Official Protocol Title:	A Phase 3, Randomized, Double-Blind Study of Pembrolizumab versus Placebo in Combination With Paclitaxel With or Without Bevacizumab for the Treatment of Platinum-resistant Recurrent Ovarian Cancer (KEYNOTE-B96 / ENGOT-ov65)
NCT number:	NCT05116189
Document Date:	31-Jan-2024

TITLE PAGE

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Protocol Title: A Phase 3, Randomized, Double-Blind Study of Pembrolizumab versus Placebo in Combination With Paclitaxel With or Without Bevacizumab for the Treatment of Platinum-resistant Recurrent Ovarian Cancer (KEYNOTE-B96 / ENGOT-ov65)

Protocol Number: B96-04 / ENGOT-ov65

Compound Number: MK-3475

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

Legal Registered Address:

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

Regulatory Agency Identifying Number(s):

NCT	NCT05116189
EU CT	2023-506177-35
EudraCT	2020-005027-37
JRCT	jRCT2051210184
WHO	Not applicable
UTN	Not applicable
IND	126,191

Approval Date: 31 January 2024

Sponsor Signatory

Typed Name: Title:	Date

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

Investigator Signatory

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

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 04/ Global Amendment	31-JAN-2024	To update the target number of events for the interim/final analyses and sample size and power calculations to reflect the actual PD-L1 CPS prevalence within the study based on blinded data review.
Amendment 03/ Global Amendment	22-JUN-2022	To add collection of blood samples for pembrolizumab PK and ADA/NAb analysis for participants receiving bevacizumab due to Health Authority request, to provide additional clarifications for inclusion/exclusion criteria, and to change the Sponsor entity name and address.
Amendment 02/ Germany-specific Amendment	22-DEC-2021	To clarify in the Schedule of Assessments that pregnancy testing is to continue in posttreatment for 120 days after the last dose of pembrolizumab/placebo or 180 days after the last dose of paclitaxel, docetaxel (if applicable), or bevacizumab (if using) and to remove the contraceptive language from the Germany country-specific appendix that was incorrectly included.
Amendment 01/ Japan-specific Amendment	13-OCT-2021	To indicate docetaxel as IMP in Japan, and permit a starting dose for docetaxel (if using) of 70 mg/m^2 for Japanese participants.
Original Protocol	27-JUL-2021	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 04

Overall Rationale for the Amendment:

To update the target number of events for the interim/final analyses and sample size and power calculations to reflect the actual PD-L1 CPS prevalence within the study based on blinded data review.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
Section 9.1 Statistical Analysis Plan Summary	The target number of events for the interim/final analyses and sample size and power calculations were updated to reflect the actual PD-L1 CPS prevalence within the study based on blinded data review.	To align with new data.

Section Number and Name	Description of Change	Brief Rationale
Additional Changes		
Throughout	The structure of the protocol has been updated.	To comply with current industry regulations and guidelines. This restructuring does not affect the clinical or regulatory integrity of the protocol. All other changes and their reasons are included for completeness.
Title Page	The NCT number was added.	To include all available and applicable regulatory agency numbers.
	The EU CT number was added.	See rationale for Title Page (NCT number).
	The jRCT number was added.	See rationale for Title Page (NCT number).
Section 1.1 Synopsis	Indication: The indication was updated to ovarian cancer recurrent.	To align with MedDRA coding.
Section 1.3 Schedule of Activities	A statement referring to Table 1 and Table 2 was added.	To correctly cite tables in text.

Section Number and Name	Description of Change	Brief Rationale
Section 1.3.1 First Course Treatment	Table 1: An "X" was added to the Cycle 1 column of the ECOG performance status row and the related note in the comments column was clarified.	To accurately depict the intended collection timepoints.
	Table 1: An "X" was added to the Cycle 1 column of the chemistry row and the related note in the comments column was clarified.	See rationale for Section 1.3.1 (ECOG).
	Table 1: An "X" was added to the Cycle 1 column of the hematology row and the related note in the comments column was clarified.	See rationale for Section 1.3.1 (ECOG).
	Table 1: An "X" was added to the Cycle 1 column of the urinalysis (for participants receiving bevacizumab) row and the related note in the comments column was clarified.	See rationale for Section 1.3.1 (ECOG).
Section 1.3.2 Second Course (Retreatment)	Table 2: Details of pregnancy test requirements posttreatment were added to the comments column of the pregnancy test row.	To correct a previous erroneous omission.
	Table 2: An "X" was added to the Cycle 1 column of the urinalysis row.	See rationale for Section 1.3.2 (pregnancy test requirements).
Section 4.4 Beginning and End-of-Study Definition	The description of lost to follow-up was replaced with a citation to Section 7.3.	To allow a participant to be considered lost to follow-up as appropriate for the study.
Section 5.2 Exclusion Criteria	Exclusion Criterion 21: A statement referring to Appendix 7 was added.	See rationale for Section 1.3.2 (pregnancy test requirements).
	Exclusion Criterion 22: A statement referring to Appendix 7 was added.	See rationale for Section 1.3.2 (pregnancy test requirements).
Section 6.1 Study Intervention(s) Administered	Table 4: The descriptions for the dose formulations for pembrolizumab, paclitaxel, docetaxel, bevacizumab, and placebo were updated to Solution.	To align with ISO standards.
	Table 4: A note regarding duration of treatment with paclitaxel and bevacizumab was added.	To align with the rest of the protocol.
Section 7.3 Lost to Follow-up	The definition for when a participant is considered lost to follow-up and how the missing data will be handled were deleted.	See rationale for Section 4.4.
Section 9.7.1 Efficacy Interim Analysis	Table 11: The target number of events for the interim/final analyses and sample size and power calculations were updated to reflect the actual PD-L1 CPS prevalence within the study based on blinded data review.	See rationale for Section 9.1.
Section 9.8.1 Progression-free Survival	Table 12:The target number of events for the interim/final analyses and sample size and power calculations were updated to reflect the actual PD-L1 CPS prevalence within the study based on blinded data review.	See rationale for Section 9.1.

Section Number and Name	Description of Change	Brief Rationale
Section 9.8.2 Overall Survival	Table 13: The target number of events for the interim/final analyses and sample size and power calculations were updated to reflect the actual PD-L1 CPS prevalence within the study based on blinded data review.	See rationale for Section 9.1.
Section 9.9 Sample Size and Power Calculations	The target number of events for the interim/final analyses and sample size and power calculations were updated to reflect the actual PD-L1 CPS prevalence within the study based on blinded data review.	See rationale for Section 9.1.
Section 10.3.2 Definition of AE	Reference to Sponsor's product was removed.	To align terminology throughout the protocol.
Section 10.3.5 Recording AE and SAE	References to Sponsor's product were replaced with study intervention.	See rationale for Section 10.3.2.
Section 10.7.5 Japan	The Japan-specific requirement regarding the bevacizumab dosing regimen was updated to include the newly approved, 10-mg/kg Q2W bevacizumab dosing regimen in Japan.	To allow participants in Japan the option to receive either of the bevacizumab dosing regimens now approved for treatment of ovarian cancer in Japan.
	The Japan-specific requirement regarding the docetaxel dose was updated to refer to Section 4.3.2 instead of Section 4.3.3.	To correct a previous error.
Throughout document	Minor administrative, formatting, grammatical, and/or typographical changes were made throughout the document.	To ensure clarity and accurate interpretation of the intent of the protocol.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3, Randomized, Double-Blind Study of Pembrolizumab versus Placebo in Combination With Paclitaxel With or Without Bevacizumab for the Treatment of Platinum-resistant Recurrent Ovarian Cancer (KEYNOTE-B96 / ENGOT-ov65)

Short Title: Pembrolizumab/placebo plus paclitaxel with or without bevacizumab for platinum-resistant recurrent ovarian cancer

Acronym: KEYNOTE-B96

Hypotheses, Objectives, and Endpoints:

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

Throughout this protocol, the term Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 refers to the modification of RECIST 1.1 to include a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Refer to Section 4.2.1.1 for additional details.

In female participants with platinum-resistant recurrent ovarian cancer who have received ≤2 prior lines of therapy:

Primary Objective	**Primary Endpoint**
To compare pembrolizumab plus paclitaxel with or without bevacizumab to placebo plus paclitaxel with or without bevacizumab, with respect to progression-free survival (PFS) per RECIST 1.1 as assessed by the investigator Hypothesis (H1): pembrolizumab plus paclitaxel with or without bevacizumab is superior to placebo plus paclitaxel with or without bevacizumab, with respect to PFS per RECIST 1.1 as assessed by the investigator for participants with programmed cell death ligand 1 (PD-L1) positive tumors (Combined Positive Score [CPS] ≥1) Hypothesis (H2): pembrolizumab plus paclitaxel with or without bevacizumab is superior to placebo plus paclitaxel with or without bevacizumab, with respect to PFS per RECIST 1.1 as assessed by the investigator for all participants	PFS: The time from randomization to the first documented disease progression or death due to any cause, whichever occurs first

Secondary Objectives	Secondary Endpoints
To compare pembrolizumab plus paclitaxel with or without bevacizumab to placebo plus paclitaxel with or without bevacizumab, with respect to overall survival (OS) Hypothesis (H3): Pembrolizumab plus paclitaxel with or without bevacizumab is superior to placebo plus paclitaxel with or without bevacizumab, with respect to OS for participants with PD-L1 positive tumors (CPS ≥1) Hypothesis (H4): Pembrolizumab plus paclitaxel with or without bevacizumab is superior to placebo plus paclitaxel with or without bevacizumab, with respect to OS for all participants	OS: The time from randomization to death due to any cause
To compare pembrolizumab plus paclitaxel with or without bevacizumab to placebo plus paclitaxel with or without bevacizumab, with respect to PFS per RECIST 1.1 by blinded independent central review (BICR) for participants with PD-L1 positive tumors (CPS ≥1) and all participants	PFS
To evaluate the safety and tolerability of pembrolizumab in combination with paclitaxel with or without bevacizumab	-Adverse events (AEs) -Study treatment discontinuation due to AEs
To compare pembrolizumab plus paclitaxel with or without bevacizumab to placebo plus paclitaxel with or without bevacizumab, with respect to 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 (GI) symptoms using the EORTC Ovarian Cancer-Specific Quality of Life Questionnaire (QLQ-OV28) abdominal/GI symptom scale for participants with PD-L1 positive tumors (CPS ≥1) and all participants	Change from baseline and time to deterioration (TTD) of the QoL and symptom scores from the GHS/QoL scale (items 29 and 30) of the EORTC QLQ-C30 and the abdominal/GI symptom scale (items 31 to 36) of the EORTC QLQ-OV28

Overall Design:

Study Phase	Phase 3
Primary Purpose	Treatment
Indication	Ovarian cancer recurrent
Population	Participants with platinum-resistant recurrent ovarian cancer who have received ≤2 prior lines of therapy
Study Type	Interventional
Intervention Model	Parallel This is a multi-site study.
Type of Control	Placebo
Study Blinding	Double-blind
Blinding Roles	Participants or Subjects Investigator Outcomes Assessor Sponsor
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 65 months from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact. Extension Portion of the Study in China: The study may remain open longer than 65 months to complete an extension portion of the study in China.

Number of Participants:

Approximately 616 eligible participants are expected to be randomized to 1 of 2 treatment arms as described in Section 6.3.1. Crossover between treatment arms is not permitted.

Intervention Groups and Duration:

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/Treatment Period	Use
Arm 1	Pembrolizumab (MK-3475)	25 mg/mL	400 mg	IV Infusion	Q6W for 18 cycles	Test Product
Arm 1	Paclitaxel	Variable	80 mg/m^2	IV Infusion	Days 1, 8, 15 of each Q3W cycle until disease progression or prohibitive toxicity	Background Treatment
Arm 1	Docetaxel (in place of paclitaxel, only after Sponsor consultation)	Variable	75 mg/m^2	IV Infusion	Q3W until disease progression or prohibitive toxicity	Background Treatment
Arm 1	Bevacizumab (if using)	25 mg/mL	10 mg/kg	IV Infusion	Optional, Q2W until disease progression or prohibitive toxicity	Background Treatment
Arm 2	Placebo	Normal Saline or Dextrose	0 mg/mL	IV Infusion	Q6W for 18 cycles	Placebo
Arm 2	Paclitaxel	Variable	80 mg/m^2	IV Infusion	Days 1, 8, 15 of each Q3W cycle until disease progression or prohibitive toxicity	Background Treatment
Arm 2	Docetaxel (in place of paclitaxel, only after Sponsor consultation)	Variable	75 mg/m^2	IV Infusion	Q3W until disease progression or prohibitive toxicity	Background Treatment
Arm 2	Bevacizumab (if using)	25 mg/mL	10 mg/kg	IV Infusion	Optional, Q2W until disease progression or prohibitive toxicity	Background Treatment

Abbreviations: IV=intravenous; QW=weekly; Q2/3/6W=every 2/3/6 weeks.

The unit dose strength for background treatment may vary depending on market availability.

Pembrolizumab/placebo may be administered for a maximum of 18 Q6W cycles. Paclitaxel and bevacizumab may continue until disease progression, prohibitive toxicity, other protocol-defined reasons for discontinuation, or the participant has received the maximum duration (if applicable) per the respective approved labels or local practice.

Paclitaxel-related toxicities should be managed according to local practice and institutional guidelines with supportive care measures, dose interruptions and reductions before consideration of discontinuation, if clinically appropriate. Docetaxel (75 mg/m^2 Q3W) may be considered for participants who experience either a severe hypersensitivity reaction to paclitaxel or an adverse event requiring discontinuation of paclitaxel only after consultation with the Sponsor. Refer to Appendix 7 for country-specific requirements.

The use of bevacizumab is optional and may be administered to eligible participants at the investigator's discretion. Use of bevacizumab must be decided before randomization as it is a stratification factor. Refer to Section 8.1.8.1.3 for additional information on use of bevacizumab and biosimilars. Refer to Appendix 7 for country-specific requirements.

Other current or former name(s) or alias(es) for study intervention(s) are as follows: MK-3475.

Total Number of Intervention Groups/Arms	2
Duration of Participation	Each participant will participate in the study from the time that the participant provides documented informed consent through the final protocol-specified contact. After a screening phase of up to 28 days, each participant will be assigned to receive study intervention until one of the conditions for discontinuation of study intervention is met. Participants who complete study intervention after receiving 18 administrations of pembrolizumab/placebo (18 Q6W 400 mg infusions), and participants who attain a complete response and stop study intervention may be eligible for up to 9 additional administrations of Q6W pembrolizumab (approximately 1 year) upon experiencing disease progression. After the end of treatment, each participant will be followed for the occurrence of adverse events and spontaneously reported pregnancy. Participants who discontinue for reasons other than radiographic disease progression will have posttreatment follow-up imaging for disease status until any of the conditions for discontinuation of imaging are met. All participants will be followed for overall survival until death, withdrawal of consent, or the end of the study.

Study Governance Committees:

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

Study governance considerations are outlined in Appendix 1.

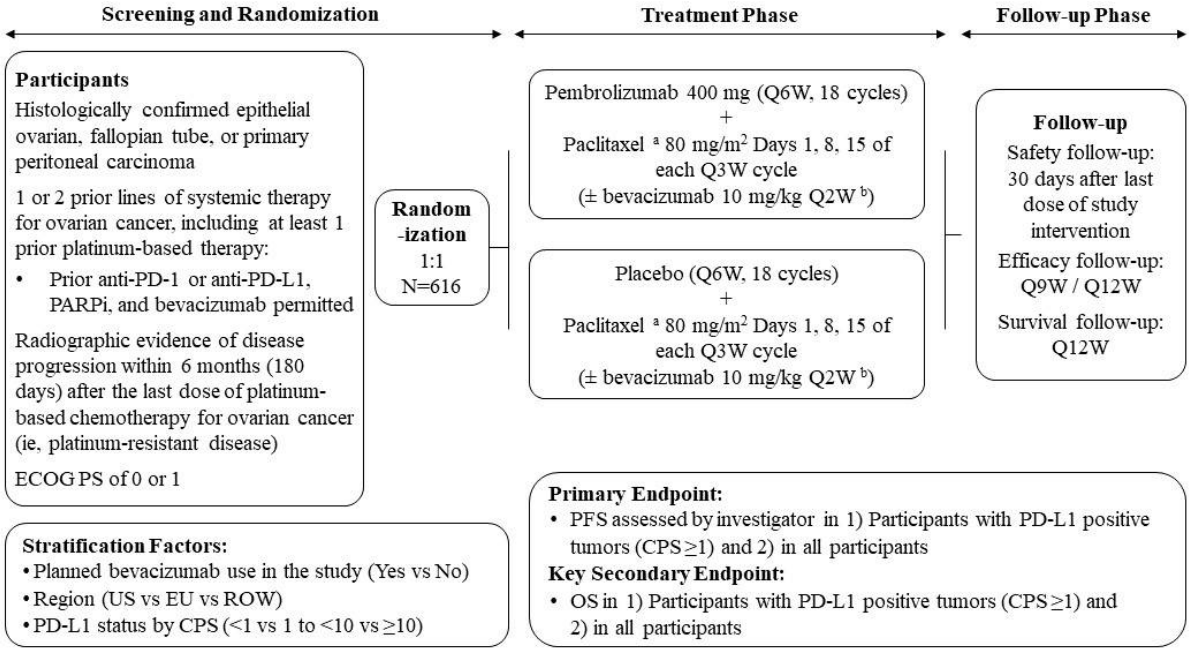
Study Accepts Healthy Participants: No

A list of abbreviations is in Appendix 9.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Diagram



Abbreviations: CPS=combined positive score; ECOG PS =Eastern Cooperative Oncology Group Performance Status; EU=European Union; OS=overall survival; PARPi=poly(adenosine-ribose) polymerase inhibitor; PD-1=programmed cell death 1; PD-L1=programmed cell death 1 ligand 1; PFS=progression-free survival; Q2/3/6/9/12W=every 2/3/6/9/12 weeks; ROW=Rest of World; US=United States.

Pembrolizumab/placebo may only be administered for 18 Q6W cycles. Paclitaxel and/or bevacizumab may continue until disease progression, prohibitive toxicity, other protocol-defined reason for discontinuation or the participant has received the maximum duration (if applicable) per the respective approved label or local practice.

a Paclitaxel-related toxicities should be managed according to local practice and institutional guidelines with supportive care measures, dose interruptions and reductions before consideration of discontinuation, if clinically appropriate. Docetaxel (75 mg/m^2 Q3W) may be considered for participants who experience either a severe hypersensitivity reaction to paclitaxel or an adverse event requiring discontinuation of paclitaxel only after consultation with the Sponsor. Refer to Appendix 7 for country-specific requirements.

b The use of bevacizumab is optional and may be administered to eligible participants at the investigator's discretion. Use of bevacizumab must be decided before randomization as it is a stratification factor. Refer to Appendix 7 for country-specific requirements.

1.3 Schedule of Activities

The schedules of activities for First Course Treatment and Second Course Retreatment are presented in Table 1 and Table 2, respectively.

1.3.1 First Course Treatment

Table 1 First Course Treatment – Study Schedule of Activities

Period	**Screening**	**Study Intervention (Q6W Cycles)[a]**								**EOT**	**Posttreatment**			**Comments**
Cycle		**C1**	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C8+**	**DC**	**Safety follow-up[b]**	**Efficacy follow-up[c]**	**Survival follow-up[d]**	**Note: Window for pembrolizumab/placebo and bevacizumab (if applicable) dosing is ±3 days. Window for paclitaxel dosing is ±1 day, except on C1D1, which has a window of +3 days.**
Scheduling Window	**-28 d to -1 d**	**+3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**		**30 d after last dose (+7 d)**	**Q9W or Q12W (±7 d)**	**Q12W (± 7 d)**	
Administrative Procedures														
Informed consent	X													Rescreened participants do not need to provide additional documented consent if original consent was obtained more than 28 days before C1, unless required per local regulations. Treatment beyond initial radiographic disease progression per RECIST 1.1 requires an additional consent.
Informed Consent for Future Biomedical Research (optional)	X													Participant may participate in main study without signing Future Biomedical Research consent.
Participant ID Card	X	X												Distribute at screening and add the randomization number at the time of randomization
Eligibility Assessment (Inclusion / Exclusion)	X													Screening procedures may be performed on the date of randomization as long as they are performed before randomization.
Demographics	X													
Medical History	X													
Ovarian Cancer History Details	X													Collect disease details including histology, prior treatments, and surgery.
Prior BRCA status	X													Record local results if performed/available.

Period	**Screen-ing**	**Study Intervention (Q6W Cycles)[a]**								**EOT**	**Posttreatment**			**Comments**
Cycle		**C1**	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C8+**	**DC**	**Safety follow-up[b]**	**Efficacy follow-up[c]**	**Survival follow-up[d]**	**Note: Window for pembrolizumab/placebo and bevacizumab (if applicable) dosing is ±3 days. Window for paclitaxel dosing is ±1 day, except on C1D1, which has a window of +3 days.**
Scheduling Window	**-28 d to -1 d**	**+3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**		**30 d after last dose (+7 d)**	**Q9W or Q12W (±7 d)**	**Q12W (± 7 d)**	
Prior HRD status	X													Record local results if performed/available.
Review FIGO (2014) Staging from Initial Diagnosis	X													Refer to Appendix 8.
Prior / Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X		Record medications taken within 28 days before the start of study intervention. Record concomitant medications at every visit that study intervention is administered. Concomitant medications will be recorded for 30 days after last dose. All concomitant medications administered during SAEs or ECIs are to be recorded.
Treatment Eligibility Assessment 1 Form for Bevacizumab	X													The investigator must record whether or not bevacizumab is selected and, if applicable, document the justification for adding bevacizumab to SOC paclitaxel before randomization.
Treatment Eligibility Assessment 2 Form for Bevacizumab	X													The investigator must record whether or not bevacizumab is selected and, if applicable, document the reason why bevacizumab was not selected before randomization.
Randomization (via IRT)		X												First dose of study intervention may be administered up to 3 days after randomization.
Register Visit in IRT	X	X	X	X	X	X	X	X	X	X				Each time drug is dispensed, IRT is to be contacted.
Subsequent Anticancer Treatment										X	X	X	X	Participants should be contacted by telephone to monitor new anticancer treatment if there is no corresponding clinic visit.
Date of Progression on Subsequent Anticancer Treatment											X	X	X	Participants will be followed for PFS2.

