Official Protocol Title:	A Randomized, Phase 2 Study of Pembrolizumab And Chemotherapy With or Without MK-4830 as Neoadjuvant Treatment for High-Grade Serous Ovarian Cancer
NCT number:	NCT05446870
Document Date:	10-APR-2024

Title Page

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Protocol Title: A Randomized, Phase 2 Study of Pembrolizumab And Chemotherapy With or Without MK-4830 as Neoadjuvant Treatment for High-Grade Serous Ovarian Cancer

Protocol Number: 002-04

Compound Number: MK-4830

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):

IND	160197
EudraCT	2021-005458-27
EUCT	2023-505005-16

Approval Date: 10 April 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	10-APR-2024	To address a health authority request
Amendment 03	07-NOV-2022	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.
Amendment 02	22-MAR-2022	To address health authority comments.
Amendment 01	02-FEB-2022	To allow exploratory histological confirmation of high-grade serous carcinoma of tumor samples from enrolled participants to be conducted.
Original Protocol	21-DEC-2021	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 04

Overall Rationale for the Amendment:

To address a health authority request.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
Title page	Added EU CT number.	This change was made to address Health Authority feedback to align with Regulation (EU) 536/2014

Section Number and Name	Description of Change	Brief Rationale
Additional Changes		
Section 4.4, Beginning and End of Study Definition	Added text estimating the duration of the study.	Refer to title page rationale.
Section 8.4.4, Regulatory Reporting Requirements for SAE	Added text for SUSAR reporting in the EU.	Refer to title page rationale.
Section 10.1.1, Code of Conduct for Clinical Studies	Added text that the study will be conducted in compliance with Regulation (EU) 536/2014.	Refer to title page rationale.
Section 10.1.3, Data Protection	Added text on privacy rules.	Refer to title page rationale.
Section 10.1.6, Compliance with Study Registration and Results Posting Requirements	Revised text to include reference to Regulation 536/2014.	Refer to title page rationale.
Section 10.1.7, Compliance with Law, Audit, and Debarment	Added text on serious breach reporting.	Refer to title page rationale.
Section 10.1.8, Data Quality Assurance	Added text to specify record retention period for EU.	Refer to title page rationale.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Randomized, Phase 2 Study of Pembrolizumab And Chemotherapy With or Without MK-4830 as Neoadjuvant Treatment for High-Grade Serous Ovarian Cancer

Short Title: Genomic and immune markers of response in ILT4- and pembrolizumab-treated ovarian cancer

Acronym: None

Hypotheses, Objectives, and Endpoints:

In participants with high-grade serous ovarian cancer:

Objectives	Endpoints
Primary	
Objective: Among patients with detectable ctDNA at baseline, to evaluate whether the reduction from baseline in circulating tumor DNA at Cycle 3 (ΔctDNA) is larger in participants receiving MK-4830 + pembrolizumab in combination with standard of care (SOC) therapy than in those receiving pembrolizumab + SOC therapy.	ctDNA, the continuous mean mutant/tumor molecules per mL.
Secondary	
Objective: Among patients with detectable ctDNA at baseline, to evaluate the association between neoadjuvant ΔctDNA at Cycle 3 from baseline and surgical outcomes.	ctDNA pCR, all surgical specimens collected during the interval debulking surgery are microscopically negative for residual tumor. CRS, tiered response score based omental assessment of residual disease.
Objective: To estimate the difference in pCR and CRS following neoadjuvant treatment between arms.	pCR CRS
Objective: To evaluate the safety and tolerability of the study intervention administered.	Adverse events (AEs) Study intervention discontinuation due to AEs

Overall Design:

Study Phase	Phase 2
Primary Purpose	Treatment
Indication	First-line treatment of advanced HGSOC
Population	Participants with advanced HGSOC who are candidates for interval debulking surgery.
Study Type	Interventional
Intervention Model	Parallel This is a multi-site study.
Type of Control	Active control
Study Blinding	Unblinded Open-label
Blinding Roles	No Blinding
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 35 months from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Approximately 160 participants will be randomly assigned.

