4.1, Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information	Added text about collecting safety event information in an extension study.	See rationale for Section 1.1, Duration of Participation - strategy, extension study.
	Table 10: Revised text for Pregnancy/Lactation Exposure row.	To add details not previously specified.
	Table 10: Updated periods and duration for potential DILI events meeting biochemical criteria of Hy's Law.	To maintain continued regulatory reporting compliance in alignment with new health authority DILI reporting requirements.
	Table 10: Revised text for ECI (requiring regulatory reporting) row.	For consistency with language in Section 8.4.3.
Section 8.4.3, Follow-up of AE, SAE, and Other Reportable Safety Event Information	Added potential DILI events meeting biochemical criteria of Hy's Law to list of other reportable safety events.	See Section 8.4.1 rationale, DILI reporting requirements.
Section 8.4.4, Regulatory Reporting Requirements for SAE	Added a statement describing the process for reporting SUSARs.	See Section 4.4 rationale pertaining to the EU CTR.
Section 8.4.7, Events of Clinical Interest	ECIs updated to include potential DILI meeting biochemical criteria of Hy's Law, with associated reporting requirements.	See Section 8.4.1 rationale, DILI reporting requirements.
Section 10.1, Appendix 1: Regulatory, Ethical and Study Oversight Considerations	Added numbering (10.1.3.1 through 10.1.10) to subheadings where missing.	To streamline the flow of content.
Section 10.1.1, Code of Conduct for Clinical Trials	Updated wording to include reference to additional standards and regulations.	See Section 4.4 rationale pertaining to the EU CTR.
Section 10.1.3, Data Protection	Added text regarding Sponsor's EU-approved Binding Corporate Rules.	See Section 4.4 rationale pertaining to the EU CTR.

Section Number and Name	Description of Change	Brief Rationale
Section 10.1.6, Compliance With Study Registration and Results Posting Requirements	Updated referenced EU regulation and added a submission website link.	See Section 4.4 rationale pertaining to the EU CTR.
Section 10.1.7, Compliance with Law, Audit, and Debarment	Added text for investigators located in countries with serious breach reporting requirements.	See Section 4.4 rationale pertaining to the EU CTR.
Section 10.1.8, Data Quality Assurance	Added the EU CTR requirement for a 25-year retention period for records and documents.	See Section 4.4 rationale pertaining to the EU CTR.
Section 10.3, Appendix 3: Contraceptive Guidance and Pregnancy Testing	Added numbering (10.3.1 through 10.3.3) to subheadings.	See Section 10.1 rationale.
Section 10.4, Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Added numbering (10.4.1 through 10.4.7) to subheadings.	See Section 10.1 rationale.
Section 10.4.3, Definition of SAE	Added potential DILI events meeting biochemical criteria of Hy's Law to definition of SAE.	See Section 8.4.1 rationale, DILI reporting requirements.
Section 10.4.4, Definition of a Suspected Unexpected Serious Adverse Reaction (SUSAR)	Added this section.	See Section 8.4.1 rationale, details not previously specified.
Section 10.6, Appendix 6: Collection and Management of Specimens for Future Biomedical Research	Added numbering (10.6.1 through 10.6.8) to subheadings.	See Section 10.1 rationale.
Section 10.10, Appendix 10: Weighted Parametric Group Sequential Design	Removed multiple pages of code at the end of this section.	To meet journal publication requirements.
	Updated Figure 5 by replacing study intervention names with the respective study arm (#) and adding list of abbreviations.	To align with the otherwise identical Figure 4 in Section 9.8.
Throughout document	Minor administrative, formatting, grammatical, and/or typographical changes were made throughout the document.	To ensure clarity and accurate interpretation of the intent of the protocol.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. Protocol Summary

1.1 Synopsis

Protocol Title:

A Randomized Phase 3, Double-Blind Study of Chemotherapy With or Without Pembrolizumab Followed by Maintenance With Olaparib or Placebo for the First-Line Treatment of BRCA non-mutated Advanced Epithelial Ovarian Cancer (EOC) (KEYLYNK-001 / ENGOT-ov43 / GOG-3036)

Short Title:

First-line chemotherapy plus pembrolizumab and olaparib for BRCA non-mutated advanced EOC (KEYLYNK-001 / ENGOT-ov43 / GOG-3036)

Objectives/Hypotheses and Endpoints:

In participants with previously untreated *BRCA1/2* non-mutated advanced EOC treated with pembrolizumab plus carboplatin/paclitaxel followed by continued pembrolizumab treatment plus olaparib maintenance (Arm 1) or pembrolizumab plus carboplatin/paclitaxel followed by continued pembrolizumab treatment (Arm 2) versus carboplatin/paclitaxel alone (Arm 3):

Objective/Hypothesis	Endpoint
Primary	
• Objective: To compare the progression-free survival (PFS) as assessed by the investigator according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) Hypothesis (H1): The combination of pembrolizumab plus carboplatin/paclitaxel followed by continued pembrolizumab treatment and olaparib maintenance (Arm 1) is superior to carboplatin/paclitaxel alone (Arm 3) with respect to PFS per	• PFS, the time from the date of randomization until either the earliest date of documented disease progression or death due to any cause, whichever occurs first

RECIST 1.1 in participants with PD-L1 positive tumors (CPS ≥10). Hypothesis (H2): The combination of pembrolizumab plus carboplatin/paclitaxel followed by continued pembrolizumab treatment and olaparib maintenance (Arm 1) is superior to carboplatin/paclitaxel alone (Arm 3) with respect to PFS per RECIST 1.1 in All Participants. Hypothesis (H3): The combination of pembrolizumab plus carboplatin/paclitaxel followed by continued pembrolizumab treatment (Arm 2) is superior to carboplatin/paclitaxel alone (Arm 3) with respect to PFS per RECIST 1.1 in participants with PD-L1 positive tumors (CPS ≥10). Hypothesis (H4): The combination of pembrolizumab plus carboplatin/paclitaxel followed by continued pembrolizumab treatment (Arm 2) is superior to carboplatin/paclitaxel alone (Arm 3) with respect to PFS per RECIST 1.1 in All Participants.	
Secondary	
• Objective: To compare the overall survival (OS) Hypothesis (H5): The combination of pembrolizumab plus carboplatin/paclitaxel followed by continued pembrolizumab treatment and olaparib maintenance (Arm 1) is superior to carboplatin/paclitaxel alone (Arm 3) with respect to OS in All Participants. Hypothesis (H6): The combination of pembrolizumab plus carboplatin/paclitaxel followed by	• OS, the time from the date of randomization to death due to any cause

continued pembrolizumab treatment (Arm 2) is superior to carboplatin/paclitaxel alone (Arm 3) with respect to OS in All Participants. Hypothesis (H7): The combination of pembrolizumab plus carboplatin/paclitaxel followed by continued pembrolizumab treatment (Arm 2) is superior to carboplatin/paclitaxel alone (Arm 3) with respect to OS in participants with PD-L1 positive tumors (CPS ≥10).	
• Objective: To compare the PFS as assessed by blinded independent central review according to RECIST 1.1 in participants with PD-L1 positive tumors (CPS ≥10) and in All Participants.	• PFS
• Objective: To compare the PFS after second-line treatment as determined by the investigator according to the local standard of clinical practice (PFS2) following discontinuation of study treatment administration in participants with PD-L1 positive tumors (CPS ≥10) and in All Participants.	• PFS2, the time from date of randomization until disease progression (clinical or radiological) after second-line treatment or death due to any cause, whichever occurs first
• Objective: To evaluate the safety and tolerability of pembrolizumab administered with chemotherapy and olaparib maintenance	• Adverse events (AEs) • Study treatment discontinuation due to AEs

• Objective: To compare the mean change from baseline of Global Health Status/Quality-of-Life (GHS/QoL) score using the European Organisation for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire Core 30 (QLQ-C30) and abdominal and gastrointestinal (abdominal/GI) symptoms using the EORTC Ovarian Cancer-Specific Quality-of-Life Questionnaire (QLQ-OV28) abdominal/GI symptom scale	Change from baseline in: • EORTC QLQ-C30 GHS/QoL score • EORTC QLQ-OV28 abdominal/GI symptom scale
• Objective: To compare time to deterioration (TTD) of GHS/QoL score using EORTC QLQ-C30 and abdominal/GI symptoms using EORTC QLQ-OV28	Time to deterioration in: • EORTC QLQ-C30 GHS/QoL score • EORTC QLQ-OV28 abdominal/GI symptom scale
• Objective: To compare the time to first subsequent anticancer treatment (TFST), the time to second subsequent anticancer treatment (TSST), and the time to discontinuation of study treatment or death (TDT)	• 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 • TDT, the time from the date of randomization to discontinuation of study treatment or death due to any cause, whichever occurs first
• Objective: To compare the rate of locally determined pathological complete response (pCR) of pembrolizumab in combination with carboplatin/paclitaxel versus carboplatin/paclitaxel alone when administered as neoadjuvant therapy	• pCR, all surgical specimens collected during the interval debulking surgery are microscopically negative for malignancy

Overall Design:

Study Phase	Phase 3
Clinical Indication	First-line treatment of advanced EOC
Population	Participants with *BRCA1/2* non-mutated advanced EOC
Study Type	Interventional
Type of Design	Multi-site, randomized, parallel, 3 arm
Type of Control	Placebo-control
Study Blinding	Double-blind
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 7 years from the time the first participant provides documented informed consent until the last participant's last study-related telephone call or visit.

Number of Participants:

Approximately 1284 participants will be randomized.

Treatment Groups and Duration:

Treatment Groups	Following a Lead-in Period, during which all participants will receive a single cycle of carboplatin/paclitaxel*, participants will be randomly assigned in a 1:1:1 ratio to the following treatment arms: **Arm 1** Treatment: Carboplatin/paclitaxel* for 5 cycles plus pembrolizumab 200 mg every 3 weeks (Q3W) for up to 35 infusions Maintenance: Olaparib 300 mg (twice daily [BID]) **Arm 2** Treatment: Carboplatin/paclitaxel* for 5 cycles plus pembrolizumab 200 mg Q3W for up to 35 infusions

	Maintenance: Olaparib placebo (BID) **Arm 3** Treatment: Carboplatin/paclitaxel* for 5 cycles plus pembrolizumab placebo Q3W for up to 35 infusions Maintenance: Olaparib placebo (BID) *Crossover between treatment arms is not permitted.* **At the investigator's discretion and determined prior to the participant being randomly assigned to study treatment, 1 of the following regimens may be selected:* • *Carboplatin area under the concentration-time curve (AUC)5 or AUC6 Q3W plus paclitaxel 175 mg/m^2 Q3W* • *Carboplatin AUC5 or AUC6 Q3W plus paclitaxel 80 mg/m^2 every week (QW)* • *Carboplatin AUC2 or AUC2.7 QW plus paclitaxel 60 mg/m^2 QW* *Docetaxel may be considered for participants who experience either a severe hypersensitivity reaction to paclitaxel or an AE requiring discontinuation of paclitaxel only after consultation with the Sponsor. The recommended dose, as determined by the SGCTG group [Vasey, P. A., et al 2004], is as follows:* • *Docetaxel 75 mg/m^2 Q3W plus carboplatin AUC 5 Q3W* *Note: At the investigator's discretion, bevacizumab may be used, but the investigator must decide on the use of bevacizumab prior to the participant being randomly assigned to study treatment. For participants eligible for interval debulking surgery, bevacizumab, if using, should be started with lead-in chemotherapy, stopped following Cycle 1 (prior to surgery), and resumed in Cycle 4 (after surgery). For participants eligible for primary debulking surgery, bevacizumab, if using, should be initiated in Cycle 1. The investigator may wait to administer the first dose of bevacizumab, as long as it is administered by Cycle 4 (but it may be started sooner). Any delay in restarting/starting bevacizumab beyond what is defined in the protocol requires Sponsor approval.*

Duration of Participation	Each participant will participate in the study from the time the participant signs the Informed Consent Form through the final protocol-specified contact. After the Screening/Lead-in Period, each participant will be randomly assigned to receive study treatment until any of the following occur: • Disease progression is radiographically documented per RECIST 1.1 by the investigator, and when clinically appropriate, confirmed by the site per modified RECIST 1.1 for immune-based therapeutics (iRECIST) • Clinical progression without radiographic disease progression defined by elevated CA-125 (based on GCIG criteria [see Appendix 9]) in conjunction with any of the following criteria for malignant bowel obstruction: ▪ Any of the following: new or worsening abdominal pain, nausea, or vomiting ▪ Abdominal distension, constipation, and/or diarrhea ▪ No evidence of metabolic or electrolyte abnormalities leading to impaired intestinal motility *Note: Symptoms must be assessed as not related to study treatment and/or concomitant medication AND other non-malignant causes must be excluded by supplementary diagnostic measures* *Note: Participants who discontinue study treatment due to clinical progression will have posttreatment follow-up imaging to evaluate disease status until disease progression is radiographically documented per RECIST 1.1 by the investigator* • Initiation of a new anticancer treatment • Unacceptable AEs • Intercurrent illness that prevents further administration of study treatment • Investigator's decision to discontinue the participant • The participant has received 35 infusions of either pembrolizumab or pembrolizumab placebo (approximately 2 years), the participant has received 2 years of olaparib or olaparib placebo, or the participant has received the maximum duration of bevacizumab per the approved label or local practice

	Note: Only participants with no evidence of disease will stop treatment with olaparib or olaparib placebo following 2 years of treatment. The total duration of treatment is calculated starting with the first dose of olaparib or olaparib placebo. Additional discontinuation criteria are outlined in Section 7.1. After the end of study treatment, each participant will be followed for the occurrence of AEs and spontaneously reported pregnancy as described under Section 8.4.1. Participants who discontinue for reasons other than radiographic disease progression will have posttreatment follow-up imaging to evaluate disease status until disease progression is radiographically documented per RECIST 1.1 by the investigator, and when clinically appropriate, confirmed by the site per iRECIST, initiating a new anticancer treatment, withdrawal of consent, becoming lost to follow-up, pregnancy, or death. All participants will be followed by telephone for OS until death, withdrawal of consent, or the end of the study. Upon study completion, participants are to be discontinued, and those who remain on study treatment upon study completion may be enrolled in an extension study to continue treatment as per the current study. **As of Amendment 05, all blood collections for ctDNA analysis and all PRO collections will be discontinued.**

Study Governance:

Study Governance Committees

Committee	Included in this study?
Steering Committee	Yes
Executive Oversight Committee	Yes
Data Monitoring Committee	Yes
Clinical Adjudication Committee	No

Study governance considerations are outlined in Appendix 1.

A list of abbreviations used in this document can be found in Appendix 8.

1.2 Schema

The study design is depicted in Figure 1. A schematic detailing the intervals for screening and debulking surgery for participants eligible for primary and interval debulking is presented in Figure 2 and Figure 3, respectively.

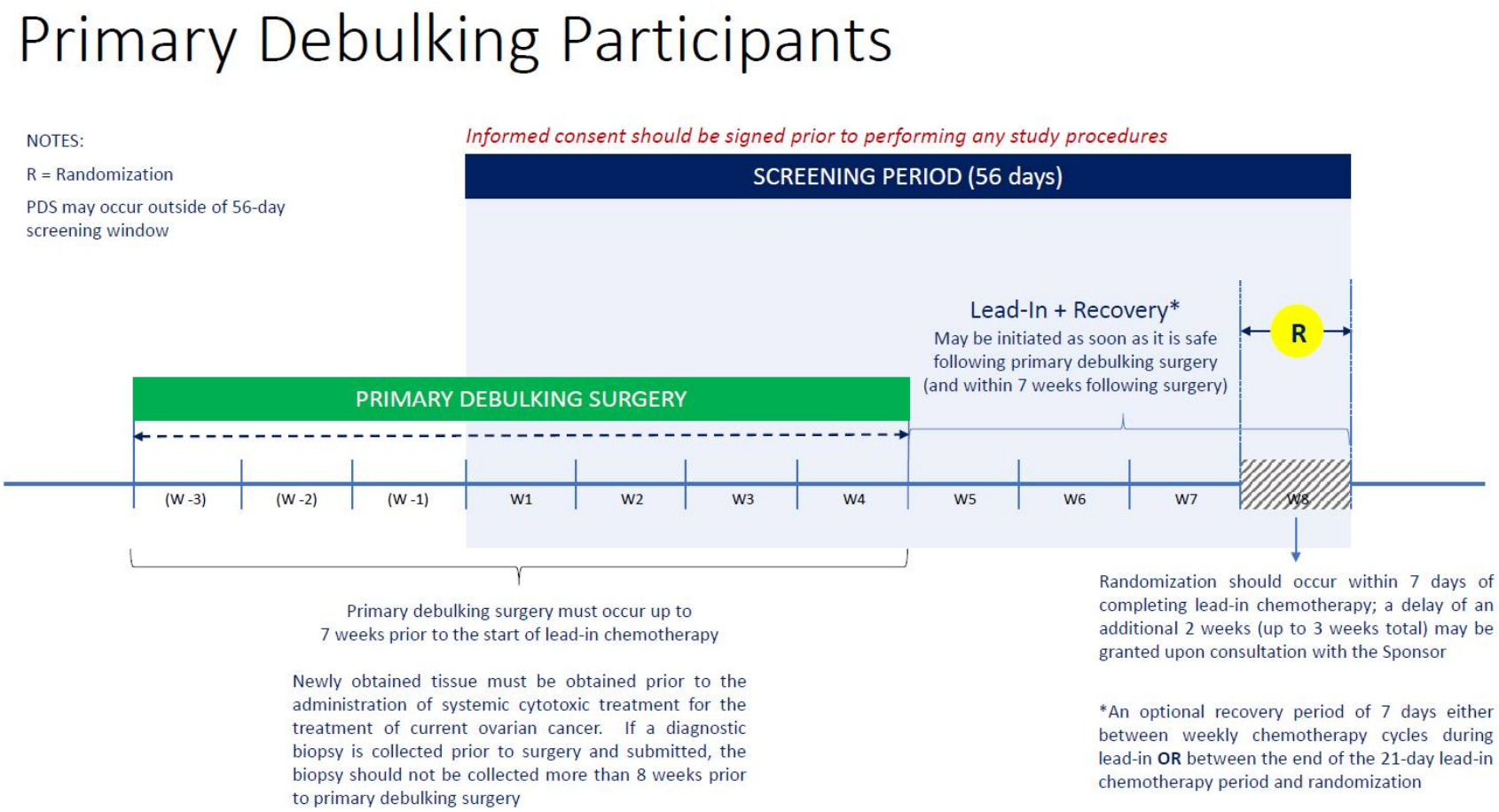
CCI

[redacted]

CCI

[redacted]

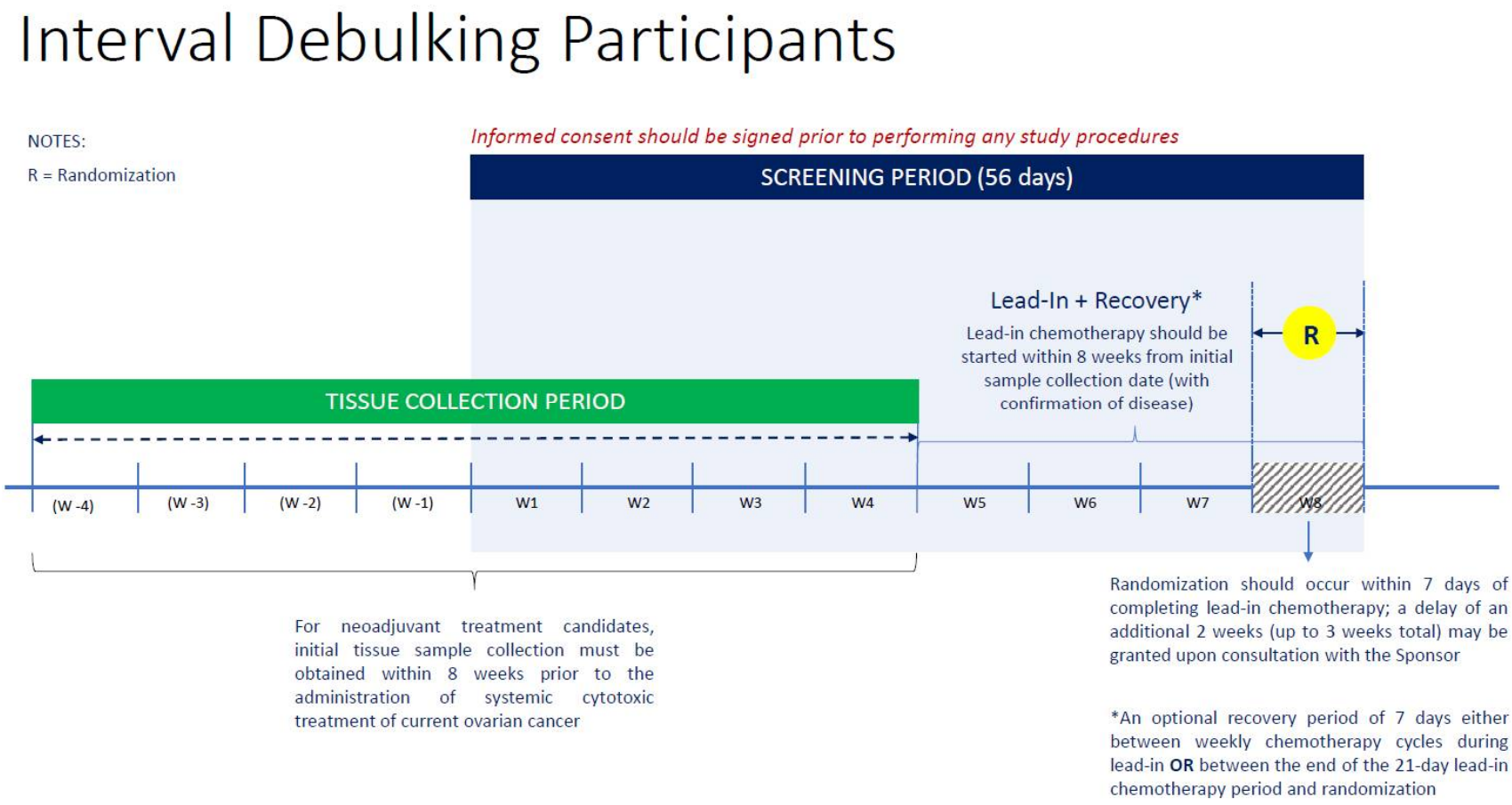
Figure 2 Study Intervals for Participants Eligible for Primary Debulking



PDS=primary debulking surgery; W=week.

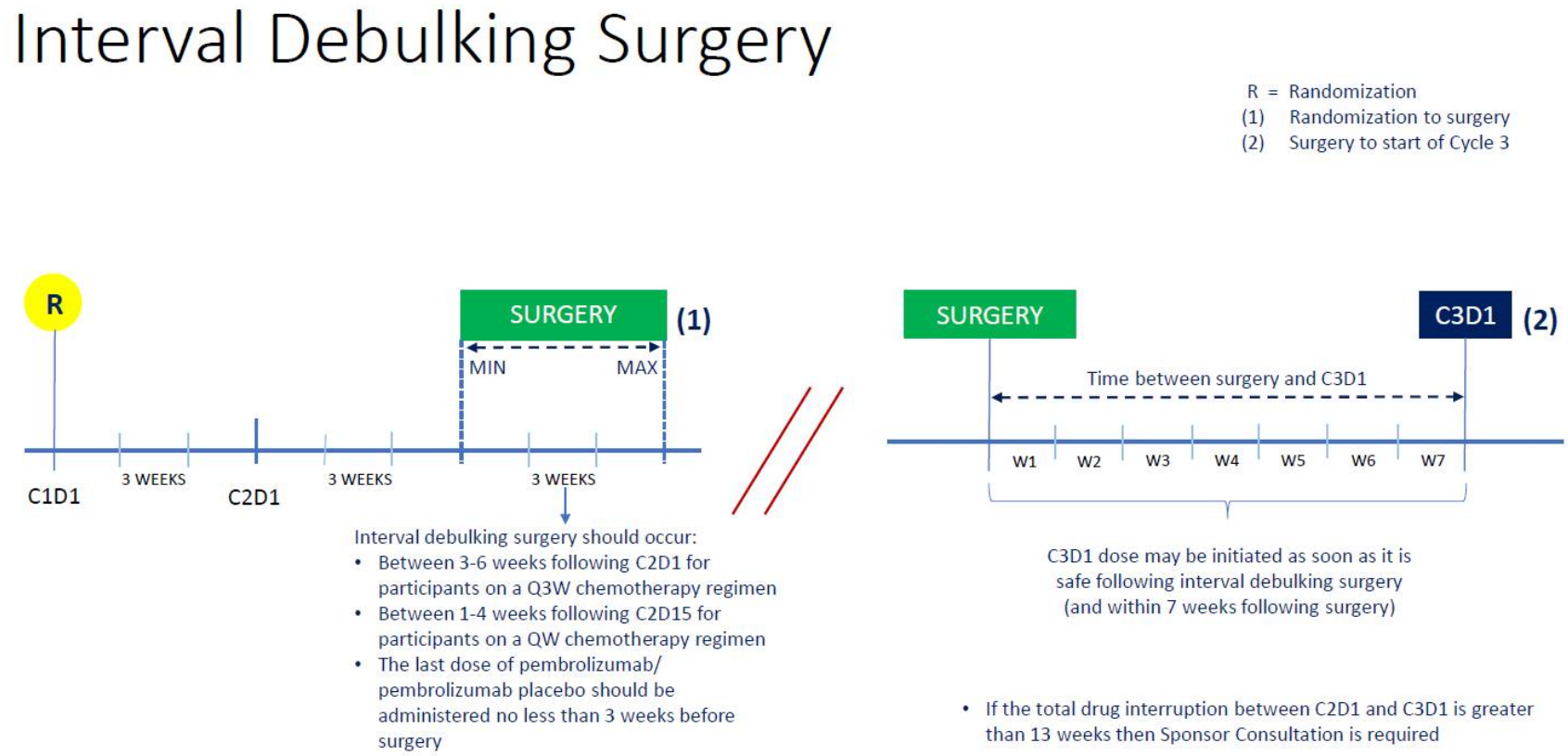
Figure 3 Study Intervals for Participants Eligible for Interval Debulking

A) Screening/Lead-in



C1D1=Cycle 1, Day 1; C2D1=Cycle, 2 Day 1; C3D1=Cycle 3, Day 1; IDS=interval debulking surgery; W=week.

B) Interval Debulking Surgery



C1D1=Cycle 1 Day 1; C2D1=Cycle 2 Day 1, C2D15=Cycle 2 Day 15; C3D1=Cycle 3 Day 1; QW=once weekly; Q3W=every 3 weeks.

1.3 Schedule of Activities (SoA)

1.3.1 SoA – Adjuvant Treatment Period With Primary Debulking Followed by Maintenance

Primary Debulking Followed by Adjuvant Treatment and Maintenance														
Study Period	**Screening + Lead-in**		**Treatment (C1 – C6) Maintenance (C7+)[a] (3-Week Cycles)**							**EOT**	**Posttreatment Visits**			**Notes**
Treatment Cycle	**Screen[b]**	**Lead-In**	**1**	**2**	**3**	**4**	**5**	**6**	**7+**	**DC**	**Safety FU[c]**	**Efficacy FU[d]**	**Survival FU**	**The Screening Period is a total of 56 days, which includes the 21-day Lead-in Period and an optional 7-day recovery period during or following lead-in chemotherapy. Maintenance is for participants without radiographic disease progression; participants must have SD, PR, CR, or non-PD.**
Scheduling Window (Days):	**–56 to start of lead-in**	**Start of lead-in to –1**	**–3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC**	**30 Days After Last Dose (+ 7)**	**Q9W, Q12W, or Q24W post DC (± 7)**	**Q12W (± 7)**	
Administrative Procedures														
ICF	X													Consent must be obtained prior to performing any protocol-specific procedures. If the signature falls outside of the 56-day screening window, the participant does not need to be reconsented. Participant must be reconsented prior to continuing study treatment after initial disease progression.
FBR ICF (optional)	X													Participants may participate in main study without signing FBR ICF.
Inclusion /Exclusion	◄----------►													
Participant ID Card	X		X											Distribute at screening and add randomization number at C1D1.
Demographics and Medical History	X													

Primary Debulking Followed by Adjuvant Treatment and Maintenance														
Study Period	**Screening + Lead-in**		**Treatment (C1 – C6) Maintenance (C7+)[a] (3-Week Cycles)**							**EOT**	**Posttreatment Visits**			**Notes**
Treatment Cycle	**Screen[b]**	**Lead-In**	**1**	**2**	**3**	**4**	**5**	**6**	**7+**	**DC**	**Safety FU[c]**	**Efficacy FU[d]**	**Survival FU**	**The Screening Period is a total of 56 days, which includes the 21-day Lead-in Period and an optional 7-day recovery period during or following lead-in chemotherapy. Maintenance is for participants without radiographic disease progression; participants must have SD, PR, CR, or non-PD.**
Scheduling Window (Days):	**–56 to start of lead-in**	**Start of lead-in to –1**	**–3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC**	**30 Days After Last Dose (+ 7)**	**Q9W, Q12W, or Q24W post DC (± 7)**	**Q12W (± 7)**	
Ovarian Cancer History	X													Assess and record presurgery tumor burden per imaging and postsurgery tumor burden per imaging and surgical report. R0 and R1 will be determined based on the outcome of surgery; however, radiological findings at the baseline imaging (postsurgery) needs to be considered when defining R0.
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	X	X	X	X	X		Record medications taken within 56 days prior to randomization. Concomitant medications will be recorded for 30 days after last dose (or for up to 90 days after last dose for SAEs). Include blood transfusions during review of concomitant medications.

Primary Debulking Followed by Adjuvant Treatment and Maintenance														
Study Period	**Screening + Lead-in**		**Treatment (C1 – C6) Maintenance (C7+)[a] (3-Week Cycles)**							**EOT**	**Posttreatment Visits**			**Notes**
Treatment Cycle	**Screen[b]**	**Lead-In**	**1**	**2**	**3**	**4**	**5**	**6**	**7+**	**DC**	**Safety FU[c]**	**Efficacy FU[d]**	**Survival FU**	**The Screening Period is a total of 56 days, which includes the 21-day Lead-in Period and an optional 7-day recovery period during or following lead-in chemotherapy. Maintenance is for participants without radiographic disease progression; participants must have SD, PR, CR, or non-PD.**
Scheduling Window (Days):	**–56 to start of lead-in**	**Start of lead-in to –1**	**–3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC**	**30 Days After Last Dose (+ 7)**	**Q9W, Q12W, or Q24W post DC (± 7)**	**Q12W (± 7)**	
Primary Debulking Surgery	X													Primary debulking surgery does not need to be performed within the 56-day Screening Period. Surgery must occur up to 7 weeks (maximum) prior to the start of lead-in chemotherapy.
Rationale for Carboplatin	X													Investigator must provide rationale for not choosing cisplatin prior to randomization.
Randomization (using IRT)			X											Randomization via IRT may occur up to 3 days prior to C1D1.
Subsequent Anticancer Therapy Review										X	X	X	X	
Survival Status			←----------										X	Upon Sponsor request, participants may be contacted to assess survival status at any point during the study.