Period	Screening	Study Intervention (Q6W Cycles)[a]								EOT	Posttreatment			Comments
Cycle		**C1**	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C8+**	**DC**	**Safety follow-up[b]**	**Efficacy follow-up[c]**	**Survival follow-up[d]**	**Note: Window for pembrolizumab/placebo and bevacizumab (if applicable) dosing is ±3 days. Window for paclitaxel dosing is ±1 day, except on C1D1, which has a window of +3 days.**
Scheduling Window	**-28 d to -1 d**	**+3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**		**30 d after last dose (+7 d)**	**Q9W or Q12W (±7 d)**	**Q12W (± 7 d)**	
Survival Information (Vital Status)		←							→				X	After investigator-determined disease progression or start of new anticancer treatment. In addition, on Sponsor request, participants may be contacted for survival status at any time during the course of the study.
Clinical Assessments														
Adverse Event Monitoring	X	X	X	X	X	X	X	X	X	X	X	X		Report AEs at every visit that study intervention is administered through 30 days after the last dose of study intervention. Report SAEs through 90 days after the last dose of study intervention, or 30 days after the last dose if participant initiates a new anticancer treatment, whichever is earlier.
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X			Perform within 3 days before randomization. If ECOG PS is performed on the day of randomization, it should be performed before randomization. After C1D1, perform on Day 1 of every pembrolizumab/placebo cycle (Q6W) and chemotherapy cycle (Q3W).
Complete Physical Examination	X									X				
Symptom-directed Physical Examination		X	X	X	X	X	X	X	X		X			If a complete physical examination is performed within 3 days before randomization, a symptom-directed physical examination is not required at C1D1. Assess more frequently as clinically indicated.
Vital Signs (temperature, blood pressure, respiratory rate, pulse rate, weight, height [height - screening only])	X	X	X	X	X	X	X	X	X	X	X			Assess during screening and before treatment at the start of every pembrolizumab/placebo cycle (Q6W) and chemotherapy cycle (Q3W). In case of dose interruption or missed dose, assess before restarting treatment. Assess more frequently as clinically indicated.

Period	**Screen-ing**	**Study Intervention (Q6W Cycles)[a]**								**EOT**	**Posttreatment**			**Comments**
Cycle		**C1**	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C8+**	**DC**	**Safety follow-up[b]**	**Efficacy follow-up[c]**	**Survival follow-up[d]**	**Note: Window for pembrolizumab/placebo and bevacizumab (if applicable) dosing is ±3 days. Window for paclitaxel dosing is ±1 day, except on C1D1, which has a window of +3 days.**
Scheduling Window	**-28 d to -1 d**	**+3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**		**30 d after last dose (+7 d)**	**Q9W or Q12W (±7 d)**	**Q12W (± 7 d)**	
Blood Pressure (Additional Assessments Required for Participants Receiving Bevacizumab)		←	—	—	—	—	—	—	→					Measure blood pressure before each bevacizumab administration (Q2W).
12-lead ECG	X													Additional ECGs may be performed as clinically indicated.
Laboratory Assessments for Eligibility and Safety														
HIV / HBV / HCV Eligibility Testing	X													Required only when mandated by local health authority. Refer to Appendix 7 for country-specific requirements.
Urine or Serum Pregnancy Test - WOCBP Only	X	←	—	—	—	—	—	—	→	X	X			WOCBP require a negative pregnancy test within either 24 hours (urine) or 72 hours (serum) before the first dose of study intervention. A pregnancy test must be performed every month during study treatment. Pregnancy testing should continue in posttreatment until 120 days after last dose of pembrolizumab/placebo and 180 days after last dose of paclitaxel, docetaxel (if applicable) and bevacizumab (if using). More frequent pregnancy testing may be performed if required by local regulations or if clinically indicated. Refer to Appendix 7 for country-specific requirements. Home pregnancy tests are acceptable when a scheduled visit does not occur within the month (per local regulation), but the site must make monthly telephone contact with the participant to determine the results of the pregnancy test.

Period	**Screen-ing**	**Study Intervention (Q6W Cycles)[a]**								**EOT**	**Posttreatment**			**Comments**
Cycle		**C1**	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C8+**	**DC**	**Safety follow-up[b]**	**Efficacy follow-up[c]**	**Survival follow-up[d]**	**Note: Window for pembrolizumab/placebo and bevacizumab (if applicable) dosing is ±3 days. Window for paclitaxel dosing is ±1 day, except on C1D1, which has a window of +3 days.**
Scheduling Window	**-28 d to -1 d**	**+3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**		**30 d after last dose (+7 d)**	**Q9W or Q12W (±7 d)**	**Q12W (± 7 d)**	
Serum FSH - WONCBP only	X													Only required for postmenopausal women with <12 months amenorrhea and not currently on HRT or hormonal contraception (see Appendix 5). Confirmation with 2 FSH measurements in the postmenopausal range is required.
PT/INR and aPTT/PTT	X													Perform within 7 days before randomization. Perform more frequently if clinically indicated.
Chemistry	X	X	X	X	X	X	X	X	X	X	X			Perform within 7 days before randomization. After C1D1, perform within 72 hours before treatment on Day 1 of every pembrolizumab/ placebo cycle (Q6W) and chemotherapy cycle (Q3W). In case of dose interruption or missed dose, assess before restarting treatment. Perform more frequently if clinically indicated.
Hematology	X	X	X	X	X	X	X	X	X	X	X			
Urinalysis (for participants not receiving bevacizumab)	X		X		X		X		X	X	X			Perform within 7 days before randomization. After C1, perform within 72 hours before treatment on Day 1 every 2 pembrolizumab/ placebo cycles starting with C2 (ie, C2, 4, 6 etc.). Perform more frequently if clinically indicated.
Urinalysis (for participants receiving bevacizumab)	X	X	X	X	X	X	X	X	X	X	X			Perform within 7 days before randomization. After C1D1, perform within 72 hours before every bevacizumab administration (Q2W). In case of dose interruption or missed dose, assess before restarting treatment. Perform more frequently if clinically indicated.
T3 or FT3, plus FT4 and TSH	X		X	X	X	X	X	X	X	X	X			Perform within 7 days before randomization. Perform within 72 hours before treatment on Day 1 of every cycle starting with C2 (if unavailable, results may be reviewed after dosing).

Period	**Screen-ing**	**Study Intervention (Q6W Cycles)[a]**								**EOT**	**Posttreatment**			**Comments**
Cycle		**C1**	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C8+**	**DC**	**Safety follow-up[b]**	**Efficacy follow-up[c]**	**Survival follow-up[d]**	**Note: Window for pembrolizumab/placebo and bevacizumab (if applicable) dosing is ±3 days. Window for paclitaxel dosing is ±1 day, except on C1D1, which has a window of +3 days.**
Scheduling Window	**-28 d to -1 d**	**+3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**		**30 d after last dose (+7 d)**	**Q9W or Q12W (±7 d)**	**Q12W (± 7 d)**	
Study Intervention Administration														
Pembrolizumab (MK-3475) or placebo (Q6W)		X	X	X	X	X	X	X	X					Maximum of 18 cycles. Window for pembrolizumab/placebo dosing is ±3 days. Pembrolizumab: 400 mg by IV Placebo: normal saline or dextrose by IV.
Paclitaxel[e] (Q3W - D1, D8, D15)		◄———	———	———	———	———	———	———	———►					80 mg/m^2 by IV QW until disease progression, prohibitive toxicity, or other protocol-defined reason for discontinuation. Window for paclitaxel dosing is ±1 day, except on C1D1, which has a window of +3 days. Refer to Section 6.1 for treatment requirements.
Bevacizumab - optional (Q2W)		◄———	———	———	———	———	———	———	———►					10 mg/kg by IV Q2W until disease progression, prohibitive toxicity, or other protocol-defined reason for discontinuation. Bevacizumab use must be selected in IRT before randomization as it is a stratification factor. Window for bevacizumab dosing is ±3 days. Refer to Section 6.1 for treatment requirements. Refer to Appendix 7 for country-specific requirements.

Period	Screen-ing	Study Intervention (Q6W Cycles)[a]								EOT	Posttreatment			Comments
Cycle		C1	C2	C3	C4	C5	C6	C7	C8+	DC	Safety follow-up[b]	Efficacy follow-up[c]	Survival follow-up[d]	**Note: Window for pembrolizumab/placebo and bevacizumab (if applicable) dosing is ±3 days. Window for paclitaxel dosing is ±1 day, except on C1D1, which has a window of +3 days.**
Scheduling Window	-28 d to -1 d	+3 d	±3 d	±3 d	±3 d	±3 d	±3 d	±3 d	±3 d		30 d after last dose (+7 d)	Q9W or Q12W (±7 d)	Q12W (± 7 d)	
Efficacy Assessments														
Tumor Scans – Chest, Abdomen, and Pelvis	X	←	—	—	—	—	—	—	→	X		X		Baseline tumor scans must be obtained within 28 days before randomization. Postrandomization scans will be performed Q9W (±7 d) through Week 54 and Q12W (±7 d) thereafter. All time points are calculated from the date of randomization. Scan timing should follow calendar days and should not be adjusted for delays in cycle starts. Tumor scans are required at EOT if previous scans were performed more than 4 weeks before EOT. If required, EOT scans must be performed before the start of new anticancer treatment. Unscheduled scans may be performed as clinically indicated.
Bone Scan	X	←	—	—	—	—	—	—	→					Required at baseline within 28 days before randomization for participants with a history of bone metastases and/or who are clinically symptomatic. On-study bone scans should be performed if clinically indicated or to confirm CR (if other lesions indicate CR and bone lesions existed at baseline).
Brain Scan	X	←	—	—	—	—	—	—	→					Required at baseline within 28 days before randomization for participants with a history of brain metastases (to confirm stability) or who are clinically symptomatic (to rule out brain metastases). On-study brain scans should be performed if clinically indicated or to confirm CR (if other lesions indicate CR and brain lesions existed at baseline).

Period	**Screen-ing**	**Study Intervention (Q6W Cycles)[a]**								**EOT**	**Posttreatment**			**Comments**
Cycle		**C1**	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C8+**	**DC**	**Safety follow-up[b]**	**Efficacy follow-up[c]**	**Survival follow-up[d]**	**Note: Window for pembrolizumab/placebo and bevacizumab (if applicable) dosing is ±3 days. Window for paclitaxel dosing is ±1 day, except on C1D1, which has a window of +3 days.**
Scheduling Window	**-28 d to -1 d**	**+3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**		**30 d after last dose (+7 d)**	**Q9W or Q12W (±7 d)**	**Q12W (± 7 d)**	
CA-125	X	←	—	—	—	—	—	—	→	X		X		Perform within 7 days before randomization. Sample to be collected at the time of each scheduled tumor scan (±14 days of scheduled scan). An optional sample may be collected at the time of unscheduled scan at the investigator's discretion. Additional assessments may be performed if clinically indicated (eg, suspected progression). All CA-125 testing will be performed locally.
Health-Related Quality of Life (HRQoL)														
EORTC QLQ-C30		X	X	X	X	X	X	X	X	X	X			Administer PROs in the order shown before performing any procedures, assessments, and treatment. Collect at every cycle that pembrolizumab/placebo is scheduled to be administered (ie, Q6W) until completion or discontinuation. Continue to collect PROs Q6W if the participant discontinues pembrolizumab/placebo but continues chemotherapy and/or bevacizumab.
EORTC QLQ-OV28		X	X	X	X	X	X	X	X	X	X			
EQ-5D-5L		X	X	X	X	X	X	X	X	X	X			
Blood and Tissue Sample Collection for Biomarker, Pharmacokinetic, and Immunogenicity Analyses														
Archival or Newly Obtained Tissue Collection	X													Prospective analysis of PD-L1 status is required before randomization.
Blood for Genetic Analysis		X												Collect before administration of first dose of study intervention.

Period	**Screen-ing**	**Study Intervention (Q6W Cycles)[a]**								**EOT**	**Posttreatment**			**Comments**
Cycle		**C1**	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C8+**	**DC**	**Safety follow-up[b]**	**Efficacy follow-up[c]**	**Survival follow-up[d]**	**Note: Window for pembrolizumab/placebo and bevacizumab (if applicable) dosing is ±3 days. Window for paclitaxel dosing is ±1 day, except on C1D1, which has a window of +3 days.**
Scheduling Window	**-28 d to -1 d**	**+3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**		**30 d after last dose (+7 d)**	**Q9W or Q12W (±7 d)**	**Q12W (± 7 d)**	
Blood for ctDNA Analysis		X	X*		X		X	X	X†	X				Collect before administration of first dose of study intervention. Collect at C1D1, C2D1, C2D22, C4D1, C6D1, C7D1. *Collect at both C2D1 and C2D22. †Collect at C9D1 and C10D1. After C10D1, collect at D1 of Q12W (C12, C14, C16, C18). Collect at EOT. An optional sample may be collected at the time of unscheduled visit at the investigator's discretion.
Blood for Pembrolizumab PK		X	X			X								Collect up to 72 hours before pembrolizumab/placebo administration at C1D1, C2D1, C5D1 (only applicable for participants receiving bevacizumab enrolled after approval of Amendment 03).
Blood for Pembrolizumab ADA/NAb		X	X			X								

Abbreviations: ADA=antidrug antibodies; AE=adverse event; aPTT=activated partial thromboplastin time; BRCA=breast cancer gene; C=cycle; CA-125=cancer antigen-125; ctDNA=circulating tumor DNA; d/D=day; DC=discontinuation; ECG=electrocardiogram; ECI=event of clinical interest; ECOG=Eastern Cooperative Oncology Group; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EORTC QLQ-OV28=European Organisation for Research and Treatment of Cancer Ovarian Cancer-Specific Quality of Life Questionnaire; EOT=end of treatment; EQ-5D-5L=European Quality of Life Five-dimension Five-level Scale Questionnaire; FBR=future biomedical research; FIGO=International Federation of Gynecology and Obstetrics; FSH=follicle-stimulating hormone; FT3=free triiodothyronine; FT4=free thyroxine; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; HRD=homologous recombination deficiency; HRQoL=health-related quality of life; HRT=hormone replacement therapy; ID=identification; INR=International Normalized Ratio; IRT=interactive response technology; IV=intravenous; NAb=neutralizing antibodies; PD-L1=programmed cell death ligand 1; PFS2=progression-free survival after next-line treatment; PK=pharmacokinetic; PRO=patient-reported outcome; PT=prothrombin time; PTT=partial thromboplastin time; Q2/3/6/9/12/24W=every 2/3/6/9/12/24 weeks; QW=once weekly; RECIST=Response Evaluation Criteria in Solid Tumors; SAE=serious adverse event; SOC=standard of care; T3=triiodothyronine; TSH=thyroid-stimulating hormone; WOCBP=women of childbearing potential; WONCBP=women of nonchildbearing potential.

a. Pembrolizumab/placebo may only be administered for 18 Q6W cycles. Paclitaxel and/or bevacizumab may continue until disease progression, prohibitive toxicity, other protocol-defined reason for discontinuation or the participant has received the maximum duration (if applicable) per the respective approved label or local practice.
b. If the End-of-Treatment Visit occurs ≥30 days from last dose of study intervention, a separate Safety Follow-up Visit is not required.
c. Participants should continue tumor scans Q9W (±7 d) through Week 54 and Q12W (±7 d) thereafter until investigator-assessed radiographic disease progression per RECIST 1.1, the start of a new anticancer treatment, withdrawal of consent, pregnancy, or death. Tumor scan timepoints will be calculated from the date of randomization for the duration of the study.
d. Survival Follow-up Visit will be performed by telephone.
e. Paclitaxel-related toxicities should be managed according to local practice and institutional guidelines with supportive care measures, dose interruptions, and reductions before consideration of discontinuation, if clinically appropriate. Docetaxel (75 mg/m^2 Q3W) 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. Refer to Appendix 7 for country-specific requirements.

1.3.2 Second Course (Retreatment)

Second Course retreatment with pembrolizumab is only available to participants who meet the criteria in Section 6.1.2. If eligible, these participants may be able to receive 9 additional Q6W, 400 mg administrations of pembrolizumab.

Table 2 Second Course Retreatment - Study Schedule of Activities

Period	**Second Course Phase (Retreatment) Q6W Cycles**									**EOT**	**Posttreatment**			**Comments**
Cycle	**C1**	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C8**	**C9**	**DC**	**Safety follow-up[a]**	**Efficacy follow-up[b]**	**Survival follow-up[c]**	**If EOT visit occurs ≥30 days from last dose of study treatment, a Safety Follow-up Visit is not required. In this situation, all procedures required at both the EOT visit and the Safety Follow-up Visit should be performed.**
Scheduling Window		**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**		**30 d after last dose (+ 7 d)**	**Q12W (±7 d)**	**Q12W (± 7 d)**	
Administrative Procedures														
Inclusion/ Exclusion	X													
Prior/ Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X		Concomitant medications will be recorded for 30 days after last dose. All concomitant medications administered during SAEs or ECIs are to be recorded.
Subsequent Anticancer Treatment										X	X	X	X	All anticancer treatment will be recorded until time of death or termination of survival follow-up. Participants should be contacted by telephone to monitor new anticancer treatment if there is no corresponding clinic visit.
Date of Progression on Subsequent Anticancer Treatment											X	X	X	Participants will be followed for PFS2.

Period	**Second Course Phase (Retreatment) Q6W Cycles**									**EOT**	**Posttreatment**			**Comments**
Cycle	**C1**	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C8**	**C9**	**DC**	**Safety follow-up[a]**	**Efficacy follow-up[b]**	**Survival follow-up[c]**	**If EOT visit occurs ≥30 days from last dose of study treatment, a Safety Follow-up Visit is not required. In this situation, all procedures required at both the EOT visit and the Safety Follow-up Visit should be performed.**
Scheduling Window		**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**		**30 d after last dose (+ 7 d)**	**Q12W (±7 d)**	**Q12W (± 7 d)**	
Survival Information (Vital Status)	←	—	—	—	—	—	—	—	—	→			X	After investigator-determined disease progression or start of new anticancer treatment. In addition, on Sponsor request, participants may be contacted for survival status at any time during the course of the study.
Study Intervention Administration														
Pembrolizumab (MK-3475)	X	X	X	X	X	X	X	X	X					Pembrolizumab 400 mg by IV Q6W
Efficacy Assessments														
Tumor Scans – Chest, Abdomen, and Pelvis	←	—	—	—	—	—	—	—	—	→				Tumor scans to be performed within 28 days before restarting treatment in Second Course and then Q12W (±7 d) from the start of Second Course retreatment until disease progression. Scan timing should follow calendar days and should not be adjusted for delays in cycle starts. Tumor scans are required at EOT if previous scans were performed more than 4 weeks before EOT. Unscheduled scans may be performed as clinically indicated.
										X		X		

Period	**Second Course Phase (Retreatment) Q6W Cycles**									**EOT**	**Posttreatment**			**Comments**
Cycle	**C1**	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C8**	**C9**	**DC**	**Safety follow-up[a]**	**Efficacy follow-up[b]**	**Survival follow-up[c]**	**If EOT visit occurs ≥30 days from last dose of study treatment, a Safety Follow-up Visit is not required. In this situation, all procedures required at both the EOT visit and the Safety Follow-up Visit should be performed.**
Scheduling Window		**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**		**30 d after last dose (+ 7 d)**	**Q12W (±7 d)**	**Q12W (± 7 d)**	
Bone Scan	←	—	—	—	—	—	—	—	—	—	—	—	→	Only for participants with a history of bone metastases or who are clinically symptomatic. A bone scan is required before restarting treatment in the Second Course, only if the previous scan was not performed within 28 days of restarting treatment, and thereafter if clinically indicated or to confirm CR (if other lesions indicate CR and bone lesions existed at baseline).
Brain Scan	←	—	—	—	—	—	—	—	—	—	—	—	→	Only for participants with a history of protocol-eligible treated brain metastases and/or who are clinically symptomatic, a brain scan will be required within 28 days of restarting treatment in Second Course and thereafter if clinically indicated or to confirm CR (if other lesions indicate CR and brain lesions existed at baseline).
CA-125	←	—	—	—	—	—	—	—	—	X		X		Sample to be collected at the time of each tumor scan (±14 days of scheduled scan). An optional sample may be collected at the time of unscheduled scan at the investigator's discretion. Additional assessments may be performed if clinically indicated (eg, suspected progression). All CA-125 testing will be performed locally.

Period	**Second Course Phase (Retreatment) Q6W Cycles**									**EOT**	**Posttreatment**			**Comments**
Cycle	**C1**	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C8**	**C9**	**DC**	**Safety follow-up[a]**	**Efficacy follow-up[b]**	**Survival follow-up[c]**	**If EOT visit occurs ≥30 days from last dose of study treatment, a Safety Follow-up Visit is not required. In this situation, all procedures required at both the EOT visit and the Safety Follow-up Visit should be performed.**
Scheduling Window		**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**		**30 d after last dose (+ 7 d)**	**Q12W (±7 d)**	**Q12W (± 7 d)**	
Clinical Assessments														
Adverse Event Monitoring	X	X	X	X	X	X	X	X	X	X	X	X		Report all AEs through 30 days after the last dose of study intervention. Report SAEs through 90 days after the last dose of study intervention, or 30 days after the last dose if participant initiates a new anticancer treatment, whichever is earlier.
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X			Perform within 7 days before starting Second Course retreatment and on Day 1 of each treatment cycle starting at C2.
Complete Physical Examination	X									X				
Symptom-directed Physical Examination		X	X	X	X	X	X	X	X		X			Assess more frequently as clinically indicated.
Vital Signs (temperature, blood pressure, respiratory rate, pulse rate, weight, height [height - screening only])	X	X	X	X	X	X	X	X	X	X	X			Assess before pembrolizumab is administered in each cycle.
12-lead ECG	X													An ECG is required before restarting treatment only if it was not already completed within 28 days previously. Additional ECGs may be performed as clinically indicated.

Period	**Second Course Phase (Retreatment) Q6W Cycles**									**EOT**	**Posttreatment**			**Comments**
Cycle	**C1**	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C8**	**C9**	**DC**	**Safety follow-up[a]**	**Efficacy follow-up[b]**	**Survival follow-up[c]**	**If EOT visit occurs ≥30 days from last dose of study treatment, a Safety Follow-up Visit is not required. In this situation, all procedures required at both the EOT visit and the Safety Follow-up Visit should be performed.**
Scheduling Window		**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**		**30 d after last dose (+ 7 d)**	**Q12W (±7 d)**	**Q12W (± 7 d)**	
Laboratory Assessments														
Urine or Serum Pregnancy Test - WOCBP Only	←	—	—	—	—	—	—	—	→	X	X			WOCBP require a negative pregnancy test within either 24 hours (urine) or 72 hours (serum) before starting Second Course retreatment. A pregnancy test must be performed every month during Second Course treatment. Pregnancy testing should continue in posttreatment until 120 days after last dose of pembrolizumab and 180 days after the last dose of paclitaxel, docetaxel (if applicable) and bevacizumab (if using) in first course treatment, if applicable. More frequent pregnancy testing may be performed if required by local regulations or if clinically indicated. Refer to Appendix 7 for country-specific requirements. Home pregnancy tests are acceptable when a scheduled visit does not occur within the month (per local regulation), but the site must make monthly telephone contact with the participant to determine the results of the pregnancy test.