Intervention Groups and Duration:

Eligible participants will be randomized to one of the following study intervention arms:

- Arm 1:
  Neoadjuvant phase: 3 cycles of carboplatin/paclitaxel* plus pembrolizumab (200 mg Q3W plus MK-4830 (800 mg Q3W) before surgery.
  Adjuvant phase: 3 cycles of carboplatin/paclitaxel* plus pembrolizumab (200 mg Q3W) plus MK-4830 (800 mg Q3W) ± Avastin® (or biosimilar) after surgery

- Arm 2:
  Neoadjuvant phase: 3 cycles of carboplatin/paclitaxel* plus pembrolizumab (200 mg Q3W) prior to surgery.
  Adjuvant phase: 3 cycles of carboplatin/paclitaxel* plus pembrolizumab (200 mg Q3W) ± Avastin (or biosimilar) after surgery.

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

    - Carboplatin AUC 5 or AUC 6 Q3W plus paclitaxel 175 mg/m^2 Q3W

The optional use of Avastin (or biosimilar) in the adjuvant phase (ie, after surgery in Cycles 4 to 6) is permitted according to local practice and at the choice of the investigator; however, the investigator must decide on the use of Avastin (or biosimilar) after surgery and it must be selected in IRT (interactive response technology) prior to starting treatment in the adjuvant phase.

A safety lead-in will be performed to determine the tolerability of pembrolizumab + MK-4830 + carboplatin/paclitaxel when Avastin (or biosimilar) is added. Participants treated with pembrolizumab + MK-4830 + carboplatin/paclitaxel + Avastin (or biosimilar) will be closely followed for DLTs for the first cycle after the first dose of study intervention (the DLT evaluation period). ***Note: Use of Avastin (or biosimilar) is not permitted in the neoadjuvant phase (ie, prior to surgery in Cycles 1 to 3).***

Intervention Groups

Intervention Group Name	Drug	Dose Strength	Dose Frequency	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use
Arm 1	Carbo	AUC 5 or AUC 6	Q3W	IV	Day 1 of each 3-week cycle	Bgd
	Pac[a]	175 mg/m^2	Q3W	IV	Day 1 of each 3-week cycle	Bgd
	Pembro	200 mg	Q3W	IV	Day 1 of each 3-week cycle	Test Prod
	MK-4830	800 mg	Q3W	IV	Day 1 of each 3-week cycle	Test Prod
	Avastin (or biosimilar)	Variable	Q3W	IV	Day 1 of each 3-week cycle[b]	Bgd
Arm 2	Carbo	AUC 5 or AUC 6	Q3W	IV	Day 1 of each 3-week cycle	Bgd
	Pac[a]	175 mg/m^2	Q3W	IV	Day 1 of each 3-week cycle	Bgd
	Pembro	200 mg	Q3W	IV	Day 1 of each 3-week cycle	Test Prod
	Avastin (or biosimilar)	Variable	Q3W	IV	Day 1 of each 3-week cycle[b]	Bgd

Abbreviations: AUC = area under the concentration-time curve; Bgd = background; Carbo = carboplatin; IV = intravenous; Pac = paclitaxel; Pembro = pembrolizumab; Prod = product; Q3W = every 3 weeks; QW = once weekly.

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

b. The option to use Avastin (or biosimilar) in the adjuvant phase (ie, after surgery in Cycles 4 to 6) is permitted according to local practice and at the choice of the investigator; however, the investigator must decide on the use of Avastin (or biosimilar) after surgery but prior to the participant starting study intervention in the adjuvant phase.
Note: Use of Avastin (or biosimilar) is not permitted in the neoadjuvant phase (ie, prior to surgery in Cycles 1 to 3).

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

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. After the end-of-treatment, each participant will be followed for the occurrence of AEs and spontaneously reported pregnancy.

Study Governance Committees:

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

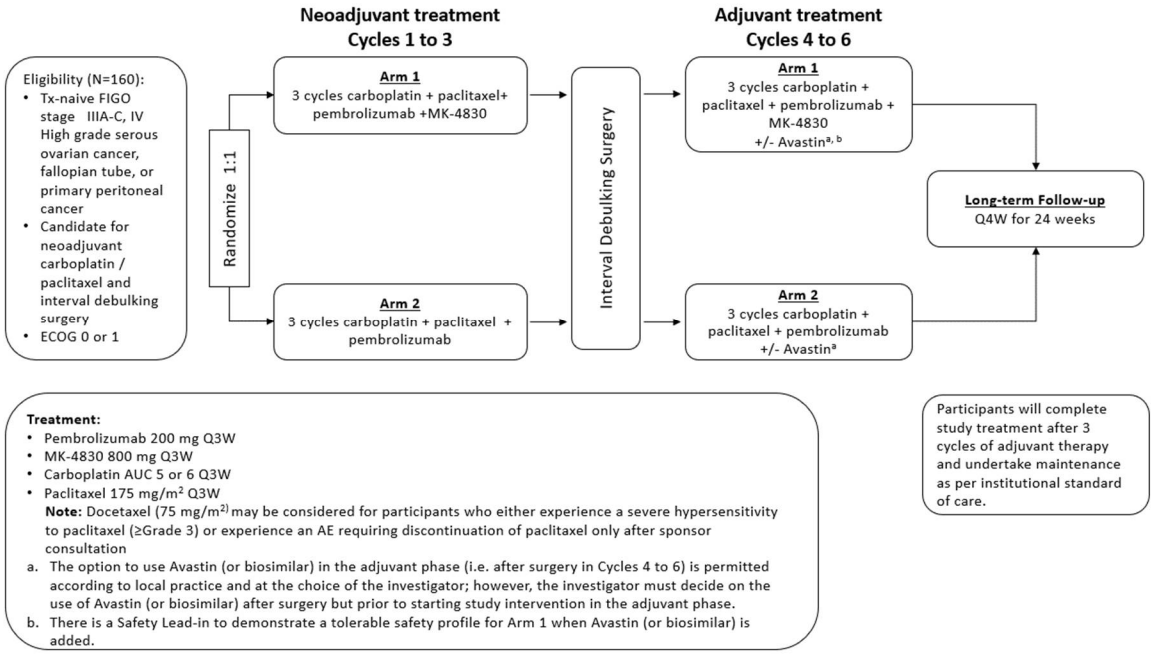
Study Accepts Healthy Volunteers: No

A list of abbreviations is in Appendix 8.

1.2 Schema

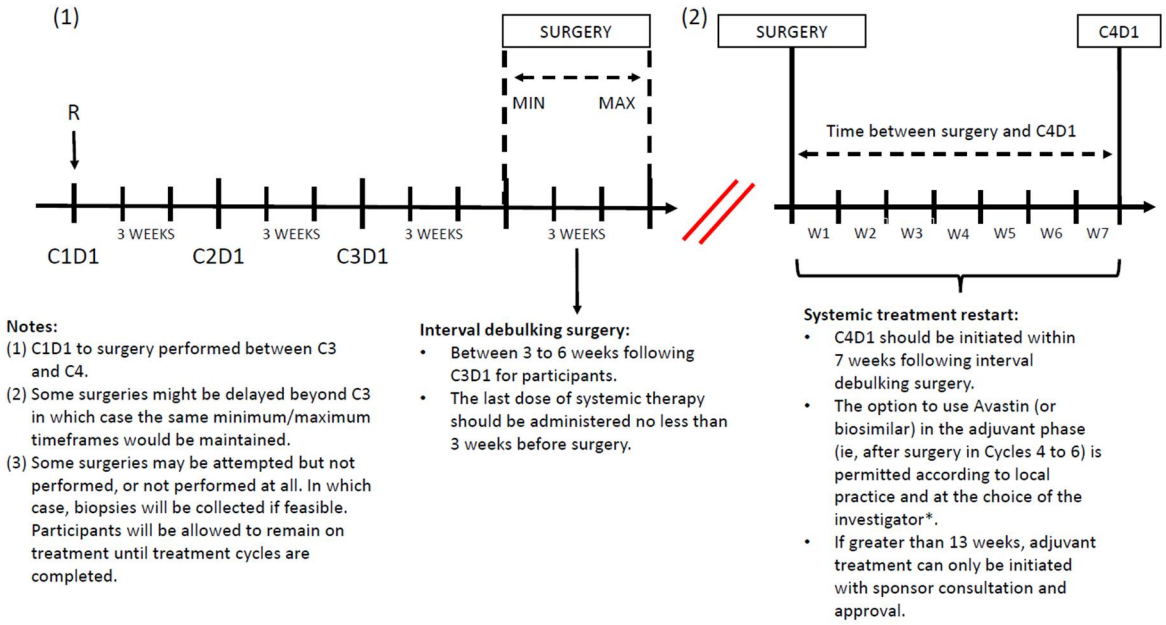
The study design is depicted in Figure 1 and Figure 2.