Primary Debulking Followed by Adjuvant Treatment and Maintenance														
Study Period	**Screening + Lead-in**		**Treatment (C1 – C6) Maintenance (C7+)[a] (3-Week Cycles)**							**EOT**	**Posttreatment Visits**			**Notes**
Treatment Cycle	**Screen[b]**	**Lead-In**	**1**	**2**	**3**	**4**	**5**	**6**	**7+**	**DC**	**Safety FU[c]**	**Efficacy FU[d]**	**Survival FU**	**The Screening Period is a total of 56 days, which includes the 21-day Lead-in Period and an optional 7-day recovery period during or following lead-in chemotherapy. Maintenance is for participants without radiographic disease progression; participants must have SD, PR, CR, or non-PD.**
Scheduling Window (Days):	**–56 to start of lead-in**	**Start of lead-in to –1**	**–3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC**	**30 Days After Last Dose (+ 7)**	**Q9W, Q12W, or Q24W post DC (± 7)**	**Q12W (± 7)**	
Study Treatment Administration														
Lead-in Carboplatin / Paclitaxel		X												Lead-in chemotherapy should start when clinically appropriate but no longer than 7 weeks after primary debulking surgery. Investigator's choice of 3 regimens: 1) Carboplatin AUC5 or AUC6 + paclitaxel 175 mg/m^2 Q3W, or 2) Carboplatin AUC5 or AUC6 Q3W + paclitaxel 80 mg/m^2 QW, or 3) Carboplatin AUC2 or AUC2.7 QW + paclitaxel 60 mg/m^2 QW Q3W dosing on Day 1 and QW dosing on Days 1, 8, and 15 of each cycle. Docetaxel (75 mg/m^2 Q3W) may be considered for participants who either experience a severe hypersensitivity reaction or an AE that requires discontinuation of paclitaxel only after Sponsor consultation

Primary Debulking Followed by Adjuvant Treatment and Maintenance														
Study Period	**Screening + Lead-in**		**Treatment (C1 – C6) Maintenance (C7+)[a] (3-Week Cycles)**							**EOT**	**Posttreatment Visits**			**Notes**
Treatment Cycle	**Screen[b]**	**Lead-In**	**1**	**2**	**3**	**4**	**5**	**6**	**7+**	**DC**	**Safety FU[c]**	**Efficacy FU[d]**	**Survival FU**	**The Screening Period is a total of 56 days, which includes the 21-day Lead-in Period and an optional 7-day recovery period during or following lead-in chemotherapy. Maintenance is for participants without radiographic disease progression; participants must have SD, PR, CR, or non-PD.**
Scheduling Window (Days):	**–56 to start of lead-in**	**Start of lead-in to –1**	**–3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC**	**30 Days After Last Dose (+ 7)**	**Q9W, Q12W, or Q24W post DC (± 7)**	**Q12W (± 7)**	
Carboplatin / Paclitaxel			X	X	X	X	X							Investigator's choice of 3 regimens: 1) Carboplatin AUC5 or AUC6 + paclitaxel 175 mg/m^2 Q3W, or 2) Carboplatin AUC5 or AUC6 Q3W + paclitaxel 80 mg/m^2 QW, or 3) Carboplatin AUC2 or AUC2.7 QW + paclitaxel 60 mg/m^2 QW Q3W dosing on Day 1 and QW dosing on Days 1, 8 and 15 of each cycle. Day 1 of Cycle 1 must be at least 20 days after the first dose of lead-in chemotherapy. Docetaxel (75 mg/m^2 Q3W) may be considered for participants who either experience a severe hypersensitivity reaction or an AE that requires discontinuation of paclitaxel only after Sponsor consultation.

Primary Debulking Followed by Adjuvant Treatment and Maintenance														
Study Period	**Screening + Lead-in**		**Treatment (C1 – C6) Maintenance (C7+)[a] (3-Week Cycles)**							**EOT**	**Posttreatment Visits**			**Notes**
Treatment Cycle	**Screen[b]**	**Lead-In**	**1**	**2**	**3**	**4**	**5**	**6**	**7+**	**DC**	**Safety FU[c]**	**Efficacy FU[d]**	**Survival FU**	**The Screening Period is a total of 56 days, which includes the 21-day Lead-in Period and an optional 7-day recovery period during or following lead-in chemotherapy. Maintenance is for participants without radiographic disease progression; participants must have SD, PR, CR, or non-PD.**
Scheduling Window (Days):	**–56 to start of lead-in**	**Start of lead-in to –1**	**–3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC**	**30 Days After Last Dose (+ 7)**	**Q9W, Q12W, or Q24W post DC (± 7)**	**Q12W (± 7)**	
Bevacizumab (optional)			X	X	X	X	X	X	X					Bevacizumab use must be selected in IRT prior to randomization. Day 1 of Cycle 1 must be at least 20 days after the first dose of lead-in chemotherapy. The investigator may wait to administer the first dose of bevacizumab, as long as the first dose is administered by Cycle 4 (but it may be started as early as Cycle 1).
Pembrolizumab / Placebo			X	X	X	X	X	X	X					200 mg Q3W / normal saline or dextrose Q3W. Participant may receive up to 35 infusions. Day 1 of Cycle 1 must be at least 20 days after the first dose of lead-in chemotherapy.

Primary Debulking Followed by Adjuvant Treatment and Maintenance														
Study Period	**Screening + Lead-in**		**Treatment (C1 – C6) Maintenance (C7+)[a] (3-Week Cycles)**							**EOT**	**Posttreatment Visits**			**Notes**
Treatment Cycle	**Screen[b]**	**Lead-In**	**1**	**2**	**3**	**4**	**5**	**6**	**7+**	**DC**	**Safety FU[c]**	**Efficacy FU[d]**	**Survival FU**	**The Screening Period is a total of 56 days, which includes the 21-day Lead-in Period and an optional 7-day recovery period during or following lead-in chemotherapy. Maintenance is for participants without radiographic disease progression; participants must have SD, PR, CR, or non-PD.**
Scheduling Window (Days):	**–56 to start of lead-in**	**Start of lead-in to –1**	**–3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC**	**30 Days After Last Dose (+ 7)**	**Q9W, Q12W, or Q24W post DC (± 7)**	**Q12W (± 7)**	
Olaparib / Placebo									X[a]					300 mg BID / placebo BID. Participants with no evidence of disease after 2 years of treatment with olaparib or olaparib placebo will stop olaparib or olaparib placebo at the next scheduled visit following radiographic assessment of CR or NED. Participants with continued evidence of disease after 2 years of treatment with olaparib or olaparib placebo and without evidence of disease progression may continue olaparib or olaparib placebo until any one of the discontinuation criteria is met.
Efficacy Procedures														
Tumor Imaging	X		X							X		X		Refer to Section 1.3.3.
Bone imaging	X		X							X		X		Refer to Section 1.3.3.
Brain imaging	X		X							X		X		Refer to Section 1.3.3.

Primary Debulking Followed by Adjuvant Treatment and Maintenance														
Study Period	**Screening + Lead-in**		**Treatment (C1 – C6) Maintenance (C7+)[a] (3-Week Cycles)**							**EOT**	**Posttreatment Visits**			**Notes**
Treatment Cycle	**Screen[b]**	**Lead-In**	**1**	**2**	**3**	**4**	**5**	**6**	**7+**	**DC**	**Safety FU[c]**	**Efficacy FU[d]**	**Survival FU**	**The Screening Period is a total of 56 days, which includes the 21-day Lead-in Period and an optional 7-day recovery period during or following lead-in chemotherapy. Maintenance is for participants without radiographic disease progression; participants must have SD, PR, CR, or non-PD.**
Scheduling Window (Days):	**–56 to start of lead-in**	**Start of lead-in to –1**	**–3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC**	**30 Days After Last Dose (+ 7)**	**Q9W, Q12W, or Q24W post DC (± 7)**	**Q12W (± 7)**	
Safety Procedures (during treatment visits safety assessments and procedures must be done prior to treatment administration)[e]														
AE Monitoring	◄----------►		X	X	X	X	X	X	X	X	X	X		Report all AEs through 30 days following last dose of study treatment. Report SAEs through 90 days following last dose of study treatment (or 30 days following last dose if participant initiates new anticancer therapy, whichever is earlier).
Complete PE	X									X				
Directed PE		X	X	X	X	X	X	X	X		X			Perform as clinically indicated.
Weight		X	X	X	X	X	X	X	X	X	X			Perform within 7 days prior to starting lead-in chemotherapy.
Vital Signs		X	X	X	X	X	X	X	X	X	X			Assess BP, heart rate, RR, temperature. Height only assessed once prior to starting lead-in chemotherapy. Perform within 7 days prior to starting lead-in chemotherapy.
12-lead ECG		X								X				Additional ECGs may be performed as clinically indicated. Perform within 7 days prior to starting lead-in chemotherapy.

Primary Debulking Followed by Adjuvant Treatment and Maintenance														
Study Period	**Screening + Lead-in**		**Treatment (C1 – C6) Maintenance (C7+)[a] (3-Week Cycles)**							**EOT**	**Posttreatment Visits**			**Notes**
Treatment Cycle	**Screen[b]**	**Lead-In**	**1**	**2**	**3**	**4**	**5**	**6**	**7+**	**DC**	**Safety FU[c]**	**Efficacy FU[d]**	**Survival FU**	**The Screening Period is a total of 56 days, which includes the 21-day Lead-in Period and an optional 7-day recovery period during or following lead-in chemotherapy. Maintenance is for participants without radiographic disease progression; participants must have SD, PR, CR, or non-PD.**
Scheduling Window (Days):	**–56 to start of lead-in**	**Start of lead-in to –1**	**–3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC**	**30 Days After Last Dose (+ 7)**	**Q9W, Q12W, or Q24W post DC (± 7)**	**Q12W (± 7)**	
PT or INR and aPTT/PTT		X												Perform within 7 days prior to starting lead-in chemotherapy. PT or INR and aPTT/PTT should be monitored more closely in participants receiving anticoagulant therapy during treatment and Safety Follow-up Period.
Chemistry		X	X	X	X	X	X	X	X	X	X			Perform within 7 days prior to starting lead-in chemotherapy and again within 3 days prior to C1D1 treatment.
Hematology		X	X	X	X	X	X	X	X	X	X			Perform within 7 days prior to starting lead-in chemotherapy and again within 3 days prior to C1D1 treatment.
Urinalysis (dipstick or laboratory analysis)		X	X			X			X	X	X			Perform within 7 days prior to starting lead-in chemotherapy and again within 3 days prior to C1D1 treatment. Continue to perform urinalysis testing every 4 cycles starting with Cycle 4 (ie, Cycles 8, 12, 16 etc).

Primary Debulking Followed by Adjuvant Treatment and Maintenance														
Study Period	**Screening + Lead-in**		**Treatment (C1 – C6) Maintenance (C7+)[a] (3-Week Cycles)**							**EOT**	**Posttreatment Visits**			**Notes**
Treatment Cycle	**Screen[b]**	**Lead-In**	**1**	**2**	**3**	**4**	**5**	**6**	**7+**	**DC**	**Safety FU[c]**	**Efficacy FU[d]**	**Survival FU**	**The Screening Period is a total of 56 days, which includes the 21-day Lead-in Period and an optional 7-day recovery period during or following lead-in chemotherapy. Maintenance is for participants without radiographic disease progression; participants must have SD, PR, CR, or non-PD.**
Scheduling Window (Days):	**–56 to start of lead-in**	**Start of lead-in to –1**	**–3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC**	**30 Days After Last Dose (+ 7)**	**Q9W, Q12W, or Q24W post DC (± 7)**	**Q12W (± 7)**	
Urinalysis (dipstick or laboratory analysis) – Participants Receiving Bevacizumab		X	X	X	X	X	X	X	X	X	X			Perform within 7 days prior to starting lead-in chemotherapy. Participants receiving bevacizumab require urinalysis at every dosing cycle while receiving bevacizumab.
T3 or FT3 / FT4 / TSH		X		X		X		X	X	X	X			Perform within 7 days prior to starting lead-in chemotherapy. Perform every other cycle (C2, C4, C6, C8, etc).
Cortisol Levels		X												Perform within 7 days prior to starting lead-in chemotherapy.
CA-125		X	<---------->							X		X		Perform within 7 days prior to starting lead-in chemotherapy. Sample to be collected at the time of each tumor imaging assessment (±14 days of scheduled imaging assessment) (Section 1.3.3). An optional sample may be collected at the time of unscheduled imaging at the investigator's discretion. All CA-125 testing will be performed locally.

Primary Debulking Followed by Adjuvant Treatment and Maintenance														
Study Period	**Screening + Lead-in**		**Treatment (C1 – C6) Maintenance (C7+)[a] (3-Week Cycles)**							**EOT**	**Posttreatment Visits**			**Notes**
Treatment Cycle	**Screen[b]**	**Lead-In**	**1**	**2**	**3**	**4**	**5**	**6**	**7+**	**DC**	**Safety FU[c]**	**Efficacy FU[d]**	**Survival FU**	**The Screening Period is a total of 56 days, which includes the 21-day Lead-in Period and an optional 7-day recovery period during or following lead-in chemotherapy. Maintenance is for participants without radiographic disease progression; participants must have SD, PR, CR, or non-PD.**
Scheduling Window (Days):	**–56 to start of lead-in**	**Start of lead-in to –1**	**–3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC**	**30 Days After Last Dose (+ 7)**	**Q9W, Q12W, or Q24W post DC (± 7)**	**Q12W (± 7)**	
Urine or serum pregnancy test - WOCBP only		X	X	X	X	X	X	X	X[a]	X	X			WOCBP require a negative pregnancy test within either 24 hours (urine) or 72 hours (serum) prior to starting lead-in chemotherapy and again within either 24 hours (urine) or 72 hours (serum) prior to C1D1 treatment as outlined in Appendix 3. A pregnancy test must be performed at the cycle the participant enters maintenance and then test at each cycle that olaparib/olaparib placebo is administered. More frequent pregnancy testing may be performed if required by local regulations or if clinically indicated. Refer to Appendix 7 for country-specific requirements.
Serum Follicle-Stimulating Hormone (FSH) - WOCBP only	◄----------►													Only to be determined once for women <45 years old with no menses for ≥1 year (12 months) prior to screening and not currently on HRT or hormonal contraception.

Primary Debulking Followed by Adjuvant Treatment and Maintenance														
Study Period	**Screening + Lead-in**		**Treatment (C1 – C6) Maintenance (C7+)[a] (3-Week Cycles)**							**EOT**	**Posttreatment Visits**			**Notes**
Treatment Cycle	**Screen[b]**	**Lead-In**	**1**	**2**	**3**	**4**	**5**	**6**	**7+**	**DC**	**Safety FU[c]**	**Efficacy FU[d]**	**Survival FU**	**The Screening Period is a total of 56 days, which includes the 21-day Lead-in Period and an optional 7-day recovery period during or following lead-in chemotherapy. Maintenance is for participants without radiographic disease progression; participants must have SD, PR, CR, or non-PD.**
Scheduling Window (Days):	**–56 to start of lead-in**	**Start of lead-in to –1**	**–3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC**	**30 Days After Last Dose (+ 7)**	**Q9W, Q12W, or Q24W post DC (± 7)**	**Q12W (± 7)**	
HIV / HBV / HCV	◄----------►													Testing is only required once at screening if mandated by local health authority. Refer to Appendix 7 for country-specific requirements.
ECOG Performance Status		X	X	X	X	X	X	X	X	X				Perform within 7 days prior to starting lead-in chemotherapy and again within 3 days prior to C1D1 treatment.
CCI														
CCI														**As of Amendment 05, all PRO collections will be discontinued. Original protocol text in this section has been retained for historical perspective.** Administer PROs on Day 1 of the following cycles: C1, C2, C3, C4, every 3 cycles through C16 (C7, C10, C13, C16), and every 4 cycles thereafter in the second year (C20, C24, C28, C32, C36) for as long as participant is receiving study treatment.

Primary Debulking Followed by Adjuvant Treatment and Maintenance														
Study Period	**Screening + Lead-in**		**Treatment (C1 – C6) Maintenance (C7+)[a] (3-Week Cycles)**							**EOT**	**Posttreatment Visits**			**Notes**
Treatment Cycle	**Screen[b]**	**Lead-In**	**1**	**2**	**3**	**4**	**5**	**6**	**7+**	**DC**	**Safety FU[c]**	**Efficacy FU[d]**	**Survival FU**	**The Screening Period is a total of 56 days, which includes the 21-day Lead-in Period and an optional 7-day recovery period during or following lead-in chemotherapy. Maintenance is for participants without radiographic disease progression; participants must have SD, PR, CR, or non-PD.**
Scheduling Window (Days):	**–56 to start of lead-in**	**Start of lead-in to –1**	**–3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC**	**30 Days After Last Dose (+ 7)**	**Q9W, Q12W, or Q24W post DC (± 7)**	**Q12W (± 7)**	
Biomarker Sample Collection														**Biomarker samples may be collected up to 3 days prior to C1D1.**
Blood for Genetic Analysis			X											Collect prior to administration of study treatment. Refer to Section 8.9 for additional collection information.
Blood for Plasma Biomarker Analysis			X	X			X		X	X				Collect prior to administration of study treatment. A sample needs to be collected at the cycle the participants enters maintenance (C7 or earlier); no additional on-treatment samples are required following this collection.
Blood for Serum Biomarker Analysis			X	X			X		X	X				Collect prior to administration of study treatment. A sample needs to be collected at the cycle the participants enters maintenance (C7 or earlier); no additional on-treatment samples are required following this collection.

Primary Debulking Followed by Adjuvant Treatment and Maintenance														
Study Period	**Screening + Lead-in**		**Treatment (C1 – C6) Maintenance (C7+)[a] (3-Week Cycles)**							**EOT**	**Posttreatment Visits**			**Notes**
Treatment Cycle	**Screen[b]**	**Lead-In**	**1**	**2**	**3**	**4**	**5**	**6**	**7+**	**DC**	**Safety FU[c]**	**Efficacy FU[d]**	**Survival FU**	**The Screening Period is a total of 56 days, which includes the 21-day Lead-in Period and an optional 7-day recovery period during or following lead-in chemotherapy. Maintenance is for participants without radiographic disease progression; participants must have SD, PR, CR, or non-PD.**
Scheduling Window (Days):	**–56 to start of lead-in**	**Start of lead-in to –1**	**–3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC**	**30 Days After Last Dose (+ 7)**	**Q9W, Q12W, or Q24W post DC (± 7)**	**Q12W (± 7)**	
Blood for RNA Analysis			X	X			X		X	X				Collect prior to administration of study treatment. A sample needs to be collected at the cycle the participants enters maintenance (C7 or earlier); no additional on-treatment samples are required following this collection.
Blood for ctDNA Analysis			X	X			X		X	X		X		**As of Amendment 05, all blood collections for ctDNA will be discontinued. Original protocol text in this section has been retained for historical perspective.** Collect prior to administration of study treatment. A sample needs to be collected at the cycle the participants enters maintenance (C7 or earlier); during maintenance, a sample to be collected every second regularly scheduled imaging assessment (±14 days). A sample may be collected at the time of unscheduled imaging (±14 days) at the investigator's discretion. Refer to imaging timing outlined in Section 1.3.3.

Primary Debulking Followed by Adjuvant Treatment and Maintenance														
Study Period	**Screening + Lead-in**		**Treatment (C1 – C6) Maintenance (C7+)[a] (3-Week Cycles)**							**EOT**	**Posttreatment Visits**			**Notes**
Treatment Cycle	**Screen[b]**	**Lead-In**	**1**	**2**	**3**	**4**	**5**	**6**	**7+**	**DC**	**Safety FU[c]**	**Efficacy FU[d]**	**Survival FU**	**The Screening Period is a total of 56 days, which includes the 21-day Lead-in Period and an optional 7-day recovery period during or following lead-in chemotherapy. Maintenance is for participants without radiographic disease progression; participants must have SD, PR, CR, or non-PD.**
Scheduling Window (Days):	**–56 to start of lead-in**	**Start of lead-in to –1**	**–3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC**	**30 Days After Last Dose (+ 7)**	**Q9W, Q12W, or Q24W post DC (± 7)**	**Q12W (± 7)**	
PD-L1 Status	X													Required for stratification; results must be available prior to randomization. Sponsor consultation is required to delay randomization if the results are not available at the planned time of randomization.
BRCA1/2 Status	X													Required for stratification; results must be available prior to randomization and must be *BRCA1/2* non-mutated. Sponsor consultation is required to delay randomization if the results are not available at the planned time of randomization.
Submission of Newly obtained Tissue Collection	X													Newly obtained tissue must be obtained prior to the administration of systemic cytotoxic treatment for the treatment of current ovarian cancer. If a diagnostic biopsy is performed prior to surgery and submitted, the biopsy should not be collected more than 8 weeks prior to primary debulking surgery.

Primary Debulking Followed by Adjuvant Treatment and Maintenance														
Study Period	**Screening + Lead-in**		**Treatment (C1 – C6) Maintenance (C7+)[a] (3-Week Cycles)**							**EOT**	**Posttreatment Visits**			**Notes**
Treatment Cycle	**Screen[b]**	**Lead-In**	**1**	**2**	**3**	**4**	**5**	**6**	**7+**	**DC**	**Safety FU[c]**	**Efficacy FU[d]**	**Survival FU**	**The Screening Period is a total of 56 days, which includes the 21-day Lead-in Period and an optional 7-day recovery period during or following lead-in chemotherapy. Maintenance is for participants without radiographic disease progression; participants must have SD, PR, CR, or non-PD.**
Scheduling Window (Days):	**–56 to start of lead-in**	**Start of lead-in to –1**	**–3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC**	**30 Days After Last Dose (+ 7)**	**Q9W, Q12W, or Q24W post DC (± 7)**	**Q12W (± 7)**	
Tumor Biopsy										X				A core or excisional biopsy to be collected from visual tumor upon confirmed PD, if possible.

AE=adverse event; aPTT=activated partial thromboplastin time; AUC=area under the concentration-time curve; BICR=blinded independent central review; BID=twice daily; *BRCA1/2*=breast cancer susceptibility gene 1/2; C1D1=Cycle 1, Day 1; C5D1=Cycle 5, Day 1; C7=Cycle 7; CA-125=cancer antigen-125; CR=complete response; ctDNA=circulating tumor DNA; DBP=diastolic blood pressure; DC=discontinuation; ECG=electrocardiogram; ECOG=Eastern Cooperative Cancer Group CCI CCI FT3=free triiodothyronine; FT4=free thyroxine; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; HRT=hormone replacement therapy; ICF=informed consent form; ID=identification; INR=International Normalized Ratio; iRECIST=modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; IRT=interactive response technology; NED=no evidence of disease; pCR=pathological complete response; PD=progressive disease; PD-L1=programmed cell death ligand 1; PR=partial response; PRO=patient-reported outcome; PT=prothrombin time; PTT=partial thromboplastin time; Q3W=every 3 weeks; Q9W=every 9 weeks; Q12W=every 12 weeks; Q24W=every 24 weeks; QW=once weekly; RECIST=Response Evaluation Criteria in Solid Tumors; RR=respiratory rate; SBP=systolic blood pressure; SD=stable disease; SOC=standard of care; T3=triiodothyronine; TSH=thyroid-stimulating hormone; WOCBP=women of childbearing potential.

a. Following consultation with the Sponsor, participants who are unable to complete 6 treatment cycles (including lead-in) of chemotherapy due to toxicity, may be eligible to start the Maintenance Period earlier.
b. All screening procedures should be performed prior to starting lead-in chemotherapy unless otherwise noted. The Lead-in Period occurs within the 56-day window. The optional recovery period, if needed, should not exceed 7 days between cycles (weekly chemotherapy regimen) or at the end of lead-in chemotherapy. Randomization should occur within 7 days of completing lead-in chemotherapy; a delay of an additional 2 weeks (up to 3 weeks total) may be granted upon consultation with the Sponsor.
c. If the DC visit occurs ≥30 days from last dose of study treatment, a Safety Follow-up Visit is not required.
d. For participants who DC for reasons other than radiographic PD, imaging continues until radiographically documented PD by the investigator (and, when clinically appropriate, confirmed by iRECIST), initiation of a new anticancer treatment, withdrawal of consent, becoming lost to follow-up, pregnancy, or death, whichever occurs first. Efficacy follow-up visits may be scheduled to coincide with follow-up imaging. Refer to Section 1.3.3 for the imaging schedule during the treatment and posttreatment Efficacy Follow-up Period.
e. All procedures and laboratory testing should be conducted on the day of, or within the specified window, but prior to dosing. Laboratory results must be assessed by a qualified investigator prior to dosing; thyroid function testing is an exception as outlined in Appendix 5.

1.3.2 SoA – Neoadjuvant/Adjuvant Treatment Period With Interval Debulking Followed by Maintenance

Neoadjuvant / Adjuvant Treatment Period With Interval Debulking Followed by Maintenance															
Study Period	**Screening +Lead-in**		**Treatment (C1 – C6) Maintenance (C7+)[a] (3-Week Cycles)**								**EOT**	**Posttreatment Visits**			**Notes**
Treatment Cycle	**Screen [b]**	**Lead-in**	**1**	**2**	**SURGERY**	**3**	**4**	**5**	**6**	**7+**	**DC**	**Safety FU[c]**	**Efficacy FU[d]**	**Survival FU**	**The Screening Period is a total of 56 days, which includes the 21-day Lead-in Period and an optional 7-day recovery period during or following lead-in chemotherapy. Maintenance is for participants without radiographic disease progression; participants must have SD, PR or CR, or non-PD.**
Scheduling Window (Days):	**-56 to start of lead-in**	**Start of lead-in to -1**	**-3**	**± 3**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC**	**30 Days After Last Dose (+ 7)**	**Q9W, Q12W, or Q24W post DC (± 7)**	**Q12W (± 7)**	
Administrative Procedures															
ICF	X														Consent must be obtained prior to performing any protocol-specific procedures. If the signature falls outside of the 56-day screening window, the participant does not need to be reconsented. Participant must be reconsented prior to continuing study treatment after initial disease progression.
FBR ICF (optional)	X														Participants may participate in main study without signing FBR ICF.
Inclusion /Exclusion	◄--------►														
Participant ID Card	X		X												Distribute at screening and add randomization number at C1D1.
Demographics and Medical History	X														
Ovarian Cancer History	X														Assess and record tumor burden per imaging.

Neoadjuvant / Adjuvant Treatment Period With Interval Debulking Followed by Maintenance															
Study Period	**Screening +Lead-in**		**Treatment (C1 – C6) Maintenance (C7+)[a] (3-Week Cycles)**								**EOT**	**Posttreatment Visits**			**Notes**
Treatment Cycle	**Screen [b]**	**Lead-in**	**1**	**2**	**SURGERY**	**3**	**4**	**5**	**6**	**7+**	**DC**	**Safety FU[c]**	**Efficacy FU[d]**	**Survival FU**	**The Screening Period is a total of 56 days, which includes the 21-day Lead-in Period and an optional 7-day recovery period during or following lead-in chemotherapy. Maintenance is for participants without radiographic disease progression; participants must have SD, PR or CR, or non-PD.**
Scheduling Window (Days):	**-56 to start of lead-in**	**Start of lead-in to -1**	**-3**	**± 3**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC**	**30 Days After Last Dose (+ 7)**	**Q9W, Q12W, or Q24W post DC (± 7)**	**Q12W (± 7)**	
History of Blood Transfusion	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	X	X	X	X	X	X		Record medications taken within 56 days prior to randomization. Concomitant medications will be recorded for 30 days after last dose (or for up to 90 days after last dose for SAEs). Include blood transfusions during review of concomitant medications.
Interval Debulking Surgery (if indicated)					X										Surgery should occur: • Between 3 to 6 weeks following C2D1 for participants on Q3W chemotherapy regimen; or • Between 1 to 4 weeks following C2D15 for participants on QW chemotherapy regimen. The last dose of pembrolizumab/ pembrolizumab placebo should be administered at least 3 weeks before surgery. Study treatment may resume when clinically appropriate but no later than 7 weeks following surgery.

Neoadjuvant / Adjuvant Treatment Period With Interval Debulking Followed by Maintenance															
Study Period	**Screening +Lead-in**		**Treatment (C1 – C6) Maintenance (C7+)[a] (3-Week Cycles)**								**EOT**	**Posttreatment Visits**			**Notes**
Treatment Cycle	**Screen [b]**	**Lead-in**	**1**	**2**	**SURGERY**	**3**	**4**	**5**	**6**	**7+**	**DC**	**Safety FU[c]**	**Efficacy FU[d]**	**Survival FU**	**The Screening Period is a total of 56 days, which includes the 21-day Lead-in Period and an optional 7-day recovery period during or following lead-in chemotherapy. Maintenance is for participants without radiographic disease progression; participants must have SD, PR or CR, or non-PD.**
Scheduling Window (Days):	**-56 to start of lead-in**	**Start of lead-in to -1**	**-3**	**± 3**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC**	**30 Days After Last Dose (+ 7)**	**Q9W, Q12W, or Q24W post DC (± 7)**	**Q12W (± 7)**	
Rationale for Carboplatin	X														Investigator must provide rationale for not choosing cisplatin prior to randomization.
Randomization (using IRT)			X												Randomization via IRT may occur up to 3 days prior to C1D1.
Subsequent Anticancer Therapy Review											X	X	X	X	
Survival Status			<----------											X	Upon Sponsor request, participants may be contacted to assess survival status at any point during the study.

Neoadjuvant / Adjuvant Treatment Period With Interval Debulking Followed by Maintenance															
Study Period	**Screening +Lead-in**		**Treatment (C1 – C6) Maintenance (C7+)[a] (3-Week Cycles)**								**EOT**	**Posttreatment Visits**			**Notes**
Treatment Cycle	**Screen [b]**	**Lead-in**	**1**	**2**	**SURGERY**	**3**	**4**	**5**	**6**	**7+**	**DC**	**Safety FU[c]**	**Efficacy FU[d]**	**Survival FU**	**The Screening Period is a total of 56 days, which includes the 21-day Lead-in Period and an optional 7-day recovery period during or following lead-in chemotherapy. Maintenance is for participants without radiographic disease progression; participants must have SD, PR or CR, or non-PD.**
Scheduling Window (Days):	**-56 to start of lead-in**	**Start of lead-in to -1**	**-3**	**± 3**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC**	**30 Days After Last Dose (+ 7)**	**Q9W, Q12W, or Q24W post DC (± 7)**	**Q12W (± 7)**	
Study Treatment Administration															
Lead-in Carboplatin/ Paclitaxel		X													Investigator's choice of 3 regimens: 1) Carboplatin AUC5 or AUC6 + paclitaxel 175 mg/m^2 Q3W, or 2) Carboplatin AUC5 or AUC6 Q3W + paclitaxel 80 mg/m^2 QW, or 3) Carboplatin AUC2 or AUC2.7 QW + paclitaxel 60 mg/m^2 QW Q3W dosing on Day 1 and QW dosing on Days 1, 8 and 15 of each cycle. Docetaxel (75 mg/m^2 Q3W) may be considered for participants who either experience a severe hypersensitivity reaction or an AE that requires discontinuation of paclitaxel only after Sponsor consultation.

Neoadjuvant / Adjuvant Treatment Period With Interval Debulking Followed by Maintenance															
Study Period	**Screening +Lead-in**		**Treatment (C1 – C6) Maintenance (C7+)[a] (3-Week Cycles)**								**EOT**	**Posttreatment Visits**			**Notes**
Treatment Cycle	**Screen [b]**	**Lead-in**	**1**	**2**	**SURGERY**	**3**	**4**	**5**	**6**	**7+**	**DC**	**Safety FU[c]**	**Efficacy FU[d]**	**Survival FU**	**The Screening Period is a total of 56 days, which includes the 21-day Lead-in Period and an optional 7-day recovery period during or following lead-in chemotherapy. Maintenance is for participants without radiographic disease progression; participants must have SD, PR or CR, or non-PD.**
Scheduling Window (Days):	**-56 to start of lead-in**	**Start of lead-in to -1**	**-3**	**± 3**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC**	**30 Days After Last Dose (+ 7)**	**Q9W, Q12W, or Q24W post DC (± 7)**	**Q12W (± 7)**	
Carboplatin / Paclitaxel			X	X		X	X	X							Investigator's choice of 3 regimens: 1) Carboplatin AUC5 or AUC6 + paclitaxel 175 mg/m^2 Q3W, or 2) Carboplatin AUC5 or AUC6 Q3W + paclitaxel 80 mg/m^2 QW, or 3) Carboplatin AUC2 or AUC2.7 QW + paclitaxel 60 mg/m^2 QW Q3W dosing on Day 1 and QW dosing on Days 1, 8 and 15 of each cycle. Day 1 of Cycle 1 must be at least 20 days after the first dose of lead-in chemotherapy. Docetaxel (75 mg/m^2 Q3W) may be considered for participants who either experience a severe hypersensitivity reaction or an AE that requires discontinuation of paclitaxel only after Sponsor consultation.

Neoadjuvant / Adjuvant Treatment Period With Interval Debulking Followed by Maintenance															
Study Period	**Screening +Lead-in**		**Treatment (C1 – C6) Maintenance (C7+)[a] (3-Week Cycles)**								**EOT**	**Posttreatment Visits**			**Notes**
Treatment Cycle	**Screen [b]**	**Lead-in**	**1**	**2**	**SURGERY**	**3**	**4**	**5**	**6**	**7+**	**DC**	**Safety FU[c]**	**Efficacy FU[d]**	**Survival FU**	**The Screening Period is a total of 56 days, which includes the 21-day Lead-in Period and an optional 7-day recovery period during or following lead-in chemotherapy. Maintenance is for participants without radiographic disease progression; participants must have SD, PR or CR, or non-PD.**
Scheduling Window (Days):	**-56 to start of lead-in**	**Start of lead-in to -1**	**-3**	**± 3**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC**	**30 Days After Last Dose (+ 7)**	**Q9W, Q12W, or Q24W post DC (± 7)**	**Q12W (± 7)**	
Bevacizumab (optional)		X	X				X	X	X	X					Bevacizumab use must be selected in IRT prior to randomization. Day 1 of Cycle 1 must be at least 20 days after the first dose of lead-in chemotherapy. The investigator may wait to administer the first dose of bevacizumab, as long as the first dose is administered by Cycle 4 (but it may be started with lead-in).
Pembrolizumab / Placebo			X	X		X	X	X	X	X					200 mg Q3W / normal saline or dextrose Q3W. Participant may receive up to 35 infusions. Day 1 of Cycle 1 must be at least 20 days after the first dose of lead-in chemotherapy.