Period	**Second Course Phase (Retreatment) Q6W Cycles**									**EOT**	**Posttreatment**			**Comments**
Cycle	**C1**	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C8**	**C9**	**DC**	**Safety follow-up[a]**	**Efficacy follow-up[b]**	**Survival follow-up[c]**	**If EOT visit occurs ≥30 days from last dose of study treatment, a Safety Follow-up Visit is not required. In this situation, all procedures required at both the EOT visit and the Safety Follow-up Visit should be performed.**
Scheduling Window		**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**		**30 d after last dose (+ 7 d)**	**Q12W (±7 d)**	**Q12W (± 7 d)**	
PT/INR and aPTT/PTT	X													Perform within 7 days before starting Second Course retreatment. Additional testing to be conducted as clinically indicated.
Chemistry	X	X	X	X	X	X	X	X	X	X	X			Perform within 7 days before starting Second Course retreatment. Perform within 72 hours before treatment on Day 1 of every cycle starting with Second Course C2. Perform more frequently as clinically indicated.
Hematology	X	X	X	X	X	X	X	X	X	X	X			
Urinalysis	X	X		X		X		X		X	X			Perform within 7 days before starting Second Course retreatment. After C1, perform within 72 hours before treatment on Day 1 every 2 cycles starting with C2 (ie, C2, 4, 6, 8).
T3 or FT3, plus FT4 and TSH	X	X	X	X	X	X	X	X	X	X	X			Perform within 7 days before starting Second Course retreatment, then within 72 hours before treatment every cycle.

Abbreviations: AE=adverse event; aPTT=activated partial thromboplastin time; C=cycle; CA-125=cancer antigen-125; d=day; DC=discontinuation; ECG=electrocardiogram; ECI=events of clinical interest; ECOG=Eastern Cooperative Oncology Group; EOT=end of treatment; FT3=free triiodothyronine; FT4=free thyroxine; INR=International Normalized Ratio; IV=intravenous; PFS2=progression-free survival after next-line treatment; PT=prothrombin time; PTT=partial thromboplastin time; Q6W= every 6 weeks; Q12W=every 12 weeks; SAE=serious adverse event; T3=triiodothyronine; TSH=thyroid-stimulating hormone; WOCBP=women of childbearing potential.

a. If the End-of-Treatment Visit occurs ≥30 days from last dose of study intervention, a separate Safety Follow-up Visit is not required.

b. Participants should continue tumor scans Q12W (±7 d) until investigator-assessed radiographic disease progression per RECIST 1.1, the start of a new anticancer treatment, withdrawal of consent, pregnancy, or death. Tumor scan timepoints will be calculated from the start of Second Course retreatment.

c. Survival Follow-up Visit will be performed by telephone.

2 INTRODUCTION

OC is the 20th most common cancer, with an estimated 295,414 new cases diagnosed worldwide, yet it is the eighth primary cause of cancer-related death for women, with approximately 184,799 deaths in 2018 [Bray, F., et al 2018]. In the US, the estimated numbers of new cases and deaths occurring in 2020 are 21,750 and 13,940, respectively [Siegel, R. L., et al 2020], while in Europe, the estimated number of new cases and deaths from OC in 2018 were 67,800 and 44,600, respectively [Ferlay, J., et al 2018]. The 5-year survival rate for patients with OC is only about 48% [Siegel, R. L., et al 2020]. OC is typically diagnosed in advanced stages (FIGO Stage III-IV) [Matulonis, U. A., et al 2016]; 5-year survival in patients with distant disease is 29%, compared with 92% for patients with localized disease [Siegel, R. L., et al 2020].

OC is currently divided into several histologic subtypes that differ in genetic composition and clinical characteristics, for which increasingly tailored treatments are now used. In the 2014 World Health Organization classification guidelines, epithelial OC comprises serous (high- and low-grade), endometrioid, clear cell, mucinous, carcinosarcoma, and malignant Brenner tumors histologic subtypes. High-grade serous carcinoma is the most frequently diagnosed subtype of OC [Matulonis, U. A. 2018]. Irrespective of stages, patients with low-grade serous and endometrioid show the best survival rates. In localized and regional stages, the poorest survival rates are detected for carcinosarcoma and malignant Brenner tumors, but in distant stage, the worst prognoses are observed in mucinous, clear cell and carcinosarcoma [Lan, A. 2019].

Until recently, treatment options for patients with newly diagnosed OC were cytoreductive surgery with either adjuvant or neoadjuvant chemotherapy (most likely platinum- and taxane-based) or chemotherapy alone [National Comprehensive Cancer Network 2020]. While most patients achieve a complete remission after the combination of cytoreductive surgery and chemotherapy, the majority (>80%) will recur [Matulonis, U. A., et al 2016]. The addition of the antiangiogenic agent bevacizumab to carboplatin plus paclitaxel, followed by bevacizumab alone, is a standard option in patients eligible to receive bevacizumab with newly diagnosed advanced OC [Burger, R. A., et al 2011] [Ledermann, J. A., et al 2013]. Treatment decisions in subsequent lines of therapy are less defined. Factors that affect treatment decisions include the duration of response to the previous chemotherapy, number of lines of chemotherapy, molecular signature, histological subtype, and residual toxic effects from previous therapies [Alvarez, R. D., et al 2016].

PARP inhibitors have ultimately changed the way that patients with OC are treated. Different PARP inhibitors have obtained US FDA and/or EMA approval in OC in different settings. Early studies have shown significant efficacy for PARP inhibitors in patients with germline BRCA1/2 mutations. It has also become evident that BRCA wild-type patients with other defects in the homologous recombination repair pathway benefit from this treatment [Boussios, S., et al 2019]. Recently olaparib in combination with bevacizumab was approved in the US as maintenance treatment for patients with OC who are in response to first-line platinum-based chemotherapy and whose cancer is associated with HRD positive status [Ray-Coquard, I., et al 2019] [U.S. Prescribing Information 2021]. Niraparib was also approved as maintenance treatment for OC patients who are in response to first-line

platinum-based chemotherapy regardless of BRCA or HRD status [Gonzalez-Martin, A., et al 2019] [U.S. Prescribing Information 2021a].

Patients with platinum-sensitive relapsed OCs (where disease progression occurs ≥6 months after the last dose of platinum-based chemotherapy) may initially be managed with different treatments such as chemotherapies and targeted therapies, if indicated. However, almost all patients will ultimately relapse. Patients who experience relapse during chemotherapy (ie, have platinum-refractory disease) or those who experience relapse within 6 months of completing the last platinum therapy (ie, have platinum-resistant disease) typically have low response rates to subsequent chemotherapy (<20%), a median PFS of 3 to 4 months, and a median OS in the range of 12 to 15 months [Pujade-Lauraine, E., et al 2019].

Several chemotherapeutic treatment options are globally approved and available for patients with PRROC including PLD, topotecan, cyclophosphamide, gemcitabine, docetaxel, and paclitaxel. The sequential use of single-agent therapy with a nonplatinum compound is considered standard [Pujade-Lauraine, E., et al 2019]. The major goals of therapy in this setting are to improve disease symptoms and prolong survival, while minimizing treatment toxicity. Weekly administration of paclitaxel has shown the highest response rate in platinum-resistant cancers [Markman, M., et al 2006], with less neurotoxicity than the standard Q3W regimen. The AURELIA study showed that the addition of bevacizumab to single-agent chemotherapy (weekly paclitaxel, PLD, or topotecan) significantly improved PFS and ORR in patients with PRROC [Pujade-Lauraine, E., et al 2014], leading to approval of bevacizumab in combination with paclitaxel, topotecan, and PLD for the treatment of second-line and third-line PRROC. Weekly paclitaxel plus bevacizumab was the most active of the combination regimens in the AURELIA study [Poveda, A. M., et al 2015], and is thus considered an ideal option, although only approximately 30% of patients with PRROC are eligible for bevacizumab treatment. Given the high toxicity with the current SOC chemotherapeutic regimens, limited activity in radiological/biochemical response, and no clear improvement in OS [Bogani, G., et al 2020], there remains an urgent requirement for novel therapies to be identified for women with platinum-resistant disease.

2.1 Study Rationale

Several clinical studies have shown efficacy of immune checkpoint inhibitors (anti-CTLA-4 antibody, anti-PD-1 antibody and/or anti-PD-L1 antibody) in patients with various types of solid malignancies, with response rates of 5.9% to 20.0% in OC [Hamanishi, J., et al 2016]. In KEYNOTE-100, pembrolizumab monotherapy elicited modest antitumor efficacy (ORR of 8.0%), but a durable activity in mostly heavily pretreated patients with advanced recurrent OC (including those with platinum-refractory, resistant, and sensitive disease). KEYNOTE-100 showed a trend toward higher ORR with increasing PD-L1 CPS. In the "training set" used to establish CPS cutoff points, ORR was 2.9% in patients with CPS <1 (n=34), 16.9% in patients with CPS ≥1 (n=59), and 30.0% in patients with CPS ≥10 (n=20), while in the total population (training + confirmation sets; N=376), ORR was 5.0% for CPS <1 (n=141), 10.2% for CPS ≥1 (n=197), and 17.1% for CPS ≥10 (n=82) [Matulonis, U. A., et al 2019]. Toxicities in KEYNOTE-100 were consistent with other single-agent pembrolizumab studies.

In JAVELIN Ovarian 200, the prevalence of PD-L1+ patients was 58% [Pujade-Lauraine, E., et al 2019a], which is similar to CPS ≥1 in KEYNOTE-100. In the avelumab + PLD arm, the ORR was 18.5% (95% CI: 11.1, 27.9) in the PD-L1+ subgroup and 3.4% (95% CI: 0.4, 11.9) for the PD-L1− subgroup. In PD-L1+ patients, the median PFS with the combination was longer than with avelumab alone, indicating a potential role of PD-L1 status as predictor of clinical benefit.

The combination of chemotherapy and immune checkpoint blockade may be a rational approach for the treatment of recurrent OC; PD-L1 is over-expressed in OC; women with tumor-infiltrating lymphocytes have improved survival, and there is evidence of preclinical synergy when these 2 types of agents are combined. Pembrolizumab has a nonoverlapping toxicity profile with chemotherapy, and combination therapy has shown promising activity in recurrent OC, improving both ORR and PFS (see Section 2.2.3).

There may be additional synergistic activity between antiangiogenic therapy (bevacizumab, lenvatinib) and immunotherapy [Tartour, E., et al 2011]. A study of pembrolizumab + bevacizumab + cyclophosphamide in recurrent OC is described in Section 2.2.3. The combination of pembrolizumab + lenvatinib has shown promising antitumor activity and manageable toxicity in various advanced solid tumors, including an ORR of 32% and DCR of 74% as forth-line therapy in patients with OC [Lwin, Z., et al 2020]. Further clinical studies for combination therapies of PD-1 inhibitors with chemotherapies, targeted molecular drugs for solid tumors, PARPi, focal radiation therapy and the other cancer immunotherapies such as cancer-specific vaccines or immune modulators are currently ongoing.

Based on this rationale, and the high unmet need in patients with PRROC, the present study has been designed to compare the combination of pembrolizumab and the preferred SOC regimen (weekly paclitaxel with or without bevacizumab) with the SOC regimen alone in participants with PRROC who have received no more than 2 prior lines of systemic therapy. Due to the rapidly evolving landscape, a future approval of an immune checkpoint inhibitor in combination with other therapies in frontline OC cannot be ruled out, and such participants may benefit from the combination of pembrolizumab + paclitaxel + bevacizumab. Therefore, participants with prior exposure to anti-PD-1 or anti-PD-L1 will be eligible for this study.

2.2 Background

2.2.1 Pembrolizumab

Pembrolizumab is a potent humanized IgG4 mAb with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and PD-L2. Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an IV immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across several indications. For more details on specific indications refer to the IB.

2.2.1.1 Pharmaceutical and Therapeutic Background

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

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

The structure of murine PD-1 has been resolved [Zhang, X., et al 2004]. PD-1 and its family members are type I transmembrane glycoproteins containing an IgV–type domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. After T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ, and ZAP70, which are involved in the CD3 T-cell signaling cascade [Okazaki, T., et al 2001] [Chemnitz, J. M., et al 2004] [Sheppard, K-A, et al 2004] [Riley, J. L. 2009]. The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [Parry, R. V., et al 2005] [Francisco, L. M., et al 2010]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in OC.

2.2.1.2 Preclinical and Clinical Studies

Refer to the pembrolizumab IB for a summary of preclinical and clinical study data.

2.2.1.3 Ongoing Clinical Studies

Refer to the pembrolizumab IB for a summary of ongoing clinical study data.

2.2.2 Therapeutic Strategies in Platinum-resistant Ovarian Cancer

Preferred chemotherapeutic options for PRROC include paclitaxel, docetaxel, PLD, topotecan, and gemcitabine [National Comprehensive Cancer Network 2020]. There is

evidence that (at equivalent dose intensity) weekly paclitaxel in patients with PRROC leads to better tolerance compared with the 3-weekly regimen, without compromising efficacy, and it has gained widespread use globally as a standard treatment [Rosenberg, P., et al 2002]. Weekly paclitaxel (80 mg/m^2/week) showed an ORR of 20.9% (2 CRs, 8 PRs) among 48 patients with platinum and paclitaxel-resistant ovarian and primary peritoneal cancers in a Gynecologic Oncology Group study. SAEs were relatively uncommon with 21% and 4% of patients experiencing Grade 2 and 3 neuropathy, respectively, and Grade 3 fatigue noted in 8% [Markman, M., et al 2006]. A higher ORR was observed in another study of weekly paclitaxel (80 mg/m^2) for up to 24 weeks in patients with recurrent platinum-resistant epithelial OC; 44% of patients had a PR and 9% had a CR, with median PFS of 6.1 months (95% CI: 3.81, 8.39) and median OS of 10.4 months (95% CI: 8.49, 12.38). Five patients (15%) reported Grade 3/4 neurotoxicity at the end of 12 weeks. No dose reduction or treatment delay was required and no significant hematologic toxicity was observed[Le, T., et al 2006]. It should be noted that response was evaluated using standard RECIST criteria in the former study, and both standard RECIST criteria and CA-125 in the latter study.

Bevacizumab substantially improves efficacy in PRROC compared with chemotherapy alone, and is approved for use in eligible patients with PRROC in combination with paclitaxel, topotecan, or PLD. The AURELIA study showed that adding bevacizumab (10 mg/kg Q2W) to chemotherapy (paclitaxel 80 mg/m^2 Days 1, 8, 15, and 22 Q4W, topotecan 4 mg/m^2 on Days 1, 8, and 15 Q4W or 1.25 mg/m^2 on Days 1 to 5 Q3W, or PLD 40 mg/m^2 Day 1 Q4W) significantly improved PFS and ORR [Pujade-Lauraine, E., et al 2014]. The largest treatment effect on ORR was observed in the paclitaxel cohort (53.3% vs 30.2%; difference, 23.1%; 95% CI: 1.7, 44.5%), followed by the topotecan cohort (17.0% vs 0.0%; difference, 17.0%; 95% CI: 5.1, 28.9%), with a less pronounced effect in the PLD cohort (13.7% vs 7.8%; difference, 5.9%; 95% CI: -7.2, 19.0%) [Poveda, A. M., et al 2015]. PFS HRs were 0.46 (95% CI: 0.30, 0.71) in the paclitaxel cohort (median, 10.4 vs 3.9 months), 0.57 (95% CI: 0.39, 0.83) for PLD (median 5.4 vs 3.5 months favoring bevacizumab-containing therapy), and 0.32 (95% CI: 0.21, 0.49) for topotecan (median 5.8 vs 2.1 months, respectively). The median duration of therapy was 3 cycles (range: 1 to 17 cycles) in the chemotherapy arm versus 6 cycles (range: 1 to 24 cycles) in the combination arm, reflecting the substantially longer PFS in the combination arm. Grade ≥2 hypertension and proteinuria were more common with the combination than with chemotherapy alone. However, there were no new safety signals. GI perforation occurred in 2.2% of bevacizumab-treated patients [Pujade-Lauraine, E., et al 2014].

PARP inhibitors have also shown significant efficacy in relapsed OC patients with germline BRCA1/2 mutations who have been treated with ≥2 prior lines of chemotherapy and in patients whose cancer is associated with HRD that were treated with ≥3 prior lines of chemotherapy [U.S. Prescribing Information 2020] [U.S. Prescribing Information 2020a]. In KEYNOTE-162, niraparib in combination with pembrolizumab was tolerable, and showed promising antitumor activity for patients with ovarian carcinoma who have limited treatment options regardless of platinum status, biomarker status, or prior treatment with bevacizumab [Konstantinopoulos, P. A., et al 2019].

2.2.3 Immunotherapy Plus Chemotherapy in Platinum-resistant Recurrent Ovarian Cancer

Multiple studies are exploring the augmentation of chemotherapy efficacy and ways to overcome drug resistance by combining standard chemotherapy with immunotherapy. In the 3-arm, randomized JAVELIN Ovarian 200 study, avelumab alone or in combination with PLD did not provide a statistically significant improvement in PFS or OS compared with PLD alone in 566 patients with PRROC . The ORR for the combination was 13.3% (95% CI: 8.8, 19.0%) compared with 4.2% (95% CI: 1.8, 8.1%) for PLD monotherapy; median PFS was 3.7 versus 3.5 months, respectively, and median OS was 15.7 versus 13.1 months, respectively. However, the retrospective PD-L1 subgroup analysis revealed that for the avelumab plus PLD arm, patients with PD-L1+ tumors had a higher ORR (18.5%; 95% CI: 11.1, 27.9%) than those with PD-L1– tumors (3.4%; 95% CI: 0.4, 11.9%) [Pujade-Lauraine, E., et al 2019a].

Despite the inconclusive results of the JAVELIN Ovarian 200 study, other immunotherapy and chemotherapy combinations are being explored.

Studies have shown that pembrolizumab improves the efficacy of chemotherapy with or without bevacizumab in PRROC. The combination of pembrolizumab (200 mg Q3W) and PLD (40 mg/m^2 Q4W) showed only modest improvement with an ORR of ~13% among 23 evaluable patients [Matulonis, U. A., et al 2018a]. Grade 3 toxicities included 19% rash, 8% ALT increase, 4% each of AST increase, anemia, diarrhea, fever, and mucositis; there was 8% Grade 2 pneumonitis. Substantial efficacy improvement was observed when pembrolizumab was added to paclitaxel as combination partner in patients with PRROC, with an ORR of 51.4% [Wenham, R. M., et al 2018] (see Section 2.2.4).

In another investigator-initiated study, 30 patients with platinum-resistant disease and 10 patients with platinum-sensitive disease who declined platinum-based therapy were treated with pembrolizumab (200 mg Q3W) added to oral cyclophosphamide (50 mg once daily), and bevacizumab (15 mg/kg Q3W) [Zsiros, E., et al 2020]. The ORR in patients with PRROC was 43.3% (3 CR and 10 PR) with median DOR of 5.5 months (range: 0 to 26 months) and DCR (CR+PR+SD) of 93.3%. Median PFS in patients with PRROC was 7.6 months (90% CI: 5.7, 10.3). Cyclophosphamide plus bevacizumab without pembrolizumab is associated with an ORR of approximately 24% [Garcia, A. A., et al 2008]. The combination was well tolerated; any grade of treatment-related AEs occurred in 33 (82.5%) patients, with ≥Grade 3 AEs in 13 (32.5%). The most frequently reported AEs included fatigue (18 [45.0%]), diarrhea (13 [32.5%]), and hypertension (11 [27.5%]) and the most common Grade 3 to 4 treatment-related AEs were bevacizumab-induced hypertension (6 [15.0%]) and lymphopenia attributed to oral cyclophosphamide (3 [7.5%]). One Grade 4 AE was noted due to low white blood cell and platelet counts that resolved without clinical intervention. No treatment-related deaths occurred during the study and treatment-related AEs led to treatment discontinuation for 4 patients (10%) and dose interruption in 17 patients (42.5%).

Based on the published results and preliminary data, combination therapy of PD-1/PD-L1 inhibitors and chemotherapy with or without an antiangiogenic therapy certainly has the potential to be superior to chemotherapy alone.

2.2.4 Pembrolizumab and Paclitaxel in Platinum-resistant Recurrent Ovarian Cancer

Pembrolizumab 200 mg Q3W in combination with weekly paclitaxel (80 mg/m^2 on Days 1, 8, and 15 Q3W) has shown a signal of activity in a single arm Phase 2 study of 42 women with PRROC who had received up to 3 prior cytotoxic chemotherapeutic regimens [Wenham, R. M., et al 2018]. The ORR and disease control rate were 51.4% (all PR) and 86.5%, respectively, in the 37 evaluable patients. This response rate is similar to the 53% response rate seen with the combination of bevacizumab and paclitaxel in AURELIA [Poveda, A. M., et al 2015]. The 6-month PFS was 64.5%, with median PFS of 7.6 (4.8, 12.0) months and median OS of 13.4 (12.1, 27.0) months. Among the 42 treated patients, the most frequent AEs were anemia (77%), fatigue (65%), neutropenia (56%), and nausea (51%). The most frequent Grade 3 AEs were leukocytosis (18.6%), anemia (14%), neutropenia (11.6%), and lymphopenia (7.0%). There were 3 Grade 4 AEs (neutropenia, glucose intolerance, and hyponatremia) and no Grade 5 AEs [Wenham, R. M., et al 2018].

2.2.5 Safety Data on the Combination of Pembrolizumab and Chemotherapy in Other Malignancies

Safety data for pembrolizumab + chemotherapy in other tumor types show an acceptable tolerability profile of combination therapy.

In KEYNOTE-407, participants with previously untreated metastatic squamous NSCLC were randomized 1:1 to chemotherapy (carboplatin plus paclitaxel/nab-paclitaxel for four 3-week cycles) plus either pembrolizumab (N=278) or placebo (N=281) Q3W for up to 35 cycles [Paz-Ares, L., et al 2020]. ≥Grade 3 AEs occurred in 74.1% of participants in the pembrolizumab plus chemotherapy group and in 69.6% of participants in the placebo plus chemotherapy group; discontinuation of any study drug due to AEs occurred in 27.3% and 13.2%; immune-mediated AEs occurred in 35.3% and 8.9%, and AEs led to death in 11.2% and 6.8%. The most frequently occurring AEs in both treatment groups were anemia, alopecia, neutropenia, and nausea. Most immune-mediated AEs and infusion reactions were Grade 1/2.

The combination of pembrolizumab plus carboplatin and paclitaxel has also been investigated in participants with previously untreated Stage II or Stage III triple negative breast cancer in study KEYNOTE-522 [Schmid, P., et al 2020]. Participants received neoadjuvant pembrolizumab (N=784) or placebo (N=390) plus paclitaxel and carboplatin Q3W for 4 cycles, followed by an additional 4 cycles of pembrolizumab or placebo, and both groups received doxorubicin-cyclophosphamide or epirubicin-cyclophosphamide. After definitive surgery, the participants received adjuvant pembrolizumab or placebo Q3W for up to 9 cycles. Across all treatment phases, the incidence of ≥Grade 3 treatment-related AEs was 76.8% in the pembrolizumab plus chemotherapy group and 72.2% in the placebo plus chemotherapy group; treatment-related AEs led to discontinuation of any study drug in 23.3% and 12.3%, and deaths across both phases were reported in 0.4% and 0.3%. The only AEs of interest ≥Grade 3 occurring in ≥10 participants in the pembrolizumab plus chemotherapy group were severe skin reactions (3.8%), infusion reactions (2.6%), and adrenal insufficiency (1.3%).