Figure 1 Study Design



Abbreviations: AE = adverse event; AUC = area under the concentration-time curve; ECOG = Eastern Cooperative Oncology Group; FIGO = International Federation of Gynecology and Obstetrics; IV = intravenous; Q3W = every 3 weeks; Tx = treatment.

Figure 2 Interval Debulking Surgery



Abbreviations: C1D1 = Cycle 1, Day 1; C2D1 = Cycle 2, Day 1; C3D1 = Cycle, 3 Day 1; C4D1 = Cycle 4, Day 1; FFPE = formalin-fixed-paraffin-embedded; Q3W = every 3 weeks; R = Randomization.

*Note: The investigator must decide on the use of Avastin (or biosimilar) after surgery but prior to starting study intervention in the adjuvant phase. The use of Avastin (or biosimilar) is not permitted in the neoadjuvant phase (ie, prior to surgery in Cycles 1 to 3).

1.3 Schedule of Activities

Study Period:	**Screening**	**Intervention Treatment Cycle = 21 days**							**EOT**	**Safety Follow-up[a]**	**Long-term Follow-up**	**Notes**
		Neoadjuvant Phase			**Debulking Surgery**	**Adjuvant Phase**						
Visit Timing/Cycle Number:	**–28 to –1**	**1**	**2**	**3**	**–**	**4**	**5**	**6**	**At DC**	**30 Days post last dose**	**Q4W for 24 Weeks**	**If surgery is delayed (only after Sponsor approval), the number of cycles in the neoadjuvant and adjuvant phase will alter but should not exceed 6 total cycles.**
Cycle Day:		**1**	**1**	**1**	**–**	**1**	**1**	**1**	**–**	**–**	**–**	
Screening Window (Days):		**+3**	**±3**	**±3**	**–**	**±3**	**±3**	**±3**	**At DC**	**+7**	**±3**	
	Administrative Procedures											
Informed Consent	X											Documented informed consent must be obtained before any protocol-specific screening procedures are performed. If the investigator plans to treat beyond disease progression, additional consent is required.
Informed Consent for Future Biomedical Research	X											Participants may participate in main study without consenting to FBR.
Inclusion/ Exclusion Criteria	X					X*						Refer to Appendix 7 for country-specific requirements. *Confirm that participants are still eligible to receive Avastin (or biosimilar) in the adjuvant phase (if administered)
Participant ID Card	X	X										Update with randomization number at C1D1
Demographics and Medical History	X											

Study Period:	Screen-ing	Intervention Treatment Cycle = 21 days							EOT	Safety Follow-up[a]	Long-term Follow-up	Notes
		Neoadjuvant Phase			Debulking Surgery	Adjuvant Phase						
Visit Timing/Cycle Number:	**–28 to –1**	**1**	**2**	**3**	**–**	**4**	**5**	**6**	**At DC**	**30 Days post last dose**	**Q4W for 24 Weeks**	**If surgery is delayed (only after Sponsor approval), the number of cycles in the neoadjuvant and adjuvant phase will alter but should not exceed 6 total cycles.**
Cycle Day:		**1**	**1**	**1**	**–**	**1**	**1**	**1**	**–**	**–**	**–**	
Screening Window (Days):		**+3**	**±3**	**±3**	**–**	**±3**	**±3**	**±3**	**At DC**	**+7**	**±3**	
Ovarian Cancer History	X*	X**										*Assess and record tumor burden per imaging. **Additional details on OC should be recorded, including BRCA and HRD status, if known, at any point during treatment.
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	Concomitant medications, including those administered at the time of surgery, will be recorded for 30 days after last dose (or for up to 90 days after last dose for SAEs).
Interval debulking surgery					X							Surgery should occur between 3 to 6 weeks following C3D1. Study intervention may resume when clinically appropriate but no later than 7 weeks following surgery.
Intervention Randomization (using IRT)		X										Randomization via IRT may occur up to 3 days prior to C1D1.
Vital Status									X	X	X	On Sponsor request, participants may be contacted for survival information at any time during the study.