Neoadjuvant / Adjuvant Treatment Period With Interval Debulking Followed by Maintenance															
Study Period	**Screening +Lead-in**		**Treatment (C1 – C6) Maintenance (C7+)[a] (3-Week Cycles)**								**EOT**	**Posttreatment Visits**			**Notes**
Treatment Cycle	**Screen [b]**	**Lead-in**	**1**	**2**	**SURGERY**	**3**	**4**	**5**	**6**	**7+**	**DC**	**Safety FU[c]**	**Efficacy FU[d]**	**Survival FU**	**The Screening Period is a total of 56 days, which includes the 21-day Lead-in Period and an optional 7-day recovery period during or following lead-in chemotherapy. Maintenance is for participants without radiographic disease progression; participants must have SD, PR or CR, or non-PD.**
Scheduling Window (Days):	**-56 to start of lead-in**	**Start of lead-in to -1**	**-3**	**± 3**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC**	**30 Days After Last Dose (+ 7)**	**Q9W, Q12W, or Q24W post DC (± 7)**	**Q12W (± 7)**	
Olaparib / Placebo										X[a]					300 mg BID / placebo BID. Participants with no evidence of disease after 2 years of treatment with olaparib or olaparib placebo will stop olaparib or olaparib placebo at the next scheduled visit following radiographic assessment of CR or NED. Participants with continued evidence of disease after 2 years of treatment with olaparib or olaparib placebo and without evidence of disease progression may continue olaparib or olaparib placebo until any one of the discontinuation criteria is met.
Efficacy Procedures															
Pathological Tumor Assessment					X										Detailed pathological assessment of all tumor tissue collected during interval debulking for determination of pCR.
Tumor Imaging	X		X								X		X		Refer to Sections 1.3.4 and 1.3.5
Bone imaging	X		X								X		X		Refer to Sections 1.3.4 and 1.3.5
Brain Imaging	X		X								X		X		Refer to Sections 1.3.4 and 1.3.5

Neoadjuvant / Adjuvant Treatment Period With Interval Debulking Followed by Maintenance															
Study Period	**Screening +Lead-in**		**Treatment (C1 – C6) Maintenance (C7+)[a] (3-Week Cycles)**								**EOT**	**Posttreatment Visits**			**Notes**
Treatment Cycle	**Screen [b]**	**Lead-in**	**1**	**2**	**SURGERY**	**3**	**4**	**5**	**6**	**7+**	**DC**	**Safety FU[c]**	**Efficacy FU[d]**	**Survival FU**	**The Screening Period is a total of 56 days, which includes the 21-day Lead-in Period and an optional 7-day recovery period during or following lead-in chemotherapy. Maintenance is for participants without radiographic disease progression; participants must have SD, PR or CR, or non-PD.**
Scheduling Window (Days):	**-56 to start of lead-in**	**Start of lead-in to -1**	**-3**	**± 3**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC**	**30 Days After Last Dose (+ 7)**	**Q9W, Q12W, or Q24W post DC (± 7)**	**Q12W (± 7)**	
Safety Procedures (during treatment visits safety assessments and procedures must be done prior to treatment administration)[e]															
AE Monitoring	◄--------►		X	X	X	X	X	X	X	X	X	X	X		Report all AEs through 30 days following last dose of study treatment. Report SAEs through 90 days following last dose of study treatment (or 30 days following last dose if participant initiates new anticancer therapy, whichever is earlier).
Complete PE	X										X				
Directed PE		X	X	X		X	X	X	X	X		X			Perform as clinically indicated.
Weight		X	X	X		X	X	X	X	X	X	X			Perform within 7 days prior to starting lead-in chemotherapy.
Vital Signs		X	X	X		X	X	X	X	X	X	X			Assess BP, heart rate, RR, temperature. Height only assessed once prior to starting lead-in chemotherapy. Perform within 7 days prior to starting lead-in chemotherapy.
12-lead ECG		X									X				Additional ECGs may be performed as clinically indicated. Perform within 7 days prior to starting lead-in chemotherapy.

Neoadjuvant / Adjuvant Treatment Period With Interval Debulking Followed by Maintenance															
Study Period	**Screening +Lead-in**		**Treatment (C1 – C6) Maintenance (C7+)[a] (3-Week Cycles)**								**EOT**	**Posttreatment Visits**			**Notes**
Treatment Cycle	**Screen [b]**	**Lead-in**	**1**	**2**	**SURGERY**	**3**	**4**	**5**	**6**	**7+**	**DC**	**Safety FU[c]**	**Efficacy FU[d]**	**Survival FU**	**The Screening Period is a total of 56 days, which includes the 21-day Lead-in Period and an optional 7-day recovery period during or following lead-in chemotherapy. Maintenance is for participants without radiographic disease progression; participants must have SD, PR or CR, or non-PD.**
Scheduling Window (Days):	**-56 to start of lead-in**	**Start of lead-in to -1**	**-3**	**± 3**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC**	**30 Days After Last Dose (+ 7)**	**Q9W, Q12W, or Q24W post DC (± 7)**	**Q12W (± 7)**	
PT or INR and aPTT/PTT		X													Perform within 7 days prior to starting lead-in chemotherapy. PT or INR and aPTT/PTT should be monitored more closely in participants receiving anticoagulant therapy during treatment and Safety Follow-up Period.
Chemistry		X	X	X		X	X	X	X	X	X	X			Perform within 7 days prior to starting lead-in chemotherapy and again within 3 days prior to C1D1 treatment.
Hematology		X	X	X		X	X	X	X	X	X	X			Perform within 7 days prior to starting lead-in chemotherapy and again within 3 days prior to C1D1 treatment.
Urinalysis (dipstick or laboratory analysis)		X	X				X			X	X	X			Perform within 7 days prior to starting lead-in chemotherapy and again within 3 days prior to C1D1 treatment. Continue to perform urinalysis testing every 4 cycles starting with Cycle 4 (ie, Cycles 8, 12, 16 etc).

Neoadjuvant / Adjuvant Treatment Period With Interval Debulking Followed by Maintenance															
Study Period	**Screening +Lead-in**		**Treatment (C1 – C6) Maintenance (C7+)[a] (3-Week Cycles)**								**EOT**	**Posttreatment Visits**			**Notes**
Treatment Cycle	**Screen [b]**	**Lead-in**	**1**	**2**	**SURGERY**	**3**	**4**	**5**	**6**	**7+**	**DC**	**Safety FU[c]**	**Efficacy FU[d]**	**Survival FU**	**The Screening Period is a total of 56 days, which includes the 21-day Lead-in Period and an optional 7-day recovery period during or following lead-in chemotherapy. Maintenance is for participants without radiographic disease progression; participants must have SD, PR or CR, or non-PD.**
Scheduling Window (Days):	**-56 to start of lead-in**	**Start of lead-in to -1**	**-3**	**± 3**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC**	**30 Days After Last Dose (+ 7)**	**Q9W, Q12W, or Q24W post DC (± 7)**	**Q12W (± 7)**	
Urinalysis (dipstick or laboratory analysis) – Participants Receiving Bevacizumab		X	X				X	X	X	X	X	X			Perform within 7 days prior to starting lead-in chemotherapy. Participants receiving bevacizumab require urinalysis at every dosing cycle while receiving bevacizumab.
T3 or free T3 / FT4 / TSH		X		X			X		X	X	X	X			Perform within 7 days prior to starting lead-in chemotherapy. Perform at every other cycle (C2, C4, C6, C8, etc).
Cortisol Levels		X			X	X	X								Perform within 7 days prior to starting lead-in chemotherapy. Perform within 7 days prior to surgery and within 7 days prior to administration of study treatment for the 2 treatment cycles following surgery.

Neoadjuvant / Adjuvant Treatment Period With Interval Debulking Followed by Maintenance														
Study Period	**Screening +Lead-in**		**Treatment (C1 – C6) Maintenance (C7+)[a] (3-Week Cycles)**								**EOT**	**Posttreatment Visits**			**Notes**
Treatment Cycle	**Screen [b]**	**Lead-in**	**1**	**2**	**SURGERY**	**3**	**4**	**5**	**6**	**7+**	**DC**	**Safety FU[c]**	**Efficacy FU[d]**	**Survival FU**	**The Screening Period is a total of 56 days, which includes the 21-day Lead-in Period and an optional 7-day recovery period during or following lead-in chemotherapy. Maintenance is for participants without radiographic disease progression; participants must have SD, PR or CR, or non-PD.**
Scheduling Window (Days):	**-56 to start of lead-in**	**Start of lead-in to -1**	**-3**	**± 3**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC**	**30 Days After Last Dose (+ 7)**	**Q9W, Q12W, or Q24W post DC (± 7)**	**Q12W (± 7)**	
CA-125		X	←----------	----------	----------	----------	----------	----------	----------	----------→	X		X		Perform within 7 days prior to starting lead-in chemotherapy. Sample to be collected at the time of each tumor imaging assessment (±14 days of scheduled imaging assessment) (Section 1.3.4 and 1.3.5). An optional sample may be collected at the time of unscheduled imaging at the investigator's discretion. All CA-125 testing will be performed locally.
CEA	X														Perform within 7 days prior to starting lead-in chemotherapy.

Neoadjuvant / Adjuvant Treatment Period With Interval Debulking Followed by Maintenance															
Study Period	**Screening +Lead-in**		**Treatment (C1 – C6) Maintenance (C7+)[a] (3-Week Cycles)**								**EOT**	**Posttreatment Visits**			**Notes**
Treatment Cycle	**Screen [b]**	**Lead-in**	**1**	**2**	**SURGERY**	**3**	**4**	**5**	**6**	**7+**	**DC**	**Safety FU[c]**	**Efficacy FU[d]**	**Survival FU**	**The Screening Period is a total of 56 days, which includes the 21-day Lead-in Period and an optional 7-day recovery period during or following lead-in chemotherapy. Maintenance is for participants without radiographic disease progression; participants must have SD, PR or CR, or non-PD.**
Scheduling Window (Days):	**-56 to start of lead-in**	**Start of lead-in to -1**	**-3**	**± 3**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC**	**30 Days After Last Dose (+ 7)**	**Q9W, Q12W, or Q24W post DC (± 7)**	**Q12W (± 7)**	
Urine or serum pregnancy test - WOCBP only		X	X	X		X	X	X	X	X[a]	X	X			WOCBP require a negative pregnancy test within either 24 hours (urine) or 72 hours (serum) prior to starting lead-in chemotherapy and again within either 24 hours (urine) or 72 hours (serum) prior to C1D1 treatment as outlined in Appendix 3. A pregnancy test must be performed at the cycle the participant enters maintenance and test at each cycle that olaparib/olaparib placebo is administered. More frequent pregnancy testing may be performed if required by local regulations or if clinically indicated. Refer to Appendix 7 for country-specific requirements.
Serum Follicle-Stimulating Hormone (FSH) - WOCBP only	◄--------►														Only to be determined once for women <45 years old with no menses for ≥1 year (12 months) prior to screening and not currently on HRT or hormonal contraception.

Neoadjuvant / Adjuvant Treatment Period With Interval Debulking Followed by Maintenance															
Study Period	**Screening +Lead-in**		**Treatment (C1 – C6) Maintenance (C7+)[a] (3-Week Cycles)**								**EOT**	**Posttreatment Visits**			**Notes**
Treatment Cycle	**Screen [b]**	**Lead-in**	**1**	**2**	**SURGERY**	**3**	**4**	**5**	**6**	**7+**	**DC**	**Safety FU[c]**	**Efficacy FU[d]**	**Survival FU**	**The Screening Period is a total of 56 days, which includes the 21-day Lead-in Period and an optional 7-day recovery period during or following lead-in chemotherapy. Maintenance is for participants without radiographic disease progression; participants must have SD, PR or CR, or non-PD.**
Scheduling Window (Days):	**-56 to start of lead-in**	**Start of lead-in to -1**	**-3**	**± 3**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC**	**30 Days After Last Dose (+ 7)**	**Q9W, Q12W, or Q24W post DC (± 7)**	**Q12W (± 7)**	
HIV / HBV / HCV	◄---------►														Testing is only required once at screening if mandated by local health authority. Refer to Appendix 7 for country-specific requirements.
ECOG Performance Status		X	X	X		X	X	X	X	X	X				Perform within 7 days prior to starting lead-in chemotherapy and again within 3 days prior to C1D1 treatment.
CCI															
															As of Amendment 05, all PRO collections will be discontinued. Original protocol text in this section has been retained for historical perspective. Administer PROs on Day 1 of the following cycles: C1, C2, C3, C4, every 3 cycles through C16 (C7, C10, C13, C16), and every 4 cycles thereafter in the second year (C20, C24, C28, C32, C36) for as long as participant is receiving study treatment.
CCI															

Neoadjuvant / Adjuvant Treatment Period With Interval Debulking Followed by Maintenance															
Study Period	**Screening +Lead-in**		**Treatment (C1 – C6) Maintenance (C7+)[a] (3-Week Cycles)**								**EOT**	**Posttreatment Visits**			**Notes**
Treatment Cycle	**Screen [b]**	**Lead-in**	**1**	**2**	**SURGERY**	**3**	**4**	**5**	**6**	**7+**	**DC**	**Safety FU[c]**	**Efficacy FU[d]**	**Survival FU**	**The Screening Period is a total of 56 days, which includes the 21-day Lead-in Period and an optional 7-day recovery period during or following lead-in chemotherapy. Maintenance is for participants without radiographic disease progression; participants must have SD, PR or CR, or non-PD.**
Scheduling Window (Days):	**-56 to start of lead-in**	**Start of lead-in to -1**	**-3**	**± 3**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC**	**30 Days After Last Dose (+ 7)**	**Q9W, Q12W, or Q24W post DC (± 7)**	**Q12W (± 7)**	
Biomarker Sample Collection															**Biomarker samples may be collected up to 3 days prior to C1D1.**
Blood for Genetic Analysis			X												Collect prior to administration of study treatment. Refer to Section 8.9 for additional collection information.
Blood for Plasma Biomarker Analysis			X	X				X		X	X				Collect prior to administration of study treatment. A sample needs to be collected at the cycle the participants enters maintenance (C7 or earlier); no additional on-treatment samples are required following this collection.
Blood for Serum Biomarker Analysis			X	X				X		X	X				Collect prior to administration of study treatment. A sample needs to be collected at the cycle the participants enters maintenance (C7 or earlier); no additional on-treatment samples are required following this collection.

Neoadjuvant / Adjuvant Treatment Period With Interval Debulking Followed by Maintenance															
Study Period	**Screening +Lead-in**		**Treatment (C1 – C6) Maintenance (C7+)[a] (3-Week Cycles)**								**EOT**	**Posttreatment Visits**			**Notes**
Treatment Cycle	**Screen [b]**	**Lead-in**	**1**	**2**	**SURGERY**	**3**	**4**	**5**	**6**	**7+**	**DC**	**Safety FU[c]**	**Efficacy FU[d]**	**Survival FU**	**The Screening Period is a total of 56 days, which includes the 21-day Lead-in Period and an optional 7-day recovery period during or following lead-in chemotherapy. Maintenance is for participants without radiographic disease progression; participants must have SD, PR or CR, or non-PD.**
Scheduling Window (Days):	**-56 to start of lead-in**	**Start of lead-in to -1**	**-3**	**± 3**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC**	**30 Days After Last Dose (+ 7)**	**Q9W, Q12W, or Q24W post DC (± 7)**	**Q12W (± 7)**	
Blood for RNA Analysis			X	X				X		X	X				Collect prior to administration of study treatment. A sample needs to be collected at the cycle the participants enters maintenance (C7 or earlier); no additional on-treatment samples are required following this collection.
Blood for ctDNA Analysis			X	X				X		X	X		X		**As of Amendment 05, all blood collections for ctDNA will be discontinued. Original protocol text in this section has been retained for historical perspective.** Collect prior to administration of study treatment. A sample needs to be collected at the cycle the participants enters maintenance (C7 or earlier); during maintenance, a sample to be collected every second regularly scheduled imaging assessment (±14 days). A sample may be collected at the time of unscheduled imaging (±14 days) at the investigator's discretion. Refer to imaging timing outlined in Sections 1.3.4 and 1.3.5.

Neoadjuvant / Adjuvant Treatment Period With Interval Debulking Followed by Maintenance															
Study Period	**Screening +Lead-in**		**Treatment (C1 – C6) Maintenance (C7+)[a] (3-Week Cycles)**								**EOT**	**Posttreatment Visits**			**Notes**
Treatment Cycle	**Screen [b]**	**Lead-in**	**1**	**2**	**SURGERY**	**3**	**4**	**5**	**6**	**7+**	**DC**	**Safety FU[c]**	**Efficacy FU[d]**	**Survival FU**	**The Screening Period is a total of 56 days, which includes the 21-day Lead-in Period and an optional 7-day recovery period during or following lead-in chemotherapy. Maintenance is for participants without radiographic disease progression; participants must have SD, PR or CR, or non-PD.**
Scheduling Window (Days):	**-56 to start of lead-in**	**Start of lead-in to -1**	**-3**	**± 3**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC**	**30 Days After Last Dose (+ 7)**	**Q9W, Q12W, or Q24W post DC (± 7)**	**Q12W (± 7)**	
PD-L1 Status	X														Required for stratification; results must be available prior to randomization. Sponsor consultation is required to delay randomization if the results are not available at the planned time of randomization.
BRCA1/2 Status	X														Required for stratification; results must be available prior to randomization and must be *BRCA1/2* non-mutated. Sponsor consultation is required to delay randomization if the results are not available at the planned time of randomization.
Submission of Newly obtained Tissue Collection	X														Newly obtained tissue must be obtained within 8 weeks prior to the administration of systemic cytotoxic treatment for the treatment of current ovarian cancer.

Neoadjuvant / Adjuvant Treatment Period With Interval Debulking Followed by Maintenance															
Study Period	**Screening +Lead-in**		**Treatment (C1 – C6) Maintenance (C7+)[a] (3-Week Cycles)**								**EOT**	**Posttreatment Visits**			**Notes**
Treatment Cycle	**Screen [b]**	**Lead-in**	**1**	**2**	**SURGERY**	**3**	**4**	**5**	**6**	**7+**	**DC**	**Safety FU[c]**	**Efficacy FU[d]**	**Survival FU**	**The Screening Period is a total of 56 days, which includes the 21-day Lead-in Period and an optional 7-day recovery period during or following lead-in chemotherapy. Maintenance is for participants without radiographic disease progression; participants must have SD, PR or CR, or non-PD.**
Scheduling Window (Days):	**-56 to start of lead-in**	**Start of lead-in to -1**	**-3**	**± 3**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC**	**30 Days After Last Dose (+ 7)**	**Q9W, Q12W, or Q24W post DC (± 7)**	**Q12W (± 7)**	
Tumor Biopsy					X						X				If possible, a core or excisional biopsy should be obtained at the following time points and submitted to the central lab: 1) Tumor tissue removed during interval debulking 2) If participant is unable to undergo interval debulking 3) Visual tumor upon confirmed PD

Neoadjuvant / Adjuvant Treatment Period With Interval Debulking Followed by Maintenance															
Study Period	**Screening +Lead-in**		**Treatment (C1 – C6) Maintenance (C7+)[a] (3-Week Cycles)**								**EOT**	**Posttreatment Visits**			**Notes**
Treatment Cycle	**Screen [b]**	**Lead-in**	**1**	**2**	**SURGERY**	**3**	**4**	**5**	**6**	**7+**	**DC**	**Safety FU[c]**	**Efficacy FU[d]**	**Survival FU**	**The Screening Period is a total of 56 days, which includes the 21-day Lead-in Period and an optional 7-day recovery period during or following lead-in chemotherapy. Maintenance is for participants without radiographic disease progression; participants must have SD, PR or CR, or non-PD.**
Scheduling Window (Days):	**-56 to start of lead-in**	**Start of lead-in to -1**	**-3**	**± 3**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC**	**30 Days After Last Dose (+ 7)**	**Q9W, Q12W, or Q24W post DC (± 7)**	**Q12W (± 7)**	

AE=adverse event; aPTT=activated partial thromboplastin time; AUC=area under the concentration-time curve; BICR=blinded independent central review; BID=twice daily; *BRCA1/2*=breast cancer susceptibility gene 1/2; C1D1=Cycle 1, Day 1; C2=Cycle 2; C5D1=Cycle 5, Day 1; C7=Cycle 7; CA-125=cancer antigen-125; CEA=cancer embryonic antigen; CR=complete response; ctDNA=circulating tumor DNA; DBP=diastolic blood pressure; DC=discontinuation; ECG=electrocardiogram; ECOG=Eastern Cooperative Cancer Group; CCI [redacted] CCI [redacted] CCI [redacted] FT3=free triiodothyronine; FT4=free thyroxine; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; HRT=hormone replacement therapy; ICF=informed consent form; ID=identification; INR=International Normalized Ratio; iRECIST=modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; IRT=interactive response technology; NED=no evidence of disease; pCR=pathological complete response; PD=progressive disease; PD-L1=programmed cell death ligand 1; PR=partial response; PRO=patient-reported outcome; PT=prothrombin time; PTT=partial thromboplastin time; Q3W=every 3 weeks; Q9W=every 9 weeks; Q12W=every 12 weeks; Q24W=every 24 weeks; QW=once weekly; RECIST=Response Evaluation Criteria in Solid Tumors; RR=respiratory rate; SBP=systolic blood pressure; SD=stable disease; SOC=standard of care; T3=triiodothyronine; TSH=thyroid-stimulating hormone; WOCBP=women of childbearing potential.

a. Following consultation with the Sponsor, participants who are unable to complete 6 treatment cycles (including lead-in) of chemotherapy due to toxicity, may be eligible to start the Maintenance Period earlier.

b. All screening procedures should be performed prior to starting lead-in chemotherapy unless otherwise noted. The Lead-in Period occurs within the 56-day window. The optional recovery period, if needed, should not exceed 7 days between cycles (weekly chemotherapy regimen) or at the end of lead-in chemotherapy. Randomization should occur within 7 days of completing lead-in chemotherapy; a delay of an additional 2 weeks (up to 3 weeks total) may be granted upon consultation with the Sponsor.

c. If the DC visit occurs ≥30 days from last dose of study treatment, a Safety Follow-up Visit is not required.

d. For participants who DC for reasons other than radiographic PD, imaging continues until radiographically documented PD by the investigator (and, when clinically appropriate, confirmed by iRECIST), initiation of a new anticancer therapy, withdrawal of consent, becoming lost to follow-up, pregnancy, or death, whichever occurs first. Efficacy Follow-up Visits may be scheduled to coincide with follow-up imaging. Refer to Sections 1.3.4 and 1.3.5 for the imaging schedule during the treatment and posttreatment Efficacy Follow-up Period.

e. All procedures and laboratory testing should be conducted on the day of, or within the specified window, but prior to dosing. Laboratory results must be assessed by a qualified investigator prior to dosing; thyroid function testing is an exception as outlined in Appendix 5.

1.3.3 Imaging Assessments for Primary Debulking Followed by Adjuvant Treatment and Maintenance

Primary Debulking Followed by Adjuvant Treatment and Maintenance	
Imaging Visit	**Description**
Baseline	Perform imaging after primary debulking surgery and within 28 days prior to starting lead-in chemotherapy.
Treatment Period	Imaging performed 9 weeks (63 days ± 7) from the date of randomization.
Maintenance Eligibility	To confirm SD, PR, CR, or non-PD, imaging must be performed: • A minimum of 21 days following C5D1 (for Q3W regimen) or a minimum of 7 days following C5D15 (for QW regimen) and prior to starting olaparib or olaparib placebo in the Maintenance Period (for participants completing 6 cycles of chemotherapy [including lead-in dose]) **OR** • A minimum of 21 days after Day 1 of the last cycle of chemotherapy (if discontinued due to toxicity) and prior to starting olaparib or olaparib placebo in the Maintenance Period. Imaging obtained within 4 weeks (28 days) prior to the planned start of maintenance may be used as the maintenance eligibility scan following Sponsor approval. Participants with radiographic evidence of PD (but clinically stable) can start the Maintenance Period (pembrolizumab/pembrolizumab placebo only) and must have PD ruled out per iRECIST (Section 8.2.1.5) prior to starting olaparib or olaparib placebo in the Maintenance Period.
Maintenance	Imaging is to be performed Q9W (63 days ± 7 days) from the date of the maintenance eligibility assessment through Week 54, Q12W (84 days ± 7 days) through Week 156, and Q24 weeks (168 days ± 7 days) thereafter. Week 54 and Week 156 are calculated from the date of randomization.
Imaging For Eligibility to Continue Olaparib/ Olaparib Placebo at 2 years	Imaging should be performed within 4 weeks prior to reaching 2 years of maintenance with olaparib/olaparib placebo: • If at this scan, the participant has CR or NED, this is the final tumor imaging in the Maintenance Phase and the participant must discontinue olaparib/olaparib placebo. Note: the participant will continue to have imaging in the Efficacy Follow-up Phase (see below and Section 8.11.3.2). • If at this scan the participant does not have a CR and is not NED, the participant may continue olaparib/olaparib placebo until CR or NED by RECIST 1.1. Note: Thereafter, the participant will continue to have imaging in the Efficacy Follow-up Phase (see below and Section 8.11.3.2).
Posttreatment Efficacy Follow-up Imaging	Participants who discontinue study treatment without documented disease progression should continue monitoring disease status by tumor imaging Q9W (63 days ± 7) through Week 54, Q12W (84 days ± 7 days) through Week 156, and Q24 weeks (168 days ± 7 days) thereafter or until meeting discontinuation criteria. Week 54 and Week 156 are calculated from the date of randomization.

Primary Debulking Followed by Adjuvant Treatment and Maintenance	
Imaging Visit	**Description**
End of Treatment	Imaging performed at the time of treatment discontinuation (±4 weeks) and prior to starting a new anticancer treatment. If previous imaging was obtained within 4 weeks (28 days) before the date of discontinuation, then imaging at treatment discontinuation is not mandatory. For participants who discontinue study treatment due to documented PD (Table 9), this is the final required tumor imaging if the investigator elects not to implement iRECIST.
CR=complete response; CxDx=Cycle 1, Day 1; iRECIST=modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; NED=no evidence of disease; PD=progressive disease; PR=partial response; QW=every week; QxW=every x weeks; SD=stable disease. Note: Chest, abdomen, and pelvis imaging - required at baseline and every timepoint according to the schedule above. Note: Bone imaging – required at baseline for participants with a history of bone metastases or who are clinically symptomatic. If positive for bone metastases at baseline, perform bone imaging according to the schedule above. Note: Brain imaging – required at baseline for participants with a history of brain metastases (to confirm stability) or who are clinically symptomatic (to rule out brain metastases). If positive for brain metastases but eligible per exclusion criterion 7, perform brain imaging according to the schedule above. Note: Unscheduled imaging may be performed as clinically indicated.	

1.3.4 Imaging Assessments for Neoadjuvant / Adjuvant Treatment Period With Interval Debulking Followed by Maintenance

Neoadjuvant / Adjuvant Treatment Period With Interval Debulking Followed by Maintenance	
Imaging Visit	**Description**
Baseline	Perform imaging within 28 days prior to starting lead-in chemotherapy.
Peri-surgery	• Presurgery: Imaging performed a minimum of 21 days after C2D1 • Postsurgery: Imaging performed prior to resuming treatment at C3D1 Note: If surgery is attempted but not performed (with or without biopsy collection), continue imaging as specified here.
Maintenance Eligibility	To confirm SD, PR, CR, or non-PD, imaging must be performed: • A minimum of 21 days following C5D1 (for Q3W regimen) or a minimum of 7 days following C5D15 (for QW regimen) and prior to starting olaparib or olaparib placebo the Maintenance Period (for participants completing 6 cycles of chemotherapy [including lead-in dose]). **OR** • A minimum of 21 days after Day 1 of the last cycle of chemotherapy (if discontinued due to toxicity) and prior to starting olaparib or olaparib placebo in the Maintenance Period. Imaging obtained within 4 weeks (28 days) prior to the planned start of maintenance, including postsurgery imaging, may be used as the maintenance eligibility scan following Sponsor approval. Participants with radiographic evidence of PD (but clinically stable) can start the Maintenance Period (pembrolizumab/pembrolizumab placebo only) and must have PD ruled out per iRECIST (Section 8.2.1.5) prior to starting olaparib or olaparib placebo in the Maintenance Period.
Maintenance	Imaging is to be performed Q9W (63 days ± 7) from the date of the maintenance eligibility assessment through Week 54, Q12W (84 days ± 7 days) through Week 156, and Q24 weeks (168 days ± 7 days) thereafter or until meeting discontinuation criteria. Week 54 and Week 156 are calculated from the date of randomization.

Neoadjuvant / Adjuvant Treatment Period With Interval Debulking Followed by Maintenance	
Imaging Visit	**Description**
Imaging For Eligibility to Continue Olaparib/ Olaparib Placebo at 2 years	Imaging should be performed within 4 weeks prior to reaching 2 years of maintenance with olaparib/olaparib placebo: • If at this scan, the participant has CR or NED, this is the final tumor imaging in the Maintenance Phase and the participant must discontinue olaparib/olaparib placebo. Note: the participant will continue to have imaging in the Efficacy Follow-up Phase (see below and Section 8.11.3.2). • If at this scan the participant does not have a CR and is not NED, the participant may continue olaparib/olaparib placebo until CR or NED by RECIST 1.1. Note: Thereafter, the participant will continue to have imaging in the Efficacy Follow-up Phase (see below and Section 8.11.3.2).
Posttreatment Efficacy Follow-up Imaging	Participants who discontinue study treatment without documented disease progression should continue monitoring disease status by tumor imaging Q9W (63 days ± 7) through Week 54, Q12W (84 days ± 7 days) through Week 156, and Q24 weeks (168 days ± 7 days) thereafter. Week 54 and Week 156 are calculated from the date of randomization.
End of Treatment	Imaging performed at the time of treatment discontinuation (±4 weeks) and prior to starting a new anticancer treatment. If previous imaging was obtained within 4 weeks (28 days) before the date of discontinuation, then imaging at treatment discontinuation is not mandatory. For participants who discontinue study treatment due to documented PD (Table 9), this is the final required tumor imaging if the investigator elects not to implement iRECIST.
CR=complete response; CxDx=Cycle x, Day x; iRECIST=modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; NED=no evidence of disease; PD=progressive disease; PR=partial response; QW=every week; QxW=every x weeks; SD=stable disease. Note: Chest, abdomen, and pelvis imaging - required at baseline and every timepoint according to the schedule above. Note: Bone imaging – required at baseline for participants with a history of bone metastases or who are clinically symptomatic. If positive for bone metastases at baseline, perform bone imaging according to the schedule above. Note: Brain imaging – required at baseline for participants with a history of brain metastases (to confirm stability) or who are clinically symptomatic (to rule out brain metastases). If positive for brain metastases, but eligible per exclusion criterion 7, perform brain imaging according to the schedule above. Note: Unscheduled imaging may be performed as clinically indicated.	

1.3.5 Imaging Assessments for Neoadjuvant / Adjuvant Treatment Period Without Interval Debulking Followed by Maintenance

Neoadjuvant / Adjuvant Treatment Period Without Interval Debulking Followed by Maintenance	
Imaging Visit	**Description**
Baseline	Perform imaging within 28 days prior to starting lead-in chemotherapy.
Treatment Period	Imaging performed 9 weeks (63 days ± 7) from the date of randomization. If surgery is not performed (with or without biopsy collection), continue imaging as specified here.
Maintenance Eligibility	To confirm SD, PR, CR, or non-PD, imaging must be performed: • A minimum of 21 days following C5D1 (for Q3W regimen) or a minimum of 1 week following C5D15 (for QW regimen) and prior to starting olaparib or olaparib placebo in the Maintenance Period (for participants completing 6 cycles of chemotherapy [including lead-in dose]) **OR** • A minimum of 21 days after Day 1 of the last cycle of chemotherapy (if discontinued due to toxicity) and prior to starting olaparib or olaparib placebo in the Maintenance Period. Imaging obtained within 4 weeks (28 days) prior to the planned start of maintenance may be used as the maintenance eligibility scan following Sponsor approval Participants with radiographic evidence of PD (but clinically stable) can start the Maintenance Period (pembrolizumab/pembrolizumab placebo only) and must have PD ruled out per iRECIST (Section 8.2.1.5) prior to starting olaparib or olaparib placebo in the Maintenance Period.
Maintenance	Imaging is to be performed Q9W (63 days ± 7) from the date of the maintenance eligibility assessment through Week 54, Q12W (84 days ± 7 days) through Week 156, and Q24 weeks (168 days ± 7 days) thereafter. Week 54 and Week 156 are calculated from the date of randomization.
Imaging For Eligibility to Continue Olaparib/ Olaparib Placebo at 2 years	Imaging should be performed within 4 weeks prior to reaching 2 years of maintenance with olaparib/olaparib placebo: • If at this scan, the participant has CR or NED, this is the final tumor imaging in the Maintenance Phase and the participant must discontinue olaparib/olaparib placebo. Note: the participant will continue to have imaging in the Efficacy Follow-up Phase (see below and Section 8.11.3.2). • If at this scan the participant does not have a CR and is not NED, the participant may continue olaparib/olaparib placebo until CR or NED by RECIST 1.1. Note: Thereafter, the participant will continue to have imaging in the Efficacy Follow-up Phase (see below and Section 8.11.3.2).
Posttreatment Efficacy Follow-up Imaging	Participants who discontinue study treatment without documented disease progression should continue monitoring disease status by tumor imaging Q9W (63 days ± 7) through Week 54, Q12W (84 days ± 7 days) through Week 156, and Q24 weeks (168 days ± 7 days) thereafter or until meeting discontinuation criteria. Week 54 and Week 156 are calculated from the date of randomization.