In KEYNOTE-826, participants with persistent, recurrent, or metastatic cervical cancer were randomized 1:1 to receive pembrolizumab 200 mg or placebo Q3W, each in combination with paclitaxel 175 mg/m^2 and cisplatin 50 mg/m^2 or carboplatin AUC 5 Q3W plus, per investigator discretion, bevacizumab 15 mg/kg Q3W [Colombo, N., et al 2021]. ≥Grade 3 AEs occurred in 81.8% of 307 treated participants in the pembrolizumab plus chemotherapy group and in 75.1% of 309 treated participants in the placebo plus chemotherapy group; SAEs occurred in 49.8% and 42.4%; discontinuation of any study drug due to AEs occurred in 37.5% and 26.5%; immune-mediated AEs occurred in 33.9% and 15.2%; and AEs led to death in 4.6% and 4.5%. The most common ≥Grade 3 AEs were anemia (30.3% in the pembrolizumab group and 26.9% in the placebo group) and neutropenia (12.4% and 9.7%, respectively).

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.

Given the low response rates to subsequent chemotherapy without clear improvement in OS in women with PRROC, new treatment modalities and paradigms are needed to improve the prognosis of this patient group. Immunotherapy is emerging as a potential strategy to enhance traditional PRROC treatments. Pembrolizumab and chemotherapy may be more beneficial to the patient via enhancing immunostimulatory activity of pembrolizumab as a single agent. Investigator-initiated study data discussed in Sections 2.2.3 and 2.2.4 suggest that standard chemotherapy may be administered safely in combination with pembrolizumab in patients with OC. The addition of bevacizumab to single-agent chemotherapy has been shown to significantly improve PFS and ORR in patients with PRROC [Poveda, A. M., et al 2015], and may therefore also be administered to eligible participants in this study.

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

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

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

Throughout this protocol, the term Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 refers to the modification of RECIST 1.1 to include a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Refer to Section 4.2.1.1 for additional details.

In female participants with platinum-resistant recurrent ovarian cancer who have received ≤2 prior lines of therapy:

Primary Objective	**Primary Endpoint**
To compare pembrolizumab plus paclitaxel with or without bevacizumab to placebo plus paclitaxel with or without bevacizumab, with respect to progression-free survival (PFS) per RECIST 1.1 as assessed by the investigator Hypothesis (H1): pembrolizumab plus paclitaxel with or without bevacizumab is superior to placebo plus paclitaxel with or without bevacizumab, with respect to PFS per RECIST 1.1 as assessed by the investigator for participants with programmed cell death ligand 1 (PD-L1) positive tumors (Combined Positive Score [CPS] ≥1) Hypothesis (H2): pembrolizumab plus paclitaxel with or without bevacizumab is superior to placebo plus paclitaxel with or without bevacizumab, with respect to PFS per RECIST 1.1 as assessed by the investigator for all participants	PFS: The time from randomization to the first documented disease progression or death due to any cause, whichever occurs first

Secondary Objectives	Secondary Endpoints
To compare pembrolizumab plus paclitaxel with or without bevacizumab to placebo plus paclitaxel with or without bevacizumab, with respect to overall survival (OS) Hypothesis (H3): Pembrolizumab plus paclitaxel with or without bevacizumab is superior to placebo plus paclitaxel with or without bevacizumab, with respect to OS for participants with PD-L1 positive tumors (CPS ≥1) Hypothesis (H4): Pembrolizumab plus paclitaxel with or without bevacizumab is superior to placebo plus paclitaxel with or without bevacizumab, with respect to OS for all participants	OS: The time from randomization to death due to any cause
To compare pembrolizumab plus paclitaxel with or without bevacizumab to placebo plus paclitaxel with or without bevacizumab, with respect to PFS per RECIST 1.1 by blinded independent central review (BICR) for participants with PD-L1 positive tumors (CPS ≥1) and all participants	PFS
To evaluate the safety and tolerability of pembrolizumab in combination with paclitaxel with or without bevacizumab	-Adverse events (AEs) -Study treatment discontinuation due to AEs
To compare pembrolizumab plus paclitaxel with or without bevacizumab to placebo plus paclitaxel with or without bevacizumab, with respect to 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 (GI) symptoms using the EORTC Ovarian Cancer-Specific Quality of Life Questionnaire (QLQ-OV28) abdominal/GI symptom scale for participants with PD-L1 positive tumors (CPS ≥1) and all participants	Change from baseline and time to deterioration (TTD) of the QoL and symptom scores from the GHS/QoL scale (items 29 and 30) of the EORTC QLQ-C30 and the abdominal/GI symptom scale (items 31 to 36) of the EORTC QLQ-OV28

Tertiary/Exploratory Objectives	Tertiary/Exploratory Endpoints
CCI	

CCI

[redacted]

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 3, randomized, placebo-controlled, parallel-group, multisite, double-blind study of pembrolizumab versus placebo in combination with paclitaxel with or without bevacizumab in participants with PRROC who have received ≤2 prior lines of therapy. Participants must have received at least 1 line of platinum-based chemotherapy for OC with radiographic evidence of disease progression within 6 months after the last dose (ie, platinum-resistant disease). Participants should have radiographic evidence of disease progression on the most recent line of therapy to be eligible. Participants with secondary platinum-refractory disease who were either platinum resistant or platinum sensitive in the first line are eligible. Secondary platinum-refractory disease is defined as disease that has progressed per radiographic imaging while receiving or within 28 days of the last dose of second-line platinum-based therapy.

Prior anti-PD-1 or anti-PD-L1, prior PARP inhibitor, and prior bevacizumab use is permitted.

Approximately 616 eligible participants are expected to be randomized in the global portion of the study. After enrollment of the global portion of the study is complete, the study may remain open to enrollment in China alone until the target number of China participants has been enrolled to meet local regulatory requirements. This extension portion of the study, if required, will be identical to the global study (eg, inclusion and exclusion criteria, study endpoints, primary and secondary objectives, study procedures, and statistical analyses).

Eligible participants will be stratified according to planned bevacizumab use in the current study (yes vs no), region (US vs EU vs ROW), and PD-L1 status (CPS <1 vs CPS 1 to <10 vs CPS ≥10). The Sponsor, investigators, participants, and other study-site staff will be masked to participant PD-L1 status. Participants will be randomly assigned to 1 of the following 2 treatment arms in a 1:1 ratio:

Arm 1:

Pembrolizumab 400 mg Q6W for 18 cycles

PLUS paclitaxel 80 mg/m^2 on Days 1, 8, and 15 of each Q3W cycle

(with or without bevacizumab 10 mg/kg Q2W)

Arm 2:

Placebo Q6W for 18 cycles

PLUS paclitaxel 80 mg/m^2 on Days 1, 8, and 15 of each Q3W cycle

(with or without bevacizumab 10 mg/kg Q2W)

Crossover between treatment arms is not permitted.

Pembrolizumab/placebo may be administered for a maximum of 18 Q6W cycles (approximately 2 years). Paclitaxel and bevacizumab may continue until disease progression, prohibitive toxicity, other protocol-defined reasons for discontinuation, or the participant has received the maximum duration (if applicable) per the respective approved labels or local practice.

The use of bevacizumab is optional and may be administered to eligible participants at the investigator's discretion. Bevacizumab use must be decided and selected in IRT before randomization as it is a stratification factor. Refer to Appendix 7 for country-specific requirements for bevacizumab.

Paclitaxel-related toxicities should be managed according to local practice and institutional guidelines with supportive care measures, dose interruptions and reductions before consideration of discontinuation, if clinically appropriate. Docetaxel (75 mg/m^2 Q3W) may be considered after consultation with the Sponsor for participants who experience either a severe hypersensitivity reaction to paclitaxel or an AE requiring discontinuation of paclitaxel only after consultation with the Sponsor. Refer to Appendix 7 for country-specific requirements.

On-study tumor scans will be performed Q9W (±7 days) from randomization through Week 54 and Q12W (±7 days) thereafter until disease progression is radiographically documented by the investigator per RECIST 1.1, initiating a new anticancer treatment, withdrawal of consent, becoming lost to follow-up, pregnancy, or death. Tumor scans are required at EOT if previous scans were obtained more than 4 weeks before the EOT visit, and must be performed before the start of new anticancer treatment. All scans obtained on study will be submitted to the iCRO for assessment of PFS per RECIST 1.1 by BICR. Refer to Section 8.2 for details about tumor scans and assessment.

AE monitoring will be ongoing throughout the study and graded according to the guidelines outlined in the NCI CTCAE version 5.0. All AEs will be reported through 30 days after the last dose of study intervention. All SAEs will be reported through 90 days after the last dose of study intervention, or 30 days after the last dose if participant initiates a new anticancer treatment, whichever is earlier.

Participants who have completed the first course may be eligible for retreatment with pembrolizumab. If eligible, these participants may receive 9 additional Q6W, 400 mg administrations of pembrolizumab (Second Course retreatment) upon experiencing investigator-determined progressive disease by RECIST 1.1 after initial treatment or first course has been completed or stopped for confirmed CR, as specified in Section 6.1.2.

The primary efficacy endpoint is PFS per RECIST 1.1 as assessed by investigator, and the key secondary endpoint is OS. Comparisons between the 2 treatment arms will be conducted at 2 planned IAs (at approximately 27 and 38 months after the first participant is randomized) and the final analysis at approximately 64 months after the first participant is randomized. Results of the IAs will be reviewed by an eDMC. Details are provided in Section 9.7.

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

4.2 Scientific Rationale for Study Design

This multisite, randomized, double-blind, Phase 3 study is designed to compare efficacy and safety of pembrolizumab added to SOC chemotherapy with or without bevacizumab in participants with PRROC. Randomization will be used in this study to avoid bias in the assignment of participants to treatment, to increase the likelihood that known and unknown participant attributes (eg, demographics and baseline characteristics) are balanced across treatment arms, and to ensure the validity of statistical comparisons across treatment arms. Intravenous placebo will be used to reduce bias as the primary study endpoint of PFS is per investigator.

Randomization will be stratified according to planned bevacizumab use in the study, region, and PD-L1 status using CPS (Section 6.3.2). Planned bevacizumab use (yes vs no) is included as a stratification factor to ensure that bevacizumab use is equally balanced across treatment arms. PD-L1 status (CPS <1 vs CPS 1 to <10 vs CPS ≥10) is included as a stratification factor since KEYNOTE-100 showed a trend toward higher ORR with increasing PD-L1 CPS (see Section 2.1). Furthermore, in JAVELIN Ovarian 200, the prevalence of PD-L1+ patients was 58%, which is similar to CPS ≥1 in KEYNOTE-100. The PFS result of the combination of avelumab with PLD in PD-L1+ was longer than avelumab alone, indicating a potential role of PD-L1 status as predictor of clinical benefit [Pujade-Lauraine, E., et al 2019a]. Region is included as a stratification factor as regional variability may be a prognostic factor.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

This study will use PFS based on RECIST 1.1 criteria as assessed by the investigator as the primary endpoint and OS as the key secondary endpoint as outlined in Section 3.

PFS is an acceptable measure of clinical benefit for a late-stage study that shows 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, assessment of PFS based on RECIST 1.1 will be performed by BICR as a secondary objective.

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

RECIST 1.1 will be used by the investigator and BICR when assessing images for efficacy measures. Although original RECIST 1.1 publication recommends 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, if a larger number of target lesions is needed to adequately represent the tumor burden. Refer to Section 8.2.1.5 for additional detail.

4.2.1.2 Safety Endpoints

Safety parameters frequently used for evaluating investigational-systemic anticancer treatments are included as safety endpoints including, but not limited to, the incidence of, causality, and outcome of AEs/SAEs, and changes in vital signs and laboratory values. AEs will be assessed as defined by CTCAE, Version [5.0].

4.2.1.3 Patient-reported Outcomes

Symptomatic improvement is considered a clinical benefit and accepted by health authorities as additional evidence of the risk-benefit profile of any new study intervention. In this study, HRQoL and disease-related symptoms will be investigated via the following assessment tools: EORTC QLQ-C30 and EORTC QLQ-OV28 questionnaires. Health utilities will be evaluated using the EQ-5D-5L PRO instrument. These measures are not pure efficacy or safety endpoints because they are affected by both disease progression and treatment tolerability.

4.2.1.3.1 EORTC QLQ-C30

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

4.2.1.3.2 EORTC QLQ-OV28

The EORTC QLQ-OV28 is an OC-specific module to supplement the EORTC QLQ-C30. It has been translated and validated in over 70 languages. The EORTC QLQ-OV28 comprises 3 functional scales (body image, sexuality, and attitude to disease/treatment), 3 symptom scales (abdominal/gastrointestinal symptoms, peripheral neuropathy, and hormonal/menopausal symptoms), and 7 items for other chemotherapy side-effects [Greimel, E., et al 2003]. It is scored on a 4-point scale (1=not at all, 2=a little, 3=quite a bit, 4=very much).

The EORTC QLQ-OV28 is a psychometrically and clinically validated instrument appropriate for assessing QoL of participants with OC, supplementary to EORTC QLQ-C30 [Greimel, E., et al 2003]. These instruments have been commonly used in Phase 3 studies of participants with OC [Stockler, M. R., et al 2014] [Brotto, L., et al 2016] [Stark, D., et al 2013]. There are 7 items (items 31 to 37) in the QLQ-OV28 to measure abdominal/ GI symptoms, which are predominant and burdensome symptoms specific to OC. The item 37 (heartburn/indigestion) was excluded from abdominal/GI symptoms because it was judged to

be a less specific symptom of OC and less correlated with abdominal/GI symptom scale than with items for other chemotherapy side-effects [Stockler, M. R., et al 2014] [Cull, A., et al 2001]. A difference of 10 points on the 100-point scale either from baseline or between the cohorts is considered clinically relevant [Bjordal, K., et al 1994] [Bjordal, K., et al 2000].

4.2.1.3.3 EQ-5D-5L

The EQ-5D-5L is a standardized instrument for use as a measure of health outcome and will provide data to develop health utilities for use in health economic analyses [Rabin, R. and de Charro, F. 2001]. The 5 health state dimensions in the EQ-5D-5L include the following: Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression. Each dimension is rated on a 5-point scale from 1 (no problem) to 5 (unable to/extreme problems). The EQ-5D-5L also includes a graded (0 to 100) vertical visual analog scale on which the participant rates his or her general state of health at the time of the assessment. This instrument has been used extensively in cancer studies and published results from these studies support its validity and reliability [Pickard, A. S., et al 2007].

4.2.1.4 Planned Exploratory Biomarker Research

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

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

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

Genetic (DNA) analyses from tumor

The application of new technologies, such as next generation sequencing, has provided scientists the opportunity to identify tumor-specific DNA changes (ie, mutations, methylation status, microsatellite instability). Key molecular changes of interest to immuno-oncology drug development include the mutational burden of tumors and the clonality of T-cells in the tumor microenvironment. Increased mutational burden (sometimes called a ‘hyper-mutated’

state) may generate neoantigen presentation in the tumor microenvironment. To conduct this type of research, it is important to identify tumor-specific mutations that occur across all genes in the tumor genome. Thus, genome-wide approaches may be used for this effort. Note that to understand tumor-specific mutations, it is necessary to compare the tumor genome with the germline genome. Microsatellite instability may also be evaluated as this is an important biomarker for some cancers (ie, colorectal cancer). Circulating tumor DNA and/or RNA may also be evaluated from blood samples.

Tumor and/or blood RNA analyses

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

Proteomics and IHC using blood and/or tumor

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

Other blood-derived biomarkers

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

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

4.2.1.5 Future Biomedical Research

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

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

4.2.2 Rationale for the Use of Comparator/Placebo

The background regimen of single-agent chemotherapy (weekly paclitaxel) with or without bevacizumab (for clinically eligible participants) used in this study represents one of the current SOC options for PRROC. The use of a placebo for pembrolizumab will ensure the objectivity of investigator-assessed progression and safety, as well as any decisions to interrupt/discontinue therapy, and will control for knowledge of treatment effects on PRO data, while still providing all participants enrolled with the current SOC treatment.

4.3 Justification for Dose

4.3.1 Pembrolizumab

The planned dose of pembrolizumab for this study is 400 mg Q6W.

The current approved dosing regimens of pembrolizumab for IV administration are 200 mg Q3W and 400 mg Q6W for adults.

A 400 mg Q6W dosing regimen of pembrolizumab is expected to have a similar benefit-risk profile as 200 mg Q3W, in all treatment settings in which 200 mg Q3W pembrolizumab is currently appropriate [Lala, M., et al 2020]. Specifically, the dosing regimen of 400 mg Q6W for pembrolizumab is considered adequate based on M&S analyses, given the following rationale:

PK simulations demonstrating that in terms of pembrolizumab exposures:

- C_{avg} (or AUC) at 400 mg Q6W is similar to the approved 200 mg Q3W dose, thus bridging efficacy between dosing regimens.
- Trough concentrations (C_{min}) at 400 mg Q6W are generally within the range of those achieved with 2 mg/kg or 200 mg Q3W in the majority (>99%) of patients.

- Peak concentrations (C_{max}) at 400 mg Q6W are well below the C_{max} for the highest clinically tested dose of 10 mg/kg Q2W, supporting that the safety profile for 400 mg Q6W should be comparable to the established safety profile of pembrolizumab.
- E-R for pembrolizumab has been shown to be flat across indications, and OS predictions in melanoma and NSCLC show that efficacy at 400 mg Q6W is expected to be similar to 200 mg or 2 mg/kg Q3W, given the similar exposures; thus, 400 mg Q6W is expected to be efficacious across indications.

4.3.2 Paclitaxel

The regimen and dose of paclitaxel was selected based on standard clinical practice for the treatment of participants with PRROC. Weekly paclitaxel at a dose of 80 mg/m^2 is in accordance with NCCN guidelines for PRROC [National Comprehensive Cancer Network 2020] supported by evidence from a Phase 2 study of single-agent weekly paclitaxel in women with both platinum and paclitaxel-resistant OC [Markman, M., et al 2006]. The same dose and regimen was used in combination with bevacizumab in the AURELIA study [Pujade-Lauraine, E., et al 2014], although the 4-weekly cycle length in AURELIA (paclitaxel on Days 1, 8, 15, and 22 of a 4-week cycle) is adapted to Days 1, 8, and 15 of a 3-week cycle in this study to complement the Q6W pembrolizumab dosing schedule. Randomized studies in recurrent OC have used weekly paclitaxel in the control arm (eg, TRINOVA-1 [Monk, B. J., et al 2014], MITO-11 [Pignata, S., et al 2015], ESP2011-002 [NCT01485848]).

The dose of docetaxel (75 mg/m^2 Q3W), if approved by the Sponsor to be used in place of paclitaxel, reflects the recommended dose for OC as determined by the SGCTG group [Vasey, P. A., et al 2004].

All participants should receive premedication and other supportive care measures, to prevent severe hypersensitivity reactions and minimize toxicity, according to the local label and/or per local practice. Paclitaxel-related toxicities should be managed with dose interruptions and/or reductions prior to discontinuation, as clinically appropriate.

4.3.3 Bevacizumab

The use of bevacizumab is permitted for clinically eligible participants at the investigator's discretion. The regimen and dose of 10 mg/kg Q2W of bevacizumab to be used in combination with weekly paclitaxel was selected based on the approved product label and evidence from the AURELIA study [Pujade-Lauraine, E., et al 2014]. Refer to Appendix 7 for country-specific requirements for bevacizumab.

4.3.4 Maximum Dose/Exposure for This Study

The maximum dose/exposure of pembrolizumab allowed in the first course of this study is 400 mg Q6W for 18 cycles.

Paclitaxel (80 mg/m^2 on Days 1, 8, and 15 of each Q3W cycle) and bevacizumab (10 mg/kg Q2W) may continue until disease progression, prohibitive toxicity, other protocol-defined

reasons for discontinuation, or the participant has received the maximum duration (if applicable) per the respective approved labels or local practice.

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

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

4.4.1 Clinical Criteria for Early Study Termination

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

5 STUDY POPULATION

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

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

5.1 Inclusion Criteria

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

Type of Participant and Disease Characteristics

1. Has histologically confirmed epithelial (including high-grade serous or predominantly serous, low-grade serous, any-grade endometrioid, malignant mixed Müllerian tumors [carcinosarcoma], or clear cell) ovarian, fallopian tube, or primary peritoneal carcinoma.

   Note: Enrollment of participants with low-grade serous OC is permitted but will be capped at 4% of the total population.

2. Has received 1 or 2 prior lines of systemic therapy for OC, including at least 1 prior platinum-based therapy.
   - Participants must have received at least 4 cycles but not more than 9 cycles of platinum-based therapy in first line.

     Note: Participation in the study may be allowed in case of discontinuation of platinum-based therapy due to toxicity, following Sponsor consultation

   - Adjuvant ± neoadjuvant therapy is considered 1 line
   - Participants may have received a prior PARPi; this will not be considered a separate line of therapy if received in maintenance
   - Participants may have received a prior anti-PD-1/anti-PD-L1 therapy or bevacizumab; these will not be considered a separate line of therapy
   - Any chemotherapy regimen change due to toxicity in the absence of disease progression will be considered part of the same line of therapy
   - Hormonal therapy for OC (eg, tamoxifen, aromatase inhibitors etc.) will not count as a separate line of prior therapy
3. Has radiographic evidence of disease progression within 6 months (180 days) after the last dose of platinum-based chemotherapy for OC (ie, platinum-resistant disease).

   Note: Participants with secondary platinum-refractory disease who were either platinum resistant or platinum sensitive in the first line are eligible.

4. Is a candidate for paclitaxel chemotherapy (and bevacizumab, if using).

Demographics

5. Is female, and at least 18 years of age, at the time of signing the informed consent.
6. Has an ECOG performance status of 0 to 1 assessed within 3 days before randomization.

Female Participants

7. A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

- Is not a WOCBP

  OR

- Is a WOCBP and:
  - Uses 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 5 during the intervention period and for at least the time needed to eliminate each study intervention after the last dose of study intervention 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 length of time required to continue contraception for each study intervention is as follows:
  - Pembrolizumab: 120 days
  - Paclitaxel (or docetaxel, if applicable): 180 days
  - Bevacizumab (if administered): 180 days

  The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention. 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. Refer to Appendix 7 for country-specific requirements.

  - Has a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 24 hours for urine or within 72 hours for serum before the first dose of study intervention. 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 intervention are in Section 8.3.5.
  - Abstains from breastfeeding during the study intervention period and for at least 120 days after the last dose of study intervention.
  - Has had her medical history, menstrual history, and recent sexual activity reviewed by the investigator to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

8. The participant (or legally acceptable representative) has provided documented informed consent for the study. The participant may also provide consent for FBR. However, the participant may participate in the study without participating in FBR.