Study Period:	Screen-ing	Intervention Treatment Cycle = 21 days							EOT	Safety Follow-up[a]	Long-term Follow-up	Notes
		Neoadjuvant Phase			Debulking Surgery	Adjuvant Phase						
Visit Timing/Cycle Number:	**–28 to –1**	**1**	**2**	**3**	**–**	**4**	**5**	**6**	**At DC**	**30 Days post last dose**	**Q4W for 24 Weeks**	**If surgery is delayed (only after Sponsor approval), the number of cycles in the neoadjuvant and adjuvant phase will alter but should not exceed 6 total cycles.**
Cycle Day:		**1**	**1**	**1**	**–**	**1**	**1**	**1**	**–**	**–**	**–**	
Screening Window (Days):		**+3**	**±3**	**±3**	**–**	**±3**	**±3**	**±3**	**At DC**	**+7**	**±3**	
Participant contact		X*		X*							X**	* Staff to contact participants within 3 days after clinic visit to ensure CCI devices were collected and picked up by the courier. ** Staff to contact participants for pregnancy status.
	Interventions											
MK-4830 (Arm 1 only)		X	X	X		X	X	X				800 mg Q3W
Pembrolizumab		X	X	X		X	X	X				200 mg Q3W
Carboplatin		X	X	X		X	X	X				AUC 5 or AUC 6 Q3W
Paclitaxel		X	X	X		X	X	X				175 mg/m^2 Q3W Docetaxel (75 mg/m^2 Q3W) may be considered in special cases only after Sponsor consultation and approval.
Avastin or biosimilar (optional)						X	X	X				Avastin (or biosimilar) use must be selected in IRT prior to starting study intervention in the adjuvant phase. Participants will be followed for DLTs for the first cycle in the adjuvant phase.

Study Period:	Screening	Intervention Treatment Cycle = 21 days							EOT	Safety Follow-up[a]	Long-term Follow-up	Notes
		Neoadjuvant Phase			Debulking Surgery	Adjuvant Phase						
Visit Timing/Cycle Number:	**–28 to –1**	**1**	**2**	**3**	**–**	**4**	**5**	**6**	**At DC**	**30 Days post last dose**	**Q4W for 24 Weeks**	**If surgery is delayed (only after Sponsor approval), the number of cycles in the neoadjuvant and adjuvant phase will alter but should not exceed 6 total cycles.**
Cycle Day:		**1**	**1**	**1**	**–**	**1**	**1**	**1**	**–**	**–**	**–**	
Screening Window (Days):		**+3**	**±3**	**±3**	**–**	**±3**	**±3**	**±3**	**At DC**	**+7**	**±3**	
	Efficacy Procedures											
Pathological Tumor Assessment (pCR and CRS)					X							Detailed pathological assessment of all tumor tissue, including tissue from omentum, collected during interval debulking for CRS determination and pCR.
Tumor Imaging (chest, abdomen, and pelvis)	X			X		X			X			See Section 1.3.1. Presurgery scan for surgical assessment should be performed a minimum of 21 days (+5 days) after C3D1. A scan should be performed prior to resuming study intervention in Cycle 4 (-5 days)
Brain Imaging (for participants with brain metastases at baseline [to show stability] or who are clinically symptomatic)	X	X*				X*						* On-study imaging as clinically indicated or to confirm CR.
Bone Imaging (for participants with bone metastases at baseline [to show stability] or who are clinically symptomatic)	X	X*				X*						* On-study imaging as clinically indicated or to confirm CR.

Study Period:	Screening	Intervention Treatment Cycle = 21 days							EOT	Safety Follow-up[a]	Long-term Follow-up	Notes
		Neoadjuvant Phase			Debulking Surgery	Adjuvant Phase						
Visit Timing/Cycle Number:	**–28 to –1**	**1**	**2**	**3**	**–**	**4**	**5**	**6**	**At DC**	**30 Days post last dose**	**Q4W for 24 Weeks**	**If surgery is delayed (only after Sponsor approval), the number of cycles in the neoadjuvant and adjuvant phase will alter but should not exceed 6 total cycles.**
Cycle Day:		**1**	**1**	**1**	**–**	**1**	**1**	**1**	**–**	**–**	**–**	
Screening Window (Days):		**+3**	**±3**	**±3**	**–**	**±3**	**±3**	**±3**	**At DC**	**+7**	**±3**	
	Safety Procedures											
AE Monitoring		X	X	X	X	X	X	X	X	X	X	Report all AEs and SAEs as outlined in Section 8.4.1.
Complete PE	X								X			
Directed PE		X*								X		* To be performed when clinically indicated.
Height	X											
Weight	X*	X	X	X		X	X	X				* Perform within 7 days of starting study intervention.
Vital Signs	X	X	X	X	X*	X	X	X	X	X		* To be performed prior to and after surgery.
12-lead ECG	X*								X			* Perform within 7 days of starting study intervention.
Pregnancy Test (WOCBP only)	X*	X	X	X	X	X	X	X	X	X	X	* A negative pregnancy test within either 24 hours (urine) or 72 hours (serum) prior to C1D1 treatment. Refer to Appendix 7 for country-specific requirements.
Serum FSH (WONCBP only)	X											