Neoadjuvant / Adjuvant Treatment Period Without Interval Debulking Followed by Maintenance	
Imaging Visit	**Description**
End of Treatment	Imaging performed at the time of treatment discontinuation (±4 weeks) and prior to starting a new anticancer treatment. If previous imaging was obtained within 4 weeks (28 days) before the date of discontinuation, then imaging at treatment discontinuation is not mandatory. For participants who discontinue study treatment due to documented PD (Table 9), this is the final required tumor imaging if the investigator elects not to implement iRECIST.
CR=complete response; CxDx=Cycle x, Day x; iRECIST=modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; NED=no evidence of disease; PD=progressive disease; PR=partial response; QW=every week; QxW=every x weeks; SD=stable disease. Note: Chest, abdomen, and pelvis imaging - required at baseline and every timepoint according to the schedule above. Note: Bone imaging – required at baseline for participants with a history of bone metastases or who are clinically symptomatic. If positive for bone metastases at baseline, perform bone imaging according to the schedule above. Note: Brain imaging – required at baseline for participants with a history of brain metastases (to confirm stability) or who are clinically symptomatic (to rule out brain metastases). If positive for brain metastases, but eligible per exclusion criterion 7, perform brain imaging according to the schedule above. Note: Unscheduled imaging may be performed as clinically indicated.	

2. Introduction

2.1 Study Rationale

Treatment of newly diagnosed, advanced OC is determined by the stage and risk of disease recurrence at diagnosis. Treatment options include either cytoreductive surgery followed by adjuvant chemotherapy (most likely platinum- and taxane-based) or chemotherapy alone. Alternatively, when the removal of all cancer during the initial surgery would be problematic due to tumor size, chemotherapy may be administered before surgery (neoadjuvant chemotherapy) to shrink the tumor, with additional chemotherapy after surgery (adjuvant chemotherapy). Clinically, complete remission is achieved in most newly diagnosed patients through a combination of cytoreductive surgery and chemotherapy; however, 10% of patients might not respond to first-line chemotherapeutic treatment and, of those who do respond, between 55% and 75% will relapse within 2 years [du Bois, A., et al 2009] [Ledermann, J. A., et al 2013] [Edwards, S. J., et al 2015]. The overall 5-year survival rate for EOC remains poor, ranging from 28% to 57% depending on age at diagnosis [Edwards, S. J., et al 2015] [Eisenhauer, E. L., et al 2012]; in addition, toxicity is high with the current SOC chemotherapeutic regimens, urgently requiring novel therapies to be identified for women with OC.

PARP inhibitors have been recently approved as maintenance treatment in the front-line setting for patients with OC HRD positive (ie, based on PAOLA-1) or irrespective of HRR status (ie, based on PRIMA); however, *BRCA1/2* non-mutated patient population still represents high unmet need, particularly in patients with homologous recombination proficiency. OS data from PAOLA-1 presented at ESMO 2022 have shown HR=1.18 for olaparib plus bevacizumab in the HRD-negative subgroup, confirming limited efficacy of PARP inhibitors in these patient populations. HRD-negative OC represents about 70% of all *BRCA*wt OC and remains an area of high unmet clinical need.

The PD-1 antibody pembrolizumab has shown efficacy as monotherapy in patients with several advanced cancers and has a non-overlapping toxicity profile with chemotherapy. A recently published report of a randomized, controlled clinical study demonstrated that the addition of pembrolizumab to carboplatin and pemetrexed improved efficacy and had a favorable benefit-to-risk profile in patients with chemotherapy-naïve, advanced non-squamous NSCLC [Langer, C. J., et al 2016]. These are the first published data to prospectively show a benefit of the addition of a PD-1 pathway inhibitor to platinum-based doublet chemotherapy in front-line advanced non-squamous NSCLC. Ongoing studies, in several different tumor types, are currently investigating the benefit of the addition of pembrolizumab to other front-line platinum-based chemotherapies. Data from KEYNOTE-100, in participants with recurrent OC, suggest improved efficacy for pembrolizumab monotherapy in those participants whose tumors express PD-L1 with the cutoff of CPS ≥10. In addition, recent data from a Phase 3 study of atezolizumab in combination with carboplatin, paclitaxel, and bevacizumab in front-line advanced OC failed to demonstrate an advantage in PFS and OS over standard chemotherapy (IMAGYN50) [Moore, K., et al 2020]. However, a trend favoring atezolizumab was shown in the PD-L1 positive population. IMAGYN50 data suggest prevalence of PD-L1 positive cases ~60% (measured by SP142 at IC1% cutoff). Given that the prevalence of PD-L1 positivity at IC1% cutoff is slightly higher

compared with CPS ≥10, we would expect the prevalence at CPS ≥10 to be ~50%. These results are in-line with those of JAVELIN 200 Ovarian, which tested avelumab alone or in combination with PLD versus PLD in platinum refractory or resistant OC. Despite being overall a negative study, JAVELIN 200 demonstrated a trend favoring the combination of PLD and avelumab in the PD-L1 positive population. In addition, the Kaplan-Meier Curve for PFS from JAVELIN 200 shows a late separation of the curves for PLD plus avelumab versus PLD, indicating that data maturity may be important to demonstrate an immunotherapy effect in this patient population.

Similarly, the final PFS analysis of IMAGYN050 was conducted with relatively immature data (~50% of events in each arm), and it was estimated that the study would have achieved the PFS endpoint in PD-L1 positive patients if they were to have more mature data (ie, more events [~70%]). A similar issue was considered as one of the main reasons the JAVELIN study failed at the interim analysis with immature data and limited number of events. The overall follow-up was also 19 months, and there was not a PARP inhibitor used in IMAGYN50, which also is an important aspect to consider along with the inclusion of patients with *BRCA1/2* mutated (*BRCA*mut) as well as those with *BRCA* non-mutated tumors in the study. All of these were considered when revising the SAP for this amendment.

The combination of immune checkpoint inhibitor pembrolizumab plus the PARP inhibitor niraparib has shown efficacy in participants with platinum-resistant, relapsed OC following initial treatment (TOPACIO/KEYNOTE-162), with responses documented irrespective of *BRCA1/2* status [Konstantinopoulos, P. A., et al 2018]. In addition, data recently presented from the MEDIOLA study, in participants with *BRCA* non-mutated, platinum-sensitive recurrent OC, comparing the triple combination of durvalumab + olaparib + bevacizumab with the doublet combination of durvalumab + olaparib, demonstrated a high ORR, particularly in triple combination arm (ORR ~87%) vs doublet (ORR ~34%) [Pujade-Lauraine, E., et al 2019]. Olaparib is currently approved for second-line maintenance in platinum-sensitive, recurrent OC, regardless of *BRCA1/2* status and is currently being investigated as maintenance treatment after response to front-line chemotherapy (SOLO-1 study) in *BRCA*mut OC patients. Based on the promising results from the TOPACIO/KEYNOTE-162 and MEDIOLA studies [Konstantinopoulos, P. A., et al 2018] [Drew, Y., et al 2018], the present study has been designed to compare carboplatin/paclitaxel alone with the novel combinations of either carboplatin/paclitaxel plus pembrolizumab or carboplatin/paclitaxel plus pembrolizumab with olaparib maintenance as a first-line treatment for *BRCA1/2* non-mutated advanced EOC. This novel combination will likely provide significant benefit for women with newly diagnosed advanced OC.

2.2 Background

2.2.1 Pembrolizumab

Pembrolizumab is a potent humanized Ig G4 monoclonal antibody 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 a number of indications.

Refer to the IB/approved labeling for detailed background information on pembrolizumab.

2.2.2 Olaparib

Olaparib (AZD2281, KU-0059436) is a potent PARP inhibitor (PARP-1, -2 and -3) that is being developed as an oral therapy, both as a monotherapy (including maintenance) and for combination with chemotherapy and other anticancer agents.

PARP inhibition is a novel approach to targeting tumors with deficiencies in DNA repair mechanisms. PARP enzymes are essential for repairing DNA SSBs. Inhibiting PARPs leads to the persistence of SSBs, which are then converted to the more serious DNA DSBs during the process of DNA replication. During the process of cell division, DSBs can be efficiently repaired in normal cells by HRR. Tumors with HRD, such as OCs in patients with *BRCA1/2* mutations, 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.

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

2.2.3 Pharmaceutical and Therapeutic Background

2.2.3.1 Inhibition of PD-1 as a Target for Cancer

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

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

The structure of murine PD-1 has been resolved [Zhang, X., et al 2004]. PD-1 and its family members are type I transmembrane glycoproteins containing an extracellular Ig-variable-type domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs,

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

2.2.3.2 Inhibition of PARP as a Target for Cancer

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 rate of errors compared with other forms of DNA repair [Prakash, R., et al 2015]. During DNA replication (S phase), pre-existing SSBs are converted to DSBs as the replication machinery passes [Fong, Peter C., et al 2009], which are ultimately repaired by HRR. Cells unable to perform HRR (eg, due to inactivation of genes required for the process, such as *BRCA1* or *BRCA2*) are more likely to use the error-prone NHEJ or alternative NHEJ pathways to repair these DSBs and are at risk for accumulating multiple lesions or loss of heterozygosity. Over time, the buildup of excessive DNA errors in combination with the inability to complete S phase (because of stalled replication forks) contributes to cell death.

Clinical studies have shown that PARP inhibitors are most effective in patients with recurrent OC who are either platinum-sensitive or platinum-resistant and harbor mutations of *BRCA1/2* [George, A., et al 2017]. PARP inhibitors have demonstrated effectiveness in patients without germline *BRCA*mut (g*BRCA*mut), although the magnitude has been smaller [Fong, Peter C., et al 2009] [Gelmon, K. A., et al 2011] [Ledermann, J., et al 2012]. For example, median PFS was significantly longer for patients with platinum-sensitive, relapsed OC and g*BRCA*mut who were treated with olaparib as maintenance therapy compared with placebo (19.1 months versus 5.5 months; HR: 0.30, $p<0.001$) [Pujade-Lauraine, E., et al 2017]. Similarly, median PFS was significantly longer in patients with platinum-sensitive, relapsed OC and any *BRCA1/2* status compared with placebo (8.4 months versus 4.8 months; HR: 0.35, $p<0.001$). Additionally, these patients had a median OS of 29.8 months compared with 27.8 months for placebo (HR: 0.73) [Ledermann, J., et al 2012].

In summary, treatment with PARP1/2 inhibitors represents a novel opportunity to selectively kill a subset of cancer cell types by exploiting their deficiencies in DNA repair. Human cancers exhibit genomic instability and an increased mutation rate due to underlying defects in DNA repair. These deficiencies render cancer cells more dependent on the remaining DNA repair pathways, and targeting these pathways is expected to have a much greater impact on the survival of the tumor cells than on normal cells.

2.2.3.3 Combined Use of an Anti-PD-1 Monoclonal Antibody and PARP Inhibitor for the Treatment of Cancer

Over recent years, research has revealed the importance of TILs in controlling the clinical progression of various cancers and their presence in a tumor is associated with response to immune checkpoint inhibitors [Fridman, W. H., et al 2012]. In OC, intraepithelial CD8+ T-cells correlated with the presence of mutation or loss of expression of *BRCA1* through promoter methylation [Clarke, B., et al 2009]. Patients with OC that were sensitive to agents targeting defects in DNA repair are likely to overlap with those tumors with an active, yet checkpoint-blocked, immune response.

Despite promising activity of PD-1 inhibitors observed in some types of cancer, including melanoma and NSCLC [Barbee, M. S., et al 2015], activity in OC has been modest [Disis, M. L., et al 2015] [Varga, A., et al 2015] [Matulonis, U. A., et al 2018]. In KEYNOTE-028, the confirmed ORR was 11.5% following pembrolizumab monotherapy in participants with advanced ovarian epithelial, fallopian tube, or primary peritoneal carcinoma who had failed prior therapy [Disis, M. L., et al 2015]. In KEYNOTE-100, the ORR was 9% for all participants with epithelial ovarian, fallopian tube, or primary peritoneal cancer and confirmed recurrence following front-line platinum-based therapy [Matulonis, U. A., et al 2018]. ORR was higher in participants who had elevated levels of PD-L1 expression: 14% in participants with a combined positive score (CPS) ≥1% and 25% in participants with a CPS ≥10% [Matulonis, U. A., et al 2018].

While the ORR of PARP inhibitors in unselected patients with OC (ie, with and without g*BRCA*mut) has been modest to date [Gelmon, K. A., et al 2011] [Ledermann, J., et al 2012] [Sandhu, S. K., et al 2013], PARP inhibition has significantly prolonged PFS when used as either monotherapy or in combination with chemotherapy [Ledermann, J., et al 2014] [Oza, A. M., et al 2015] [Mirza, M. R., et al 2016]. Additionally, synergistic interactions have been observed between immune checkpoint inhibitors and PARP inhibitors. Nonclinical experiments in syngeneic mouse models have shown an increased response rate to the combination of anti-PD-1 and a PARP inhibitor over either agent alone, providing additional support to investigate this combination in patients [Higuchi, T., et al 2015] [Huang, J., et al 2015]. A Phase 1 dose-finding combination study of pembrolizumab and a PARP inhibitor (ie, niraparib) is currently ongoing in participants with platinum-resistant recurrent OC treated with ≤5 prior lines of chemotherapy and having responded with CR or PR to first-line platinum-based chemotherapy (TOPACIO/KEYNOTE-162). In preliminary results, 4 of 8 participants with OC responded (based on RECIST 1.1), 3 of whom were g*BRCA*mut negative. No significant overlapping toxicity was noted with the combination of pembrolizumab and the PARP inhibitor, and the combination was generally well tolerated [Konstantinopoulos, P. A., et al 2018].

Exposure of a tumor in vivo to a PARP inhibitor results in increased cancer cell death by 2 independent mechanisms. First, through the mechanism of synthetic lethality, the PARP inhibitor can kill HRD tumors through apoptosis. Second, the PARP inhibitor can increase the number of CD8+ T cells and natural killer cells, as well as their production of interferon-gamma and tumor necrosis factor-alpha, resulting in an improved response to checkpoint blockade [Huang, J., et al 2015]. Furthermore, a wide array of biomarkers will be explored in this protocol to investigate tumor cell death, genomic changes, apoptosis, and immune response. Given the non-overlapping safety and metabolic profile (see the current IB for pembrolizumab and olaparib, respectively, for details) and preclinical data suggesting possible synergistic interaction between immune checkpoint inhibitors and PARP inhibitors along with a potential overlap for PD-1 and PARP-sensitive patient populations, this study is designed to evaluate pembrolizumab and the combination of pembrolizumab plus olaparib maintenance when added to the current SOC as a front-line treatment for the treatment of advanced EOC.

2.2.3.4 Overview of Epithelial Ovarian Cancer

OC is the most lethal gynecologic cancer and one of the top -leading causes of cancer death among women. In 2017, the estimated number of new cases and deaths from OC in the US is 22,440 and 14,080, respectively [Siegel, R. L., et al 2017]. Worldwide, OC represents one of the 10 most common cancer diagnoses and leading causes of cancer-related deaths in women [Torre, L. A., et al 2015]. Due to lack of tumor-specific signs and symptoms and effective screening tests for early detection, over 75% of OC patients are first diagnosed at advanced stages. Based on the US data from 2006 to 2012, at initial diagnosis, 60% had distant metastasis, 19% had regional disease and only 15% had localized disease. The overall 5-year survival rate of OC is approximately 46% counting all stages; the 5-year survival rate in patients with distant metastasis is only 29% [Siegel, R. L., et al 2017].

OC is a heterogeneous disease, with distinct histopathologic features, genetic alterations, and clinical behaviors. EOC is the most common (>90% of OCs) and most lethal of the gynecologic malignancies [Gilks, C. B. and Prat, J. 2009]. Currently, EOCs are classified into 5 main subtypes based on histopathology, immunohistochemistry, and molecular-genetic characteristics: HGSC (~ 70% of EOCs), endometrioid carcinoma (~ 10% of EOCs), clear cell carcinoma (~ 10% of EOCs), mucinous carcinoma (~ 3% of EOCs), and low-grade serous carcinoma (5% EOC) [Gilks, C. B. and Prat, J. 2009] [Prat, J. and FIGO Committee on Gynecologic Oncology 2014]. The distinction of EOC subtype at diagnosis/staging is a critical factor that will guide treatment, as each tumor type responds differently to chemotherapy [Gilks, C. B. and Prat, J. 2009]. Primary peritoneal carcinoma and fallopian tube carcinoma, while rare and distinct tumor types, have typically been managed and studied together with EOC as they share similar clinical and pathological characteristics with HGSC [Cannistra, S. A., et al 2011].

2.2.3.5 Current Standard of Care and Unmet Medical Need

The current SOC for advanced EOC (FIGO Stage II to Stage IV) includes primary cytoreductive/debulking surgery followed by postoperative front-line (ie, adjuvant) systemic treatment with IV carboplatin and paclitaxel administered Q3W for 6 cycles. However,

weekly paclitaxel has also been frequently used to replace Q3W paclitaxel. In addition, where locally approved for front-line treatment, IV bevacizumab can be added to IV carboplatin and paclitaxel for up to 6 cycles and then continued as a single agent. In suitable cases, postoperative chemotherapy, usually cisplatin plus paclitaxel, can be delivered via the intraperitoneal route. Finally, in cases with bulky disease that is initially inoperable, 3 cycles of standard platinum/taxane-based chemotherapy can be administered as neoadjuvant therapy prior to cytoreductive/debulking surgery (ie, interval cytoreductive/debulking surgery) followed by an additional 3 cycles of standard platinum/taxane-based chemotherapy [Morgan, R. J ., et al 2016] [Ledermann, J. A., et al 2013].

The goal of cytoreductive/debulking surgery is to achieve resection of all macroscopically visible tumors, while the goals of postoperative first-line chemotherapy are: 1) to help achieve complete remission in those with residual disease, and 2) to prevent disease recurrence for those with complete tumor resection. However, after these primary treatments, only a small proportion of patients will achieve long-term disease-free and survival status. A meta-analysis on data from 3 randomized studies following the standard primary treatment with surgery and platinum/taxane-based chemotherapy (N = 3126), showed that only 24% of patients were recurrence-free after a median follow-up time of 53.9 months. The remaining 76% had recurrent disease (17.2%) or had died (58.8%) [du Bois, A., et al 2009].

Recently (29-APR-2020), niraparib was approved by the FDA for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a CR or PR to first-line platinum-based chemotherapy. On 08-MAY-2020, the combination of olaparib with bevacizumab for first-line maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or PR to first-line platinum-based chemotherapy and whose cancer is associated with HRD positive status defined by either a deleterious or suspected deleterious *BRCA* mutation, and/or genomic instability was approved by the FDA. FDA also approved the Myriad myChoice® CDx (Myriad Genetic Laboratories, Inc.) as a companion diagnostic for olaparib.

While the current SOC is initially effective for the treatment of EOC, approximately 70% of patients will experience a relapse within 3 years of treatment cessation [du Bois, A., et al 2009] [Ledermann, J. A., et al 2013]. Thus, there is an unmet medical need for therapies that, when used in combination with the current SOC, significantly increases the proportion of patients with complete remission and prevents disease recurrence in patients with advanced EOC.

2.2.4 Preclinical and Clinical Studies

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

2.2.5 Ongoing Clinical Studies

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

2.2.6 Information on Other Study-related Therapy

For additional information on carboplatin, paclitaxel, docetaxel, and bevacizumab, refer to their respective approved product labels.

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.

As discussed in Section 2.2.3.3, the combination of pembrolizumab and a PARP inhibitor has shown preliminary efficacy in heavily pretreated participants with platinum-resistant OC (TOPACIO/KEYNOTE-168). Given the high rate of relapse following initial treatment for OC [Ledermann, J. A., et al 2013], there is an unmet medical need for an effective and tolerable first-line treatment regimen. The existing data suggest that a combination of PD-1 blockade with PARP inhibition, when added to carboplatin/paclitaxel, is a promising therapeutic strategy and the benefit risk assessment for participants included in this study is expected to be favorable.

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. Objectives/Hypotheses and Endpoints

In participants with previously untreated *BRCA1/2* non-mutated advanced EOC treated with pembrolizumab plus carboplatin/paclitaxel followed by continued pembrolizumab treatment plus olaparib maintenance (Arm 1) or pembrolizumab plus carboplatin/paclitaxel followed by continued pembrolizumab treatment (Arm 2) versus carboplatin/paclitaxel alone (Arm 3):

Objective/Hypothesis	**Endpoint**
Primary	
• Objective: To compare the progression-free survival (PFS) as assessed by the investigator according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) Hypothesis (H1): The combination of pembrolizumab plus carboplatin/paclitaxel followed by continued pembrolizumab treatment and olaparib maintenance (Arm 1) is superior to carboplatin/paclitaxel alone (Arm 3) with respect to PFS per RECIST 1.1 in participants with PD-L1 positive tumors (CPS ≥10). Hypothesis (H2): The combination of pembrolizumab plus carboplatin/paclitaxel followed by continued pembrolizumab treatment and olaparib maintenance (Arm 1) is superior to carboplatin/paclitaxel alone (Arm 3) with respect to PFS per RECIST 1.1 in All Participants. Hypothesis (H3): The combination of pembrolizumab plus carboplatin/paclitaxel followed by continued pembrolizumab treatment (Arm 2) is superior to carboplatin/paclitaxel alone (Arm 3) with respect to PFS per RECIST 1.1 in participants with PD-L1 positive tumors (CPS ≥10). Hypothesis (H4): The combination of pembrolizumab plus	• PFS, the time from the date of randomization until either the earliest date of documented disease progression or death due to any cause, whichever occurs first

Objective/Hypothesis	Endpoint
carboplatin/paclitaxel followed by continued pembrolizumab treatment (Arm 2) is superior to carboplatin/paclitaxel alone (Arm 3) with respect to PFS per RECIST 1.1 in All Participants.	
Secondary	
• Objective: To compare the overall survival (OS) Hypothesis (H5): The combination of pembrolizumab plus carboplatin/paclitaxel followed by continued pembrolizumab treatment and olaparib maintenance (Arm 1) is superior to carboplatin/paclitaxel alone (Arm 3) with respect to OS in All Participants. Hypothesis (H6): The combination of pembrolizumab plus carboplatin/paclitaxel followed by continued pembrolizumab treatment (Arm 2) is superior to carboplatin/paclitaxel alone (Arm 3) with respect to OS in All Participants. Hypothesis (H7): The combination of pembrolizumab plus carboplatin/paclitaxel followed by continued pembrolizumab treatment (Arm 2) is superior to carboplatin/paclitaxel alone (Arm 3) with respect to OS in participants with PD-L1 positive tumors (CPS ≥10).	• OS, the time from the date of randomization to death due to any cause
• Objective: To compare the PFS as assessed by blinded independent central review (BICR) per RECIST 1.1 in participants with PD-L1 positive tumors (CPS ≥10) and in All Participants.	• PFS

Objective/Hypothesis	Endpoint
• Objective: To compare the PFS after second-line treatment as determined by the investigator according to the local standard of clinical practice (PFS2) following discontinuation of study treatment administration in participants with PD-L1 positive tumors (CPS ≥10) and in All Participants.	• PFS2, the time from the date of randomization until disease progression (clinical or radiological) after second-line treatment or death due to any cause, whichever occurs first
• Objective: To evaluate the safety and tolerability of pembrolizumab administered with chemotherapy and olaparib maintenance	• Adverse events (AEs) • Study treatment discontinuation due to AEs
• Objective: To compare the mean change from baseline of Global Health Status/Quality-of-Life (GHS/QoL) score using the European Organisation for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire Core 30 (QLQ-C30) and abdominal and gastrointestinal (abdominal/GI) symptoms using the EORTC Ovarian Cancer-Specific Quality-of-Life Questionnaire (QLQ-OV28) abdominal/GI symptom scale	Change from baseline in: • EORTC QLQ-C30 GHS/QoL score • EORTC QLQ-OV28 abdominal/GI symptom scale
• Objective: To compare time to deterioration (TTD) of GHS/QoL score using EORTC QLQ-C30 and abdominal/GI symptoms using EORTC QLQ-OV28	Time to deterioration in: • EORTC QLQ-C30 GHS/QoL score • EORTC QLQ-OV28 abdominal/GI symptom scale

Objective/Hypothesis	Endpoint
• Objective: To compare the time to first subsequent anticancer treatment (TFST), the time to second subsequent anticancer treatment (TSST), and the time to discontinuation of study treatment (TDT)	• 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 • TDT, the time from the date of randomization to discontinuation of study treatment or death due to any cause, whichever occurs first
• Objective: To compare the rate of locally determined pathological complete response (pCR) of pembrolizumab in combination with carboplatin/paclitaxel versus carboplatin/paclitaxel alone when administered as neoadjuvant therapy	• pCR, all surgical specimens collected during the interval debulking surgery are microscopically negative for malignancy
Tertiary/Exploratory	
CCI [redacted]	

Objective/Hypothesis	Endpoint
CCI	
CCI	
CCI	

4. Study Design

4.1 Overall Design

This is a Phase 3, randomized, placebo-controlled, parallel-group, multi-site, double-blind study to evaluate chemotherapy with or without pembrolizumab followed by maintenance with olaparib or placebo for the first-line treatment of *BRCA1/2* non-mutated advanced EOC.

Following a Lead-in Period during which all participants will receive a single cycle of carboplatin/paclitaxel*, approximately 1284 participants will be randomly assigned in a 1:1:1 ratio to 1 of 3 treatment arms. Prior to randomization, participants will be stratified by surgery (planned interval debulking versus R0 [no macroscopic residual disease (0 cm) intra- or extra-abdominal (metastatic) following primary debulking] versus R1 [>0 cm macroscopic residual disease intra- or extra-abdominal (metastatic) following primary debulking]), bevacizumab use (yes versus no), and PD-L1 positivity (CPS <10 versus CPS ≥10).

Arm 1: Treatment: carboplatin/paclitaxel* for 5 cycles plus pembrolizumab 200 mg Q3W for up to 35 infusions
Maintenance: olaparib 300 mg twice daily (BID)

Arm 2: Treatment: carboplatin/paclitaxel* for 5 cycles plus pembrolizumab 200 mg Q3W for up to 35 infusions
Maintenance: olaparib placebo BID

Arm 3: Treatment: carboplatin/paclitaxel* for 5 cycles plus pembrolizumab placebo Q3W for up to 35 infusions

Maintenance: olaparib placebo BID

Crossover between treatment arms is not permitted.

*At the investigator's discretion and determined prior to the participant being randomly assigned to study treatment, one of the following regimens should be administered:

- Carboplatin area under the concentration-time curve (AUC)5 or AUC6 Q3W plus paclitaxel 175 mg/m^2 Q3W
- Carboplatin AUC5 or AUC6 Q3W plus paclitaxel 80 mg/m^2 once weekly (QW)
- Carboplatin AUC2 or AUC2.7 QW plus paclitaxel 60 mg/m^2 QW

Docetaxel may be considered for participants who experience either a severe hypersensitivity reaction to paclitaxel or an AE requiring discontinuation of paclitaxel only after consultation with the Sponsor. The recommended dose, as determined by the SGCTG group [Vasey, P. A., et al 2004], is as follows:

- *Docetaxel 75 mg/m^2 Q3W plus carboplatin AUC 5 Q3W*

  Note: At the investigator's discretion, bevacizumab may be used. Use of bevacizumab must be decided prior to randomization as it is a stratification factor. For participants eligible for interval debulking, bevacizumab (if using) should be started with carboplatin/paclitaxel during the Lead-in Period, stopped following Cycle 1 (prior to surgery), and resumed in Cycle 4. For participants eligible for primary debulking surgery, bevacizumab (if using) should be initiated in Cycle 1. The investigator may wait to administer the first dose of bevacizumab, as long as it is administered by Cycle 4 (but it may be started sooner). Any delay in starting/restarting bevacizumab beyond what is defined in the protocol require Sponsor approval. If using, bevacizumab should be continued with chemotherapy and study treatment as per the local SOC and approved product label.

Participants must be candidates for either primary or interval debulking surgery. Primary debulking surgery may be, but does not need to be, performed within the 56-day Screening Period. Participants should initiate lead-in chemotherapy when clinically appropriate but no longer than 7 weeks following primary debulking surgery. (Figure 2). Participants having primary debulking surgery should receive 6 treatment cycles (including lead-in) of adjuvant carboplatin/paclitaxel plus either pembrolizumab or pembrolizumab placebo. Alternatively, participants who are candidates for interval debulking surgery will receive 2 cycles of carboplatin/paclitaxel plus either pembrolizumab or pembrolizumab placebo prior to surgery (neoadjuvant treatment) and another 3 cycles of carboplatin/paclitaxel plus either pembrolizumab or pembrolizumab placebo after surgery (adjuvant treatment). Participants should resume study treatment when clinically appropriate but no longer than 7 weeks following interval debulking surgery (Figure 3).

Participants with stable disease (SD), PR, CR, or non-progressive disease (PD) will enter the Maintenance Period. Participants with disease progression will be discontinued from the study (Section 7.1). The Maintenance Period (continued pembrolizumab treatment plus olaparib maintenance [Arm 1], continued pembrolizumab treatment plus olaparib placebo [Arm 2], or continued pembrolizumab placebo plus olaparib placebo [Arm 3]) will start at Cycle 7. Participants who are not able to complete 6 treatment cycles (including lead-in) of chemotherapy due to toxicity, may be eligible to start the Maintenance Period as early as Cycle 2 following consultation with the Sponsor. Note: participants may be able to start the Maintenance Period and receive only pembrolizumab or pembrolizumab placebo following consultation with the Sponsor.

Pembrolizumab and pembrolizumab placebo may continue for up to 35 infusions (approximately 2 years starting with the first infusion in Cycle 1) or until meeting criteria for discontinuation of study treatment (Section 7.1). Participants who have no evidence of disease (NED) will stop olaparib or olaparib placebo after 2 years, calculated from the first dose of olaparib or olaparib placebo. Participants who continue to have evidence of disease without evidence of disease progression at this time will continue olaparib or olaparib placebo until meeting criteria for discontinuation of study treatment (Section 7.1).

Participants will be evaluated with radiographic imaging to assess response to treatment at regular intervals during the study (Section 8.2.1). Participants will continue with imaging until disease progression is radiographically documented by the investigator per RECIST 1.1 (Section 8.2.1.4), and when clinically appropriate, confirmed by the site per modified RECIST 1.1 for immune-based therapeutics (iRECIST), initiating a new anticancer treatment, withdrawal of consent, becoming lost to follow-up, pregnancy or death (Section 8.2.1.5). All imaging obtained on study will be submitted to the central imaging vendor for retrospective assessment of PFS per RECIST 1.1 by BICR.

Tumor marker data (ie, CA-125) will not be used for defining PD to evaluate progression-related primary and secondary objectives; however, CA-125 may be used to make clinical decisions, including the decision to discontinue a participant from study treatment (Section 7.1). Clinical criteria such as the Gynecologic Cancer Intergroup criteria (see Appendix 9) will also be considered for the management of clinical events (eg, bowel obstruction) without radiographic disease progression. Participants who discontinue due to CA-125 increase and concurrent malignant bowel obstruction will have posttreatment follow-up imaging to evaluate disease status until disease progression is radiographically documented per RECIST 1.1 by the investigator as outlined in Section 8.2.1.3.

AE monitoring will be ongoing throughout the study and graded in severity according to the guidelines outlined in the NCI CTCAE version 4.03 (v4). AEs will be reported by the investigator or delegate through 30 days following cessation of study treatment. Serious AEs (SAEs) will be reported by the investigator or delegate through 90 days following cessation of study treatment or 30 days following cessation of study treatment if the participant initiates new anticancer therapy, whichever is earlier.