Additional Categories

9. Has radiographically evaluable disease, either measurable or nonmeasurable per RECIST 1.1, as assessed by the local site investigator/radiology.
10. Archival tumor tissue sample or newly obtained core or incisional/excisional biopsy of a tumor lesion not previously irradiated has been provided. Details pertaining to tumor tissue submission can be found in the Laboratory Manual. Prospective determination of PD-L1 status by a central laboratory is required for all participants. Refer to Appendix 7 for country-specific requirements.
11. Have adequate organ function as defined in the following table (Table 3). Specimens must be collected within 7 days before randomization.

Table 3 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	
Measured or calculated[b] creatinine clearance	≥60 mL/min
Hepatic	
Total bilirubin	≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or PTT 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); GFR=glomerular filtration rate; ULN=upper limit of normal.

[a]Criteria must be met without erythropoietin dependency within the last 4 weeks and without packed red blood cell (pRBC) transfusion within last 2 weeks.

[b]Estimated creatinine clearance (CrCl) should be calculated per institutional standard using Cockcroft-Gault:

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

*where F = 0.85 for females.

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.

5.2 Exclusion Criteria

An individual must be excluded from the study if the individual meets any of the following criteria:

Medical Conditions

1. Has nonepithelial cancers (germ cell tumors and sex cord-stromal tumors), borderline tumors (low malignant potential), mucinous, seromucinous that is predominantly mucinous, malignant Brenner's tumor and undifferentiated carcinoma.
2. Has primary platinum-refractory disease, defined as disease that has progressed per radiographic imaging while receiving or within 28 days of the last dose of first-line platinum-based therapy.
3. Has prior disease progression on weekly paclitaxel alone.

   Note: Sponsor consultation is required if the participant experienced disease progression after paclitaxel but while receiving bevacizumab maintenance therapy.

4. Has uncontrolled hypertension.

   Note: This applies only to participants who will receive bevacizumab. Use of antihypertensive medications to control blood pressure is allowed.

5. Has current, clinically relevant bowel obstruction (including subocclusive disease) including related to underlying epithelial OC, abdominal fistula or gastrointestinal perforation, intra-abdominal abscess, or evidence of rectosigmoid involvement by pelvic exam.

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

6. Has a history of thrombotic disorders, hemorrhage, hemoptysis, or active gastrointestinal bleeding within 6 months before randomization.

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

Prior/Concomitant Therapy

7. Has received >2 prior lines of systemic therapy for OC.
8. Has received prior systemic anticancer therapy, including investigational agents or maintenance therapy (including bevacizumab maintenance therapy), within 4 weeks before randomization.

   Note: Participants must have recovered from all AEs due to previous therapies to ≤Grade 1 or baseline. Participants with ≤Grade 2 neuropathy may be eligible. Participants with endocrine-related AEs Grade ≤2 requiring treatment or hormone replacement may be eligible.

   Note: Hormonal therapy is permitted up to the time of randomization.

9. Has received prior radiation therapy within 2 weeks of start of study intervention.

   Note: Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease.

10. Has not recovered adequately from surgery and/or any complications from the surgery.

    Note: For participants who will receive bevacizumab, surgery must have been at least 28 days before randomization.

11. Has received colony-stimulating factors (eg, G-CSF, GM-CSF or recombinant erythropoietin) within 4 weeks before randomization.
12. Has received a live or live-attenuated vaccine within 30 days before the first dose of study intervention. Administration of killed vaccines are allowed.

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

Prior/Concurrent Clinical Study Experience

13. Has received an investigational agent or has used an investigational device within 4 weeks prior to study intervention administration.

Diagnostic Assessments

14. 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 before the first dose of study medication.
15. Has a known additional malignancy that is progressing or has required active treatment within the past 3 years.

    Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ, excluding carcinoma in situ of the bladder, that have undergone potentially curative therapy are not excluded.

16. Has known active CNS metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable, (ie, without evidence of progression) for at least 4 weeks by repeat imaging (Note: The repeat imaging should be performed during study screening.), clinically stable and without requirement of steroid treatment for at least 14 days before the first dose of study intervention.

    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.

17. Has severe hypersensitivity (≥Grade 3) to pembrolizumab, paclitaxel, or bevacizumab (if using) and/or any of their excipients.

    Note: participants with known sensitivity to Chinese Hamster Ovary (CHO) cell products or other recombinant human or humanized antibodies are prohibited from receiving bevacizumab during the study.

18. Has an active autoimmune disease that has required systemic treatment in the past 2 years (ie, with use of disease modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.
19. Has a history of (noninfectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease.
20. Has an active infection requiring systemic therapy.
21. Has a known history of HIV infection.

    Note: No HIV testing is required unless mandated by local health authority. Refer to Appendix 7 for country-specific requirements.

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

    Note: No testing for Hepatitis B and Hepatitis C is required unless mandated by local health authority. Refer to Appendix 7 for country-specific requirements.

23. Has a history or current evidence of any condition, therapy, laboratory abnormality, or other circumstance that might confound the results of the study or interfere with the participant's participation for the full duration of the study, such that it is not in the best interest of the participant to participate, in the opinion of the treating investigator.
24. Has a known psychiatric or substance abuse disorder that would interfere with the participant’s ability to cooperate with the requirements of the study.

Other Exclusions

25. Participant, in the judgement of the investigator, is unlikely to comply with the study procedures, restrictions, and requirements of the study.
26. Has had an allogenic tissue/solid organ transplant.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

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

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

No restrictions are required.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study, but are not subsequently randomized in the study. A minimal set of screen-failure information is required to ensure transparent reporting of screen-failure participants to meet the 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.

Participants who fail screening may be rescreened for eligibility after consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

5.5 Participant Replacement Strategy

A participant who discontinues from study intervention OR withdraws from the study will not be replaced.

6 STUDY INTERVENTION

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

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

6.1 Study Intervention(s) Administered

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

Country-specific differences are noted in Appendix 7.

Table 4 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period	Use	IMP or NIMP/ AxMP	Sourcing
Arm 1	Experimental	Pembrolizumab (MK-3475)	Drug	Solution	25 mg/mL	400 mg	IV Infusion	Q6W for 18 cycles	Test Product	IMP	Central
Arm 1	Experimental	Paclitaxel	Drug	Solution	Variable	80 mg/m^2	IV Infusion	Days 1, 8, 15 of each Q3W cycle until disease progression or prohibitive toxicity	Background Treatment	NIMP/AxMP	Local or central
Arm 1	Experimental	Docetaxel (in place of paclitaxel, only after Sponsor consultation)	Drug	Solution	Variable	75 mg/m^2	IV Infusion	Q3W until disease progression or prohibitive toxicity	Background Treatment	NIMP/AxMP	Local or central
Arm 1	Experimental	Bevacizumab (if using)	Drug	Solution	25 mg/mL	10 mg/kg	IV Infusion	Optional, Q2W until disease progression or prohibitive toxicity	Background Treatment	NIMP/AxMP	Local or central
Arm 2	Placebo Comparator	Placebo	Drug	Solution	Normal Saline or Dextrose	0 mg/mL	IV Infusion	Q6W for 18 cycles	Placebo	IMP	Local
Arm 2	Placebo Comparator	Paclitaxel	Drug	Solution	Variable	80 mg/m^2	IV Infusion	Days 1, 8, 15 of each Q3W cycle until disease progression or prohibitive toxicity	Background Treatment	NIMP/AxMP	Local or central
Arm 2	Placebo Comparator	Docetaxel (in place of paclitaxel, only after Sponsor consultation)	Drug	Solution	Variable	75 mg/m^2	IV Infusion	Q3W until disease progression or prohibitive toxicity	Background Treatment	NIMP/AxMP	Local or central

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period	Use	IMP or NIMP/ AxMP	Sourcing
Arm 2	Placebo Comparator	Bevacizumab (if using)	Drug	Solution	25 mg/mL	10 mg/kg	IV Infusion	Optional, Q2W until disease progression or prohibitive toxicity	Background Treatment	NIMP/AxMP	Local or central

Abbreviations: AxMP=auxiliary medicinal product; EEA=European Economic Area; IMP=investigational medicinal product; IV=intravenous; NIMP=noninvestigational medicinal product; QW=weekly; Q2/3/6W=every 2/3/6 weeks.

The unit dose strength for background treatment may vary depending on market availability.

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

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.

Paclitaxel and bevacizumab may continue until disease progression, prohibitive toxicity, other protocol-defined reasons for discontinuation, or the participant has received the maximum duration (if applicable) per the respective approved labels or local practice.

All study interventions will be administered on an outpatient basis.

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

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

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

6.1.1 Treatment

The initial treatment or first course of pembrolizumab consists of 18 Q6W treatments. Note: The number of treatments is calculated starting with the first dose.

These participants may be eligible for Second Course described in Section 6.1.2.

6.1.2 Second Course

All participants who have completed the first course may be eligible for up to an additional 9 Q6W cycles of pembrolizumab if there is investigator-determined progressive disease by RECIST 1.1 after initial treatment or first course has been completed or stopped for confirmed CR. This retreatment is the Second Course of this study.

Participants may enter the Second Course if all of the following criteria are met:

1. The participant received pembrolizumab, determined on unblinding if applicable
2. No new anticancer treatment was administered after the last dose of study intervention
3. The participant meets all of the inclusion criteria and none of the exclusion criteria
4. The study is ongoing

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Details on preparation and administration of pembrolizumab are provided in the Pharmacy Manual. Paclitaxel, bevacizumab (if using), and docetaxel (if used in place of paclitaxel) will be prepared and administered as per the approved product label(s) and institutional guidelines.

6.2.2 Handling, Storage, and Accountability

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

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

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

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

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Intervention randomization will occur centrally using an IRT system. There are 2 study intervention arms. Participants will be assigned randomly in a 1:1 ratio to Arm 1 (pembrolizumab + paclitaxel with or without bevacizumab) and Arm 2 (placebo + paclitaxel with or without bevacizumab), respectively.

6.3.2 Stratification

Intervention randomization will be stratified according to the following factors:

1. Planned bevacizumab use in the study (yes vs no)
2. Region (US vs EU vs ROW)
3. PD-L1 status (CPS <1 vs CPS 1 to <10 vs CPS ≥10)

A total of 18 strata will be used for this study.

6.3.3 Blinding

A double-blinding technique will be used. Pembrolizumab and pembrolizumab placebo will be prepared and/or dispensed in a blinded fashion by an unblinded pharmacist or qualified study-site personnel. The participant, the investigator, and Sponsor personnel or delegate(s) who are involved in the study intervention administration or clinical evaluation of the participants are unaware of the intervention assignments. Paclitaxel (or docetaxel) and bevacizumab (if applicable) will be administered open-label.

The Sponsor, investigators, participants, and other study-site staff will be masked to participant PD-L1 status throughout the study.

6.4 Study Intervention Compliance

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

Refer to Section 6.6.1 for Dose Modification and Toxicity Management Guidelines for irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations and for other allowed dose interruptions.

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant ID will be confirmed at the time of dosing by a member of the study-site staff other than the person administering the study intervention.

6.5 Concomitant Therapy

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

The following medications and vaccinations are prohibited during the study:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol

- Hormonal therapy
- Investigational agents other than pembrolizumab
- Radiation therapy

  Note: Palliative radiation therapy to symptomatic lesions may be allowed following Sponsor consultation after assessment of disease progression has been determined.

- Live or live-attenuated vaccines within 30 days before the first dose of study intervention and while participating in the study (see Appendix 7 for country-specific requirements for live vaccines). Note: Killed vaccines are allowed.

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

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

- Systemic glucocorticoids except when used for the following purposes:
  - To modulate symptoms of an AE that is suspected due to chemotherapy or to have an immunologic etiology
  - For the prevention of emesis or other chemotherapy-related side-effects
  - To premedicate for IV contrast allergies
  - To treat asthma or COPD exacerbations (only short-term oral or IV use in doses >10 mg/day prednisone equivalent)
  - For chronic systemic replacement not to exceed 10 mg/day prednisone equivalent
- Other glucocorticoid use except when used for the following purposes:
  - For topical use or ocular use
  - Intraarticular joint use
  - For inhalation in the management of asthma or COPD
- Prophylactic cytokines (eg, G-CSF, GM-CSF, or recombinant erythropoietin) should not be administered within 4 weeks before randomization, but may be administered during the treatment period.

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

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

For further information on the prohibited concomitant therapies for paclitaxel, docetaxel (if applicable), and bevacizumab (if applicable), please refer to their respective approved product label.

6.5.1 Cautions for Use of Paclitaxel

Caution should be exercised when paclitaxel is concomitantly administered with known substrates, inhibitors, or inducers of CYP2C8 and/or CYP3A4.

Note: A current list of strong/moderate inducers/inhibitors of CYP2C8 and CYP3A4 can be found at the below website. The link from the FDA does not provide an all-inclusive list. Any CYP2C8 or CYP3A4 inducers or inhibitors not approved in the US will not appear in the list. The investigator must review locally-approved product labels and use best medical judgment.

https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

6.5.2 Cautions for Use of Docetaxel

Docetaxel is a CYP3A4 substrate. In vitro studies have shown that the metabolism of docetaxel may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by CYP3A4. Avoid using concomitant strong CYP3A4 inhibitors with docetaxel. Close monitoring for toxicity and a 50% docetaxel dose reduction should be considered if systemic administration of a potent CYP3A4 inhibitor cannot be avoided.

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 Section 6.6.

6.6 Dose Modification (Escalation/Titration/Other)

Dose modifications in response to treatment-related AEs are permitted to keep the participant on study intervention, when appropriate. Details on the modifications for each study intervention are provided in the sections below. In general:

- If the participant experiences either a severe hypersensitivity reaction to paclitaxel or an AE requiring discontinuation of paclitaxel, then docetaxel may be substituted after consultation with the Sponsor.

- Pembrolizumab/placebo, paclitaxel (or docetaxel, if applicable), and bevacizumab (if using) may be interrupted together or separately at the investigator's discretion to determine which treatment component is the source for a given toxicity.
- Action may be taken independently for each component of study intervention (eg, chemotherapy should be discontinued for prohibitive toxicity that is chemotherapy-related, but pembrolizumab/placebo and bevacizumab, if using, may continue if well tolerated).
- Chemotherapy may be interrupted, dose reduced or discontinued.
- Pembrolizumab/placebo and bevacizumab may only be interrupted or discontinued.

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

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

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

Dose Modification and Toxicity Management Guidelines for irAEs Associated With Pembrolizumab Monotherapy, Coformulations, or IO Combinations are provided in Table 5.

Table 5 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 (CTCAE v5.0)	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 to 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea/Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 to 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 (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
AST or ALT Elevation or Increased Bilirubin	Grade 2 [a]	Withhold	• Administer corticosteroids (initial dose of 0.5 to 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 [b] or 4 [c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1 to 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 [d]	• Initiate insulin replacement therapy for participants with T1DM • Administer antihyperglycemic 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 [d]		
Hyperthyroidism	Grade 2	Continue	• Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d]		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Hypothyroidism	Grade 2, 3 or 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological Toxicities	Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Asymptomatic cardiac enzyme elevation with clinical suspicion of myocarditis (which was previously myocarditis Grade 1 using CTCAE v4.0)	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		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
All Other irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event [e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

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

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

[a] AST/ALT: >3.0 to5.0 x ULN if baseline normal; >3.0 to 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 x ULN if baseline normal; >1.5 to 3.0 x baseline if baseline abnormal

[b] AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 to 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 x ULN if baseline normal; >3.0 to 10.0 x baseline if baseline abnormal

[c] AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal

[d] 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.

[e] Events that require discontinuation include, but are not limited to: encephalitis and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

Dose Modification and Toxicity Management of Infusion Reactions Related to Pembrolizumab Monotherapy, Coformulations, or IO Combinations

Pembrolizumab monotherapy, coformulations, or IO combinations may cause severe or life-threatening infusion reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab monotherapy, coformulations, or IO combinations associated infusion reactions are provided in Table 6.

Table 6 Pembrolizumab Monotherapy, Coformulations or IO Combinations Infusion Reaction Dose Modification and Treatment Guidelines

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

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

CTCAE=Common Terminology Criteria for Adverse Events; h=hour; IV=intravenous; NCI=National Cancer Institute; NSAIDs=nonsteroidal anti-inflammatory drugs.
Note: Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration.
For further information, please refer to the CTCAE v5.0 at http://ctep.cancer.gov

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

Pembrolizumab monotherapy, coformulations, or IO combinations may be interrupted for situations other than treatment-related AEs such as medical or surgical events and/or unforeseen circumstances not related to study intervention. However, study intervention is to be restarted within 6 weeks (42 days) of the originally scheduled dose and within 12 weeks (84 days) of the previously administered dose, unless otherwise discussed with the Sponsor. The reason for study intervention interruption is to be documented in the participant's study record.

6.6.2 Dose Modification for Chemotherapy-related Toxicity

Management for participants (ie, dose reduction, interruption, or discontinuation) who experience paclitaxel-related toxicity will be in accordance with the paclitaxel prescribing information in each country/region or local institutional guidelines. For participants who have transitioned to docetaxel due to paclitaxel-related toxicity, management of docetaxel-related toxicity will be in accordance with the docetaxel prescribing information in each country/region or local institutional guidelines. Participants may not start paclitaxel with a reduced dose. Participants must initiate Cycle 1 Day 1 with the protocol-specified dose of 80 mg/m^2 QW for paclitaxel.

Interruptions from paclitaxel (or docetaxel, if applicable) of greater than 6 consecutive weeks (42 days) from the originally scheduled dose require consultation between the investigator and the Sponsor.

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. To minimize dose reductions, interruptions, and discontinuations of chemotherapy, these supportive care measures should be used before implementing dose modifications, when appropriate.

6.6.3 Dose Modification for Bevacizumab-related Toxicity

Management for participants (ie, interruption or discontinuation) who experience bevacizumab-related toxicity will be in accordance with the bevacizumab prescribing information in each country/region or local institutional guidelines.

Interruptions from bevacizumab of greater than 6 consecutive weeks (42 days) from the originally scheduled dose require consultation between the investigator and the Sponsor.

6.7 Intervention After the End of the Study

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

6.8 Clinical Supplies Disclosure

The emergency unblinding call center will use the intervention/randomization schedule for the study to unblind participants and to unmask study intervention identity. The emergency unblinding call center should only be used in cases of emergency (see Section 8.1.10). If the emergency unblinding call center is not available for a given site in this study, the central electronic intervention randomization system (IRT) should be used to unblind participants and to unmask study intervention identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

6.9 Standard Policies

Not applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

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

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention before completion of the protocol-specified treatment period will still continue to be monitored in this study and participate in the study visits and procedures as specified in Section 1.3 and Section 8.11.3 unless the participant has withdrawn from the study as specified in Section 7.2.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons.

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

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- Any prolonged interruption of study intervention beyond the permitted periods, for irAE management or other allowed dose interruptions, as noted in Section 6.6.1, require Sponsor consultation prior to restarting treatment. If treatment will not be restarted, the participant will continue to be monitored in the study and the reason for discontinuation of study intervention will be recorded in the medical record.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive serum pregnancy test.
- Radiographic disease progression outlined in Section 8.2.1.5, documented by the investigator per RECIST 1.1 (after obtaining informed consent addendum and Sponsor communication, the investigator may elect to continue treatment beyond disease progression).

  Note: Where treatment is continued beyond disease progression, Sponsor consultation should be sought after each subsequent imaging evaluation and where the investigator may continue treatment.

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

  Note: If only local treatment is performed for an occurrence of another malignancy, the participant may continue on study intervention upon Sponsor consultation and approval.

- Any study intervention-related toxicity specified as a reason for permanent discontinuation as defined in the guidelines for dose modification due to AEs in Section 6.6.

  Note: Requirement for toxicity-related discontinuation applies to each treatment component individually (eg, paclitaxel should be discontinued for prohibitive toxicity that is paclitaxel-related, but pembrolizumab/placebo and bevacizumab [if using] may continue if well tolerated).

- Completion of 18 administrations of pembrolizumab/placebo (calculated from first dose), or the participant has received the maximum duration of paclitaxel (or docetaxel, if applicable), and bevacizumab (if using) per the approved label or local practice.

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

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

7.2 Participant Withdrawal From the Study

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

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

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from FBR, are outlined in Section 8.1.9. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

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

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

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

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study-site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All study-related medical decisions must be made by an investigator who is a qualified physician.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before providing documented informed consent may be used for screening or baseline purposes provided the procedures meet the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

The maximum amount of blood collected from each participant over the duration of the study will not exceed the amount specified in the Laboratory Manual.

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

8.1 Administrative and General Procedures

8.1.1 Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented informed consent from each potential participant (or their legally acceptable representative) prior to participating in this clinical study or FBR. If there are changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate documented informed consent is in place. Refer to Appendix 7 for country-specific requirements.

8.1.1.1 General Informed Consent

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

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

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

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

Specifics about the study and the study population are to be included in the study informed consent form.

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

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator, who is a qualified physician, to ensure that the participant meets eligibility requirements before randomization.

8.1.3 Participant Identification Card

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

the participant provides documented informed consent. At the time of intervention randomization, site personnel will add the treatment/randomization number to the participant identification card.

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

8.1.4 Medical History

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

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

8.1.4.1 Ovarian Cancer History Details

Comprehensive details regarding the participant's OC history will be recorded separately and not listed as medical history. These details include, but are not limited to, FIGO stage at diagnosis (Appendix 8), histopathology, location(s) of tumor burden, investigator-assessed tumor burden at baseline per RECIST 1.1, BRCA and/or HRD status (if local results are available), and all prior treatment (including prior radiation, prior chemotherapy, and prior surgery).

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 28 days before starting the study. Treatment for the disease for which the participant has enrolled in this study will be recorded separately and not listed as a prior medication.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study and up to 30 days after the last dose of study intervention. In addition, new medications started during the Second Course and up to 30 days after the last dose of study intervention in Second Course should be recorded.

All concomitant medications administered during SAEs and ECIs (as defined in Section 8.4) are to be recorded.

8.1.5.3 Subsequent Anticancer Treatment

Details of subsequent treatments for cancer (including surgical procedures and radiation) after discontinuation of study intervention will be collected. These details include, but are not limited to, treatment start and stop dates, reason for treatment, response to treatment, dates of progression after the completion of subsequent treatment, and reason for discontinuation from treatment. This information will be required for all subsequent anticancer treatments, including, but not limited to, other PD-1/PD-L1 inhibitors, PARP inhibitors, or investigational drugs.

8.1.6 Assignment of Screening Number

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

Any individual who is screened multiple times will retain the original screening number assigned at the initial Screening Visit. Specific details on the screening/rescreening visit requirements are in Section 8.11.1.

8.1.6.1 Treatment Eligibility Assessment Form

Two TEA forms are included in this study to document the investigator's choice of selecting or not selecting bevacizumab treatment and the rationale.

TEA1 form will document the justification for adding bevacizumab to SOC paclitaxel (if applicable).