Study Period:	Screening	Intervention Treatment Cycle = 21 days							EOT	Safety Follow-up[a]	Long-term Follow-up	Notes
		Neoadjuvant Phase			Debulking Surgery	Adjuvant Phase						
Visit Timing/Cycle Number:	**–28 to –1**	**1**	**2**	**3**	**–**	**4**	**5**	**6**	**At DC**	**30 Days post last dose**	**Q4W for 24 Weeks**	**If surgery is delayed (only after Sponsor approval), the number of cycles in the neoadjuvant and adjuvant phase will alter but should not exceed 6 total cycles.**
Cycle Day:		**1**	**1**	**1**	**–**	**1**	**1**	**1**	**–**	**–**	**–**	
Screening Window (Days):		**+3**	**±3**	**±3**	**–**	**±3**	**±3**	**±3**	**At DC**	**+7**	**±3**	
HIV/HBV/HCV	X											Testing is only required once at screening if mandated by local health authority. Refer to Appendix 7 for country-specific requirements.
Hematology	X*		X	X		X	X	X	X	X		* Perform within 7 days of starting study intervention. Following Day 1 of Cycle 1, all on-study assessments collected predose. ‡ Participants receiving Avastin (or biosimilar) require urinalysis at every dosing cycle that Avastin (or biosimilar) is administered. ** CA-125 to be collected at the time of imaging.
Urinalysis	X*					X	X‡	X‡	X	X		
Chemistry	X*		X	X		X	X	X	X	X		
T3 or free T3/FT4/TSH	X*		X			X		X	X	X		
Cortisol (local laboratory only)	X*				X	X	X					
CA-125 (central laboratory)	X*			X**		X**			X			
CEA (central laboratory)	X*											

Study Period:	Screening	Intervention Treatment Cycle = 21 days							EOT	Safety Follow-up[a]	Long-term Follow-up	Notes
		Neoadjuvant Phase			Debulking Surgery	Adjuvant Phase						
Visit Timing/Cycle Number:	**–28 to –1**	**1**	**2**	**3**	**–**	**4**	**5**	**6**	**At DC**	**30 Days post last dose**	**Q4W for 24 Weeks**	**If surgery is delayed (only after Sponsor approval), the number of cycles in the neoadjuvant and adjuvant phase will alter but should not exceed 6 total cycles.**
Cycle Day:		**1**	**1**	**1**	**–**	**1**	**1**	**1**	**–**	**–**	**–**	
Screening Window (Days):		**+3**	**±3**	**±3**	**–**	**±3**	**±3**	**±3**	**At DC**	**+7**	**±3**	
CA-125 (local laboratory)	X*											Sites have the option of assessing CA-125 and CEA at the local laboratory at screening to determine eligibility. A confirmatory sample must be submitted to the central laboratory. * Perform within 7 days of starting study intervention.
CEA (local laboratory)	X*											
PT or INR and aPTT/PTT	X*											* Perform within 7 days of starting study intervention. Monitor closely in participants receiving anticoagulant therapy.
ECOG PS	X*		X	X		X	X	X	X			* Perform within 7 days of starting study intervention (C1D1). For all other visits, perform prior to study intervention administration.