As of Amendment 05, all blood collections for ctDNA analysis and all PRO collections will be discontinued.

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

After the final analysis, participants may be transitioned to an extension study, if available.

4.1.1 Data Monitoring Committee

This study will use an independent, external data monitoring committee (eDMC) to monitor safety and efficacy (Section 9.7). The eDMC will review unblinded safety data at regular intervals throughout the study and efficacy data at prespecified interim analyses, as outlined in the eDMC charter.

4.1.2 Interim Analyses

CCI

[redacted]

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

This study will use PFS as the primary endpoint and OS as a key secondary endpoint as outlined in Section 3.

This study will use PFS based on RECIST 1.1 criteria as assessed by the investigator as the primary endpoint. PFS is an acceptable measure of clinical benefit for a late stage study that demonstrates superiority of a new antineoplastic therapy, especially if the magnitude of the effect is large and the therapy has an acceptable risk/benefit profile. Additionally, as a secondary objective, images will be read by a central imaging vendor blinded to treatment assignment to minimize bias in the response assessments.

OS 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 investigator when assessing images for primary efficacy (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 an adjustment to RECIST 1.1 to allow a maximum of 10 target lesions in total and 5 per organ.

4.2.1.1.2 Modified RECIST 1.1 for Immune-based Therapeutics

RECIST 1.1 will be adapted to account for the unique tumor response seen following treatment with pembrolizumab (Section 8.2.1.5). Immunotherapeutic agents such as

pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and patients treated with pembrolizumab may manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions.

Thus, standard RECIST 1.1 may not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab. Based on an analysis of participants with melanoma enrolled in KEYNOTE-001 (KN001), 7% of evaluable participants experienced delayed or early tumor pseudoprogression. 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 response in immunotherapy and enable treatment beyond initial radiographic progression, if the participant is clinically stable.

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 non-target 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, as well as for exploratory efficacy analyses where specified.

4.2.1.2 Safety Endpoints

Safety parameters commonly used for evaluating investigational systemic anticancer treatments include, but are not limited to, the incidence of, causality, and outcome of AEs/SAEs; and changes in vital sign measurements and laboratory values. AEs will be assessed as defined by NCI CTCAE v4.03.

4.2.1.3 Patient-reported Outcomes

CCI

[redacted]

CCI [redacted]

4.2.1.3.1 CCI [redacted]

CCI [redacted]

4.2.1.3.2 CCI [redacted]

CCI [redacted]

4.2.1.3.3 CCI [redacted]

CCI [redacted]

CCI [redacted]

4.2.1.4 CCI [redacted]

CCI [redacted]

CCI [redacted]

4.2.1.5 CCI [redacted]

CCI [redacted]

CCI [redacted]

4.2.2 Rationale for the Use of Comparator/Placebo

Carboplatin and paclitaxel represent the current SOC for the first-line treatment of advanced EOC. Docetaxel may be considered for participants who either experience a severe hypersensitivity reaction or an AE that requires discontinuation of paclitaxel only after Sponsor consultation. The use of a placebo for pembrolizumab and olaparib will ensure the objectivity of investigator- and centrally-assessed progression and safety, as well as any decisions to interrupt/discontinue therapy.

4.3 Justification for Dose

4.3.1 Rationale for Pembrolizumab Dosing Regimen

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.

4.3.2 Rationale for Olaparib Dosing Regimen

The dose of olaparib used in this study is 300 mg BID (tablet formulation) and is the current approved dose.

4.3.3 Rationale for Chemotherapy and Bevacizumab Dosing Regimen

The dosing regimens of carboplatin and paclitaxel that will be used in this study are reflective of current clinical practice. The dose of docetaxel, if approved by the Sponsor, reflects the recommended dose for OC as determined by the SGCTG group [Vasey, P. A., et al 2004]. The use of bevacizumab is allowed at the investigator's discretion, where approved for the front-line treatment of EOC, as per the local SOC and approved product label.

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). 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 EEA, the local start of the study in the EEA is defined as FSR in any Member State.

The Sponsor estimates that the maximum duration of the study from first participant entered through long-term follow-up will be approximately 7 years to attain the final assessment of

the study (eg, to evaluate safety and/or long-term efficacy) for all evaluable participants. Refer to the Synopsis, Section 1.1, for the duration of participation of participants.

4.4.1 Clinical Criteria for Early Study Termination

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

5. Study Population

Female participants of at least 18 years of age with EOC, fallopian tube cancer, or primary peritoneal cancer will be enrolled in this study.

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

As stated in the Code of Conduct for Clinical Trials (Section 10.1.1), this study uses participants of varying age (as applicable), race, and ethnicity. 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.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Type of Participant and Disease Characteristics

1. Participant has histologically confirmed FIGO Stage III or Stage IV EOC (high-grade predominantly serous, endometrioid (any grade), carcinosarcoma, mixed mullerian with high-grade serous component, clear cell, or low-grade serous OC), primary peritoneal cancer, or fallopian tube cancer.
   Note: Enrollment of participants with low-grade serous OC will be capped at 4% of the total population.
2. Participant has just completed primary debulking surgery or is eligible for primary debulking surgery or is a potential candidate for interval debulking surgery.
3. Participant is a candidate for carboplatin and paclitaxel chemotherapy, to be administered in the adjuvant or neoadjuvant setting.
4. Participant that is a candidate for neoadjuvant chemotherapy has a CA-125 (kilounits/L):carcinoembryonic antigen (CEA; ng/mL) ratio greater than or equal to 25 [Vergote, I., et al 2010].
   Note: if the serum CA-125/CEA ratio is less than 25, then a workup should be negative for the presence of a non-OC to determine eligibility (eg, breast or gastrointestinal cancers [including CRC]).

5. Participant is able to provide a newly obtained core or excisional biopsy of a tumor lesion for prospective testing of *BRCA1/2* and PD-L1 status prior to randomization.
   Note: Newly obtained tissue may be obtained at any time prior to the administration of systemic cytotoxic treatment for the treatment of current OC. Both formalin-fixed paraffin-embedded (FFPE) tumor blocks and slides are acceptable. If submitting unstained cut slides, freshly cut slides should be submitted to the testing laboratory within 14 days from the date the slides are cut.

Demographics

6. Participant is female and at least 18 years of age on the day of signing informed consent.
7. Participant has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, as assessed within 7 days prior to initiating chemotherapy in the Lead-in Period and within 3 days prior to Day 1 of Cycle 1.

Female participants:

8. A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:
   - Is not a woman of childbearing potential (WOCBP)

     OR

   - Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 3 during the Treatment Period and for at least 120 days following the last dose of pembrolizumab (or pembrolizumab placebo) and bevacizumab (if administered), at least 180 days following the last dose of olaparib (or olaparib placebo), and at least 210 days following the last dose of chemotherapy and agrees not to donate eggs (ova, oocytes) to others or freeze/store for her own use for the purpose of reproduction during this period. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study treatment. Refer to Appendix 7 for country-specific requirements.
   - A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within either 24 hours (urine) or 72 hours (serum) before the first dose of study treatment.
   - If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
   - Additional requirements for pregnancy testing during and after study treatment are located in Appendix 3.
   - 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

9. The participant (or legally acceptable representative if applicable) provides written informed consent for the study. The participant may also provide consent for future biomedical research; however, the participant may participate in the main study without participating in future biomedical research.

Laboratory Values

10. Participant has adequate organ function as defined in Table 1; all screening laboratory tests should be performed within 7 days prior to starting chemotherapy in the Lead-in Period.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/µL
Platelets	≥100 000/µL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[a]
Renal	
Creatinine OR Measured or calculated[b] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN OR ≥51 mL/min for participant with creatinine levels >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT) or partial thromboplastin time (PTT)[c]	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants

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

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

a. Criteria must be met without erythropoietin dependency. Transfusion of packed red blood cells is allowed.
b. Creatinine clearance (CrCl) should be calculated per institutional standard.
c. PTT may be performed if the local lab is unable to perform aPTT.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Participant has mucinous, germ cell, or borderline tumor of the ovary.
2. Participant has a known or suspected deleterious mutation (germline or somatic) in either *BRCA1* or *BRCA*2.
3. Participant has a history of non-infectious pneumonitis that required treatment with steroids or currently has pneumonitis.
4. Participant either has myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) or has features suggestive of MDS/AML.
5. Participant has a known additional malignancy that is progressing or has required active treatment in the last 3 years.
   Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (eg, ductal carcinoma in situ, cervical carcinoma in situ) that has undergone potentially curative therapy are not excluded.

   Note: Participants with synchronous primary endometrial cancer or a past history of primary endometrial cancer that met the following conditions are not excluded: Stage not greater than I-A; no more than superficial myometrial invasion, without vascular or lymphatic invasion; no poorly differentiated subtypes, including papillary serous, clear cell or other FIGO Grade 3 lesions.
6. Participant has ongoing Grade 3 or Grade 4 toxicity, excluding alopecia, following chemotherapy administered during the Lead-in Period.
7. Participant has known active central nervous system metastases and/or carcinomatous meningitis. Participants with brain metastases may participate provided they were previously treated (except with chemotherapy) and are radiologically stable, clinically stable, and no steroids were used for the management of symptoms related to brain metastases within 14 days prior to randomization. Stable brain metastases should be established prior to the first dose of lead-in chemotherapy.
   Note: Participants with known untreated, asymptomatic brain metastases (ie, no neurological symptoms, no requirement 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.
8. Participant has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to randomization.
9. Participant has an active autoimmune disease that has required systemic treatment in the past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs).
   Note: 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.

10. Participant has a known history of active tuberculosis (TB; Bacillus Tuberculosis).
11. Participant has an active infection requiring systemic therapy.
12. Participant has a history or current evidence of any condition (eg, cytopenia, transfusion-dependent anemia, or thrombocytopenia), therapy, or laboratory abnormality that might confound the results of the study, interfere with the participant's involvement for the full duration of the study, or is not in the best interest of the participant to be involved, in the opinion of the treating investigator.
13. Participant has received colony-stimulating factors (eg, granulocyte colony-stimulating factor [G-CSF], granulocyte macrophage colony-stimulating factor [GM-CSF] or recombinant erythropoietin) within 4 weeks (28 days) prior to receiving chemotherapy during the Lead-in Period.
14. Participant is considered to be of poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, or extensive interstitial bilateral lung disease on high-resolution computed tomography (HRCT) scan.
15. Participant has had surgery <6 months prior to screening to treat borderline tumors, early-stage EOC or early-stage fallopian tube cancer.
16. Participant has a known psychiatric or substance abuse disorder that would interfere with the ability to cooperate with the requirements of the study.
17. Participant has a known history of human immunodeficiency virus (HIV) infection. HIV testing is required at screening only if mandated by local health authority. Refer to Appendix 7 for country-specific requirements.
18. Participant has a known history of hepatitis B (defined as hepatitis B surface antigen [HBsAg] reactive) or known active hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection. Testing for hepatitis B or hepatitis C is required at screening only if mandated by local health authority. Refer to Appendix 7 for country-specific requirements.
    Note: Participants with a history of hepatitis B but who are HBsAg negative are eligible for the study.
19. Participant is either unable to swallow orally administered medication or has a gastrointestinal disorder affecting absorption (eg, gastrectomy, partial bowel obstruction, malabsorption).
20. Participant has uncontrolled hypertension.
    Note: This applies only to participants who will receive bevacizumab during the Lead-in Period and should be confirmed prior to the first administration of bevacizumab. Use of antihypertensive medications to control blood pressure is allowed.
21. Participant has current, clinically relevant bowel obstruction (including sub-occlusive disease), abdominal fistula or gastrointestinal perforation, related to underlying EOC.
    Note: This applies only to participants who will receive bevacizumab.

22. Participant has a history of hemorrhage, hemoptysis or active gastrointestinal bleeding within 6 months prior to randomization.
    Note: This applies only to participants who will receive bevacizumab.
23. A WOCBP who has a positive urine pregnancy test within 72 hours before the first dose of chemotherapy in the Lead-in Period and within 72 hours prior to Day 1 of Cycle 1 (see Appendix 3), is pregnant or breastfeeding, or is expecting to conceive children within the projected duration of the study, starting with screening through 120 days following the last dose of pembrolizumab (or pembrolizumab placebo) and bevacizumab (if administered), at least 180 days following the last dose of olaparib (or olaparib placebo), and at least 210 days following the last dose of chemotherapy.
    Note: If the urine test cannot be confirmed as negative, a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

Prior/Concomitant Therapy

24. Participant has received prior treatment for any stage of OC, including radiation or systemic anticancer therapy (eg, chemotherapy, hormonal therapy, immunotherapy, investigational therapy).
    Note: Treatment with 1 cycle of standard of care chemotherapy (lead-in dose) for EOC, fallopian tube cancer, or primary peritoneal cancer prior randomization in the study is allowed.
25. Participant 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).
26. Participant has received prior therapy with either olaparib or any other PARP inhibitor.
27. Is a participant for whom intraperitoneal chemotherapy is planned or has been administered as first-line therapy.
28. Participant has received a live vaccine within 30 days prior to the first dose of study treatment on Day 1 of Cycle 1. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.
29. Participant has severe hypersensitivity (≥Grade 3) to pembrolizumab, olaparib, carboplatin, paclitaxel, or bevacizumab (if using) and/or any of their excipients.
    Note: If severe hypersensitivity to paclitaxel occurs during lead-in, docetaxel may be considered instead of paclitaxel after consultation with the Sponsor.
30. Participant 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 prior to starting olaparib or olaparib placebo and

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/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

31. Participant is currently receiving either strong (eg, phenobarbital, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine, and St John's Wort) or moderate (eg. bosentan, efavirenz, modafinil) inducers of CYP3A4 that cannot be discontinued prior to starting olaparib or olaparib placebo and for the duration of the study. The required washout period prior to starting olaparib is 5 weeks for phenobarbital and 3 weeks for other agents.
Note: A current list of strong/moderate inducers of CYP3A4 can be found at the following website: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

Prior/Concurrent Clinical Study Experience

32. Participant is currently participating or has participated in a study of an investigational agent or has used an investigational device within 4 weeks (28 days) of starting chemotherapy in the Lead-in Period.
Note: Participants who have entered the follow-up phase of an investigational study may participate as long as it has been 4 weeks (28 days) after the last dose of the previous investigational agent.

Diagnostic Assessments

33. Participant has resting electrocardiogram (ECG) indicating uncontrolled, potentially reversible cardiac conditions, as judged by the investigator (eg, unstable ischemia, uncontrolled symptomatic arrhythmia, congestive heart failure, QTcF prolongation >500 ms, electrolyte disturbances, etc.), or participant has congenital long QT syndrome.

Other Exclusions

34. Participant has had an allogenic tissue/solid organ transplant, has received previous allogenic bone marrow transplant, or has received double umbilical cord transplantation.
35. Participant either had major surgery within 3 weeks of randomization or has not recovered from any effects of any major surgery.
Note: Participants can start chemotherapy during the Lead-in Period as soon as clinically relevant after primary debulking, provided they have adequately recovered.
36. Participant, in the judgement of the investigator, is unlikely to comply with the study procedures, restrictions, and requirements of the study.

Refer to Appendix 7 for additional country-specific requirements.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

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

5.3.2 Activity Restrictions

AEs 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 randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines.

5.5 Participant Replacement Strategy

A participant who is discontinued from study treatment or withdraws from the study will not be replaced.

6. Study Intervention

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

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

6.1 Treatments Administered

The study treatment(s) to be used in this study are outlined below in Table 2.

Table 2 Study Treatment(s)

Study Treatment Name	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/Treatment Period/Vaccination Regimen	Use	IMP or NIMP/AxMP	Sourcing
Pembrolizumab	Solution for infusion	25 mg/mL	200 mg	IV	Q3W; Day 1 of each 3-week cycle	Test product	IMP	Central
Placebo for pembrolizumab (normal saline or dextrose)	Solution for infusion	N/A	N/A	IV	Q3W; Day 1 of each 3-week cycle	Placebo	IMP	Local
Olaparib	Tablet	150 mg 100 mg	300 mg	Oral	BID during each treatment cycle	Test product	IMP	Central
Placebo for olaparib	Tablet	N/A	N/A	Oral	BID during each treatment cycles	Placebo	IMP	Central
Carboplatin	Solution for infusion	10 mg/mL (60 mL)	AUC5-AUC6	IV	Q3W; Day 1 of each 3-week cycle	Background therapy	NIMP/AxMP	Local or Central
			AUC2-AUC2.7		QW; Day 1, 8, and 15 of each 3-week cycle			
Paclitaxel	Solution for infusion	6 mg/mL (16.7 mL)	175 mg/m^2	IV	Q3W; Day 1 of each cycle	Background therapy	NIMP/AxMP	Local or central
			80 mg/m^2		QW; Day 1, 8, and 15 of each 3-week cycle			
			60 mg/m^2		QW; Day 1, 8, and 15 of each 3-week cycle			
Docetaxel	Solution for infusion	20 mg/mL	75 mg/m^2	IV	Q3W, Day 1 of each cycle	Background therapy	NIMP/AxMP	Local or central
Bevacizumab	Solution for infusion	25 mg/mL (4 mL)	Variable	IV	Q3W; Day 1 of each 3-week cycle	Background therapy	NIMP/AxMP	Local

AUC=area under the concentration-time curve; BID=twice daily; EEA=European Economic Area; IMP=Investigational Medicinal Product; IV=intravenous; N/A=not applicable; NIMP/AxMP=Noninvestigational Medicinal Product/auxiliary medicinal product; Q3W=every 3 weeks; QW=every week; SOC=standard of care.

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

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

Note: The 300 mg dose of olaparib should be made up of 2 × 150 mg tablets; 100 mg tablets are provided for dose reductions as outlined in Section 6.6.2.

Note: Docetaxel may only be considered for participants who experience either a severe hypersensitivity reaction to paclitaxel or an AE requiring discontinuation of paclitaxel only after consultation with the Sponsor.

Note: The unit dose strength of chemotherapy may vary depending on market availability.

Note: Carboplatin and paclitaxel (or docetaxel) administered during the Lead-in Period will be sourced locally.

Placebo for olaparib was created to match the active product.

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

Refer to Section 8.1.9 for details regarding administration of the study treatment.

Refer to Appendix 7 for country-specific requirements.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

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

Olaparib and olaparib placebo are tablets for oral administration; no preparation is required. Olaparib and matching placebo 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.

Carboplatin, paclitaxel, docetaxel, and bevacizumab should be prepared per local and institutional guidelines according to the approved product labels.

6.2.2 Handling, Storage, and Accountability

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

Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments 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 treatment 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 treatments in accordance with the protocol and any applicable laws and regulations.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Method of Treatment Assignment

Treatment allocation/randomization will occur centrally using an interactive response technology (IRT) system. There are 3 study treatment arms. Participants will be assigned randomly in a 1:1:1 ratio to Arm 1, Arm 2, or Arm 3, respectively.

6.3.1.1 Stratification

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

1. Surgery: planned interval debulking versus R0 following primary debulking versus R1 following primary debulking
2. Bevacizumab use (yes versus no)
3. PD-L1 status (CPS <10 versus CPS ≥10)

6.3.2 Blinding

A double-blinding technique with in-house blinding will be used. Pembrolizumab and pembrolizumab placebo will be prepared and/or dispensed in a blinded fashion by an unblinded pharmacist or other qualified site personnel. Olaparib and olaparib placebo will be supplied as either 150-mg or matching tablets and will be administered orally BID continuously starting in the Maintenance Period. Additionally, either 100-mg or matching tablets will be provided for dose reductions as outlined in Section 6.6.2. The participant, the investigator and Sponsor personnel or delegate(s) who are involved in the study treatment administration or clinical evaluation of the participants are unaware of the group assignments.

See Section 8.1.11 for a description of the method of unblinding a participant during the study, should such action be warranted.

6.4 Treatment Compliance

If there are interruptions in the study intervention schedule, the details of and reason for any interruption of study intervention will be documented in the participant's medical record.

6.4.1 Pembrolizumab, Pembrolizumab Placebo, Carboplatin, Paclitaxel (or Docetaxel), and Bevacizumab Compliance

Administration of IV pembrolizumab, pembrolizumab placebo, carboplatin, paclitaxel (or docetaxel), and bevacizumab (if using) will be monitored by the investigator and/or study staff. The total volume of study treatment infused will be compared with the total volume prepared to determine compliance with each dose administered. Pembrolizumab/pembrolizumab placebo, chemotherapy, and bevacizumab (if using) can be administered on an out-patient basis.

Interruptions from either the protocol-specified pembrolizumab/pembrolizumab placebo or carboplatin/paclitaxel (or docetaxel), and bevacizumab (if using) treatment plan require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management (Section 7.1):

- Pembrolizumab or pembrolizumab placebo is interrupted for greater than 3 weeks for situations other than treatment-related AEs such as medical/surgical events or logistical reasons not related to study treatment
- Pembrolizumab or pembrolizumab placebo is interrupted for greater than 12 weeks for treatment-related AEs
- Carboplatin and paclitaxel (or docetaxel) or bevacizumab are interrupted for greater than 6 consecutive weeks
- Carboplatin and paclitaxel (or docetaxel) are discontinued

6.4.2 Olaparib Compliance

Interruptions from the protocol-specified treatment plan for ≥4 weeks (28 days) will require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

Participants should be given clear instructions on how and when to take their study intervention. Participants will self-administer olaparib or olaparib placebo except when a clinic visit is scheduled. Study site staff will make tablet counts at regular intervals during treatment. After the tablet count has been performed, the remaining tablets will not be returned to the participant but will be retained by the investigative site until reconciliation is completed by the study monitor. All participants must return their bottle(s) of olaparib/olaparib placebo at the appropriate scheduled visit, when a new bottle will be dispensed. Participants will be instructed to notify study site personnel of missed doses.

Interruptions from the protocol-specified olaparib/olaparib placebo treatment plan for >28 consecutive days require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

6.5 Concomitant Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medication or vaccination

specifically prohibited, discontinuation from study treatment may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study treatment requires the mutual agreement of the investigator, the Sponsor and the participant.

All medications received within 56 days prior to randomization and up to 30 days after the last dose of study treatment should be recorded. If a participant experiences an SAE or event of clinical interest (as defined in Section 8.4.7), all concomitant medications administered 30 days after the last dose of study treatment are to be recorded.

6.5.1 Prohibited Concomitant Medications

Listed below are specific restrictions for concomitant therapy or vaccination that are not permitted during the study (exceptions noted):

1. Antineoplastic systemic chemotherapy or biological therapy not specified in this protocol.
2. Immunotherapy not specified in this protocol.
3. Investigational agents other than pembrolizumab and olaparib.
4. Anticancer hormonal therapy (eg, antiestrogens).
   - Note: Hormone replacement therapy is allowed.
5. Radiation therapy for disease control.
   - Note: Palliative radiation therapy to symptomatic lesions may be allowed following Sponsor consultation after assessment of disease progression has been determined.
6. Live or live attenuated vaccines within 30 days prior to the first dose of study treatment on Day 1 of Cycle 1, while participating in the study, and within 30 days of the last dose of study medication. Refer to Appendix 7 for country-specific requirements.
   - Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chickenpox, yellow fever, intranasal seasonal influenza, rabies, BCG, and typhoid (oral).
   - Note: Seasonal influenza vaccines for injection are generally killed virus vaccines and 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, 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.

7. Systemic glucocorticoids for any purpose other than to modulate symptoms from an AE that is suspected to have an immunologic etiology.
    - Note: physiologic doses of corticosteroids not exceeding 10 mg daily of prednisone equivalent may be used during the study. Inhaled steroids for the management of asthma and prophylactic corticosteroids to avoid allergic reactions or to premedicate for chemotherapy and/or bevacizumab may be used during the study

8. Prophylactic cytokines (eg, G-CSF or GM-CSF) should not be administered within 4 weeks (28 days) prior to the first dose of chemotherapy administered during the Lead-in Period, but may be administered in subsequent cycles.
9. Strong and moderate inducers or inhibitors of CYP3A that cannot be discontinued prior to starting olaparib or olaparib placebo and for the duration of the study (see Section 5.2).
    - Note: A current list of strong/moderate inducers/inhibitors of CYP3A4 can be found at the following website: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers
    - Note: Exceptions are outlined in Section 6.6.2.6.

Participants who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be discontinued from study treatment but continue in the study for assessment of disease status and survival.

The exclusion criteria (Section 5.2) describe other medications which are prohibited in this study.

There are no prohibited therapies during the Posttreatment Efficacy Follow-up Phase.

6.5.2 Acceptable Concomitant Medications

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

Based on limited 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/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

6.5.3 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 3. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab or pembrolizumab placebo.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab/pembrolizumab placebo, the investigator does not need to follow the treatment guidance. Refer to Table 3 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 Immune-related Events and Dose Modification (Withhold, Treat, Discontinue)

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

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

Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations are provided in Table 3.

If pembrolizumab or pembrolizumab placebo is interrupted or discontinued during either the adjuvant/neoadjuvant or Maintenance Period, dosing with either chemotherapy or olaparib/olaparib placebo, respectively, may continue if the criteria as outlined in Section 6.6.2 and Section 6.6.3 have not been met. If both carboplatin and paclitaxel (or

docetaxel) are interrupted, pembrolizumab or pembrolizumab placebo should be continued. Refer to Appendix 7 for country-specific requirements.

The reason for interruption or discontinuation of pembrolizumab or pembrolizumab placebo should be recorded in the eCRF.

Table 3 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated With Pembrolizumab Monotherapy, Coformulations or IO Combinations

General instructions:

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

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

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

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

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

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

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

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

6.6.1.2 Dose Modification and Toxicity Management of Infusion-Reactions Related to Pembrolizumab or Pembrolizumab Placebo

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

Table 4 Pembrolizumab or Pembrolizumab Placebo 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 (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Participant may be premedicated 1.5 h (± 30 minutes) prior to infusion of pembrolizumab or pembrolizumab placebo with: • Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). • Acetaminophen 500-1000 mg PO (or equivalent dose of analgesic).

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

6.6.1.3 Other Pembrolizumab or Pembrolizumab Placebo Dose Interruptions

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

6.6.2 Olaparib Dosing Modifications

6.6.2.1 Olaparib Dose Reduction

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 treatment should be discontinued. Once dose is reduced, escalation is not permitted (except following concomitant treatment with CYP3A4 inhibitors [Table 8]).

The reason for the dose interruption or reduction should be captured on the appropriate eCRF. If either olaparib or olaparib placebo is discontinued during the maintenance phase due to toxicity, the participant may continue pembrolizumab or pembrolizumab placebo if the criteria outlined in Section 6.6.1 have not been met.

6.6.2.2 Management of Hematological Toxicity

Any hematological toxicity observed during the study could be managed by a brief interruption of study treatment or a dose reduction of olaparib or olaparib placebo (Table 5 and Table 6). Repeated interruptions, not exceeding 4 weeks (28 days) duration, are allowed as required. If the interruption is any longer, the study team must be informed.

Table 5 Management of Anemia

Toxicity	NCI CTCAE Grade	Action Taken
Hemoglobin (Hb)	Grade 2 (<10 but ≥8 g/dL)	**First Occurrence:** Give appropriate supportive treatment and investigate causality. • Investigator judgement to either continue olaparib/olaparib placebo with supportive treatment (eg, transfusion) or interrupt olaparib/olaparib placebo dosing for a maximum of 4 weeks (28 days). Treatment can be restarted if Hb has recovered to >9 g/dL. **Subsequent Recurrence:** • **Hb <9 but ≥8 g/dL**: Interrupt olaparib/olaparib placebo for a maximum of 4 weeks (28 days) until Hb improves to >9 g/dL. Upon recovery, reduce the dose of olaparib/olaparib placebo to 250 mg/matching tablet BID. A second dose reduction to 200 mg/matching tablet BID may be considered if additional decreases in Hb occur
	Grade 3 (<8 g/dL)	Give appropriate supportive treatment (eg, transfusion) and investigate causality. • Interrupt olaparib/olaparib placebo, for a maximum of 4 weeks (28 days), until Hb improves to ≥9 g/dL. • Upon recovery, reduce the dose of olaparib/olaparib placebo to 250 mg/matching tablet BID. A second dose reduction to 200 mg/matching tablet BID may be considered if additional decreases in Hb occur.

BID=twice daily; CTCAE=Common Terminology Criteria for Adverse Events; Hb=hemoglobin; NCI=National Cancer Institute.

Note: Common treatable causes of anemia (eg, iron, vitamin B12 or folate deficiencies and hypothyroidism) should be investigated and appropriately managed. In some cases management of anemia may require blood transfusions. The management of prolonged hematological toxicities is detailed in Section 6.6.2.3.

Table 6 Management of Neutropenia, Leukopenia, and Thrombocytopenia

Toxicity	NCI CTCAE Grade	Action Taken
Neutropenia, Leukopenia, or Thrombocytopenia	Grades 1 or 2	Investigator judgement to either continue olaparib/olaparib placebo or interrupt dosing for a maximum of 4 weeks (28 days). Give appropriate supportive treatment and investigate causality.
	Grades 3 or 4	• Interrupt olaparib/olaparib placebo, for a maximum of 4 weeks (28 days), until event recovers to ≤Grade 1. • Repeated incidence: reduce the dose of olaparib/olaparib placebo to 250 mg/matching tablet BID. A second dose reduction to 200 mg/matching tablet BID may be considered if additional Grade 3 or 4 events occur.

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

Note: AEs of neutropenia and leukopenia should be managed as deemed appropriate by the investigator with close follow-up and interruption of study treatment if CTCAE Grade 3 or worse neutropenia occurs.

Note: Primary prophylaxis with G-CSF is not recommended; however, if a participant develops febrile neutropenia, study treatment 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 treatment unless absolutely necessary.

Note: Platelet transfusions, if indicated, should be done according to local hospital guidelines.

Note: The management of prolonged hematological toxicities is detailed in Section 6.6.2.3.

6.6.2.3 Management of Prolonged Hematological Toxicities

If a participant develops prolonged hematological toxicity such as:

- ≥2-week interruption/delay in olaparib/olaparib placebo due to NCI CTCAE Grade 3 or worse anemia and/or the development of blood transfusion dependence
- ≥2-week interruption/delay in olaparib/olaparib placebo due to NCI CTCAE Grade 3 or worse neutropenia (absolute neutrophil count $<1 \times 10^9$/L)
- ≥2-week interruption/delay in olaparib/olaparib placebo 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 olaparib/olaparib placebo has been interrupted for 4 weeks (28 days), the participant should be referred to 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. Olaparib/olaparib placebo should be discontinued if blood counts do not recover to NCI CTCAE Grade 1 or better within 4 weeks (28 days) of dose interruption.

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

6.6.2.4 Management of Non-Hematological Toxicity

Repeat dose interruptions, not exceeding 4 weeks (28 days) duration, are allowed as required. If toxicity reoccurs following rechallenge with olaparib/olaparib placebo, and where further dose interruptions are considered inadequate for management of toxicity, either a dose reduction should be considered (Section 6.6.2.1) or the participant must permanently discontinue study treatment.

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/olaparib placebo.

6.6.2.4.1 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 treatment is recommended and further diagnostic workup (including a high-resolution CT scan) should be performed to exclude pneumonitis.

Following investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, then study treatment may be restarted, if deemed appropriate by the investigator. If significant pulmonary abnormalities are identified, these need to be discussed with the Clinical Director.

6.6.2.4.2 Management of Nausea and Vomiting

Events of nausea and vomiting are known to be associated with olaparib treatment. 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 treatment for nausea and within the first 6 months of treatment for vomiting. For nausea, the incidence generally plateaus at around 9 months, and for vomiting at around 6 to 7 months.

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

As per international guidance on antiemetic use in cancer patients (European Society for Medical Oncology, National Comprehensive Cancer Network), generally a single-agent antiemetic should be considered (eg, dopamine receptor antagonist, antihistamines, or dexamethasone).

6.6.2.4.3 Management of Renal Impairment

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

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

Table 7 Dose Reduction of Olaparib or Olaparib Placebo to Manage Moderate Renal Impairment

Initial Dose	**Moderate Renal Impairment[a]**
300 mg/matching tablet BID	200 mg/matching tablet BID

BID=twice daily.
a. Creatinine clearance of 31 to 50 mL/min as calculated by either Cockcroft-Gault equation or based on 24-hour urine test.

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

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

6.6.2.5 Interruptions for Intercurrent Non-Toxicity-Related Events

Olaparib/olaparib placebo dose interruption for conditions other than toxicity resolution should be kept as short as possible. If a participant cannot restart study treatment within 4 weeks (28 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.

Participants will be instructed to notify the study site personnel of missed doses. 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.

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

Olaparib/olaparib placebo should be discontinued for a minimum of 3 days before a participant undergoes radiation treatment and should be restarted within 4 weeks (28 days) as long as any bone marrow toxicity has recovered.