TEA2 form will document why bevacizumab was not selected (if applicable).

The investigator must complete these forms before randomization.

8.1.7 Assignment of Treatment/Randomization Number

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

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

8.1.8 Study Intervention Administration

Study intervention(s) will be administered by the investigator and/or study staff according to the specifications within the Pharmacy Manual.

Treatment sequencing:

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

1. Pembrolizumab or placebo
2. Paclitaxel (or docetaxel, if applicable)
3. Bevacizumab (if using)

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

Additional dosing details are provided in Section 8.1.8.1.

Study intervention should begin within 3 days of randomization.

8.1.8.1 Timing of Dose Administration

8.1.8.1.1 Pembrolizumab/Placebo

Pembrolizumab will be administered as a dose of 400 mg Q6W for 18 cycles using a 30-minute IV infusion. 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 25 to 40 minutes).

The first dose of pembrolizumab/placebo must be administered within 3 days after randomization. Pembrolizumab/placebo should be administered every 42 days (±3 days).

The Pharmacy Manual contains specific instructions for pembrolizumab/placebo preparation.

8.1.8.1.2 Paclitaxel (or Docetaxel)

Paclitaxel will be initiated on Cycle 1 Day 1 with the first administration of pembrolizumab/placebo, within 3 days after randomization. Paclitaxel may continue until disease progression, prohibitive toxicity, other protocol-defined reasons for discontinuation, or the participant has received the maximum duration (if applicable) per the respective approved label or local practice.

Paclitaxel will be administered by IV infusion as a dose of 80 mg/m^2 on Days 1, 8, and 15 of each Q3W cycle according to prescribing information in each country/region or local institutional guidelines. The permitted window for paclitaxel dosing after Cycle 1 Day 1 is ±1 day.

Paclitaxel-related toxicities should be managed according to local practice and institutional guidelines with supportive care measures, dose interruptions and reductions before consideration of discontinuation, if clinically appropriate. Docetaxel (75 mg/m^2 Q3W) 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. Refer to Appendix 7 for country-specific requirements. If the participant is receiving a concomitant strong CYP3A4 inhibitor, close monitoring for toxicity and a 50% docetaxel dose reduction should be considered.

The preparation and administration of paclitaxel (or docetaxel, if applicable) should follow the local label and/or institutional guidelines. 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.

8.1.8.1.3 Bevacizumab

The use of bevacizumab is optional and may be administered to eligible participants at the investigator's discretion. Use of bevacizumab must be decided before randomization as it is a stratification factor.

Bevacizumab will be initiated on Cycle 1 Day 1 with the first administration of pembrolizumab/placebo. Bevacizumab may continue until disease progression, prohibitive toxicity, other protocol-defined reason for discontinuation, or the participant has received the maximum duration (if applicable) per the respective approved label or local practice.

Bevacizumab 10 mg/kg will be administered as an IV infusion Q2W, preferably following paclitaxel (or docetaxel, if applicable). The permitted window for bevacizumab dosing is ±3 days. Refer to Appendix 7 for country-specific requirements.

The preparation and administration of bevacizumab should follow the local label and/or institutional guidelines. The bevacizumab biosimilar Zirabev™ (bevacizumab-bvzr, Pfizer Inc.) may be allowed only after consultation with the Sponsor. Other biosimilars may be considered if approved in combination with paclitaxel in this indication in the US, EU, and other regions at the same time, only after consultation with the Sponsor.

Participants should remain on the same drug for the duration of the study. If a participant starts with Avastin, she should continue with Avastin until completion or discontinuation. If she starts on Zirabev, she should continue with Zirabev until completion or discontinuation. Similarly, participants receiving other biosimilars in accordance with the conditions above should remain on that biosimilar for the duration of the study.

8.1.9 Discontinuation and Withdrawal

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

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

8.1.9.1 Withdrawal From Future Biomedical Research

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

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

8.1.10 Participant Blinding/Unblinding

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.

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

Participants whose treatment assignment has been unblinded by the investigator or medically qualified designee and/or nonstudy treating physician 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. If the emergency unblinding call center is not available for a given site in this study, the IRT system should be used for emergency unblinding if 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.

Note: In some instances (emergency and nonemergency), unblinding to study intervention may be needed for appropriate clinical management of complications, but may not necessitate discontinuation of study intervention. The Sponsor's Clinical Director must be consulted to review individual requests, and the collaborative decision to unblind and allow a participant to remain on study intervention must be documented.

8.1.10.1 Nonemergency Unblinding

Nonemergency unblinding to study intervention (pembrolizumab/placebo) administration may occur on an individual participant basis and only after consultation with the Sponsor under the following circumstances:

- Disease progression (as assessed by investigator) with discontinuation of study intervention and the participant is being considered for alternate treatment that necessitates knowledge of prior treatment on the study.
- An AE necessitating discontinuation of study intervention and unblinding is required for appropriate clinical management of complications.

8.1.11 Calibration of Equipment

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

8.1.12 Tumor Tissue for Biomarker Status

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

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

Or

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

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

Details pertaining to tumor tissue submission can be found in the Laboratory Manual. Refer to Appendix 7 for country-specific requirements.

The central laboratory will use the tissue sample to ascertain PD-L1 status using the PD-L1 IHC 22C3 pharmDx (Investigational Use Only) diagnostic kit. The diagnostic test is identical to the US FDA-approved PD-L1 IHC 22C3 pharmDx diagnostic kit except it is labeled IUO.

The PD-L1 result will be masked to the site and Sponsor. PD-L1 status must be determined before randomization as it is a stratification factor.

8.2 Efficacy Assessments

8.2.1 Tumor Imaging and Assessment of Disease

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

In addition to survival, efficacy will be assessed based on evaluation of scan changes in tumor burden over time, until the participant is discontinued from efficacy follow-up and goes into survival follow-up. The process and acceptable modality for scan collection and transmission to the iCRO can be found in the SIM. The same scan technique should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the response assessment based on scans.

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

If brain scans are performed, MRI is preferred; however, CT imaging will be acceptable, if MRI is medically contraindicated.

Bone scans may be performed to evaluate bone metastases. Any supplemental scans performed to support a positive or negative bone scan, such as plain X-rays acquired for correlation, should also be submitted to the iCRO.

Other imaging modalities that may be collected, submitted to the iCRO, and included in the response assessment include PET and X-rays. Other types of medical imaging (such as ultrasound) should not be submitted to the iCRO and will not be included in response assessment.

Participant eligibility and the primary PFS endpoint will be determined using local assessment (investigator assessment) based on RECIST 1.1. All scheduled scans for each participant will be submitted to the iCRO for assessment of the secondary PFS endpoint by BICR. In addition, unscheduled scans used to determine disease progression and scans obtained for other reasons, but which show radiologic progression, are to be submitted to the iCRO.

8.2.1.1 Initial Tumor Scans

The screening scans for randomized participants must be submitted to the iCRO.

Tumor scans performed as part of routine clinical management are acceptable for screening if they are of acceptable diagnostic quality and performed within 28 days of randomization and can be assessed by the iCRO.

If brain scans are required to document the stability of existing metastases, the brain scan should be acquired during screening. The specific methods permitted for this study are described in the SIM.

Bone scans are required at screening for participants with a history of bone metastases and/or for those participants with indicative clinical signs/symptoms such as bone pain or elevated alkaline phosphatase levels.

Bone scan refers to imaging methods used to assess bone metastasis. The specific methods permitted for this study are described in the SIM.

8.2.1.2 Tumor Scans During the Study

The first on-study scan should be performed at 9 weeks (63 days ±7 days) from the date of randomization. Subsequent tumor scans should be performed every 9 weeks (63 days ±7 days) or more frequently if clinically indicated. After 54 weeks (378 days ±7 days), participants who remain on treatment will have scans performed every 12 weeks (84 days ±7 days). Scan timing should follow calendar days and should not be adjusted for delays in cycle starts. Scans are to be performed until disease progression is identified by the investigator, or until the start of new anticancer treatment, withdrawal of consent, pregnancy, death, or the end of the study, whichever occurs first.

Objective response should be confirmed by a repeat scan performed at least 4 weeks after the first indication of a response is observed. Participants will then return to the regular scan schedule, starting with the next scheduled time point. Participants who receive additional scans for confirmation do not need to undergo the next scheduled scan if it is fewer than 4 weeks later; scans may resume at the subsequent scheduled time point.

On-study brain or bone scans should be performed if clinically indicated or to confirm CR (if other lesions indicate CR and brain or bone lesions existed at baseline).

8.2.1.3 End-of-treatment and Follow-up Tumor Scans

If participants discontinue study intervention, tumor scans should be performed at the time of discontinuation (±4-week window) unless previous scans were obtained within 4 weeks of discontinuation. If participants discontinue study intervention due to documented disease progression, this is the final required tumor scan.

If participants discontinue study intervention without documented disease progression, every effort is to be made to monitor disease status by acquiring tumor scans using the same schedule calculated from the date of randomization, refer to Section 8.2.1.2.

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

- disease progression as defined by RECIST 1.1 as assessed by the investigator
- the start of a new anticancer treatment
- pregnancy
- death
- withdrawal of consent
- the end of the study

Participants who are clinically stable may be treated beyond RECIST 1.1 radiographic progression after consultation with the Sponsor (see Section 8.2.1.5).

8.2.1.4 Second Course (Retreatment) Tumor Scans

Tumor scans must be performed within 28 days before restarting study intervention with pembrolizumab.

Response assessments and progressive disease are determined by investigator assessment.

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

The first scan should be performed at 12 weeks (84 days ±7 days) after restarting study intervention. Subsequent tumor scans are to be performed every 12 weeks (84 days ±7 days) or more frequently, if clinically indicated.

Scans are to be performed until disease progression, the start of a new anticancer treatment, withdrawal of consent, death, completion of Second Course, or notification by the Sponsor, whichever occurs first.

If participants discontinue study intervention, tumor scans are to be performed at discontinuation (±4 week window) unless previous scans were obtained within 4 weeks of discontinuation. If participants discontinue study intervention due to documented disease progression, this is the final required tumor scan.

If participants discontinue study intervention without documented disease progression, every effort is to be made to monitor disease status by acquiring tumor scans every 12 weeks (84 days ±7 days) until the start of a new anticancer treatment, disease progression, withdrawal of consent, pregnancy, death, or the end of the study, whichever occurs first.

8.2.1.5 RECIST 1.1 Assessment of Disease

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

If disease progression is established by the investigator, the process continues as follows:

- investigator judgement will determine action
- if the participant is clinically stable and study intervention is to continue, communication with the sponsor is required and a reconsent addendum must be signed
- obtain scans per original protocol schedule
- send scans to iCRO

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

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

As described above, treatment beyond documented disease progression may be permitted at the discretion of the investigator after consultation with the Sponsor and receiving appropriate documented informed consent. Sponsor consultation should be sought after each subsequent imaging evaluation and where the investigator may continue treatment.

8.2.2 Tumor Marker Assessment

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

8.2.3 Patient-reported Outcomes

The PRO questionnaire will be administered by trained site personnel and completed electronically by participants in the following order: EORTC QLQ-C30 first, then EORTC QLQ-OV28, and EQ-5D-5L. The questionnaires should be administered according to the schedule in the SoA (Section 1.3.1). It is acceptable for laboratory safety tests to be performed before administration of ePROs to accommodate institutional practice.

It is best practice and strongly recommended that ePROs are administered to randomized participants before drug administration, AE evaluation, and disease status notification. If the participant does not complete the ePROs at a scheduled time point, the MISS_MODE form must be completed to capture the reason the assessment was not performed.

Site staff must not read, administer, or complete the PRO questionnaires on behalf of the participant. If the participant is unable to read the questionnaire (eg, is blind or illiterate), that participant may still participate in the study, but is exempt from completing PRO questionnaires. Participants exempt in this regard should be documented appropriately by the site staff. Voice scripts may be used to complete the PRO questionnaires if available in the participant's local language.

8.3 Safety Assessments

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

The total amount of blood/tissue to be drawn/collected over the course of the study (from prestudy to poststudy visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant, can be found in the Laboratory and/or Procedures Manual.

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

8.3.1 Physical Examinations

A complete or symptom-directed physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standards.

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

8.3.1.1 Full Physical Examination

The investigator or qualified designee will perform a complete physical examination during the Screening period. Clinically significant abnormal findings should be recorded as medical history. The time points for full physical examinations are described in Section 1.3. After the first dose of study intervention, new clinically significant abnormal findings should be recorded as AEs.

8.3.1.2 Directed Physical Examination

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

8.3.2 Vital Signs

The investigator or qualified designee will assess vital signs at screening and as specified in the SoA (Section 1.3). Vital signs will include height (at screening only), weight, temperature, systolic and diastolic blood pressure, pulse rate, and respiratory rate. It is highly recommended that abnormal blood pressure measurements be confirmed.

For participants receiving bevacizumab, blood pressure should be measured before each bevacizumab administration (Q2W).

8.3.3 Electrocardiograms

A standard 12-lead ECG will be obtained at screening and reviewed by an investigator or medically qualified designee (consistent with local requirements) as outlined in the SoA (Section 1.3). Additional ECGs may be performed during the study as clinically indicated.

8.3.4 Clinical Safety Laboratory Assessments

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

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the Laboratory Manual and the SoA.
- If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).
- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

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

8.3.4.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

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

8.3.5 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 monthly intervals during intervention.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted for the time required to eliminate systemic exposure after the last dose of each study intervention as noted in Section 5.1. The length of time required to continue pregnancy testing for each study intervention is as follows:
  - Pembrolizumab: 120 days
  - Paclitaxel (or docetaxel, if applicable): 180 days
  - Bevacizumab (if administered): 180 days
- 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 subject's participation in the study.
- Home pregnancy tests are acceptable when a scheduled visit does not occur within the month (per local regulation), but the site must make monthly telephone contact with the participant to determine the results of the pregnancy test. The results of the test must be recorded in the participant’s eCRF.

8.3.6 Performance Assessments

8.3.6.1 Eastern Cooperative Oncology Group Performance Status

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

The investigator or qualified designee will assess ECOG performance status (see https://ecog-acrin.org/resources/ecog-performance-status) at screening (within 3 days before randomization) to determine eligibility, and at subsequent timepoints as specified in the SoA (Section 1.3).

8.4 Adverse Events, Serious Adverse Events, and Other Reportable Safety Events

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

Progression of the cancer under study is not considered an AE as described in Section 8.4.6 and Appendix 3.

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

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators need to document if an SAE was associated with a medication error, misuse, or abuse.

Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3. The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity, and causality.

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

All AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent, but before intervention randomization, must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event cause the participant to be excluded from the study, or is the result of a protocol-specified intervention, including, but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

- All AEs from the time of intervention randomization through 30 days after cessation of study intervention must be reported by the investigator.
- All AEs meeting serious criteria, from the time of intervention randomization through 90 days after cessation of study intervention or 30 days after cessation of study intervention if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator.
- All pregnancies and exposure during breastfeeding, from the time of intervention randomization through the time required to eliminate systemic exposure after cessation of study intervention as described in Sections 5.1 and 8.3.5, or 30 days after cessation of study intervention if the participant initiates new anticancer therapy must be reported by the investigator.

- Additionally, any SAE brought to the attention of an investigator at any time outside the time specified above must be reported immediately to the Sponsor if the event is considered related to study intervention.

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

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 7.

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

Table 7 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Time Period: Consent to Randomization/ Allocation**	**Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period**	**Reporting Time Period: After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Sponsor:**
NSAE	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
SAE including Cancer and Overdose	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event

Type of Event	**Reporting Time Period:** Consent to Randomization/ Allocation	**Reporting Time Period:** Randomization/ Allocation through Protocol-specified Follow-up Period	**Reporting Time Period:** After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor:
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
ECI (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - potential DILI - require regulatory reporting	Not required	Within 24 hours of learning of event
ECI (do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event

DILI=drug-induced liver injury; ECI=event of clinical interest; NSAE=nonserious adverse event; SAE=serious adverse event.

8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events, including pregnancy and exposure during breastfeeding, ECIs, cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will

make every attempt to follow all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

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

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

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

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

8.4.5 Pregnancy and Exposure During Breastfeeding

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

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

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

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

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

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

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

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

The Sponsor will ensure that unblinded aggregated efficacy endpoint events and safety data are monitored to safeguard the participants in the study.

8.4.7 Events of Clinical Interest

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

Events of clinical interest for this study include:

- An overdose of Sponsor's product, as defined in Section 8.5.
- An elevated AST or ALT laboratory value that is greater than or equal to 3X the ULN and an elevated total bilirubin laboratory value that is greater than or equal to 2X the ULN and, at the same time, an alkaline phosphatase laboratory value that is less than 2X the ULN, as 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).

8.5 Treatment of Overdose

For this study, an overdose of pembrolizumab will be defined as any dose of 1000 mg or greater.

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

8.6 Pharmacokinetics

To evaluate the immunogenicity and exposure of pembrolizumab in this indication, sample collections for analysis of ADA/NAb and PK are currently planned as shown in Section 1.3.1 (SoA). These samples will only be collected for participants receiving bevacizumab enrolled after approval of Amendment 03. Data analysis, if performed, will be reported separately.

Ongoing PK and/or ADA sampling may be reduced or discontinued upon alignment with requesting health authorities.

Sample collection, storage, and shipment instructions for PK and ADA samples will be provided in the laboratory procedure manual.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Biomarkers

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

- Blood for genetic analysis
- Blood for ctDNA analyses
- Tumor tissue

Sample collection, storage, and shipment instructions for the exploratory biomarker specimens will be in the Laboratory Manual. Refer to Appendix 7 for country-specific requirements.

8.8.1 Planned Genetic Analysis Sample Collection

The planned genetic analysis sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. 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 FBR if the participant provides documented informed consent for FBR. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.

Sample collection, storage, and shipment instructions for planned genetic analysis samples will be in the Operations/Laboratory Manual.

Refer to Appendix 7 for country-specific requirements.

8.9 Future Biomedical Research Sample Collection

If the participant provides documented informed consent for FBR, the following specimens will be obtained as part of FBR:

- Leftover from biomarker samples listed in Section 8.8.

8.10 Medical Resource Utilization and Health Economics

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

8.11 Visit Requirements

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

8.11.1 Screening

Documented informed consent must be provided before performing any protocol-specific procedure. Results of tests or procedures performed before the participant provides documented informed consent may be used for screening or baseline purposes provided the tests or procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

Screening procedures are to be completed within 28 days before the first dose of study intervention.

Participants may be rescreened after initially failing to meet the inclusion/exclusion criteria (see Section 5.4). 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 Sections 8.1, 8.2, and 8.3.

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

When a participant discontinues study intervention during the treatment period, procedures for study intervention discontinuation will be performed.

The End-of-Treatment Visit should occur at the time study intervention is discontinued for any reason. If the End-of-Treatment Visit occurs 30 days from the last dose of study intervention, at the time of the mandatory Safety Follow-up Visit, the End-of-Treatment Visit procedures and any additional safety follow-up procedures should be performed. Visit requirements are outlined in Section 1.3. Additional details regarding participant withdrawal and discontinuation are in Section 7.

8.11.4 Posttreatment Visit

Posttreatment visit requirements are outlined in the SoA (Section 1.3).

8.11.4.1 End-of-Treatment Visit

The End-of-Treatment Visit should occur at the time study intervention is completed or discontinued for any reason.

Participants who discontinue study treatment for a reason other than disease progression will still be considered on-study and should continue with regularly scheduled assessments (see Section 8.11.3), including collecting participant information on the start of new anticancer treatment, disease progression, and death. If the End-of-Treatment Visit occurs 30 days from the last dose of study intervention, at the same time as the mandatory 30-Day Safety Follow up visit, the End-of-Treatment Visit procedures and any additional Safety Follow-up procedures can be combined into a single visit.

8.11.4.2 Safety Follow-up Visit

The mandatory Safety Follow-up Visit should be conducted approximately 30 days after the last dose of study intervention or before initiation of a new anticancer treatment, whichever comes first. AEs should continue to be recorded until 30 days after the last dose of study intervention, regardless of whether or not the participant has started new anticancer treatment (see Section 8.4.1).

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

8.11.4.3 Efficacy Follow-up Visits

Participants who complete the protocol-required cycles of study intervention or who discontinue study intervention for a reason other than disease progression will begin Efficacy Follow-up and should be assessed according to the on-treatment scan schedule (Q9W [63 days ±7 days] from randomization through Week 54 and Q12W [84 days ±7 days] thereafter) to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anticancer treatment, disease progression, withdrawal of consent, pregnancy, death, end of study, or if the participant begins retreatment with pembrolizumab as detailed in Section 6.1.2. Information regarding poststudy anticancer treatment will be collected if new treatment is initiated. Participants who completed all efficacy assessments and/or will not have further efficacy assessments must enter Survival Follow-up.

Participants who are eligible to receive retreatment with pembrolizumab according to the criteria in Section 6.1.2 will move from Efficacy Follow-up to Second Course when they experience disease progression. Details are provided in the Second Course SoA (Section 1.3.2) for retreatment with pembrolizumab.

8.11.4.4 Survival Follow-up Contacts

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

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

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

8.11.5 Vital Status

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

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but before any unblinding, 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 nonconfirmatory analyses made after the protocol has been finalized, but before unblinding, will be documented in an sSAP and referenced in the 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.

Study Design Overview	A Phase 3, Randomized, Double-Blind Study of Pembrolizumab versus Placebo in Combination With Paclitaxel With or Without Bevacizumab for the Treatment of Platinum-resistant Recurrent Ovarian Cancer (KEYNOTE-B96)
Treatment Assignment	643 participants were randomized (double-blind) in a 1:1 ratio between 2 treatment arms: (1) pembrolizumab + paclitaxel ± bevacizumab and (2) placebo + paclitaxel ± bevacizumab. Stratification factors are as follows: 1. Planned bevacizumab use in the study (yes vs no) 2. Region (US vs EU vs ROW) 3. PD-L1 status (CPS <1 vs CPS 1 to <10 vs CPS ≥10)
Analysis Populations	Efficacy: ITT Safety: APaT PRO: PRO FAS
Primary Endpoints	1. PFS per RECIST 1.1 assessed by investigator in participants with PD-L1 positive tumors (CPS ≥1). 2. PFS per RECIST 1.1 assessed by investigator in all participants.
Key Secondary Endpoints	1. OS in participants with PD-L1 positive tumors (CPS ≥1). 2. OS in all participants.
Statistical Methods for Key Efficacy Analyses	The hypothesis testing for the primary endpoint of PFS and key secondary endpoint of OS will be evaluated by comparing the experimental group to the control group using a stratified log-rank test. The HR will be estimated using a stratified Cox proportional hazard model. Event rates over time will be estimated within each treatment group using the Kaplan-Meier method.
Statistical Methods for Key Safety Analyses	For analyses in which 95% CIs will be provided for between-treatment differences in the percentage of participants with events, these analyses will be performed using the Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985].