6.6.2.6 Dose Reductions for Concurrent CYP3A4 Inhibitor Use

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

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

Initial Dose	Strong CYP3A Inhibitor	Moderate CYP3A Inhibitor
300 mg BID	100 mg BID	150 mg BID
BID=twice daily; CYP=Cytochrome P450.		

6.6.3 Management of Overlapping Toxicities

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 3 (pembrolizumab) and Table 7 (olaparib). A kidney biopsy is strongly recommended to help to determine etiology of renal dysfunction.

Treatment with olaparib/olaparib placebo must be held for any grade of pneumonitis. Treatment with pembrolizumab/pembrolizumab placebo must be held for pneumonitis ≥Grade 2 (Table 3). When the pneumonitis resolves to <Grade 2, then pembrolizumab/pembrolizumab placebo may be resumed as per guidelines in Table 3. Olaparib/olaparib placebo may be restarted once pneumonitis has completely resolved. Study treatment must be discontinued for recurrent Grade 2 pneumonitis (Table 3).

6.6.4 Chemotherapy and Bevacizumab Dose Modifications

6.6.4.1 Lead-in Period

Dose modifications of chemotherapy are not allowed during the Lead-in Period; all participants must receive the full dose of chemotherapy to be eligible to move into the Treatment Period.

6.6.4.2 Treatment Period

Carboplatin and/or paclitaxel (or docetaxel) may be reduced, interrupted, or discontinued at the investigator's discretion per the approved product labels, local regulations, and/or institutional standards. If chemotherapy (either carboplatin or paclitaxel [or docetaxel] or both) is interrupted or discontinued, pembrolizumab or pembrolizumab placebo should be

continued. If pembrolizumab or pembrolizumab placebo is interrupted or discontinued, chemotherapy should be continued.

Bevacizumab, if using, may be interrupted, or discontinued at the investigator's discretion per the approved product label and local regulations. If bevacizumab is interrupted or discontinued, pembrolizumab/pembrolizumab placebo and olaparib/olaparib placebo may be continued. If pembrolizumab/pembrolizumab placebo or olaparib/olaparib placebo is interrupted or discontinued, bevacizumab may be continued as per the approved product label, local regulations, and/or institutional standards.

Interruptions from either carboplatin and paclitaxel (or docetaxel) or bevacizumab of greater than 6 weeks (42 days) from the originally scheduled dose require consultation between the investigator and the Sponsor. Discontinuation of both carboplatin and paclitaxel (or docetaxel) require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

Supportive care measures (eg. G-CSF, erythropoietin, blood transfusion) should be used according to local standards to manage chemotherapy-induced myelosuppression, including to prevent severe infections linked to febrile neutropenia. In order to minimize dose reductions, interruptions, and discontinuations of chemotherapy, these supportive care measures should be used before implementing dose modifications, when appropriate.

6.7 Treatment After the End of the Study

The study is complete upon consent of the last active treatment participant for an extension study, if available, in which participants can continue treatment as per the current study.

All study-related procedures and data collection as defined per protocol will be terminated at study completion. In addition, follow-up will be stopped upon study completion as defined in Section 4.4. For participants who enroll in an extension study, if available, investigators will follow the SoA of the extension study protocol.

6.8 Clinical Supplies Disclosure

The emergency unblinding call center will use the treatment/randomization schedule for the study to unblind participants and to unmask study treatment identity. The emergency unblinding call center should only be used in cases of emergency (see Section 8.1.11). In the event that the emergency unblinding call center is not available for a given site in this study, the central electronic treatment allocation/randomization system (IRT) should be used in order to unblind participants and to unmask study treatment identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

See Section 8.1.11 for a description of the method of unblinding a participant during the study, should such action be warranted.

6.9 Standard Policies

For studies using controlled substances, all federal, state, province, country, etc. regulations must be adhered to in regard to the shipping, storage, handling and dispensing of controlled substances. Additionally, the investigator should have the appropriate controlled drug license(s) as mandated by federal, state, province, country, etc. laws in which the study is being conducted.

At the close of the study after unblinding, a letter is to be sent by the investigator to those participants who received placebos in the image of the competitor's product to provide the following advice:

"You have participated in a study conducted by the Sponsor. This is to advise you that you were among those who received either an infusion prepared at the investigational site or a look-alike tablet created to resemble the drugs pembrolizumab or olaparib as much as possible. You did not receive the active drug pembrolizumab or olaparib as manufactured by the Sponsor or Astra Zeneca, respectively."

7. Discontinuation of Study Treatment and Participant Withdrawal

7.1 Discontinuation of Study Treatment

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

As certain data on clinical events beyond study treatment 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 treatment. Therefore, all participants who discontinue study treatment prior to completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 1.3 and Section 8.11.3.

Participants may discontinue study treatment at any time for any reason or be discontinued from the study treatment at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study treatment by the investigator or the Sponsor if study treatment is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study treatment discontinuation are provided in Section 8.1.10.

A participant must be discontinued from study treatment 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 treatment.
- Radiographic disease progression documented by the investigator per RECIST 1.1, and when clinically appropriate, confirmed by the site per iRECIST (Section 8.2.1.5).
  Note: An exception to continue study treatment beyond confirmed PD per iRECIST (iCPD) may be considered after obtaining the informed consent addendum and consultation with the Sponsor (Section 8.2.1.5).

- Clinical progression without radiographic disease progression defined by elevated CA-125 (based on GCIG criteria [see Appendix 9]) in conjunction with any of the following criteria for malignant bowel obstruction:
  - Any of the following: new or worsening abdominal pain, nausea, or vomiting
  - Abdominal distension, constipation, and/or diarrhea
  - No evidence of metabolic or electrolyte abnormalities leading to impaired intestinal motility

  Note: Symptoms must be assessed as not related to study treatment and/or concomitant medication AND other non-malignant causes must be excluded by supplementary diagnostic measures

  Note: Participants who discontinue study treatment due to clinical progression will have posttreatment follow-up imaging to evaluate disease status until disease progression is radiographically documented per RECIST 1.1 by the investigator (Section 8.2.1.4).
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active systemic treatment.
- The participant interrupts pembrolizumab or pembrolizumab placebo administration for more than 12 consecutive weeks for an AE/toxicity or for more than 3 consecutive weeks for administrative reasons without Sponsor consultation.
- The participant interrupts olaparib or olaparib placebo for more than 4 consecutive weeks (>28 consecutive days) without Sponsor consultation.
- The participant interrupts chemotherapy (both carboplatin and paclitaxel [or docetaxel]) or bevacizumab for more than 6 consecutive weeks without Sponsor consultation.
  Note: Participants who are not able to complete 6 treatment cycles (including lead-in) of chemotherapy due to toxicity, may be eligible to start the Maintenance Period as early as Cycle 2 following consultation with the Sponsor.

  Note: Docetaxel may be considered for participants who experience either a severe hypersensitivity reaction to paclitaxel or an AE requiring discontinuation of paclitaxel only after consultation with the Sponsor.
- 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 treatment.
- The participant has a confirmed positive serum pregnancy test.
- Any study treatment-related toxicity specified as a reason for permanent discontinuation as defined in the guidelines for dose modifications due to AEs in Section 6.6.
- Unacceptable AEs.
- 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 treatment.

- Completion of 35 infusions (approximately 2 years) with pembrolizumab/pembrolizumab placebo (calculated from first dose), completion of approximately 2 years of treatment with olaparib or olaparib placebo, or the participant has received the maximum duration of bevacizumab per the approved label or local practice.
  Note: Only participants with NED will stop treatment with olaparib or olaparib placebo following 2 years of treatment. The total duration of treatment is calculated starting with the first dose of olaparib or olaparib placebo.

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

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

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 treatment or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from future biomedical research are outlined in Section 8.1.10. Participants who wish to withdraw from treatment and/or imaging may retain consent specifically for the noninvasive Survival Follow-up Phase of the study. All participants are encouraged to be followed for survival status until death or the closure of the study, if they consent to do so. 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.
- If it is determined that a study procedure and/or assessment no longer needs to be performed, the Sponsor or its designee will provide ample notification to participating investigator sites so appropriate adjustments can be made.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The investigator is responsible for assuring that procedures are conducted by appropriately qualified or trained staff. Delegation of study site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All study-related medical decisions must be made by an investigator who is a qualified physician.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized 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, etc.), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

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

8.1 Administrative and General Procedures

8.1.1 Informed Consent

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

8.1.1.1 General Informed Consent

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

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

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

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

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

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

Note: If primary debulking surgery is performed within the Screening Period, the main study ICF may be signed prior to surgery.

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or medically qualified designee will explain the future biomedical research consent to the participant, answer all of his/her questions, and obtain written informed consent before performing any procedure related to future biomedical research. A copy of the informed consent will be given to the participant.

8.1.2 Inclusion/Exclusion Criteria

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

8.1.3 Participant Identification Card

All participants will be given a Participant Identification Card identifying them as participants in a research study. The card will contain study site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the participant with a Participant Identification

Card immediately after the participant provides written informed consent. At the time of treatment allocation/randomization, site personnel will add the treatment/randomization number to the Participant Identification Card.

The Participant Identification Card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about study treatment in emergency situations where the investigator is not available.

8.1.4 Medical History

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

8.1.4.1 Ovarian Cancer History

The investigator or qualified designee will obtain prior and current details regarding the participant's OC, including investigator-determined tumor size per RECIST 1.1.

8.1.5 Debulking Surgery

All eligible participants will undergo debulking surgery (primary or interval) per the local SOC. Primary debulking surgery can occur up to 7 weeks (49 days) prior to starting chemotherapy during the Lead-in Period (Figure 2); all participants eligible for primary debulking surgery may sign the main study ICF prior to surgery (Section 8.1.1). Interval debulking surgery should be performed between 3 to 6 weeks following Day 1 Cycle 2 for participants on a Q3W chemotherapy regimen or between 1 to 4 weeks following Day 15 of Cycle 2 for participants on a weekly chemotherapy regimen (Figure 3); any delay to interval debulking surgery (eg, due to an AE) requires approval from the Sponsor. The last dose of pembrolizumab or pembrolizumab placebo should be administered no less than 3 weeks before surgery. Participants should resume study treatment when clinically appropriate but no longer than 7 weeks following surgery. Details regarding the date of surgery, surgical findings, residual tumor postsurgery, surgical pathology, etc. will be recorded in the appropriate eCRF. All tumor tissue will be reviewed by the local pathologist for pathological CR (pCR) following interval debulking surgery (Section 8.2.2). Debulking surgery may be performed at a hospital/surgical unit separate from the investigator site.

If the investigator determines that a participant has inoperable disease following the 3 neoadjuvant treatment cycles (including lead-in), the participant may continue treatment in the study without undergoing the interval debulking surgery. For these participants, a tumor biopsy should be collected, if possible (Section 8.1.5.1). Participants should resume study treatment when clinically appropriate but no longer than 6 weeks following the last dose of study treatment.

8.1.5.1 Tumor Tissue Biopsy and Sample Collection

All tumor tissue collected during interval debulking will be sent for detailed pathological assessment (Section 8.2.2). A separate core or excisional biopsy will be collected from the tumor tissue at the time of debulking surgery. For those participants who do not undergo interval debulking surgery, a core or excisional biopsy should be collected, if possible, prior to resuming study medication in Cycle 3.

An optional core or excisional biopsy may be collected at the time of PD, if possible (Section 1.3).

All biopsies should be obtained and prepared according to the instructions outlined in the Procedure Manual for this study. If feasible, at least 2 separate core biopsies should be obtained. These tumor tissues will be submitted to the designated central laboratory.

8.1.6 Prior and Concomitant Medications Review

8.1.6.1 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 56 days before randomization.

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

8.1.6.2 Concomitant Medications

The investigator or qualified designee will record medication (including blood transfusions), if any, taken by the participant during the study (Section 6.5). Additionally, the investigator or qualified designee will record medication, if any, taken by the participant following PD.

8.1.6.3 Subsequent Anticancer Therapy

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

8.1.7 Assignment of Screening Number

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

Any participant who is screened multiple times will retain the original screening number assigned at the initial screening visit.

Specific details on the screening visit requirements (screening/rescreening) are provided in Section 8.11.1.

8.1.8 Assignment of Treatment/Randomization Number

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

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

The investigator must provide the rationale for not choosing cisplatin prior to randomization.

8.1.9 Treatment Administration

Carboplatin, paclitaxel (or docetaxel), bevacizumab (if using), and pembrolizumab/pembrolizumab placebo will be administered by the investigator and/or study staff according to the specifications within the Pharmacy Manual. Olaparib/olaparib placebo will be administered by the investigator and/or study staff on Day 1 of the first cycle in the Maintenance Period. Participants will then self-administer olaparib/olaparib placebo orally for the remainder of the 21-day treatment cycle (Section 8.1.9.1.5).

Study Treatment should begin within 3 days of randomization.

Note: There must be a minimum of 20 days between the start of lead-in chemotherapy and Day 1 of Cycle 1.

8.1.9.1 Timing of Dose Administration

Treatment With Chemotherapy:

Participants will receive pembrolizumab 200 mg (Day 1) or pembrolizumab placebo (Day 1) together with investigator's choice of carboplatin + paclitaxel regimen for 5 treatment cycles (± bevacizumab):

- *Carboplatin AUC5 or 6 Q3W plus paclitaxel 175 mg/m^2 Q3W*
- *Carboplatin AUC5 or 6 Q3W plus paclitaxel 80 mg/m^2 QW*
- *Carboplatin AUC2 or 2.7 QW plus paclitaxel 60 mg/m^2 QW*

Note: Docetaxel may be considered for participants who experience either a severe hypersensitivity reaction to paclitaxel or an AE requiring discontinuation of paclitaxel only after consultation with the Sponsor. The recommended dose of docetaxel [Vasey, P. A., et al 2004] is 75 mg/m^2 Q3W plus carboplatin AUC 5.

Note: the maximum duration of treatment with chemotherapy is not to exceed 6 cycles (this includes the Lead-in Period).

Between Chemotherapy and Maintenance (for assessment of eligibility for maintenance):

Participants will receive pembrolizumab 200 mg (Day 1) or pembrolizumab placebo (Day 1) (± bevacizumab).

Maintenance:

Participants will continue with pembrolizumab 200 mg (Day 1) or pembrolizumab placebo (Day 1) and maintenance therapy with olaparib 300 mg or olaparib placebo BID (± bevacizumab).

Treatment Sequencing:

Depending on which individual components of the regimen are being administered during any given cycle, administer in the following order:

1. Olaparib or olaparib placebo (starting in maintenance)
2. Pembrolizumab or pembrolizumab placebo
3. Paclitaxel (or docetaxel)
4. Carboplatin
5. Bevacizumab

Note: local practice for drug administration sequence can be followed if preferred. The date and dose of administration must be captured in the eCRF.

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

8.1.9.1.1 Pembrolizumab or Pembrolizumab Placebo

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

8.1.9.1.2 Paclitaxel (or Docetaxel)

Paclitaxel (175 mg/m^2 Q3W, 80 mg/m^2 QW, or 60 mg/m^2 QW) will be administered as an IV infusion for 6 treatment cycles (including lead-in) as per local practice and labels. For Q3W and QW infusions of paclitaxel, the infusion time should follow local practice and labels. All participants should be premedicated with oral or IV steroid and antihistamines according to

the approved product label and/or standard practice. Additional premedications should be administered as per standard practice.

Docetaxel (75 mg/m^2 Q3W), if approved by the Sponsor, will be administered as an IV infusion as per local practice and labels. The infusion time should follow local practice and labels. All participants should be premedicated with an oral steroid according to the approved product label and/or standard practice. Additional premedications should be administered as per standard practice.

8.1.9.1.3 Carboplatin

Carboplatin (AUC5-6 mg/mL•min Q3W or AUC2-2.7 mg/mL•min QW) will be administered as an IV infusion for 6 treatment cycles (including lead-in) as per local practice and labels. The infusion time of carboplatin should follow local practice and labels. The carboplatin dose should be calculated using Calvert formula (see below) and should not exceed 900 mg.

Calvert Formula:

$$\text{Total Dose (mg)} = \text{target AUC} \times (\text{GFR} + 25)$$

The estimated GFR used in the Calvert formula should not exceed 125 mL/min to calculate the maximum carboplatin dose (mg):

$$\text{Target AUC 6 (mg/mL•min)} \times (125 + 25) = 6 \times 150 \text{ mL/min} = 900 \text{ mg}$$

8.1.9.1.4 Bevacizumab

If bevacizumab is used, it should be administered, as per local practice and label, on Day 1 of each treatment cycle administered, after carboplatin. The local practice for drug administration sequence can be followed if preferred. The date and dose of bevacizumab administered will be recorded in the eCRF.

Note: Bevacizumab may be used at the investigator's discretion as per the local SOC and approved product label:

- Participants eligible for primary debulking may receive bevacizumab starting with Cycle 1.
- Participants eligible for interval debulking may receive bevacizumab starting with the lead-in dose of chemotherapy but must NOT be dosed with bevacizumab at Cycle 2 or Cycle 3. Dosing with bevacizumab should resume in Cycle 4 OR after the wound has healed, whichever is longer.
  Note: If, following Sponsor consultation, surgery is delayed, bevacizumab should be interrupted at least 4 weeks prior to the planned date of surgery. Bevacizumab should resume 4 weeks after surgery OR after the wound has healed, whichever is longer.

- For any participant who will receive bevacizumab, the investigator may wait to administer the first dose of bevacizumab, as long as it is administered by Cycle 4.
  Note: For all participants who will start bevacizumab after lead-in chemotherapy, blood pressure measurements need to be performed to ensure that the participant does not have uncontrolled hypertension (Section 8.3.2). Blood pressure must be controlled prior to starting bevacizumab.

  Note: Any delay in restarting/starting bevacizumab beyond what is defined in the protocol requires Sponsor approval.

8.1.9.1.5 Olaparib or Olaparib Placebo

Participants must complete 1 lead-in cycle with chemotherapy and 5 treatment cycles on study and have NED progression (CR, PR, SD, or non-PD) prior to starting either olaparib or olaparib placebo in the Maintenance Period (Cycle 7). Participants who are unable to complete 6 treatment cycles (including lead-in) of chemotherapy due to toxicity, may still be eligible to start the Maintenance Period earlier following consultation with the Sponsor.

Participants should begin olaparib/olaparib placebo in the Maintenance Period as soon as clinically appropriate (ie, no ongoing toxicities, completed maintenance eligibility imaging [Section 8.2.1.2], and accounting for the washout period for CYP3A4 inhibitors/inducers [Section 5.2]) but no later than 9 weeks from Day 1 of the last cycle of chemotherapy. If olaparib/olaparib placebo is started ≥9 weeks from Day 1 of the last cycle of chemotherapy, Sponsor consultation is required.

If iRECIST is implemented (Section 8.2.1.5), olaparib/olaparib placebo should not be started in the Maintenance Period until it is determined that the participant has persistent unconfirmed progression (with an overall response of iUPD), or as showing disease stability or response (iSD/iPR/iCR) (Appendix 6).

Prior to starting the recommended dose of olaparib (300 mg BID) or olaparib placebo, the participants CrCl must be ≥51 mL/min. Sponsor consultation is required for any participants with CrCl <51 mL/min. In addition, investigators should confirm that the participant does not meet any of the dose modification criteria of olaparib or olaparib placebo described in Section 6.6.2. Sponsor consultation is required for any participants with a condition meeting the dose modification criteria to initiate olaparib or olaparib placebo at a reduced dose.

Participants will self-administer olaparib/olaparib placebo except on Day 1 of each cycle, when the dose will be given at the study site clinic prior to the infusion of either pembrolizumab or pembrolizumab placebo. Olaparib/olaparib placebo tablets should be taken with one glass of water twice a day at the same time each day, approximately 12 hours between doses. The tablets should be swallowed whole and not chewed, crushed, dissolved or divided. Olaparib/olaparib placebo tablets can be taken with or without food.

If vomiting occurs shortly after the olaparib/olaparib placebo tablets are swallowed, the dose should only be replaced if all of the intact tablets can be seen and counted. Should any participant enrolled in the study miss a scheduled dose for any reason (eg, as a result of forgetting to take the tablets or vomiting), the participant will be allowed to take the

scheduled dose up to a maximum of 2 hours after that scheduled dose time. If greater than 2 hours after the scheduled dose time, the missed dose is not to be taken and the participant should take their allotted dose at the next scheduled time.

Participants with no evidence of disease after 2 years of treatment with olaparib or olaparib placebo will stop olaparib or olaparib placebo at the next scheduled visit after radiographic assessment of CR or NED. Participants with continued evidence of disease after 2 years of treatment with olaparib or olaparib placebo and without evidence of disease progression may continue olaparib or olaparib placebo until any one of the discontinuation criteria is met.

8.1.9.1.6 Antiemetic Therapy

The use of antiemetic therapy should follow Multinational Association of Supportive Care in Cancer guidelines [Roila, F., et al 2016]. For the first 6 treatment cycles (including lead-in), antiemetic therapy should include a 5-HT3 receptor antagonist, and/or dexamethasone (or equivalent) [Roila, F., et al 2016]. Aprepitant use is allowed during the Treatment Period (through the last dose of chemotherapy); however, it is not allowed during the Maintenance Period as it is a moderate inhibitor of CYP3A4.

8.1.10 Discontinuation and Withdrawal

Participants who discontinue study treatment prior to completion of the Treatment Period should be encouraged to continue to be followed for all remaining study visits.

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

8.1.10.1 Discontinuation of Study Treatment Due to Progressive Disease Prior to Interval Debulking

Due to the mechanism of action of pembrolizumab, some participants may experience a transient tumor flare within the first few months of starting treatment and then experience subsequent disease response. Because this is a double-blind study, the Sponsor, investigators, other study site personnel, and participants will be blinded to pembrolizumab versus pembrolizumab placebo administration. Therefore, if the initial imaging assessment prior to interval debulking surgery suggests PD by RECIST 1.1 (Section 8.2.1.4), investigators are encouraged to implement iRECIST (Section 8.2.1.5) prior to discontinuation of study treatment in participants that are clinically stable.

8.1.10.2 Withdrawal From Future Biomedical Research

Participants may withdraw their consent for future biomedical research. Participants may withdraw consent at any time by contacting the principal investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com). Subsequently, the participant's consent for future biomedical research will be withdrawn. A

letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the participant of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

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

8.1.11 Participant Blinding/Unblinding

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

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

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

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

Additionally, the investigator or medically qualified designee must go into the IRT system and perform the unblind in the IRT system to update drug disposition. In the event that the emergency unblinding call center is not available for a given site in this study, the IRT system should be used for emergency unblinding in the event that this is required for participant safety.

At the end of the study, random code/disclosure envelopes or lists and unblinding logs are to be returned to the Sponsor or designee.

8.1.11.1 Non-Emergency Unblinding

Unblinding to study treatment (pembrolizumab/pembrolizumab placebo and/or olaparib/olaparib placebo) administration may occur on an individual participant basis and only after consultation with the Sponsor under the following circumstances:

- PD with discontinuation of study treatment and the participant is considered for enrollment on an alternate immune-oncology protocol that requires knowledge of prior treatment with pembrolizumab and/or olaparib.
- AE necessitating discontinuation of treatment and unblinding required for appropriate clinical management of complications. Prior to unblinding any participant in this situation, the Sponsor's Clinical Director must be consulted to review individual requests for unblinding using Sponsor consultation form with reasons to unblind clearly documented.
  Note: in some instances, unblinding to study treatment may be needed for appropriate clinical management of the complications but may not necessitate discontinuation of study treatment. The Sponsor's Clinical Director must be consulted to review individual requests for unblinding using Sponsor consultation form with reasons to unblind and decision to remain on study treatment clearly documented.

8.1.12 Calibration of Equipment

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

8.1.13 Tumor Tissue

8.1.13.1 Tumor Tissue for PD-L1 and *BRCA1/2* Status

Participants are required to have an excisional or core biopsy performed during the Screening Period for the central determination of PD-L1 and *BRCA1/2* status. The results of central testing to assess *BRCA1/2* status will yield information about other genes, including those potentially involved in HRR, and will support exploratory translational science objectives.

8.1.13.2 Tumor Tissue for Biomarker Analyses

Participation in this study will be dependent upon participants supplying tumor tissue for biomarker analysis. A newly obtained core or excision biopsy of a tumor lesion is preferred. Submission of either FFPE tumor blocks or unstained slides is acceptable. For participants eligible for primary debulking surgery, newly obtained tissue must be obtained prior to the administration of systemic cytotoxic treatment for the treatment of current OC. If a diagnostic biopsy is performed prior to surgery and submitted, the biopsy should not be collected more than 8 weeks prior to primary debulking surgery For participants eligible for

interval debulking surgery, newly obtained tissue must be obtained within 8 weeks prior to the administration of systemic cytotoxic treatment for the treatment of current OC.

If submitting unstained cut slides, freshly cut slides should be submitted to the testing laboratory within 14 days from the date the slides are cut, otherwise a new sample will be requested.

Participants must sign the main study ICF prior to submitting existing tissue samples and/or undergoing a new biopsy.

8.2 Efficacy Assessments

8.2.1 Tumor Imaging

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 to be acquired by CT. For the abdomen and pelvis, contrast-enhanced magnetic resonance imaging (MRI) may be used when CT with iodinated contrast is contraindicated, or when mandated by local practice. The same imaging technique regarding modality (ideally the same scanner) and 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 to improve the accuracy of the assessment of response or progression based on imaging.

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

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 (Section 8.2.1.5). Images should continue to be submitted to the central imaging vendor.

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

8.2.1.1 Initial Tumor Imaging

Initial tumor imaging at screening must be performed within 28 days prior to administration of chemotherapy during the Lead-in Period. The screening images must be submitted to the central imaging vendor for retrospective review.

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

the administration of chemotherapy during the Lead-in Period and can be assessed by the central imaging vendor.

If brain imaging is performed to document the stability of existing metastases, MRI is preferred; however, CT imaging will be acceptable if MRI is medically contraindicated.

Bone scans are required at baseline for participants with a history of bone metastases or who are clinically symptomatic. Any supplemental imaging done to support a positive or negative bone scan, such as plain X-rays acquired for correlation, should be submitted to the central imaging vendor.

8.2.1.2 Tumor Imaging During the Study

8.2.1.2.1 Imaging for Participants Eligible for Primary Debulking

For participants eligible for primary debulking surgery, imaging during the Treatment Period will be performed as detailed in Section 1.3.3 and outlined below. An imaging assessment to confirm eligibility (ie, CR, PR, SD, or non-PD) for the Maintenance Period will be performed as follows:

- A minimum of 21 days following Day 1 of Cycle 5 (for Q3W regimen) or a minimum of 7 days following C5D15 (for QW regimen) and prior to initiating treatment with olaparib or olaparib placebo in Cycle 7; or
- A minimum of 21 days after Day 1 of the last cycle of chemotherapy for participants who cannot complete 6 treatment cycles (including lead-in) of chemotherapy due to toxicity but are deemed eligible for maintenance following Sponsor consultation
  Note: Imaging obtained within 4 weeks (28 days) prior to the planned start of maintenance may be used as the maintenance eligibility scan following Sponsor approval.

When determining eligibility for the Maintenance Period, the imaging assessment obtained prior to starting the Maintenance Period should be compared with the baseline imaging assessment to assess CR, PR, SD, or non-PD. Subsequent tumor imaging should be performed every 9 weeks (63 days ± 7 days) from the maintenance eligibility assessment or more frequently if clinically indicated. After approximately 1 year (after Week 54), participants who remain on treatment will have imaging performed every 12 weeks (84 days ± 7 days). After approximately 3 years (after Week 156), participants who remain on study will have imaging performed every 24 weeks (168 days ± 7 days). Week 54 and Week 156 are calculated from the date of randomization.

Other than the imaging assessment to determine eligibility for maintenance and eligibility to continue olaparib/olaparib placebo beyond 2 years, imaging timing should follow **calendar days** and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until PD is identified by the investigator, the start of new anticancer treatment, withdrawal of consent, pregnancy, or death, whichever occurs first; however, if the investigator elects to continue treatment and follow iRECIST after initial radiographic PD, imaging should continue, and images should be submitted to the central imaging vendor. All supplemental imaging must be submitted to the central imaging vendor.

8.2.1.2.2 Imaging for Participants Eligible for Interval Debulking

For participants eligible for interval debulking surgery, the first on-study imaging assessment should be performed at least 21 days after Day 1 of Cycle 2 and prior to the debulking surgery. An imaging assessment should be performed after debulking surgery and prior to dosing in Cycle 3 (Day 1, Cycle 3). Imaging assessments following surgery will be performed as detailed in Section 1.3.4. If surgery is not performed, the imaging assessment prior to Cycle 3 is not required and subsequent tumor imaging should be performed as detailed in Section 1.3.5. An imaging assessment to confirm eligibility (ie, non-PD) for the Maintenance Period will be performed as follows:

- A minimum of 21 days following Day 1 of Cycle 5 (for Q3W regimen) or a minimum of 7 days following C5D15 (for QW regimen) and prior to initiating treatment with olaparib or olaparib placebo in Cycle 7; or
- A minimum of 21 days following Day 1 of the last cycle of chemotherapy for participants who cannot complete 6 treatment cycles (including lead-in) of chemotherapy due to toxicity but are deemed eligible for maintenance following Sponsor consultation
  Note: Imaging obtained within 4 weeks (28 days) prior to the planned start of maintenance, including postsurgery imaging, may be used as the maintenance eligibility scan following Sponsor approval.

When determining eligibility for the Maintenance Period, the imaging assessment obtained prior to starting the Maintenance Period should be compared with the baseline imaging assessment to assess non-PD. Subsequent tumor imaging should be performed every 9 weeks (63 days ± 7 days) from the maintenance eligibility assessment or more frequently if clinically indicated. After approximately 1 year (after Week 54), participants who remain on treatment will have imaging performed every 12 weeks (84 days ± 7 days). After approximately 3 years (after Week 156), participants who remain on study will have imaging performed every 24 weeks (168 days ± 7 days). Week 54 and Week 156 are calculated from the date of randomization.

Other than the image assessments pre/post debulking surgery, to determine eligibility for maintenance, and eligibility to continue olaparib/olaparib placebo beyond 2 years imaging timing should follow **calendar days** and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until PD is identified by the investigator, the start of new anticancer treatment, withdrawal of consent, pregnancy, or death, whichever occurs first; however, if the investigator elects to continue treatment and follow iRECIST after initial radiographic PD, imaging should continue, and images should be submitted to the central imaging vendor. All supplemental imaging must be submitted to the central imaging vendor.

8.2.1.2.3 Response Evaluation Following Debulking Surgery

Following debulking surgery, tumor may still be present. PD is defined as the growth of the primary tumor or appearance of any new tumors following debulking surgery as assessed by the investigator per RECIST 1.1 and iRECIST as outlined in Section 8.2.1.4 and

Section 8.2.1.5, respectively. For those participants with NED following debulking surgery, progression is defined as the detection of new lesions on follow-up radiological assessments.

Per iRECIST (Section 8.2.1.5), PD should be confirmed by the site 4 to 8 weeks after verification of the site-assessed first radiologic evidence of PD in clinically stable participants. Participants who have unconfirmed PD may continue on treatment at the discretion of the investigator until progression is confirmed by the site per iRECIST, provided they have met the conditions detailed in Section 8.2.1.5. Participants who receive confirmatory imaging do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks (28 days) later; tumor imaging may resume at the subsequent scheduled imaging time point if clinically stable. Participants who have confirmed PD by iRECIST, as assessed by the site, will discontinue study treatment unless treatment beyond confirmed progression is approved by the Sponsor as detailed in Section 8.2.1.5.

8.2.1.2.4 Imaging for Eligibility to Continue Olaparib/Olaparib Placebo at 2 Years

Imaging should be performed within 4 weeks prior to reaching 2 years of maintenance with olaparib/olaparib placebo:

- If at this scan, the participant has CR or NED, this is the final tumor imaging in the Maintenance Phase and the participant must discontinue olaparib/olaparib placebo. Note: The participant will continue to have imaging in the Efficacy Follow-up Phase (Section 8.11.3.2).
- If at this scan the participant does not have a CR and is not NED, the participant may continue olaparib/olaparib placebo until CR or NED by RECIST 1.1. Note: Thereafter, the participant will continue to have imaging in the Efficacy Follow-up Phase (Section 8.11.3.2).

8.2.1.3 End of Treatment and Follow-up Tumor Imaging

For participants who discontinue study treatment, tumor imaging should be performed at the time of treatment discontinuation (± 4-week window) and prior to starting a new anticancer treatment. If a previous imaging was obtained within 4 weeks (28 days) prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory. For participants who discontinue study treatment due to documented PD, this is the final required tumor imaging if the investigator elects not to implement iRECIST.

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

8.2.1.4 RECIST 1.1 Assessment of Disease

RECIST 1.1 will be used by the investigator as the primary measure for assessment of tumor response, date of PD, and as a basis for all protocol guidelines related to disease status (eg,

discontinuation of treatment). 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.

Initial tumor imaging showing site-assessed PD should also be submitted to the central imaging vendor.

8.2.1.5 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.

When clinically stable, participants should not be discontinued until progression is confirmed by the investigator, working with local radiology, according to the rules outlined in Appendix 6. This allowance to continue treatment despite initial radiologic PD takes into account the observation that some participants can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. This data will be collected in the clinical database.

Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG performance status
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

Any participant deemed **clinically unstable** should be discontinued from study treatment at site-assessed first radiologic evidence of PD, and is not required to have repeat tumor imaging for confirmation of PD by iRECIST.

If the investigator decides to continue treatment, the participant may continue to receive study treatment and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per investigator assessment. For participants eligible for interval debulking surgery, the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, but prior to debulking surgery. Images should continue to be sent in to the central imaging vendor for potential retrospective BICR.

If repeat imaging does not confirm PD per iRECIST, as assessed by the investigator, and the participant continues to be clinically stable, study treatment may continue and follow the regular imaging schedule. If PD is confirmed, participants will be discontinued from study treatment.

If a participant has radiographic iCPD as defined in Appendix 6, study treatment should be discontinued; however, if the participant is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered following consultation with the Sponsor. In this case, if study treatment is continued, tumor imaging should continue to be

performed following the intervals as outlined in Section 1.3 and submitted to the central imaging vendor.

A description of the adaptations and iRECIST process is provided in Appendix 6, with additional detail in the iRECIST publication [Seymour, L., et al 2017]. A summary of imaging and treatment requirements after first radiologic evidence of progression is provided in Table 9.

Table 9 Imaging and Treatment After First Radiologic Evidence of PD

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD by RECIST 1.1	Repeat imaging at 4 to 8 weeks to confirm PD	May continue study treatment at investigator's discretion while awaiting confirmatory tumor imaging by site by iRECIST	Repeat imaging at 4 to 8 weeks to confirm PD per investigator's discretion only	Discontinue treatment
Repeat tumor imaging confirms PD (iCPD) by iRECIST per investigator assessment	No additional imaging required	Discontinue treatment (exception is possible upon consultation with Sponsor)	No additional imaging required	Not applicable
Repeat tumor imaging shows iUPD by iRECIST per investigator assessment	Repeat imaging at 4 to 8 weeks to confirm PD. May occur at next regularly scheduled visit	Continue study treatment at the investigator's discretion	Repeat imaging at 4 to 8 weeks to confirm PD per investigator's discretion only	Discontinue treatment
Repeat tumor imaging shows iSD, iPR, or iCR by iRECIST per investigator's assessment	Continue regularly scheduled imaging assessments	Continue study treatment at the investigator's discretion	Continue regularly scheduled imaging assessments	May restart study treatment if condition has improved and/or clinically stable per investigator's discretion. Next tumor imaging should occur according to the regular imaging schedule

iCPD=iRECIST confirmed progressive disease; iCR=iRECIST confirmed complete response; iPR=iRECIST confirmed partial response; iRECIST=modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; iSD=iRECIST confirmed stable disease; iUPD=iRECIST unconfirmed progressive disease; PD=progressive disease; RECIST 1.1=Response Evaluation Criteria in Solid Tumors 1.1.

Note: If progression has been verified by the site, further management is by the site, based on iRECIST. Any further imaging should still be submitted to the central imaging vendor. If RECIST 1.1 disease progression has not been verified by the site, ideally the site should continue treatment. Whether or not treatment continues, imaging should be collected and submitted to the central imaging vendor until RECIST 1.1 progression is verified by the site.

8.2.2 Pathological Tumor Assessment

Following interval debulking surgery, detailed pathological assessment will be performed by the local pathologist on all tumor tissue removed during the surgery and recorded in the appropriate eCRF. A redacted copy of the detailed pathological assessment will be requested following review of pCR worksheet. A pCR is defined as the disappearance of all known disease noted prior to surgery; all biopsies (and peritoneal washings if performed) collected during the interval debulking surgery are microscopically negative for malignancy.

All pathologists reviewing and interpreting surgical specimens for assessment of pCR will be blinded to treatment assignment.

Any leftover tissue will be archived for future biomedical research if the participant has documented the optional informed consent for future biomedical research as specified in Section 8.1.1.2.

8.2.3 Tumor Marker Assessment

Tumor markers alone cannot be used to assess response. However, some disease-specific and validated tumor markers (eg, CA-125 for OC) can be integrated as non-target disease markers. An increase in markers coincident with a decline in clinical stability and other signs of disease progression could indicate clinical progression (Section 7.1). For CA-125, this would be an increase of either ≥2 × the normal value or ≥2 × the lowest level it has been [Pepin, K., et al 2014] [Rustin, G. J., et al 2011].

Blood samples for tumor markers (ie, CA-125) will be obtained at time points indicated in Section 1.3, as clinically appropriate for the participant. Additional assessments may be done if clinically indicated (eg, suspected progression). CA-125 will be assessed by a local laboratory.

8.2.4 Quality-of-Life Assessment

As of Amendment 05, all PRO collections will be discontinued. Original protocol text in this section has been retained for historical perspective.

For patient-reported outcomes (PROs), the EQ-5D-5L, EORTC QLQ-C30, and EORTC QLQ-OV28 questionnaires will be administered by trained study site personnel and completed by the participants themselves.

It is strongly recommended that PROs are administered prior to other study procedures assessments including drug administration, AE evaluation, and disease status notification. The PROs are completed in the following order: EQ-5D-5L first, then EORTC QLQ-C30, and lastly EORTC QLQ-OV28 at the time points specified in the Section 1.3 and briefly summarized below.

The PROs will be completed on Day 1 of C1, C2, C3, C4, every 3 cycles through C16 (C7, C10, C13, C16), and every 4 cycles thereafter in the second year (C20, C24, C28, C32, C36) for as long as participant is receiving study treatment. The PROs will also be completed at

the treatment discontinuation visit and 30-day Safety Follow-up Visit. If the participant does not complete the PROs for any reason, the "Miss Mode" form must be completed to capture the reason the assessment was not performed.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided below. The total amount of blood to be drawn over the course of the study (from prestudy to poststudy visits), including approximate blood volumes drawn by visit and by sample type per participant can be found in the Procedure Manual. Safety monitoring and assessments should be performed in accordance with the approved product labels and local practice for paclitaxel (or docetaxel), carboplatin and bevacizumab.

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) as per institutional standard during the Screening Period. 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) as per institutional standard as clinically indicated, prior to administration of study treatment. Weight will also be measured and recorded.

Clinically significant abnormal findings should be recorded as medical history. After the first dose of chemotherapy in the Lead-in Period, new clinically significant abnormal findings should be recorded as AEs.

The time points for complete and directed physical examinations are described in the SoA (Section 1.3). Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.2 Vital Signs

The investigator or qualified designee will measure vital signs at the time points specified in the SoA (Section 1.3) and will include temperature, systolic and diastolic blood pressure, heart rate, and respiratory rate. For participants who will start bevacizumab after the Lead-in Period, blood pressure must be measured prior to the first administration of bevacizumab to ensure the participant does not have uncontrolled hypertension.

8.3.3 Electrocardiograms

A standard 12-lead ECG will be obtained and reviewed by an investigator or medically qualified designee (consistent with local requirements) at the time points specified in the SoA (Section 1.3). Clinically significant abnormal findings at Screening should be recorded as medical history. An additional ECG should be performed when clinically necessary.

8.3.4 Clinical Safety Laboratory Assessments

Refer to Appendix 5 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 5, must be conducted in accordance with the SoA.
- If laboratory values from non-protocol-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 treatment, 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.

The total amount of blood to be drawn/collected over the course of the study (from prestudy to poststudy visits), including approximate blood volumes drawn/collected by visit and by sample type per participant can be found in the Procedures Manual. Refer to the SoA (Section 1.3) for the timing of laboratory assessments.

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 6.6.2.3.

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

8.3.5 Performance Assessments

8.3.5.1 Eastern Cooperative Oncology Group Performance Status

The investigator or qualified designee will assess ECOG status at screening and prior to the administration of each dose of study treatment 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 4.

Progression of the cancer under study is not considered an AE as described in Section 8.4.5 and Appendix 4.

AE, 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 AE, 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.

AEs will not be collected for participants during the prescreening period (for determination of archival tissue status) as long as that participant has not undergone any protocol-specified procedure or intervention. If the participant requires a blood draw, fresh tumor biopsy etc., the participant is first required to provide consent to the main study and AEs will be captured according to guidelines for standard AE reporting.

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

- All AEs, SAEs, and other reportable safety events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event causes the participant to be excluded from the study, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.
- All AEs from the time of treatment allocation/randomization through 30 days following cessation of study treatment must be reported by the investigator.
- All AEs meeting serious criteria, from the time of treatment allocation/randomization through 90 days following cessation of study treatment, or 30 days following cessation of study treatment 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 treatment allocation/randomization through 180 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy must be reported by the investigator.

- Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately to the Sponsor if the event is considered to be drug related.
- Any SAE of MDS/AML or new primary malignancy occurring ≥30 days after the last dose of olaparib/olaparib placebo should be reported regardless of the investigator's assessment of causality or knowledge of the treatment arm.

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

If an extension study is available and a participant has been consented for the extension study, then safety events, including those considered related to study intervention, will be collected as instructed in the extension study.

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 10.

Table 10 Reporting 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 AE Collection Period**	**Reporting Period: After the Protocol-specified AE Collection 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, Cancer, or Overdose	Report if: – due to protocol-specified intervention – causes exclusion – participant is receiving placebo run-in or other run-in treatment	Report all	eport if: drug related (Follow ongoing to outcome)	Within 24 hours of learning of event

Type of Event	Reporting Period: Consent to Randomization/ Allocation	Reporting Period: Randomization/ Allocation Through Protocol-specified AE Collection Period	Reporting Period: After the Protocol-specified AE Collection Period	Time Frame to Report Event and Follow-up Information to Sponsor
Pregnancy/Lactation Exposure	Report if: – participant has been exposed to any protocol-specified intervention (eg, procedure, washout, or run-in treatment including placebo run-in) Exception: A positive pregnancy test at the time of initial screening is not a reportable event.	Report all	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event
Potential DILI events meeting biochemical criteria of Hy's Law (requiring regulatory reporting)	Report if: – due to intervention – causes exclusion	Report - regardless of suspected etiology - to be reported as an ECI and SAE with OME criteria in the absence of other serious criteria	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 if: – requiring regulatory reporting	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event
ECI (does not require regulatory reporting)	Report if: – due to intervention – causes exclusion	Report – those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event (unless an SAE)
Abbreviations: DILI=drug-induced liver injury; ECI=event of clinical interest; NSAE=nonserious adverse event; OME=other important medical 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 AE and/or SAE 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 potential DILI events meeting biochemical criteria of Hy's Law, 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 all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 4.

8.4.4 Regulatory Reporting Requirements for SAE

- Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment 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 treatment under clinical investigation. All AEs will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, ie, per ICH Topic E6 (R2) Guidelines for GCP.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAE) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

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

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

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

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

8.4.6 Pregnancy and Exposure During Breastfeeding

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

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

8.4.7 Events of Clinical Interest (ECIs)

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

All potential DILI events meeting biochemical criteria of Hy's Law will be reported to the Sponsor, regardless of suspected etiology, as both an ECI and SAE, with OME criteria in the absence of other SAE criteria, within 24 hours of learning of the event. Potential DILI events are defined as:

- An elevated AST or ALT laboratory value that is greater than or equal to 3× the ULN and,
- An elevated total bilirubin laboratory value that is greater than or equal to 2× the ULN and,
- At the same time, an alkaline phosphatase laboratory value that is less than 2× the ULN,

determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based on 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).

Additional ECIs for this study include:

1. An overdose of study intervention, as defined in Section 8.5, that is not associated with clinical symptoms or abnormal laboratory results.
2. Any event of MDS/AML, new primary malignancy, or pneumonitis should be reported whether it is considered a nonserious AE (eg, non-melanoma skin cancer) or SAE and regardless of investigator's assessment of causality as defined in Section 8.4.1.

8.5 Treatment of Overdose

For this study, an overdose of pembrolizumab will be defined as any dose of 1000 mg or greater (≥5 times the indicated dose). Olaparib must only be used in accordance with the dosing recommendations in this protocol. Any dose or frequency of dosing that exceeds the dosing regimen specified in this protocol should be reported as an overdose.

No specific information is available on the treatment of overdose of pembrolizumab, chemotherapy, bevacizumab, or olaparib. 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

PK 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 in this study as specified in the SoA:

- Blood for genetic analysis
- Blood for RNA analysis
- Blood for plasma biomarker analysis
- Blood for serum biomarker analysis
- Blood for circulating tumor DNA
- Newly obtained tissue collection
- Tumor tissue

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

The sample for genetic analysis should be drawn for planned exploratory biomarker research. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for future biomedical research if the participant signs the future biomedical research consent. If the genetic sample collection is not approved, but future biomedical research is approved and consent is given, this sample will be collected for the purpose of future biomedical research.

8.9 Future Biomedical Research Sample Collection

If the participant signs the future biomedical research consent, leftover samples listed in Section 8.8 will be obtained as part of future biomedical research.

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

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

8.11 Visit Requirements

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

8.11.1 Screening

Within 56 days prior to randomization, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.

Written consent must be obtained prior to performing any protocol-specific procedure. Results of a test performed prior to the participant signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 56-day Screening Period, except for the following:

- Laboratory tests are to be performed within 7 days prior to the initiating chemotherapy in the Lead-in Period. An exception is HIV and hepatitis testing which may be done up to 56 days prior to randomization if required by the local health authority. Refer to Appendix 7 for country-specific requirements.
- Baseline imaging to be performed within 28 days prior to starting lead-in chemotherapy administration.
- Clinical chemistry and hematological parameters are to be reassessed within 3 days of Cycle 1 Day 1.
- Evaluation of ECOG is to be performed within 7 days prior to initiating chemotherapy in the Lead-in Period and within 3 days of Cycle 1 Day 1.

- For WOCBP, a pregnancy test (urine or serum) will be performed within either 24 hours (urine) or 72 hours (serum) prior to initiating chemotherapy during the Lead-in Period and within either 24 hours (urine) or 72 hours (serum) prior to Day 1 of Cycle 1. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory). Refer to Appendix 7 for country-specific requirements.
- Newly obtained tissue may be obtained at any time prior to the administration of systemic cytotoxic treatment for the treatment of current OC.

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

8.11.2 Treatment Period

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

8.11.3 Posttreatment Visits

8.11.3.1 Safety Follow-up Visit

The mandatory Safety Follow-up Visit should be conducted 30 days (+7 days) after the last dose of study treatment or before the initiation of a new anticancer treatment, whichever comes first. If the discontinuation visit occurs ≥30 days from last dose of study intervention, a Safety Follow-up Visit is not required.

8.11.3.2 Efficacy Follow-up Visits

Participants who complete the protocol-required cycles of study intervention or who discontinue study treatment for a reason other than PD will begin the Efficacy Follow-up Phase and should be assessed approximately every 9 weeks (63 days ± 7 days) during the first year (through Week 54), approximately every 12 weeks (84 days ± 7 days) through Week 156, and Q24 weeks (168 days ± 7 days) thereafter by radiologic imaging to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anticancer therapy, disease progression, pregnancy, death, or the end of study.

Information regarding poststudy anticancer treatment will be collected if new treatment is initiated. Participants who will not have further efficacy assessments must enter the Survival Follow-up Phase.

8.11.3.3 Survival Follow-up Assessments

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 detailed below:

- For participants who discontinue study treatment and who will not enter the Efficacy Follow-up Phase, the first survival follow-up contact will be scheduled 12 weeks after the discontinuation visit and/or Safety Follow-up Visit (whichever is last).
- For participants who entered but are no longer being assessed during the Efficacy Follow-up Phase, the first survival follow-up contact will be scheduled 12 weeks after the last efficacy assessment follow-up visit has been performed.

Investigators should ask during survival follow-up assessments if the participant has developed MDS/AML or a new primary malignancy and prompted to report any such cases.

8.11.3.4 Survival Status

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

9. Statistical Analysis Plan

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to the conduct of any analysis, will be documented in a supplemental Statistical Analysis Plan (sSAP) and referenced in the Clinical Study Report (CSR) for the study. A separate biomarker analysis plan will be provided. Posthoc exploratory analyses will be clearly identified in the CSR. The PRO analysis plan will also 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 Sections 9.2 through 9.12.

Key Elements of the Statistical Analysis Plan	
Study Design Overview	**A Randomized Phase 3, Double-Blind Study of Chemotherapy With or Without Pembrolizumab Followed by Maintenance With Olaparib or Placebo for the First-Line Treatment of BRCA non-mutated Advanced Epithelial Ovarian Cancer (EOC) (KEYLYNK-001 / ENGOT-ov43 / GOG-3036)**
Treatment Assignment	Approximately 1284 participants will be randomized in a 1:1:1 ratio between 3 treatment arms: • Arm 1: Treatment: carboplatin/paclitaxel for 5 cycles plus pembrolizumab Q3W for up to 35 infusions. Maintenance: olaparib BID • Arm 2: Treatment: carboplatin/paclitaxel Q3W for 5 cycles plus pembrolizumab Q3W for up to 35 infusions Maintenance: olaparib placebo BID • Arm 3 (control Arm): Treatment: carboplatin/paclitaxel plus pembrolizumab placebo Q3W for 5 cycles plus pembrolizumab placebo Q3W for up to 35 infusions. Maintenance: olaparib placebo BID Stratification factors are as follows: 1. Surgery (planned interval debulking versus R0 following primary debulking versus R1 following primary debulking) 2. Bevacizumab use (yes versus no) 3. PD-L1 status (CPS <10 versus CPS ≥10)
Analysis Populations	Efficacy: Intention-to-Treat (ITT) Safety: All Participants as Treated (APaT)
Primary Endpoints	• Progression-free survival (PFS) based on RECIST 1.1 as assessed by investigator in participants with PD-L1 positive tumors (CPS ≥10) • PFS per RECIST 1.1 assessed by investigator in all participants.
Key Secondary Endpoints	• Overall survival (OS) in participants with PD-L1 positive tumors (CPS ≥10) • OS in all participants
Statistical Methods for Key Efficacy Analyses	The primary and key secondary hypotheses will be evaluated by comparing the treatment arms (Arm 1 vs Arm 3 and Arm 2 vs Arm 3) with respect to PFS and OS 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 group using the Kaplan-Meier method.
Statistical Methods for Key Safety Analyses	The analysis of safety results will follow a tiered approach. The tiers differ with respect to the analyses that will be performed. There are no events of interest that warrant elevation to Tier 1 events in this study. Tier 2 parameters will be assessed via point estimates with 95% confidence intervals (CIs) provided for between-group 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.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9.2 Responsibility for Analyses/In-house Blinding

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

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

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

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

9.3 Hypotheses/Estimation

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

9.4 Analysis Endpoints

Efficacy, safety and PRO endpoints that will be evaluated for within- and/or between-treatment differences are listed below. Other endpoints will be described in the sSAP.

Primary

PFS: The time from randomization to the first documented PD as assessed by the investigator according to RECIST 1.1, or death due to any cause, whichever occurs first.

Secondary

OS: The time from randomization to death due to any cause.

PFS: The time from randomization to the first documented PD as assessed by BICR according to RECIST 1.1, or death due to any cause, whichever occurs first.

PFS2: The time from randomization to subsequent disease progression (clinical or radiological) after second-line therapy, or death from any cause, whichever first.

TFST: The time from the date of randomization until initiation of first subsequent anticancer therapy or death due to any cause, whichever occurs first.

TSST: The time from the date of randomization until initiation of second subsequent anticancer therapy or death due to any cause, whichever occurs first.

TDT: The time from the date of randomization to discontinuation of study treatment or death due to any cause, whichever occurs first.

pCR: The disappearance of all known disease noted prior to surgery; all biopsies (and peritoneal washings if performed) collected during the interval debulking surgery are microscopically negative for malignancy.

PRO: Change from baseline and time to deterioration in EORTC QLQ-C30 GHS/QoL (items 29 and 30), and the abdominal/GI symptom subscale (items 31 to 36) from EORTC QLQ-OV28 will be evaluated as secondary endpoints.

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9.5 Analysis Populations

9.5.1 Efficacy Analysis Population

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

The analysis population for ORR consists of all randomly assigned participants with measurable disease.

9.5.2 Safety Analysis Population

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/allocated participants who received at least 1 dose of study treatment. Participants will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the APaT population. This will be the treatment group to which they are randomized except for participants who take incorrect study treatment for the entire Treatment Period; such participants will be included in the treatment group corresponding to the study treatment actually received.

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

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

9.5.3 PRO Analysis Population

The PRO analyses are based on the PRO Full Analysis Set (PRO FAS) population, defined as all randomized participants who have at least 1 PRO assessment available for the specific endpoint and have received at least 1 dose of the study intervention. Participants will be analyzed in the treatment group to which they are randomized.

9.6 Statistical Methods

9.6.1 Statistical Methods for Efficacy Analyses

Statistical testing and inference for safety analyses are described in Section 9.6.2. Efficacy results that will be deemed to be statistically significant after consideration of the Type-I error control strategy are described in Section 9.8. Nominal p-values will be computed for

other efficacy analyses, but should be interpreted with caution due to potential issues of multiplicity.

9.6.1.1 Progression-free Survival

The non-parametric Kaplan-Meier method will be used to estimate the PFS curve in each treatment group. The treatment difference in PFS will be assessed by the stratified log-rank test. 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 6.3.1.1) will be applied to both the stratified log-rank test and the stratified Cox model. Median PFS and its 95% confidence intervals (CIs) will be updated post the second interim analysis; however, no formal statistical test will be performed.

Since disease progression is assessed periodically, PD can occur any time in the time interval between the last assessment where PD was not documented and the assessment when PD is documented. The true date of disease progression will be approximated by the date of the first assessment at which PD is objectively documented per RECIST 1.1 (based on investigator for primary analysis). Death is always considered as a confirmed PD event. Participants who do not experience a PFS event will be censored at the last disease assessment.

In order to evaluate the robustness of the PFS endpoint per RECIST 1.1 based on investigator assessment, 1 primary and 2 sensitivity analyses with a different set of censoring rules will be performed. For the primary analysis, if the events (PD or death) are immediately after more than 1 missed disease assessment, the data are censored at the last disease assessment prior to missing visits. Also, data after new anticancer therapy are censored at the last disease assessment prior to the initiation of new anticancer therapy. The first sensitivity analysis follows the complete follow-up intention-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, it considers discontinuation of treatment or initiation of an anticancer treatment subsequent to discontinuation of study-specified treatments, whichever occurs later, to be a PD event for participants without documented PD or death. If a participant meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied. The censoring rules for primary and sensitivity analyses are summarized in Table 11.

Table 11 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 therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death	Progressed at date of documented PD or death
PD or death documented immediately after ≥2 consecutive missed disease assessments or after new anticancer therapy, if any	Censored at last disease assessment prior to the earlier date of ≥2 consecutive missed disease assessment and new anticancer therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death
No PD and no death; and new anticancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment	Progressed at treatment discontinuation due to reasons other than complete response; otherwise censored at last disease assessment if still on study or completed study treatment.
No PD and no death; new anticancer treatment is initiated	Censored at last disease assessment before new anticancer treatment	Censored at last disease assessment	Progressed at date of new anticancer treatment

Abbreviation: PD = progressive disease.

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Similar analyses will be performed for the secondary endpoint of PFS per RECIST 1.1 by BICR assessment. Only the primary censoring rule will be applied for the analysis of PFS by BICR assessment.

An analysis of PFS2, defined as the time from randomization to subsequent disease progression after second-line therapy, or death from any cause, whichever first, will be carried out. Participants alive and for whom a disease progression following initiation of new anticancer treatment has not been observed will be censored at the third-line therapy start date if any or the last time the participant was known to be alive and without second disease progression. The same stratified Cox proportional hazard model will be used to estimate the HR and its 95% CI.

9.6.1.2 Overall Survival

The non-parametric Kaplan-Meier method will be used to estimate the survival curves. The treatment difference in survival will be assessed by the stratified log-rank test (based on the stratification factors defined in Section 6.3.1.1). A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, the HR). The HR and its 95% CI from the stratified Cox model with a single treatment covariate will be reported. The stratification factors used for randomization (Section 6.3.1.1) will be applied to both the stratified log-rank test and the stratified Cox model. Participants without documented death at the time of analysis will be censored at the date of last known contact. The Restricted Mean Survival Time method may be conducted for OS to account for the possible non-proportional hazards effect.

A summary of the primary analysis strategy for the key efficacy endpoints is provided in Table 12.

Table 12 Efficacy Analysis Methods for Key Efficacy Endpoints

Endpoint/Variable	Statistical Method	Analysis Population	Missing Data Approach
Primary Analyses:			
PFS (RECIST 1.1) by investigator	Testing: Stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT (in participants with CPS ≥10 and in all participants)	Censored according to rules in Table 11.
Secondary Analyses:			
OS	Testing: Stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT (in participants with CPS ≥10 and in all participants)	Censored at last known alive date
PFS (RECIST 1.1) by BICR	Estimation: Stratified Cox model with Efron's tie handling method	ITT (in participants with CPS ≥10 and in all participants)	Primary censoring rule in Table 11.
PFS2	Estimation: Stratified Cox model with Efron's tie handling method	ITT (in participants with CPS ≥10 and in all participants)	Participants alive and for whom no secondary disease progression has been served will be censored at the third-line therapy start date, if any, or the last time known to be alive and without second disease progression.

Abbreviations: BICR = blinded independent central review; CPS = combined positive score; ITT = intention-to-treat; OS = overall survival; PFS = progression-free survival; PFS2 = progression-free survival after next-line treatment; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors version 1.1.

9.6.2 Statistical Methods for Safety Analyses

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

The analysis of safety results will follow a tiered approach (Table 13). The tiers differ with respect to the analyses that will be performed. AEs (specific terms as well as system organ class terms) and events that meet predefined limits of change (PDLCs) in laboratory values, vital signs, and ECG parameters are either prespecified as "Tier 1" endpoints, or will be classified as belonging to "Tier 2" or "Tier 3" based on the observed proportions of participants with an event.

Tier 1 Events

Safety parameters that are identified a priori constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance. AEs of special interest that are immune-mediated or potentially immune-mediated are well documented and will be evaluated separately; however, these events have been characterized consistently throughout the pembrolizumab clinical development program and determination of statistical significance is not expected to add value to the safety evaluation. Additionally, there are no known AEs associated with participants for which determination of a p-value is expected to impact the safety assessment. Therefore, there are no Tier 1 events 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 (via the Miettinen and Nurminen method [1985]).

Membership in Tier 2 requires that at least 10% of participants in any treatment group exhibit the event; all other AEs and predefined limits of change will belong to Tier 3. The threshold of at least 10% of participants was chosen for Tier 2 events because the population enrolled in this study 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 the overall safety profile and add little to the interpretation of potentially meaningful treatment differences. In addition, Grade 3 to 5 AEs (≥5% of participants in 1 of the treatment groups) and SAEs (≥5% of participants in 1 of the treatment groups) will be considered Tier 2 endpoints. Because many 95% CIs may be provided without adjustment for multiplicity, the CIs should be regarded as a helpful descriptive measure to be used in safety review, not as a formal method for assessing the statistical significance of the between-group differences.

Tier 3 Events

Safety endpoints that are not Tier 1 or 2 events are considered Tier 3 events. The broad AE categories consisting of the proportion of participants with any AE, a drug-related AE, a serious AE, an AE which is both drug related and serious, a Grade 3-5 AE, a drug-related

Grade 3-5 AE, and discontinuation due to an AE will be considered Tier 3 endpoints. Only point estimates by treatment group are provided for Tier 3 safety parameters.

Continuous Safety Measures

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

Table 13 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	Grade 3-5 AE (incidence ≥5% of participants in one of the treatment groups)	X	X
	Serious AE (incidence ≥5% of participants in one of the treatment groups)	X	X
	AEs (incidence ≥10% of participants in one of the treatment groups)	X	X
Tier 3	Any AE		X
	Any Grade 3-5 AE		X
	Any Serious AE		X
	Any Drug-Related AE		X
	Any Serious and Drug-Related AE		X
	Any Grade 3-5 and Drug-Related AE		X
	Discontinuation due to AE		X
	Death		X
	Specific AEs, SOCs (incidence <10% of participants in all of the treatment groups)		X
	Change from Baseline Results (lab toxicity shift, vital signs)		X

Abbreviations: AE=adverse event; CI=confidence interval; SOC=system organ class.

9.6.3 Statistical Methods for PRO Analyses

To evaluate the treatment effect on the HRQoL outcomes at prespecified time points, a constrained longitudinal data analysis model will be applied, with the PRO score as the response variable, and the treatment by time interaction and stratification factors as covariates. Least square mean (lsmean) change from baseline will be summarized. Group-wise comparisons will be performed and the model-based lsmean score will be provided by treatment group and study visit.

A difference of 10 points in PRO score on the 100-point scale is perceived to be clinically meaningful to participants according to previous research. Correspondingly, a participant's postbaseline PRO score will be classified as "improvement", "stable", or "deterioration" according to a 10-point or greater change for EORTC QLQ-C30 GHS/QoL and EORTC

QLQ-OV28 abdominal/GI symptom scale. The number and proportion of participants with "improved", "stable", or "deteriorated" scales will be summarized by treatment arm.

The Kaplan-Meier method will be used to estimate times to deterioration survival curve for each treatment arm and the Cox proportional hazards regression model will be used to estimate the magnitude of treatment difference.

Details of other PRO analyses will be described in the sSAP.

9.6.4 Summaries of Baseline Characteristics and Demographics

The comparability of the treatment groups for each relevant characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants randomized, and the primary reason for discontinuation will be displayed. Demographic variables (such as age) and baseline characteristics will be summarized by treatment either by descriptive statistics or categorical tables. The reasons for exclusion from the ITT population (if any) will be summarized.

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9.8 CCI [redacted]

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9.8.2 Safety Analyses

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

9.9 Sample Size and Power Calculations

The study plans to randomize ~1284 participants with CCI [redacted] in a 1:1:1 ratio into the 3 arms. Of note, the assumption of CCI [redacted] CCI [redacted] was made in the sample size and power calculations.

PFS is the primary endpoint and OS is the key secondary endpoint for the study.

For PFS in participants with CPS ≥10 of Arm 1 versus Arm 3 comparison, [redacted] the study has ~ 85% power to detect a HR of 0.70 [redacted]

For PFS in all participants of Arm 1 versus Arm 3 comparison, [redacted] the study has ~ 93% power to detect a HR of 0.72 at the initially allocated α=0.005 (1-sided).

For PFS in participants with CPS ≥10 of Arm 2 versus Arm 3 comparison [redacted] the study has ~ 87% power to detect a HR of 0.70 at the α=0.025 (1-sided).

For OS in participants with CPS ≥10 of Arm 2 versus Arm 3 comparison, [redacted] he study has ~ 74% power to detect a HR of 0.70 at the α=0.025 (1-sided).

For PFS in all participants of Arm 2 versus Arm 3 comparison, [redacted] the study has ~ 98% power to detect a HR of 0.72 at the α=0.025 (1-sided).

For OS in all participants for both comparisons (Arm 2 versus Arm 3 and Arm 1 versus Arm 3), [redacted] the study has ~ 85% power to detect a HR of 0.75 at the α=0.025 (1-sided).

Note that the above power calculations are based on a constant HR assumption. The interim analysis timing and spending have been designed to ensure the final alpha available is maximized to make testing most sensitive when follow-up is available across both early and late parts of the survival and PFS distributions.

The above sample size and power calculations for PFS and OS assume the following:

- PFS follows an exponential distribution with a median of 16 months for the control group.
- OS follows an exponential distribution with a median of 46 months for the control group.

[redacted]

The sample size and power calculations were performed using R (“gsDesign” package).

9.10 Subgroup Analyses

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

- Stratification factors
  - Surgery (planned interval debulking versus R0 following primary debulking versus R1 following primary debulking)
  - Bevacizumab use (yes versus no)
  - PD-L1 status (CPS <10 versus CPS ≥10)
- Race (white, non-white)
- ECOG performance status (0, 1)

A Forest plot will be produced, which provides the point estimates and CIs for the treatment effect across the categories of subgroups listed above. The consistency of the treatment effect will be assessed descriptively via summary statistics by category for the classification variables listed above.

9.11 Compliance (Medication Adherence)

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

9.12 Extent of Exposure

Extent of exposure for a participant is defined as number of cycles in which the participant receives the study treatment infusion for pembrolizumab/pembrolizumab placebo, and the number of days in which the participant receives olaparib/olaparib placebo. Summary statistics will be provided on the extent of exposure for pembrolizumab/pembrolizumab placebo and olaparib/olaparib placebo, separately, for the APaT population.

10. Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical and Study Oversight Considerations

10.1.1 Code of Conduct for Clinical Trials

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD)
Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with MSD's global standards, local and/or national regulations (including all applicable data protection laws and regulations), Regulation (EU) 536/2014, the International Council for Harmonisation Good Clinical Practice (ICH-GCP) E6 and ICH General Considerations for Clinical Studies E8, 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 (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials which 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 (i.e., 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-non-compliance 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 the 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 (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices.

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

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

10.1.3 Data Protection

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

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

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

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 in order to verify worksheet/CRF data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

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

10.1.3.3 Confidentiality of IRB/IEC Information

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

10.1.4 Committees Structure

10.1.4.1 Steering Committee

This study will be conducted in consultation with a Steering Committee. The Steering Committee may be comprised of some or all of the following members:

- 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 and evaluate recommendations from the DMC.

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

10.1.4.3 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 Executive Oversight Committee 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 (see Section 9.7 [Interim Analyses]) and recommend to the Executive Oversight Committee whether the study should continue in accordance with the protocol.

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

10.1.5 Publication Policy

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

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

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

10.1.6 Compliance With Study Registration and Results Posting Requirements

Under the terms of the 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. For studies conducted under the EMA Clinical Trials Regulation 546/2014, a summary of the study results will be submitted in compliance with the regulation. 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 site contact information.

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

10.1.7 Compliance With Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP (eg, International Conference for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: 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.

For investigators located in countries with serious breach reporting requirements, the investigator will promptly report to the Sponsor any serious breach or suspected serious breach that occurs in compliance with those requirements. Unless more specifically defined

in the applicable requirements, a serious breach is any breach of the applicable clinical trial regulation or of the clinical trial protocol that is likely to affect to a significant degree: (i) the safety or rights of a trial participant, or (ii) the reliability and robustness of the data generated in the clinical trial.

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 clinical 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. 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 may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.10 Study and Site Closure

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

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

10.2 Appendix 2: 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. CCI [redacted]

CCI [redacted]

3. CCI [redacted]

CCI [redacted]

CCI

[redacted]

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

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

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

5. Biorepository Specimen Usage[3,4]

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

biomedical research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

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

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

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

7. Retention of Specimens[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 main study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

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

8. Data Security[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 e-mailed directly to clinical.specimen.management@MSD.com.

13. References

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

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

10.3 Appendix 3: Contraceptive Guidance and Pregnancy Testing

10.3.1 Definitions

Women of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP:

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

  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.

10.3.2 Contraception Requirements

Female Participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 17 during the protocol-defined time frame in Section 5.1.

Table 17 Highly Effective Contraception Methods

Contraceptive allowed during the study include[a]:
Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
● Progestogen-only subdermal contraceptive implant[b, c] ● Intrauterine hormone-releasing system (IUS)[c, d] ● Nonhormonal intrauterine device (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.
● 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 treatment. 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.
LAM=lactational amenorrhea method; WOCBP=woman of childbearing potential. Note: The following are not acceptable methods of contraception: - Periodic abstinence (calendar, symptothermal, postovulation 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). a. Contraceptive use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. b. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. c. For participants who receive olaparib (or olaparib placebo): male condoms must be used in addition to female hormonal contraception during the Treatment Period and for at least 180 days following the last dose of olaparib (or olaparib placebo). d. IUS is a progestin-releasing IUD.

10.3.3 Pregnancy Testing

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 cycle during study treatment.
- Pregnancy testing (urine or serum [as required by local regulations]) should be conducted at the time of discontinuation and at 30 days after the last dose of study treatment.
- 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 individual's participation in the study.
- Refer to Appendix 7 for country-specific requirements.

10.4 Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.4.1 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.

10.4.2 Definition of AE

AE definition
● An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment. ● 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 treatment. ● NOTE: for purposes of AE definition, study treatment includes any pharmaceutical product, biological product, vaccine, device, diagnostic agent or protocol-specified procedure whether investigational (including placebo or active comparator product) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use in this study.

Events meeting the AE definition
● Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, or are considered clinically significant in the medical and scientific judgement of the investigator. ● Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. ● New conditions detected or diagnosed after study treatment 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 treatment 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 of study treatment without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect." ● Any new cancer (that is not a condition of the study). Note: Progression of the cancer under study is not a reportable event. Refer to Section 8.4.5 for additional details.

Events NOT meeting the AE definition
● Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. ● Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). ● Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen. ● Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened. ● Refer to Section 8.4.5 for protocol-specific exceptions

10.4.3 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 pre-existing condition that has not worsened is not an SAE. A pre-existing condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the patient'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) which 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 judgement 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 one 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. ● All potential DILI events meeting biochemical criteria of Hy's Law will be reported to the Sponsor, regardless of suspected etiology, as an ECI and SAE with OME criteria in the absence of other SAE criteria within 24 hours of learning of the event.

10.4.4 Definition of a Suspected Unexpected Serious Adverse Reaction (SUSAR)

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is an adverse event that occurs during a clinical trial and meets the following criteria:
● Unexpected, meaning the nature or severity of the event doesn't match the reference safety information (RSI) ● Serious adverse event as defined in Section 10.4.3 ● Reasonable possibility the event was caused by the study drug

10.4.5 Additional Events Reported in the Same Manner as SAE

Additional events which 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.

10.4.6 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

- 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 Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. Any AE which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.
  - Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
  - Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).
  - Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
  - Grade 4: Life-threatening consequences; urgent intervention indicated.
  - Grade 5: Death related to AE.

Assessment of causality

- Did the 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 investigational medicinal product)?

- **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors
- **Dechallenge:** Was the 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 one time.)
- **Rechallenge:** Was the participant re-exposed 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, or (2) the study is a single-dose drug study); or (3) study intervention(s) is/are used only one time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE STUDY INTERVENTION, OR IF RE-EXPOSURE 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 INIRB/IEC.

- **Consistency with Study treatment 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 CRFs/worksheets by an investigator who is a qualified physician according to his/her best clinical judgement, 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.)

- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one 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.

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

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

- The primary mechanism for reporting to the Sponsor will be the electronic data collection (EDC) tool.
  - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
  - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
    - Reference Section 8.4.1 for reporting time requirements
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Trial File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

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

10.5 Appendix 5: Clinical Laboratory Tests

- The tests detailed in Table 18 will be performed by the local laboratory.
- Following Cycle 1 Day 1, collection of samples for predose laboratory assessments may be performed up to 3 days (72 hours) prior to dosing in subsequent cycles.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.1 and Section 5.2 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 18 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH	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 (fasting or nonfasting)	Calcium	Alkaline phosphatase	Magnesium
	Thyroid-stimulating hormone[d] (TSH)	Triiodothyronine (T3) or free T3 (where T3 cannot be determined)[d]	Free thyroxine (FT4)[d]	Lactate dehydrogenase
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick or laboratory analysis • Microscopic examination (if blood or protein is abnormal)			

Laboratory Assessments	Parameters
Other Screening Tests	• Serum or urine pregnancy test (as needed for WOCBP). Refer to Appendix 3 for additional testing requirements. • Follicle-stimulating hormone (as needed in women of childbearing potential only). • Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody) if required by local health authority. Refer to Appendix 7 for country-specific requirements. • PT or INR and aPTT/PTT is required during screening to establish eligibility; additional testing to be conducted as clinically indicated for participants taking anticoagulation therapy. • CEA (participants eligible for interval debulking surgery). • Cortisol (at screening for both primary and interval debulking participants). • CA-125 will be assessed at screening and then according to the same schedule as imaging (±14 days) by a local laboratory.
Other Tests	• Bone marrow or blood cytogenetic analysis for prolonged hematological toxicities (Section 6.6.2.3). This should include an aspirate for cellular morphology, cytogenetic analysis and flow cytometry, and a core biopsy for bone marrow cellularity. • Cortisol – to be collected within 7 days prior to interval debulking surgery and prior to administration of study treatment in the next 2 treatment cycles following surgery for participants undergoing interval debulking only.

aPTT=activated partial thromboplastin time; CA-125=cancer antigen 125; CEA=cancer embryonic antigen; GFR=glomerular filtration rate; 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; WBC=white blood cell; WOCBP=women of childbearing potential.

a. BUN is preferred; if not available, urea may be tested.
b. Performed only if considered local standard of care.
c. GFR (measured or calculated) or creatinine clearance can be used in place of creatinine.
d. There may be instances when sites are unable to obtain the thyroid function testing results prior to scheduled dosing. After Cycle 1 (randomization) review of thyroid function test results after dosing is acceptable.

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

10.6 Appendix 6: Description of the iRECIST Process for Assessment of Disease Progression

10.6.1 Assessment at Screening and Prior to RECIST 1.1 Progression

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

10.6.2 Assessment and Decision at RECIST 1.1 Progression

For participants who show evidence of radiological PD by RECIST 1.1, as determined by the investigator, the investigator will decide whether to continue a participant on study treatment until repeat imaging is obtained (using iRECIST for participant management) (see Table 9). This decision by the investigator should be based on the participant's overall clinical stability. Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG performance status
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

Any participant deemed **clinically unstable** should be discontinued from study treatment at site-assessed first radiologic evidence of PD, and is not required to have repeat tumor imaging for confirmation of PD by iRECIST.

If the investigator decides to continue treatment, the participant may continue to receive study treatment and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per investigator assessment. For participants eligible for interval debulking surgery, the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, but prior to debulking surgery. Images should continue to be sent in to the central imaging vendor for potential retrospective BICR.

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 non-target lesion(s) identified at baseline
- Development of new lesion(s)

iRECIST defines new response categories, including iUPD (unconfirmed PD) and iCPD (confirmed PD). 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 non-target lesions identified at baseline by RECIST 1.1 will be assessed as usual.

New lesions will be classified as measurable or non-measurable, 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 – Non-target.

10.6.3 Assessment at the Confirmatory Imaging

On the confirmatory imaging, the participant will be classified as disease 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).

10.6.4 Confirmation of Disease 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 initial iUPD 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 non-target 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 non-target lesions
    - The appearance of additional new lesions
- Any new factor appears that would have triggered PD by RECIST 1.1

10.6.5 Persistent iUPD

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

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

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

10.6.6 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 initial PD 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.

10.6.7 Management Following the Confirmatory Imaging

If repeat imaging does not confirm PD per iRECIST, as assessed by the investigator, and the participant continues to be clinically stable, study treatment may continue and follow the regular imaging schedule. If PD is confirmed, participants will be discontinued from study treatment.

NOTE: If a participant has confirmed radiographic progression (iCPD) as defined above, but the participant is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered following consultation with the Sponsor. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 1.3 and submitted to the central imaging vendor.

10.6.8 Detection of Progression at Visits After Pseudoprogression Resolves

After resolution of pseudoprogression (ie, achievement of iSD/iPR/iCR), iUPD is indicated by any of the following events:

- Target lesions
  - Sum of diameters reaches the PD threshold (≥20% and ≥5 mm increase from nadir) either for the first time, or after resolution of previous pseudoprogression. The nadir is always the smallest sum of diameters seen during the entire study, either before or after an instance of pseudoprogression.

- Non-target lesions
  - If non-target lesions have never shown unequivocal progression, their doing so for the first time results in iUPD.
  - If non-target lesions have shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of non-target 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 non-target 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 Imaging above) is repeated. Progression must be confirmed before iCPD can occur.

The decision process is identical to the iUPD confirmation process for the initial PD, with one exception: if new lesions occurred at a prior instance of iUPD, and at the confirmatory imaging the burden of new lesions has increased from its smallest value (for new target lesions, the sum of diameters is ≥ 5 mm increased from its nadir), 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 a confirmatory factor causes iCPD.

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

10.7 Appendix 7: Country-Specific Requirements

10.7.1 Germany

Section 1.3.1 SoA – Adjuvant Treatment Period With Primary Debulking Followed by Maintenance

Primary Debulking Followed by Adjuvant Treatment and Maintenance														
Study Period	**Screening**		**Treatment (C1 – C6) Maintenance (C7+)[a] (3-Week Cycles)**							**EOT**	**Posttreatment Visits**			**Notes**
Treatment Cycle	**Screen[b]**	**Lead-in**	**1**	**2**	**3**	**4**	**5**	**6**	**7+**	**DC**	**Safety FU[c]**	**Efficacy FU[d]**	**Survival FU**	**The Screening Period is a total of 56 days, which includes the 21-day Lead-in Period and an optional 7-day recovery period during or following lead-in chemotherapy. Maintenance is only for participants without radiographic evidence of disease progression. Participant must have SD, PR, CR, non-PD in order to enter maintenance.**
Scheduling Window (Days):	**–56 to start of lead-in**	**Start of lead-in to –1**	**– 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC**	**30 Days After Last Dose (+ 7)**	**Q9W, Q12W, or Q24W post DC (± 7)[e]**	**Q12W (± 7)**	
Safety Procedures														
Pregnancy test - WOCBP only	X	X	X	X	X	X	X	X	X	X	X			WOCBP require a negative pregnancy test within either 24 hours (urine) or 72 hours (serum) prior to starting lead-in chemotherapy and again within either 24 hours (urine) or 72 hours (serum) prior to C1D1 as outlined in Appendix 3. More frequent pregnancy testing may be performed if required by local regulations or clinically indicated.
HIV / HBV / HCV	X													Testing required

Section 1.3.2 SoA – Neoadjuvant/Adjuvant Treatment Period With Interval Debulking Followed by Maintenance

Neoadjuvant / Adjuvant Treatment Period with Interval Debulking Followed by Maintenance															
Study Period	**Screening**		**Treatment (C1 – C6) Maintenance (C7+)[a] (3-Week Cycles)**								**EOT**	**Posttreatment Visits**			**Notes**
Treatment Cycle	**Screen [b]**	**Lead-in**	**1**	**2**	**SURGERY**	**3**	**4**	**5**	**6**	**7+**	**DC**	**Safety FU[c]**	**Efficacy FU[d]**	**Survival FU**	**The Screening Period is a total of 56 days, which includes the 21-day Lead-in Period and an optional 7-day recovery period following lead-in chemotherapy. Maintenance is only for participants without radiographic evidence of disease progression. Participant must have SD, PR, CR, or non-PD in order to enter maintenance.**
Scheduling Window (Days):	**-56 to start of lead-in**	**Start of lead-in to -1**	**– 3**	**± 3**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC**	**30 Days After Last Dose (+ 7)**	**Q9W, Q12W, or Q24W post DC (± 7)[e]**	**Q12W (± 7)**	
Safety Procedures															
Pregnancy test - WOCBP only	X	X	X	X		X	X	X	X	X	X	X			WOCBP require a negative pregnancy test within either 24 hours (urine) or 72 hours (serum) prior to starting lead-in chemotherapy and again within either 24 hours (urine) or 72 hours (serum) prior to C1D1 as outlined in Appendix 3. More frequent pregnancy testing may be performed if required by local regulations or clinically indicated.
HIV / HBV / HCV	X														Testing is required

Section 5.2 Exclusion Criteria

17. Participant has a known history of human immunodeficiency virus (HIV) infection. Testing for HIV is required at screening.
18. Participant has a known history of hepatitis B (defined as hepatitis B surface antigen [HBsAg] reactive) or known active hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection. Testing for hepatitis B or hepatitis C is required at screening. *Note: Participants with a history of hepatitis B but who are HBsAg negative are eligible for the study.*

Section 8.11.1 – Screening

- Laboratory tests are to be performed within 7 days prior to the initiating chemotherapy in the Lead-in Period. An exception is HIV and hepatitis testing which may be done up to 56-day Screening Period prior to randomization.
- For women of reproductive potential, a pregnancy test (urine or serum) will be performed within either 24 hours (urine) or 72 hours (serum) prior to initiating chemotherapy during the Lead-in Period and within either 24 hours (urine) or 72 hours (serum) prior to Day 1 of Cycle 1. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory). Monthly pregnancy testing should be conducted per local regulation.

Appendix 3: Contraceptive Guidance and Pregnancy Testing

Pregnancy Testing

Monthly pregnancy testing should be performed as per local regulations.

Appendix 5: Clinical Laboratory Tests

Other Screening Tests: Serology (HIV RNA, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody).

10.7.2 United Kingdom

Section 1.3.1 SoA – Adjuvant Treatment Period With Primary Debulking Followed by Debulking

Primary Debulking Followed by Adjuvant Treatment and Maintenance														
Study Period	**Screening**		**Treatment (C1 – C6) Maintenance (C7+)[a] (3-Week Cycles)**							**EOT**	**Posttreatment Visits**			**Notes**
Treatment Cycle	**Screen[b]**	**Lead-in**	**1**	**2**	**3**	**4**	**5**	**6**	**7+**	**DC**	**Safety FU[c]**	**Efficacy FU[d]**	**Survival FU**	**The Screening Period is a total of 56 days, which includes the 21-day Lead-in Period and an optional 7-day recovery period during or following lead-in chemotherapy. Maintenance is only for participants without radiographic evidence of disease progression. Participant must have SD, PR, CR, or non-PD in order to enter maintenance.**
Scheduling Window (Days):	**–56 to start of lead-in**	**Start of lead-in to –1**	**– 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC**	**30 Days After Last Dose (+ 7)**	**Q9W, Q12W, or Q24W post DC (± 7)[e]**	**Q12W (± 7)**	
Safety Procedures														
HIV / HBV / HCV	X													Testing required

Section 1.3.2 SoA – Neoadjuvant/Adjuvant Treatment Period With Interval Debulking Followed by Maintenance

Neoadjuvant / Adjuvant Treatment Period with Interval Debulking Followed by Maintenance															
Study Period	**Screening**		**Treatment (C1 – C6) Maintenance (C7+)[a] (3-Week Cycles)**								**EOT**	**Posttreatment Visits**			**Notes**
Treatment Cycle	**Screen [b]**	**Lead-in**	**1**	**2**	**SURGERY**	**3**	**4**	**5**	**6**	**7+**	**DC**	**Safety FU[c]**	**Efficacy FU[d]**	**Survival FU**	**The Screening Period is a total of 56 days, which includes the 21-day Lead-in Period and an optional 7-day recovery period during or following lead-in chemotherapy. Maintenance is only for participants without radiographic evidence of disease progression. Participant must have SD, PR, CR, or non-PD in order to enter maintenance.**
Scheduling Window (Days):	**-56 to start of lead-in**	**Start of lead-in to -1**	**– 3**	**± 3**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC**	**30 Days After Last Dose (+ 7)**	**Q9W, Q12W, or Q24W post DC (± 7)[e]**	**Q12W (± 7)**	
Safety Procedures															
HIV / HBV / HCV	X														Testing is required

Section 5.2 Exclusion Criteria

17. Participant has a known history of human immunodeficiency virus (HIV) infection. Testing for HIV is required at screening.
18. Participant has a known history of hepatitis B (defined as hepatitis B surface antigen [HBsAg] reactive) or known active hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection. Testing for hepatitis B or hepatitis C is required at screening. *Note: Participants with a history of hepatitis B but who are HBsAg negative are eligible for the study.*

Section 6.5.1 Prohibited Concomitant Medications

6. Live vaccines within 30 days prior to the first dose of study treatment on Day 1 of Cycle 1, while participating in the study, and within 90 days of the last dose of study medication.
    - Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chickenpox, yellow fever, intranasal seasonal influenza, rabies, BCG, and typhoid (oral).
    - Note: Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed.

Section 8.11.1 – Screening

- Laboratory tests are to be performed within 7 days prior to the initiating chemotherapy in the Lead-in Period. An exception is HIV and hepatitis testing which may be done up to 56-day Screening Period prior to randomization.

Appendix 5: Clinical Laboratory Tests

Other Screening Tests: Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody).

10.7.3 France

Section 1.3.1 SoA – Adjuvant Treatment Period With Primary Debulking Followed by Maintenance

Primary Debulking Followed by Adjuvant Treatment and Maintenance														
Study Period	**Screening**		**Treatment (C1 – C6) Maintenance (C7+)[a] (3-Week Cycles)**							**EOT**	**Posttreatment Visits**			**Notes**
Treatment Cycle	**Screen[b]**	**Lead-in**	**1**	**2**	**3**	**4**	**5**	**6**	**7+**	**DC**	**Safety FU[c]**	**Efficacy FU[d]**	**Survival FU**	**The Screening Period is a total of 56 days, which includes the 21-day Lead-in Period and an optional 7-day recovery period during or following lead-in chemotherapy. Maintenance is only for participants without radiographic evidence of disease progression. Participant must have SD, PR, CR, non-PD in order to enter maintenance.**
Scheduling Window (Days):	**–56 to start of lead-in**	**Start of lead-in to –1**	**– 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC**	**30 Days After Last Dose (+ 7)**	**Q9W, Q12W, or Q24W post DC (± 7)**	**Q12W (± 7)**	
Safety Procedures														
Pregnancy test - WOCBP only	X	X	X	X	X	X	X	X	X	X	X			WOCBP require a negative pregnancy test within either 24 hours (urine) or 72 hours (serum) prior to starting lead-in chemotherapy and again within either 24 hours (urine) or 72 hours (serum) prior to C1D1 as outline in Appendix 3. Monthly pregnancy testing is required.
HIV	X													Testing is required at screening if mandated by local health authority
HBV/HCV	X													Testing is required

Section 1.3.2 SoA – Neoadjuvant/Adjuvant Treatment Period With Interval Debulking Followed by Maintenance

Neoadjuvant / Adjuvant Treatment Period with Interval Debulking Followed by Maintenance															
Study Period	**Screening**		**Treatment (C1 – C6) Maintenance (C7+)[a] (3-Week Cycles)**								**EOT**	**Posttreatment Visits**			**Notes**
Treatment Cycle	**Screen [b]**	**Lead-in**	**1**	**2**	**SURGERY**	**3**	**4**	**5**	**6**	**7+**	**DC**	**Safety FU[c]**	**Efficacy FU[d]**	**Survival FU**	**The Screening Period is a total of 56 days, which includes the 21-day Lead-in Period and an optional 7-day recovery period during or following lead-in chemotherapy. Maintenance is only for participants without radiographic evidence of disease progression. Participant must have SD, PR, CR, or non-PD in order to enter maintenance.**
Scheduling Window (Days):	**-56 to start of lead-in**	**Start of lead-in to -1**	**– 3**	**± 3**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC**	**30 Days After Last Dose (+ 7)**	**Q9W, Q12W, or Q24W post DC (± 7)[e]**	**Q12W (± 7)**	
Safety Procedures															
Pregnancy test - WOCBP only	X	X	X	X		X	X	X	X	X	X	X			WOCBP require a negative pregnancy test within either 24 hours (urine) or 72 hours (serum) prior to starting lead-in chemotherapy and again within either 24 hours (urine) or 72 hours (serum) prior to C1D1. Monthly pregnancy testing is required.
HIV	X														Testing is required at screening if mandated by local health authority
HBV/HCV	X														Testing is required

Section 5.1 Inclusion Criteria

Female participants:

8. A female participant is eligible to participate if she is not pregnant (see Appendix 3), not breastfeeding, and at least 1 of the following conditions applies:

   a) Not a woman of childbearing potential (WOCBP) as defined in Appendix 3

   OR

   b) A WOCBP who agrees to follow the contraceptive guidance in Appendix 3 during the Treatment Period and for at least 120 days following the last dose of pembrolizumab (or pembrolizumab placebo), at least 30 days following the last dose of olaparib (or olaparib placebo), and at least 210 days following the last dose of chemotherapy or bevacizumab (if administered).

Section 5.2 Exclusion Criteria

18. Participant has a known history of hepatitis B (defined as hepatitis B surface antigen [HBsAg] reactive) or known active hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection. Testing for hepatitis B or hepatitis C is required at screening.

    Note: Participants with a history of hepatitis B but who are HBsAg negative are eligible for the study.

37. Participant has a hypersensitivity to Chinese hamster ovary (CHO) cell products or other recombinant human or humanized antibodies.

    Note: This only applies to participants who will receive bevacizumab.

Section 6.6.1.1 Dose Modification and Toxicity Management for Immune-Related AEs Associated With Pembrolizumab or Placebo

- Permanent discontinuation of pembrolizumab/pembrolizumab placebo is required for Grade 4 or confirmed cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).

Section 8.11.1 – Screening

- For women of reproductive potential, a pregnancy test (urine or serum) will be performed within either 24 hours (urine) or 72 hours (serum) prior to initiating chemotherapy during the Lead-in Period and within either 24 hours (urine) or 72 hours (serum) prior to Day 1 of Cycle 1. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory). Monthly pregnancy testing is required.

Appendix 3: Contraceptive Guidance and Pregnancy Testing

Participants of childbearing potential must adhere to the contraception requirement (Appendix 3) from the day of study treatment initiation (or 14 days prior to the initiation of study treatment for oral contraception) throughout the study period up to 120 days following the last dose of pembrolizumab (or pembrolizumab placebo), up to 30 days following the last dose of olaparib (or olaparib placebo), and up to 210 days following the last dose of chemotherapy or bevacizumab (if administered).

Pregnancy Testing

Monthly pregnancy testing is required.

Appendix 5: Clinical Laboratory Tests

Screening Tests: Serology (HIV RNA [if required], hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody).

10.7.4 Japan

Section 6.1 Treatments Administered

Table 2 Study Treatment(s)

Study Treatment Name	Dose Formula-tion	Unit Dose Strength(s)	Dosage Level(s)	Route of Adminis-tration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP/ NIMP[a]	Sourcing
Placebo for pembrolizumab	Solution for infusion	N/A	N/A	IV	Q3W; Day 1 of each 3-week cycle	Placebo	IMP	Local

Intravenous solution, not provided by the Sponsor, as placebo for pembrolizumab in this protocol is not categorized as “product(s) used in the clinical trial”.

10.8 Appendix 8: Abbreviations

Abbreviation	Definition
ADL	activities of daily living
ADP	adenosine diphosphate
AE	adverse event
ALT	alanine aminotransferase
AML	acute myeloid leukemia
APaT	All Participants as Treated
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BCG	Bacillus Calmette–Guérin
BICR	blinded independent central review
BID	twice daily
BRCA	breast cancer
BRCA1/2	breast cancer susceptibility gene 1/2
*BRCA*mut	breast cancer susceptibility gene mutated
CA-125	cancer antigen-125
CD	cluster of differentiation
CEA	cancer embryonic antigen
CFR	Code of Federal Regulations
CI	confidence interval
CPS	combined positive score
CR	complete response
CRF	case report form
CrCl	creatinine clearance
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor deoxyribonucleic acid
CTLA-4	cytotoxic T-lymphocyte-associated antigen-4
CTR	Clinical Trial Regulation
CYP	cytochrome P450
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
DSB	double-strand break
ECG	electrocardiogram

Abbreviation	Definition
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
eDMC	external data monitoring committee
EEA	European Economic Area
ELISA	enzyme-linked immunoassay
EMA	European Medicines Agency
EOC	epithelial ovarian cancer
CCI [redacted]	
ESMO	European Society for Medical Oncology
FDA	US Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FFPE	formalin-fixed paraffin-embedded
FIGO	International Federation of Gynecology and Obstetrics
FSH	follicle-stimulating hormone
FSR	First site ready
G-CSF	granulocyte colony-stimulating factor
g*BRCA*mut	germline breast cancer susceptibility gene 1/2 mutation
GCIG	Gynecologic Cancer Intergroup
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GHS	global health status
GI	gastrointestinal
GM-CSF	granulocyte-monocyte colony-stimulating factor
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HGSC	high-grade serous carcinoma
HIV	human immunodeficiency virus
HR	hazard ratio
HRD	homologous recombination repair-deficient
HRQoL	health-related quality-of-life
HRR	homologous recombination repair
HRT	hormone replacement therapy
IB	investigator's brochure
IC1%	1% of immune cells

Abbreviation	Definition
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
iCPD	Modified Response Evaluation Criteria 1.1 for immune-based therapeutics confirmed progressive disease
iCR	Modified Response Evaluation Criteria 1.1 for immune-based therapeutics confirmed complete response
ICSR	individual case safety report
IDS	interval debulking surgery
IEC	Independent Ethics Committee
Ig	immunoglobulin
IHC	immunohistochemistry
IMP	investigational medicinal product
IO	immune-oncology
iPR	Modified Response Evaluation Criteria 1.1 for immune-based therapeutics confirmed partial response
irAE	immune-related adverse event
IRB	Institutional Review Board
iRECIST	Modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics
IRT	Interactive response technology
iSD	Modified Response Evaluation Criteria 1.1 for immune-based therapeutics confirmed stable disease
ITT	intention-to-treat
iUPD	Modified Response Evaluation Criteria 1.1 for immune-based therapeutics unconfirmed progressive disease
IV	intravenous(ly)
IVD	in vitro diagnostic
lsmean	least square mean
MDS	myelodysplastic syndrome
MRI	magnetic resonance imaging
mRNA	messenger RNA
MSI	microsatellite instability
NCI	National Cancer Institute
NED	no evidence of disease
NHEJ	nonhomologous end-joining
NSCLC	non-small cell lung cancer

Abbreviation	Definition
OC	ovarian cancer
OME	other important medical event
ORR	objective response rate
OS	overall survival
PARP	poly(adenosine-ribose) polymerase
pCR	pathological complete response
PD	progressive disease
PD-1	programmed cell death 1
PD-L1	programmed cell death 1 ligand 1
PD-L2	programmed cell death 1 ligand 2
PDLC	predefined limits of change
PDS	primary debulking surgery
PFS	progression-free survival
PFS2	progression-free survival after second-line treatment
PK	pharmacokinetics
PLD	pegylated liposomal doxorubicin
PR	partial response
CCI [redacted]	
Q3W	every 3 weeks
QLQ-C30	Quality-of-Life Questionnaire Core 30
QLQ-OV28	Ovarian Cancer-Specific Quality-of-Life Questionnaire
QoL	quality-of-life
QW	once weekly
R0	no residual tumor following primary debulking
R1	residual tumor following primary debulking
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RNA	ribonucleic acid
SAE	serious adverse event
SD	stable disease
SGCTG	Scottish Gynaecological Cancer Trials Group
SHP	src homology region 2 domain-containing phosphatase
SLAB	supplemental laboratory test(s)
SNP	single nucleotide polymorphism
SoA	Schedule of Assessments
SOC	standard of care
sSAP	supplemental Statistical Analysis Plan

Abbreviation	Definition
SSB	single-strand break
SUSAR	suspected unexpected serious adverse reaction
TDT	time to discontinuation of study treatment or death
TFST	time to first subsequent anticancer treatment
TIL	tumor-infiltrating lymphocytes
TSST	time to second subsequent anticancer treatment
TWiST	time without symptoms of disease progression or toxicity of treatment
ULN	upper limit of normal
US	United States
WOCBP	woman of childbearing potential
WPGSD	Weighted Parametric Group Sequential Design
wt	wild type

10.9 Appendix 9: Assessment of Response in Ovarian Cancer by Gynecologic Cancer Intergroup (CGIG) Criteria

Because of the pelvic location of the primary tumor in patients with OC and the frequent occurrence of peritoneal disease, imaging may not always be reliable for documentation of PD in patients with OC. Criteria other than RECIST may be applicable to define PD in these patients. For this protocol, the Gynecologic Cancer Intergroup (GCIG) criteria for disease progression will also be considered for patients with OC [Rustin, G. J., et al 2011]. Based on these criteria, PD may also be determined if at least 1 of the following criteria is met:

1. Additional diagnostic tests (eg, histology/cytology, ultrasound techniques, endoscopy, positron emission tomography) identify new lesions or determine existing lesions qualify for unequivocal PD AND CA-125 progression according to GCIG criteria:

   An increase in CA-125 either ≥2 × the normal value or ≥2 × the lowest level it has been during the study
2. Definitive clinical signs and symptoms of PD unrelated to non-malignant or iatrogenic causes ([a] intractable cancer-related pain; [b] malignant bowel obstruction/worsening dysfunction; or [c] unequivocal symptomatic worsening of ascites or pleural effusion) AND CA-125 progression according to GCIG criteria:

   An increase in CA-125 either ≥2 × the normal value or ≥2 × the lowest level it has been during the study

Abnormal CA-125 levels on study do not represent disease progression; however, they may prompt imaging if clinically indicated. Progressive disease will not be diagnosed in case of CA-125 progression in the absence of at least 1 of the criteria defined above.

The investigator will describe how PD was diagnosed in the eCRF.

The date of PD is defined as the earliest time point when one of the PD criteria is met. If CT/MRI shows existing (baseline) lesions that only equivocally suggest PD and additional diagnostic tests are required to determine unequivocal PD, the official date of PD will be the date PD was unequivocally determined. Alternatively, with new lesions (except ascites and effusions) that are initially equivocal that are later unequivocally determined, the date of progression will be the date the lesion was initially identified.

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

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CCI

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