Interim Analyses	**Efficacy** Two efficacy interim analyses will be performed in this study. Results will be reviewed by an external data monitoring committee. These interim analyses are summarized below. Details are provided in Section 9.7. • Interim Analysis 1: ◦ Timing: To be performed when ~ 9 months after last participant randomized, and ~ 331 PFS events have been observed in participants with CPS ≥1, and ~ 460 PFS events have been observed in all participants. ◦ Testing: First interim PFS analysis and first interim OS analysis. • Interim Analysis 2: ◦ Timing: To be performed when ~ 20 months after last participant randomized, and ~ 389 PFS events have been observed in participants with CPS ≥1, and ~ 541 PFS events have been observed in all participants. ◦ Testing: Final PFS analysis and second interim OS analysis. • Final Analysis: ◦ Timing: To be performed after ~ 369 OS events have been observed in participants with CPS ≥1, and ~ 512 OS events have been observed in all participants. ◦ Testing: Final OS analysis. **Safety** An interim safety analysis may be performed and reviewed by the eDMC ~ 10 months after first participant is randomized. Afterwards, the eDMC will review safety data periodically in the study. Details will be specified in the DMC Charter.
Multiplicity	The overall type I error over the 2 primary hypotheses of PFS and the 2 secondary hypotheses of OS is strongly controlled at 2.5% (1-sided), with 2% initially allocated to PFS in participants with CPS ≥1 [H1] and 0.5% to PFS in all participants [H2]. By using the graphical approach of Maurer and Bretz [Maurer, W. and Bretz, F. 2013], if one null hypothesis is rejected, the alpha will be reallocated to other hypotheses. The study will be considered positive if it is successful for either PFS in participants with CPS ≥1 [H1] or PFS in all participants [H2].

Sample Size and Power	The sample size is 643 participants. • For PFS in participants with PD-L1 positive tumors (CPS ≥1), with ~ 389 estimated events at the final PFS analysis, the study has ~ 98% power to detect a HR of 0.66 at the initially allocated α=0.02 (1-sided). • For PFS in all participants, with ~ 541 estimated events at the final PFS analysis, the study has ~ 94% power to detect a HR of 0.70 at the initially allocated α=0.005 (1-sided). • For OS in participants with PD-L1 positive tumors (CPS ≥1), with ~ 369 estimated events at the final OS analysis, the study has ~ 96% power to detect a HR of 0.68 at the α=0.025 (1-sided). • For OS in all participants, with ~ 512 estimated events at the final OS analysis, the study has ~ 98% power to detect a HR of 0.70 at α=0.025 (1-sided).

9.2 Responsibility for Analyses/In-house Blinding

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

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

The investigator, site staff, participants, and study team at the Sponsor consisting of clinical, statistical, statistical programming and data management personnel, will be masked to participant-level PD-L1 biomarker results. An unblinded Sponsor clinical scientist, unblinded data management personnel, unblinded Sponsor statistician and unblinded Sponsor statistical programmer will have access to the participant-level PD-L1 results for the purpose of data review and will have no other responsibilities associated with the study. Summaries by PD-L1 status may be provided to the study team at the Sponsor by the unblinded Sponsor statistician or the IVRS vendor and will be limited and documented. In addition, efficacy assessments will be by investigator and by BICR without knowledge of treatment assignments or PD-L1 status.

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.

PRO: Change from baseline and TTD of the QoL and symptom scores from the EORTC QLQ-C30 GHS/QoL (items 29 and 30), and the Abdominal/GI symptom subscale (items 31 to 36) from EORTC QLQ-OV28.

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9.5 Analysis Populations

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9.5.1 Efficacy Analysis Populations

The analyses of efficacy endpoints are based on the ITT population. All randomized participants will be included in this population. Participants will be analyzed in the treatment group to which they are randomized.

9.5.2 Safety Analysis Populations

Safety analyses will be conducted in the APaT population, which consists of all randomized participants who received at least 1 dose of study 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 or vital sign 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.

9.5.3 PRO Analysis Populations

The PRO analyses are based on the 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

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 may be computed for other efficacy analyses, but should be interpreted with caution due to potential issues of multiplicity, sample size, etc.

9.6.1 Statistical Methods for Efficacy Analyses

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

The stratification factors used for randomization (see Section 6.3.2) will be applied to all stratified analyses, in particular, the stratified log-rank test, stratified Cox model, and stratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985]. If there are small strata, for the purpose of analysis, strata may be combined to ensure sufficient data in each stratum. Details regarding the pooling strategy will be prespecified in the sSAP prior to the database lock for the first efficacy analysis when each applicable endpoint will be analyzed, and decisions regarding the pooling will be based on a blinded review of data by stratum.

The efficacy analyses for PFS and ORR will include responses and documented progression events that occur before Second Course treatment.

9.6.1.1 Progression-Free Survival

The nonparametric 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, HR) between the treatment arms. The HR and its 95% CI from the stratified Cox model with a single treatment covariate will be reported. The stratification factors used for randomization (See Section 6.3.2) will be applied to both the stratified log-rank test and the stratified Cox model.

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

For the primary analysis, any participant who experiences an event (PD or death) immediately after 2 or more missed disease assessments will be censored at the last disease assessment prior to the missed visits. In addition, any participant who initiates new anticancer treatment prior to documented progression will be censored at the last disease assessment prior to the initiation of new anticancer treatment. Participants who do not start new anticancer treatment and who do not experience an event will be censored at the last disease assessment. If a participant meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied.

To evaluate the robustness of the PFS endpoint per RECIST 1.1 by investigator, 2 sensitivity analyses with different sets of censoring rules will be performed. The first sensitivity analysis follows the ITT principle. That is, PDs/deaths are counted as events regardless of missed study visits or initiation of new anticancer treatment. The second sensitivity analysis considers initiation of new anticancer treatment or discontinuation of treatment due to

reasons other than CR, whichever occurs later, to be a PD event for participants without documented PD or death. If a participant meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied. The censoring rules for the primary and sensitivity analyses are summarized in Table 8.

Table 8 Censoring Rules for Primary and Sensitivity 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 treatment, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death	Progressed at date of documented PD or death
Death or progression immediately after ≥2 consecutive missed disease assessments, or after new anticancer treatment	Censored at last disease assessment prior to the earlier date of ≥2 consecutive missed disease assessment and new anticancer treatment, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death
No PD and no death; and new anticancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment	Progressed at treatment discontinuation due to reasons other than complete response; otherwise censored at last disease assessment if still on study treatment or completed study treatment.
No PD and no death; new anticancer treatment is initiated	Censored at last disease assessment before new anticancer treatment	Censored at last disease assessment	Progressed at date of new anticancer treatment

Abbreviation: PD=progressive disease

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 initiation of new anticancer treatment, or death from any cause, whichever occurs 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 last time the participant was known to be alive and without 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 nonparametric Kaplan-Meier method will be used to estimate the OS curves. The treatment difference in survival will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the

magnitude of the treatment difference (ie, the HR). 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 (See Section 6.3.2) will be applied to both the stratified log-rank test and the stratified Cox model. Participants without documented death at the time of analysis will be censored at the date the participant was last known to be alive.

9.6.1.3 Analysis Strategy for Key Efficacy Variables

A summary of the primary analysis strategy for the key efficacy endpoints is provided in Table 9.

Table 9 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable	Statistical Method	Analysis Population	Missing Data Approach
Primary Analyses			
Primary Hypothesis 1			
PFS per RECIST 1.1 by investigator in participants with CPS ≥1	Testing: stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	• Primary censoring rule • Sensitivity analysis 1 • Sensitivity analysis 2 (More details are in Table 8)
Primary Hypothesis 2			
PFS per RECIST 1.1 by investigator in all participants	Testing: stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	• Primary censoring rule • Sensitivity analysis 1 • Sensitivity analysis 2 (More details are in Table 8)
Key Secondary Analyses			
Key Secondary Hypothesis 1 (Hypothesis 3)			
OS in participants with CPS ≥1	Testing: stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored at the date participant last known to be alive
Key Secondary Hypothesis 2 (Hypothesis 4)			
OS in all participants	Testing: stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored at the date participant last known to be alive
Other Secondary Analyses			
PFS per RECIST 1.1 by BICR in participants with CPS ≥1 and in all participants	Estimation: Stratified Cox model with Efron's tie handling method	ITT	Primary censoring rule (More details are in Table 8)
Abbreviations: BICR=blinded independent central review; CPS=combined positive score; ITT=intent-to-treat; OS=overall survival; PFS=progression-free survival; RECIST 1.1=Response Evaluation Criteria in Solid Tumors.			

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, and vital signs.

The analysis of safety results will follow a tiered approach (Table 10). The tiers differ with respect to the analyses that will be performed. AEs (specific terms as well as system organ class terms) 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

AEs that are immune-mediated or potentially immune-mediated are well documented and will be evaluated separately; however, these events have been characterized consistently throughout the pembrolizumab clinical development program and determination of statistical significance is not expected to add value to the safety evaluation. Similarly, the combination of pembrolizumab and paclitaxel has not been associated with any new safety signals. 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 using the Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985], an unconditional, asymptotic method.

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

Tier 3 Events

Safety 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 will be provided for Tier 3 safety parameters.

Continuous Safety Measures

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

Table 10 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 (laboratory toxicity shift, vital signs)		X
Abbreviations: AE=adverse event; CI=confidence interval; SOC=system organ class.			

9.6.3 Statistical Methods for PRO Analyses

This section describes the planned analyses for the PRO endpoints. Details of PRO analyses including exploratory PRO analysis will be described in the sSAP.

Change From Baseline

The time point for the change from baseline will be determined based on blinded data review before the database lock for any PRO analysis and the criteria will be documented in the sSAP.

To assess the treatment effects on the PRO score change from baseline in the QoL and symptom scores from the GHS/QoL scale of the EORTC QLQ-C30 and the abdominal/GI

symptom scores of the EORTC QLQ-OV28, a cLDA model proposed by Liang and Zeger [Liang, K.-Y. and Zeger, S. L. 2000] will be applied, with the PRO score as the response variable, and treatment, time, the treatment by time interaction, and stratification factors used for randomization (see Section 6.3.2) as covariates. The treatment difference in terms of least square (LS) mean change from baseline will be estimated from this model together with 95% CI. Model-based LS mean with 95% CI will be provided by treatment group for PRO scores at baseline and postbaseline time point.

Time to Deterioration

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

9.6.4 Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant demographic and baseline characteristic will be assessed by tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants screened and randomized and the primary reasons for screening failure and discontinuation will be displayed. Demographic variables, baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

9.7 Interim Analyses

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

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

9.7.1 Efficacy Interim Analysis

Two efficacy interim analyses are planned in addition to the final analysis for this study. For the interim and final analyses, all randomized participants will be included. Results of the interim analyses will be reviewed by the eDMC. Details of the boundaries for establishing statistical significance with regard to efficacy are discussed further in Section 9.8.

The analyses planned, endpoints evaluated, and drivers of timing are summarized in Table 11.

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9.7.2 Safety Interim Analysis

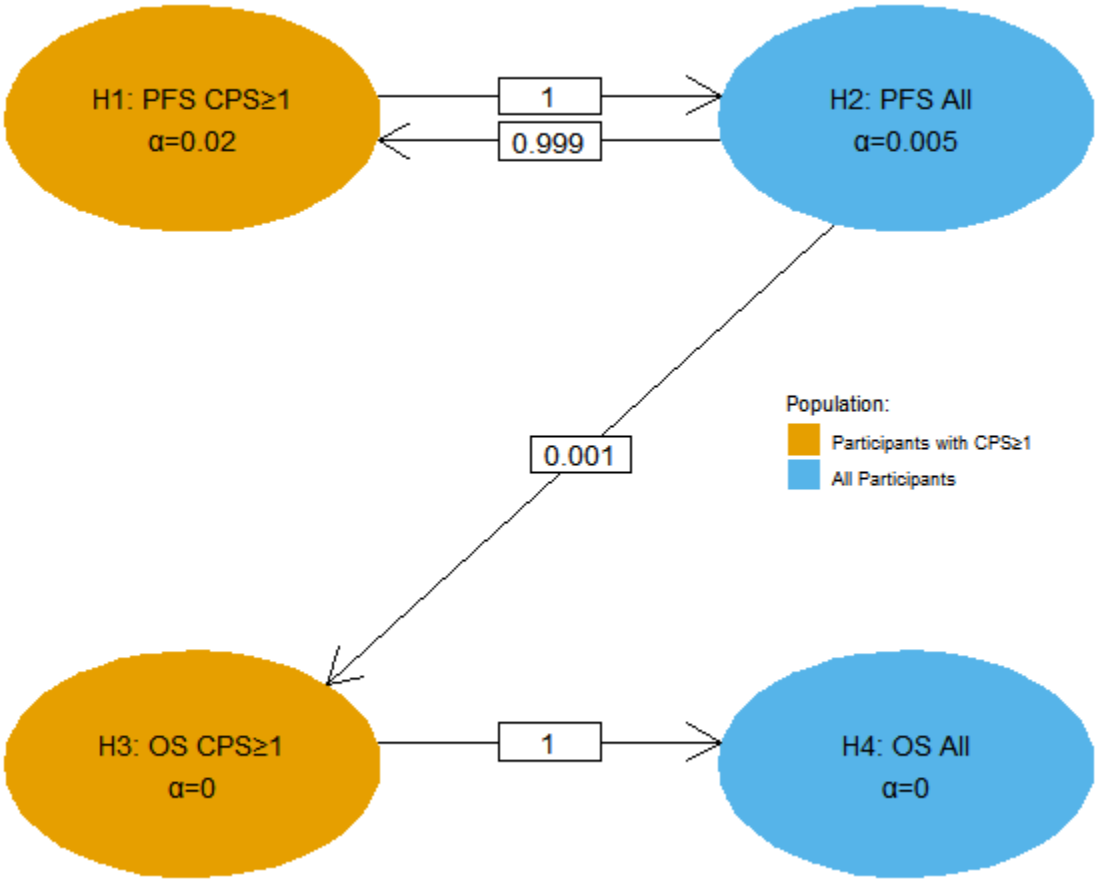
The eDMC will be responsible for periodic interim safety reviews as specified in the DMC charter. An interim safety analysis may be performed after ~ 10 months have elapsed after the first participant is randomized. Afterwards, the eDMC will review safety data periodically in the study. Interim safety analyses will also be performed at the time of interim efficacy analyses. Details will be specified in the DMC charter.

9.8 Multiplicity

The study uses the graphical method of Maurer and Bretz [Maurer, W. and Bretz, F. 2013] to provide strong multiplicity control for multiple hypotheses as well as interim analyses. According to this approach, study hypotheses may be tested more than once, and when a particular null hypothesis is rejected, the α allocated to that hypothesis can be reallocated to other hypothesis tests. Figure 2 shows the initial 1-sided α allocation for each hypothesis in the ellipse representing the hypothesis. The weights for reallocation from each hypothesis to the others are shown in the boxes on the lines connecting hypotheses.

The family-wise Type I error rate for this study is strongly controlled at 0.025 (one-sided) across the 2 primary hypotheses on PFS and the 2 secondary hypotheses on OS. The initial α assigned to PFS endpoints will be 0.02 to PFS in participants with CPS ≥1 and 0.005 assigned to PFS in all participants, respectively. No initial α will be assigned to OS endpoints. The study will be considered a success if PFS in participants with CPS ≥1 or PFS in all participants is shown to be statistically significant under multiplicity control. If the null hypothesis of PFS in participants with CPS ≥1 (H1) is rejected, the corresponding alpha can be reallocated to PFS in all participants (H2). If the null hypothesis of PFS in all participants (H2) is rejected, the corresponding alpha can be reallocated to PFS in participants with CPS ≥1 (H1). If both H1 and H2 are rejected, the corresponding alpha can be reallocated to OS in participants with CPS ≥1 (H3). If the null hypothesis of OS in participants with CPS ≥1 is rejected (H3), the corresponding alpha can be reallocated to OS in all participants (H4). A detailed graphical illustration of multiplicity will be provided in the sSAP.

Figure 2 Multiplicity Diagram for Type I Error Control



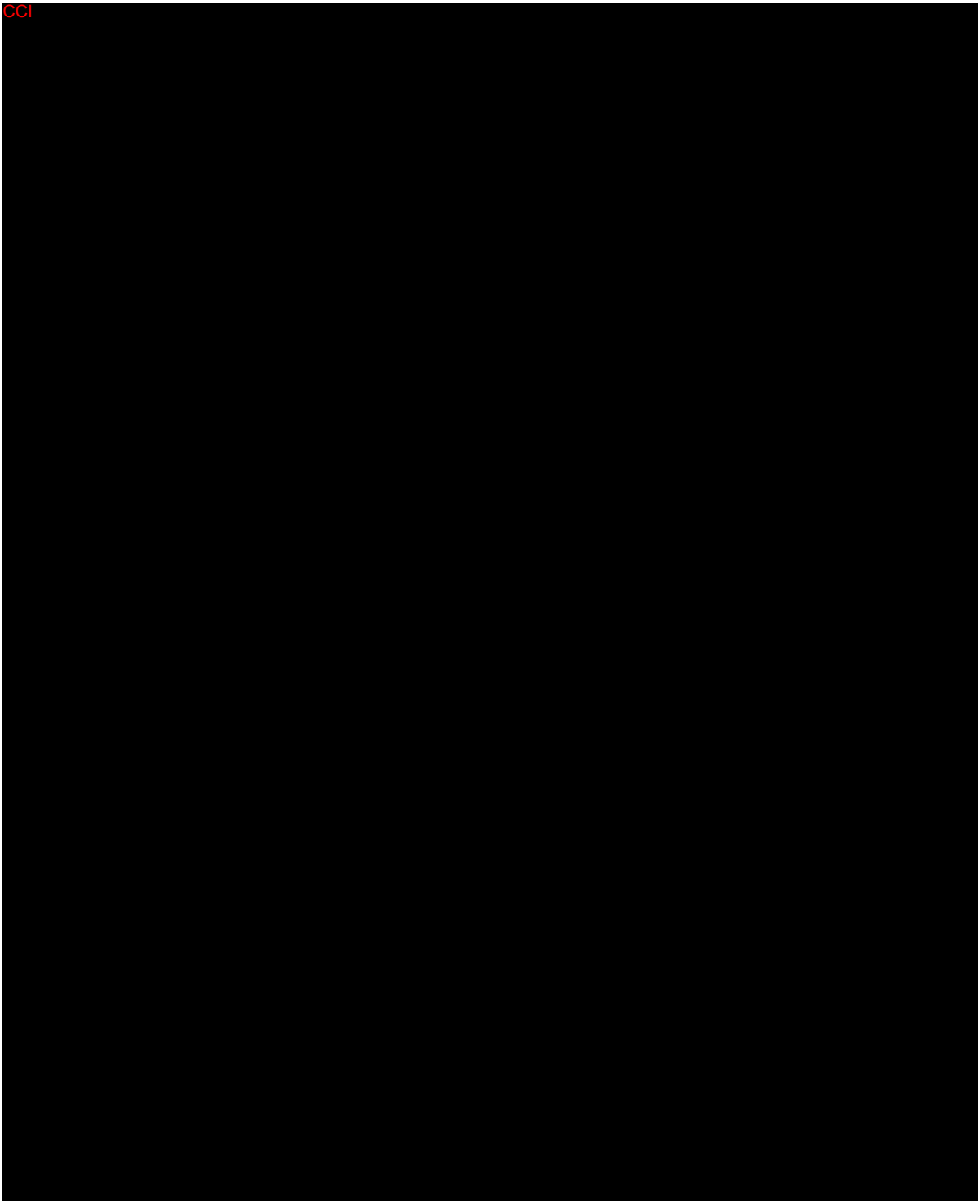
Abbreviations: CPS=combined positive score; H=hypothesis; OS=overall survival; PFS=progression-free survival.

9.8.1 Progression-free Survival

The study will test PFS hypothesis at IA1 and IA2 only, with IA2 being the final analysis of PFS endpoint. CCI [redacted] CCI Note that the final row for PFS endpoint at IA2 indicates the total power to reject the corresponding null hypothesis. If the null hypothesis of PFS in participants with CPS ≥1 is rejected, the corresponding alpha can be reallocated to PFS in all participants. If the null hypothesis of PFS is rejected in all participants, 99.9% of the alpha can be reallocated to PFS in participants with CPS ≥1. Thus, PFS hypothesis in all participants may be tested at α=0.005 (initial α), or α=0.025 (if the null hypothesis for the PFS in participants with CPS ≥1 is rejected). PFS hypothesis in participants with CPS ≥1 may be tested at α=0.02 (initial α), or α= ~ 0.025 (if the null hypothesis for the PFS in all participants is rejected).

Table 12 CCI

CCI



9.8.2 Overall Survival

The study will test OS at IA1, IA2 and FA. CCI [redacted] CCI [redacted] CCI [redacted] If the null hypothesis for PFS is rejected, the alpha initially allocated to the PFS hypothesis will be reallocated to the OS hypothesis. Technically the hypotheses for OS in both populations may be tested at α=0.000005 (0.005*0.001) if the null hypothesis for PFS is rejected in all participants, but not in participants with CPS ≥1. However, this extremely small amount is negligible. Thus, in practice the hypothesis for OS in participants with CPS ≥1 may only be tested at α=0.025 if the null hypotheses for both the PFS in all participants and in participants with CPS ≥1 are rejected. The hypothesis for OS in all participants may only be tested at α=0.025 if the null hypotheses for the OS in participants with CPS ≥1 is rejected.

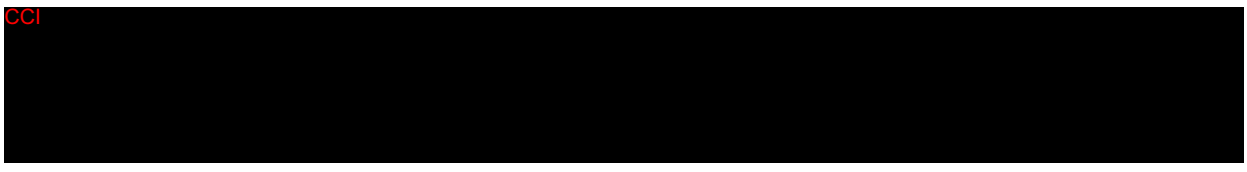
Table 13 CCI [redacted]

CCI [redacted]

CCI

CCI

CCI



CCI

[redacted]

9.8.3 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 DMC review of unplanned efficacy data prompted by safety concerns, a sensitivity analysis for PFS and OS adopting a conservative multiplicity adjustment will be specified in the sSAP if DMC explicitly requests a review of efficacy comparison beyond the standard safety eDMC package.

9.9 Sample Size and Power Calculations

The study randomized 643 participants in a 1:1 ratio into the pembrolizumab plus paclitaxel with or without bevacizumab and placebo plus paclitaxel with or without bevacizumab arms. Based on blinded review of study data, the observed prevalence of PD-L1 CPS ≥1 in this study was approximately 72%.

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

CCI

[redacted]

CCI

[redacted]

CCI [redacted]

CCI [redacted]
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.

CCI [redacted]

CCI [redacted].
CCI [redacted].
CCI [redacted]
CCI [redacted]
CCI [redacted]
CCI [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 subgroup variables. The subgroup analyses will be performed in participants with CPS ≥1 and in all participants, with the exception of the analysis by tumor PD-L1 expression level, which will only be performed in all participants.

- Stratification factors:
  - Planned bevacizumab use in the study (yes vs no)
  - Region (US vs EU vs ROW)
  - PD-L1 status (CPS <1 vs CPS 1 to <10 vs CPS ≥10)
- Race (white vs non-white)
- ECOG performance status (0 vs 1)
- Prior PARPi use (yes vs no)

- Platinum free interval (<3 months vs 3-6 months from last platinum therapy to subsequent progression)
- Planned bevacizumab use (10 mg/kg Q2W vs 15 mg/kg Q3W vs no bevacizumab)

  Note: Bevacizumab dosing (if used) in this study is 10 mg/kg Q2W except per country-specific requirements in Appendix 7.

CCI

[redacted]

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 the number of administrations and number of days in which the participant receives the study medication. Summary statistics will be provided on the Extent of Exposure for the APaT population.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Code of Conduct for Clinical Trials

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

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (including all applicable data protection laws and regulations), and International Council for Harmonisation Good Clinical Practice (ICH-GCP), and also 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 that are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials, which are not under the full control of MSD.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data

protection rights of all participants, trial site staff and, where applicable, third parties. All trial protocols are and will be assessed for the need and capability to enroll underrepresented groups. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD's clinical trials are conducted globally in many different countries and in diverse populations, including people of varying age, race, ethnicity, gender, and accounting for other potential disease related factors. MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel (or individuals acting on behalf of MSD) to assess the ability to successfully conduct the trial.

Where appropriate, and in accordance with regulatory authority guidance, MSD will make concerted efforts to raise awareness of clinical trial opportunities in various communities. MSD will seek to engage underrepresented groups and those disproportionately impacted by the disease under study. MSD will support clinical trial investigators to enroll underrepresented groups and expand access to those who will ultimately use the products under investigation.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and 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 potential fraud, scientific/research misconduct, privacy incidents/breaches or Clinical Trial-related Significant Quality Issues are reported, such matters are investigated. When necessary, appropriate corrective and/or preventative actions are defined and regulatory authorities and/or ethics review committees are 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 pre-specified 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. Regulatory Authority and Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All protocols and protocol amendments will be submitted by MSD for regulatory authority acceptance/authorization prior to implementation of the trial or amendment, in compliance with local and/or national regulations.

The protocol, protocol amendment(s), informed consent form, investigator's brochure, and other relevant trial documents must be reviewed and approved by an IRB/IEC before being implemented at each site, in compliance with local and/or national regulations. Changes to the protocol that are required urgently to eliminate an immediate hazard and to protect participant safety may be enacted in anticipation of ethics committee approval. MSD will inform regulatory authorities of such new measures to protect participant safety, in compliance with local and/or national regulations.

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, as well as all applicable data protection rights. Unless required by law, only the investigator, Sponsor (or individuals acting on behalf of MSD), 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 and medical evaluation 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, frequently known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this

information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.1.3 Data Protection

The Sponsor will conduct this study in compliance with all applicable data protection regulations.

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

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

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

10.1.3.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the IRB, IEC, or similar or expert committee, affiliated institution, and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution, and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.3.2 Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents to verify worksheet/CRF data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant will be identified by unique code only; full names/initials will be masked before transmission to the Sponsor.

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

10.1.3.3 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names

and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.1.4 Committees Structure

10.1.4.1 Executive Oversight Committee

The EOC is comprised of members of Sponsor Senior Management. The EOC will receive and decide on any recommendations made by the eDMC OR SAC regarding the study.

10.1.4.2 External Data Monitoring Committee

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

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

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

10.1.4.3 Scientific Advisory Committee (SAC)

This study was developed in collaboration with a SAC. The SAC is comprised of both Sponsor and non-Sponsor scientific experts who provide scientific and strategic guidance on various aspects of the clinical trial and/or development, which may include study design, interpretation of study results, and subsequent peer-reviewed scientific publications.

10.1.5 Publication Policy

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

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

Authorship will be determined by mutual agreement and in line with ICMJE authorship requirements.

10.1.6 Compliance with Study Registration and Results Posting Requirements

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

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

10.1.7 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP (eg, ICH GCP: Consolidated Guideline and other generally accepted standards of GCP); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical study.

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

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

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

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

Persons debarred from conducting or working on clinical studies by any court or regulatory authority will not be allowed to conduct or work on this Sponsor’s studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in

conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

10.1.8 Data Quality Assurance

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

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

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

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

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

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

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

Records and documents, including participants' documented informed consent, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.9 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's participants. Source documents and data should be attributable, legible,

contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source documents are filed at the investigator's site.

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

10.1.10 Study and Site Closure

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

In the event the Sponsor prematurely terminates a particular study site, the Sponsor or designee will promptly notify that study site's IRB/IEC as specified by applicable regulatory requirement(s).

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 14 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 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. Refer to Appendix 7 for country-specific requirements.

Table 14 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	BUN or urea[a]	Potassium	AST/SGOT	Total bilirubin (and direct bilirubin, if total bilirubin is above the ULN)
	Albumin	Carbon dioxide (CO2 or bicarbonate)[b]	Chloride	Phosphorous
	Creatinine[c]	Sodium	ALT/SGPT	Total Protein
	Glucose (either fasting or nonfasting)	Calcium	Alkaline phosphatase	Magnesium
	Thyroid-stimulating hormone (TSH)[d]	Triiodothyronine (T3) or free T3 thyroid hormone (FT3)[d]	Free thyroxine (FT4)[d]	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase[e] by dipstick • Microscopic examination (if blood or protein is abnormal)			
Pregnancy Testing	• Highly sensitive serum or urine hCG pregnancy test (as needed for WOCBP per local regulations)			
Other Screening Tests	• Coagulation: PT/INR and aPTT/PTT • FSH (as needed in WONCBP only) • Serology (HIV antibody, HBsAg, and hepatitis C virus antibody) per local requirements • CA-125 (perform within 7 days before randomization and within ±14 days of each scheduled tumor scan).			

Laboratory Assessments	Parameters
ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CA-125=cancer antigen 125; FSH=follicle-stimulating hormone; FT3=free T3 thyroid hormone; FT4=free thyroxine; GFR=glomerular filtration rate; HBsAg=hepatitis B surface antigen; hCG=human chorionic gonadotropin; INR=international normalized ratio; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; PT=prothrombin time; PTT=partial thromboplastin time; RBC=red blood cell; SGOT=serum glutamic oxaloacetic transaminase; SGPT=serum glutamic pyruvic transaminase; ULN=upper limit of normal; WOCBP=women of childbearing potential; WONCBP=women of nonchildbearing potential [a.] Blood urea nitrogen 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.] Free T3 is acceptable where T3 cannot be determined. There may be instances when sites are unable to obtain the thyroid function testing results before scheduled dosing. Review of thyroid function test results after dosing is acceptable. [e.] Leukocyte testing can be performed when leukocyte esterase is not possible.	

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

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

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication error

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

Misuse

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

Abuse

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

10.3.2 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.
- Note: For purposes of AE definition, study intervention includes any pharmaceutical product, biological product, vaccine, diagnostic agent, medical device, combination product, or protocol-specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

- Any new cancer (that is not a condition of the study). Progression of the cancer under study is not a reportable event. Refer to Section 8.4.6 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 preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgical procedure(s) planned prior to informed consent to treat a preexisting condition that has not worsened.
- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.3 Definition of SAE

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

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

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

worsened is not an SAE.) A preexisting condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant's medical history.

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

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

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

10.3.4 Additional Events Reported in the Same Manner as SAE

Additional events that require reporting in the same manner as SAE

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

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

10.3.5 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.

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

Assessment of intensity/toxicity

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.
- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI CTCAE, version 5.0. Any AE that changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.
  - Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
  - Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
  - Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
  - Grade 4: Life-threatening consequences; urgent intervention indicated.
  - Grade 5: Death related to AE.

Assessment of causality

- Did the study intervention cause the AE?
- The determination of the likelihood that the study intervention caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.

- **The following components are to be used to assess the relationship between the study intervention and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the study intervention caused the AE:**
  - **Exposure:** Is there evidence that the participant was actually exposed to the study intervention such as: reliable history, acceptable compliance assessment (pill count, diary, etc), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
  - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the study intervention? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with IMP)?
  - **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.
  - **Dechallenge:** Was the study intervention discontinued or dose/exposure/frequency reduced?
    - If yes, did the AE resolve or improve?
    - If yes, this is a positive dechallenge.
    - If no, this is a negative dechallenge.

    (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the study intervention; (3) the study is a single-dose drug study; or (4) study intervention (s) is/are only used 1 time.)
  - **Rechallenge:** Was the participant reexposed to the study intervention in this study?
    - If yes, did the AE recur or worsen?
    - If yes, this is a positive rechallenge.
    - If no, this is a negative rechallenge.

    (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability; (2) the study is a single-dose drug study; or (3) study intervention (s) is/are used only 1 time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY THE STUDY INTERVENTION, OR IF REEXPOSURE TO THE STUDY INTERVENTION POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL, AND IF REQUIRED, THE IRB/IEC.

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the study intervention or drug class pharmacology or toxicology?
- The assessment of relationship will be reported on the case report forms/worksheets by an investigator who is a qualified physician according to their best clinical judgment, including consideration of the above elements.

- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a study intervention relationship).
  - Yes, there is a reasonable possibility of study intervention relationship:
    - There is evidence of exposure to the study intervention. The temporal sequence of the AE onset relative to the administration of the study intervention is reasonable. The AE is more likely explained by the study intervention than by another cause.
  - No, there is not a reasonable possibility of study intervention relationship:
    - Participant did not receive the study intervention OR temporal sequence of the AE onset relative to administration of the study intervention is not reasonable OR the AE is more likely explained by another cause than the study intervention. (Also entered for a participant with overdose without an associated AE.)
- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.
- For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each AE causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (ie, to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the investigator's opinion, there is sufficient data to support full attribution of the AE to the single agent.

Follow-up of AE and SAE

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

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

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

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

SAE reporting to the Sponsor via paper CRF

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

10.4 Appendix 4: Medical Device and Drug–Device Combination Products: Product Quality Complaints/Malfunctions: Definitions, Recording, and Follow-up

Not applicable.

10.5 Appendix 5: Contraceptive Guidance

Refer to Appendix 7 for country-specific requirements.

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

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

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

Women in the following categories are not considered WOCBP:

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

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

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

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

10.5.2 Contraception Requirements

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

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

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research[3, 4]

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

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

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

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

3. Summary of Procedures for Future Biomedical Research[3, 4]

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

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

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

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

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

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

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

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

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

5. Biorepository Specimen Usage[3, 4]

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

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

Participants may withdraw their consent for FBR and ask that their biospecimens not be used for FBR. Participants may withdraw consent at any time by contacting the study investigator. If medical records for the study are still available, the investigator will contact the Sponsor using the designated mailbox

(clinical.specimen.management@MSD.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to study use only. If specimens were collected from study participants specifically for FBR, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed before the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

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

7. Retention of Specimens[3, 4]

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

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

8. Data Security[3, 4]

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

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

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

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

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

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

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

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

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

12. Questions

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

13. References

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

10.7 Appendix 7: Country-specific Requirements

10.7.1 China

4.1 Overall Design

After enrollment of the global portion of the study is complete, the study may remain open to enrollment in China alone until the target number of participants in China has been enrolled to meet local regulatory requirements.

5.1 Inclusion Criteria

10. Archival tumor tissue sample or newly obtained core or incisional/excisional biopsy of a tumor lesion not previously irradiated has been provided. Details pertaining to tumor tissue submission can be found in the Laboratory Manual. Prospective determination of PD-L1 status by a central laboratory is required for all participants.

For study sites in China, tissue sample collected at screening for PD-L1 central analysis is required, to support a potential requirement from health authority.

8.1.12 Tumor Tissue for Biomarker Status

In China, the below samples, including tumor tissue or slides, will be collected for the participants who enrolled after HGRAC approval of the biomarker testing:

- Tumor tissue

8.8 Biomarkers

Biomarker sample collection for participants enrolled in China will be dependent on approval by the HGRAC. FBR will not be conducted in China.

10.7.2 Germany

Section 5.2 Exclusion Criteria

Exclusion Criterion: Participant has a known history of HIV infection. HIV testing is required for participants.

Exclusion Criterion: hepatitis B and C testing is required for participants.

Legally Acceptable Representative protocol sections

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

10.7.3 Ireland

Section 1.3 Schedule of Activities

HBV, HCV, HIV, and tuberculosis testing at screening is mandatory.

Section 5.2 Exclusion Criteria

Exclusion Criterion: Has a known history of HIV infection. Testing for HIV at screening is mandatory.

Exclusion Criterion: Has a known history of Hepatitis B (defined as HBsAg reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection. Testing for HBV and HCV at screening is mandatory.

10.7.4 Italy

Section 1.3 Schedule of Activities

HBV, HCV, and HIV testing is required at screening.

Section 5.2 Exclusion Criteria

- Exclusion Criterion: Has a known history of HIV infection. Testing for HIV is required at screening.
- Exclusion Criterion: Has a known history of Hepatitis B (defined as HBsAg reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection. Testing for HBV and HCV is required at screening.

10.7.5 Japan

Section 6.1 Study Intervention(s) Administered

The classification of Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product (NIMP) in Section 6.1 is based upon guidance issued by the European Commission and applies to countries in the European Economic Area (EEA). As country differences with respect to the definition/classification of IMP/NIMP may exist, local legislation is followed. Local legislation in Japan requires that the agent paclitaxel for this study is considered as IMP. Diluent placebo (normal saline and/or dextrose) for this study is not considered as IMP in Japan.

Synopsis: Intervention Groups and Duration; Section 1.2 Schema; Section 1.3.1 Schedule of Activities – First Course Treatment; Section 4.1 Overall Design; Section 4.3.2 Paclitaxel; Section 6.1 Study Intervention(s) Administered; Section 8.1.8.1.2 Paclitaxel (or Docetaxel)

The starting dose of docetaxel, if approved by the Sponsor to be used in place of paclitaxel, will be 70 mg/m^2 Q3W for participants in Japan.

Synopsis: Intervention Groups and Duration; Section 1.2 Schema; Section 1.3.1 Schedule of Activities – First Course Treatment; Section 4.1 Overall Design; Section 4.3.3 Bevacizumab; Section 6.1 Study Intervention(s) Administered; Section 8.1.8.1.3 Bevacizumab

Sites in Japan have the option to use the 10-mg/kg Q2W or the 15-mg/kg Q3W bevacizumab dosing regimen in accordance with the approved local product label. Participants in Japan are allowed to switch dosing regimens (ie, from 15 mg/kg Q3W to 10 mg/kg Q2W or vice versa) only once and only with prior approval of the Sponsor using an SCF.

10.7.6 United Kingdom

Section 5.2 Exclusion Criteria

Exclusion Criterion: HIV testing is required for participants.

Exclusion Criterion: hepatitis B and C testing is required for participants.

Section 6.5 Concomitant Therapy

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

- Live vaccines must not be administered for 90 days after the last dose of study intervention. Refer to Section 6.5 for information on COVID-19 vaccines.

10.8 Appendix 8: 2014 Federation of Gynecology and Obstetrics (FIGO) Ovarian, Fallopian Tube, and Peritoneal Cancer Staging System

Stage	Description	TNM
I	Tumor confined to ovaries or fallopian tube(s)	T1
IA	Tumor limited to one ovary (capsule intact) or fallopian tube, No tumor on ovarian or fallopian tube surface No malignant cells in the ascites or peritoneal washings	T1a
IB	Tumor limited to both ovaries (capsules intact) or fallopian tubes No tumor on ovarian or fallopian tube surface No malignant cells in the ascites or peritoneal washings	T1b
IC	Tumor limited to one or both ovaries or fallopian tubes, with any of the following: IC1 Surgical spill intraoperatively IC2 Capsule ruptured before surgery or tumor on ovarian or fallopian tube surface IC3 Malignant cells present in the ascites or peritoneal washings	T1c
II	Tumor involves one or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or peritoneal cancer (Tp)	T2
IIA	Extension and/or implants on the uterus and/or fallopian tubes/and/or ovaries	T2a
IIB	Extension to other pelvic intraperitoneal tissues	T2b
III	Tumor involves one or both ovaries, or fallopian tubes, or primary peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes	T3
IIIA	Metastasis to the retroperitoneal lymph nodes with or without microscopic peritoneal involvement beyond the pelvis	T1,T2,T3aN1
IIIA1	Positive retroperitoneal lymph nodes only (cytologically or histologically proven)	
IIIA1(i)	Metastasis ≤10 mm in greatest dimension (note this is tumor dimension and not lymph node dimension)	T3a/T3aN1
IIIA1(ii)	Metastasis >10 mm in greatest dimension	
IIIA2	Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes	T3a/T3aN1
IIIB	Macroscopic peritoneal metastases beyond the pelvic brim ≤2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes	T3b/T3bN1
IIIC	Macroscopic peritoneal metastases beyond the pelvic brim >2 cm in greatest dimension, with or without metastases to the retroperitoneal nodes (Note 1)	T3c/T3cN1
IV	Distant metastasis excluding peritoneal metastases	
IVA	Pleural effusion with positive cytology	Any T, Any N
IVB	Metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside abdominal cavity) (Note 2)	M1

Note 1 Includes extension of tumor to capsule of liver and spleen without parenchymal involvement of either organ.
Note 2 Parenchymal metastases are Stage IV B.
Adapted from the Federation of Gynecology and Obstetrics Guidelines 2014 [Prat, J. and FIGO Committee on Gynecologic Oncology 2014].

10.9 Appendix 9: Abbreviations

Abbreviation	Expanded Term
ADA	antidrug antibodies
ADL	activities of daily living
AE	adverse event
ALT	alanine aminotransferase
APaT	All-Participants-as-Treated
AST	aspartate aminotransferase
AUC	area under the curve
AxMP	auxiliary medicinal product
BICR	blinded independent central review
BRCA	breast cancer gene
CA-125	cancer antigen 125
CD	cluster of differentiation
C_{avg}	average plasma concentration
CD3ζ	CD3 zeta
CI	confidence interval
cLDA	constrained longitudinal data analysis
C_{max}	maximum plasma concentration
C_{min}	trough plasma concentration
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease caused by severe acute respiratory syndrome coronavirus 2
CPS	combined positive score
CR	complete response
CrCl	creatinine clearance
CRF	Case Report Form
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTCAE 5.0	Common Terminology Criteria for Adverse Events, Version 5.0
ctDNA	circulating tumor deoxyribonucleic acid
CTFG	Clinical Trials Facilitation Group
CTLA-4	cytotoxic T-lymphocyte-associated protein 4

Abbreviation	Expanded Term
CYP	P450 cytochrome
DCR	disease control rate
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data collection
eDMC	external Data Monitoring Committee
EEA	European Economic Area
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOC	Executive Oversight Committee
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
EORTC QLQ-OV28	European Organisation for Research and Treatment of Cancer Ovarian Cancer-Specific Quality of Life Questionnaire
EOT	end of treatment
ePROs	electronic patient-reported outcomes
EQ-5D-5L	European Quality of Life Five-dimension Five-level Scale Questionnaire
E-R	exposure-response
EU	European Union
EU CTR	European Union Clinical Trials Regulation
EuroQoL	European Quality of Life
FA	final analysis
FAS	Full Analysis Set
FBR	Future Biomedical Research
FDA	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

Abbreviation	Expanded Term
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony-Stimulating Factor
GFR	glomerular filtration rate
GHS	Global Health Status
GI	gastrointestinal
GM-CSF	Granulocyte Macrophage Colony-Stimulating Factor
H	hypothesis
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HGRAC	Human Genetic Resources Administration of China
HIV	human immunodeficiency virus
HR	hazard ratio
HRD	homologous recombination deficiency
HRQoL	health-related quality of life
HRT	hormone replacement therapy
IA	interim analysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
iCRO	imaging CRO
ID	identification
IEC	Independent Ethics Committee
Ig	immunoglobulin
IgG4	immunoglobulin G4
IgV	immunoglobulin-variable
IHC	immunohistochemistry
IL-10	interleukin 10
IMP	investigational medicinal product
IO	immuno-oncology
irAEs	immune-related AEs
IRB	Institutional Review Board

Abbreviation	Expanded Term
iRECIST	Modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics
IRT	interactive response technology
ISO	International Standards Organization
ITT	intention-to-treat
IUD	intrauterine device
IUO	investigational use only
IUS	intrauterine hormone-releasing system
IV	intravenous
IVD	in vitro diagnostic
IVRS	interactive voice response system
LAM	lactational amenorrhea method
LS	least square
M&S	modelling and simulation
mAb	monoclonal antibody
MRI	magnetic resonance imaging
mRNA	messenger RNA
MSI	microsatellite instability
NAb	neutralizing antibodies
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NIMP	noninvestigational medicinal product
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non–small cell lung cancer
OC	ovarian cancer
ORR	objective response rate
OS	overall survival
OTC	over-the-counter
PARP(i)	poly(adenosine-ribose) polymerase (inhibitor)
PCL	Protocol Clarification Letter
PD	progressive disease
PD-1	programmed cell death 1 protein
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PET	positron emission tomography

Abbreviation	Expanded Term
PFS	progression-free survival
PFS2	progression-free survival after next-line treatment
PK	pharmacokinetic
PKCθ	protein kinase C-theta
PLD	pegylated liposomal doxorubicin
PO	by mouth (*per os*)
PR	partial response
PRO	patient-reported outcome
PRROC	platinum-resistant recurrent ovarian cancer
QW	every week
Q2/3/6/9/12W	every 2/3/6/9/12 weeks
QoL	quality of life
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	ribonucleic acid
ROW	Rest of World
SAC	Scientific Advisory Committee
SAE	serious adverse event
SCF	Sponsor Consultation Form
SGCTG	Scottish Gynaecological Cancer Trials Group
SD	stable disease
SGOT	serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SHP-1, SHP-2	Src homology region 2 domain-containing phosphatase-1/2
SIM	Site Imaging Manual
SLAB	Supplemental laboratory test(s)
SoA	schedule of activities
SOC	standard of care
sSAP	supplemental Statistical Analysis Plan
SUSAR	suspected unexpected serious adverse reaction
TDT	time to discontinuation of study treatment
TEA	Treatment Eligibility Assessment (form)
TFST	time to first subsequent anticancer treatment
TSST	time to second subsequent anticancer treatment
TTD	time to deterioration

Abbreviation	Expanded Term
TWiST	time without symptoms of disease progression or toxicity of treatment
ULN	upper limit of normal
US	United States
WOCBP	woman/women of childbearing potential
WONCBP	woman/women of nonchildbearing potential
ZAP70	zeta-chain-associated protein kinase

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