Study Period:	Screening	Intervention Treatment Cycle = 21 days							EOT	Safety Follow-up[a]	Long-term Follow-up	Notes
		Neoadjuvant Phase			Debulking Surgery	Adjuvant Phase						
Visit Timing/Cycle Number:	**–28 to –1**	**1**	**2**	**3**	**–**	**4**	**5**	**6**	**At DC**	**30 Days post last dose**	**Q4W for 24 Weeks**	**If surgery is delayed (only after Sponsor approval), the number of cycles in the neoadjuvant and adjuvant phase will alter but should not exceed 6 total cycles.**
Cycle Day:		**1**	**1**	**1**	**–**	**1**	**1**	**1**	**–**	**–**	**–**	
Screening Window (Days):		**+3**	**±3**	**±3**	**–**	**±3**	**±3**	**±3**	**At DC**	**+7**	**±3**	
	Biomarkers											
Blood for genetic analysis		X										Collect prior to administration of study intervention. Refer to Section 8.8 for additional collection information.
Blood for RNA analysis		X	X	X		X		X				
Blood for ctDNA		X	X	X		X	X	X				
Plasma for BMx analysis		X		X		X		X				
Blood for BMx analysis		X										
	Microsampling Device Collection											
CCI microsampling device (In Clinic)		X		X		X		X				Collect prior to administration of study intervention. Two CCI devices to be collected in clinic
CCI microsampling device (At Home)		X		X								Two CCI devices to be collected within +3 days of C1D1 and C3D1.
CCI device (In Clinic) for participants at select investigational sites		X		X		X		X				Collect prior to administration of study intervention. Refer to laboratory manual for list of select sites.

Study Period:	Screening	Intervention Treatment Cycle = 21 days							EOT	Safety Follow-up[a]	Long-term Follow-up	Notes
		Neoadjuvant Phase			Debulking Surgery	Adjuvant Phase						
Visit Timing/Cycle Number:	**–28 to –1**	**1**	**2**	**3**	**–**	**4**	**5**	**6**	**At DC**	**30 Days post last dose**	**Q4W for 24 Weeks**	**If surgery is delayed (only after Sponsor approval), the number of cycles in the neoadjuvant and adjuvant phase will alter but should not exceed 6 total cycles.**
Cycle Day:		**1**	**1**	**1**	**–**	**1**	**1**	**1**	**–**	**–**	**–**	
Screening Window (Days):		**+3**	**±3**	**±3**	**–**	**±3**	**±3**	**±3**	**At DC**	**+7**	**±3**	
Device collection failure assessment		X		X		X		X				Collect information when the device(s) fails to collect the full volume of blood due to cartridge or device failure.
Tissue Collection												
Tumor tissue at baseline	X											Prior to randomization, archival or newly obtained tissue at Screening must be confirmed to be of sufficient quality and quantity to analyze the primary endpoint by the designated laboratory.
Tumor tissue at surgery					X							Newly obtained tumor tissue removed during interval debulking must be submitted. If participant is unable to undergo interval debulking, core or excisional biopsies should be obtained, if possible.
Newly obtained fresh tumor tissue from participants at select investigational sites	X				X							Refer to the laboratory manual for list of select sites. Leftover fresh tissue may be frozen for translational oncology research as defined in Section 4.2.1.5.1, only if there is documented optional translational oncology research informed consent. If risk of sample collection is deemed medically unsafe for the study participant, site should consult with Sponsor

Study Period:	Screening	Intervention Treatment Cycle = 21 days							EOT	Safety Follow-up[a]	Long-term Follow-up	Notes
		Neoadjuvant Phase			Debulking Surgery	Adjuvant Phase						
Visit Timing/Cycle Number:	–28 to –1	1	2	3	–	4	5	6	At DC	30 Days post last dose	Q4W for 24 Weeks	If surgery is delayed (only after Sponsor approval), the number of cycles in the neoadjuvant and adjuvant phase will alter but should not exceed 6 total cycles.
Cycle Day:		1	1	1	–	1	1	1	–	–	–	
Screening Window (Days):		+3	±3	±3	–	±3	±3	±3	At DC	+7	±3	

Abbreviations: AE = adverse event; aPTT = activated partial thromboplastin time; AUC = area under the concentration-time curve; BMx = biomarker; BRCA = breast cancer susceptibility gene; C1D1 = Cycle 1 Day 1; C3D1 = Cycle 3 Day 1; CA-125 = cancer antigen 125; CEA = carcinoembryonic antigen; CRS = chemotherapy response score; ctDNA = circulating tumor DNA; DC = discontinuation; DLT = dose-limiting toxicity; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance score; EOT = end-of-treatment; FBR=future biomedical research; FSH=follicle-stimulating hormone; FT4 = free thyroxine; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HRD = homologous repair deficiency; ICF = informed consent form; ID=identification; INR = International Normalized Ratio; IRT = interactive response technology; OC = ovarian cancer; pCR = pathological complete response; PE = physical examination; PT = prothrombin time; PTT = partial thromboplastin time; Q3W = every 3 weeks; RNA = ribonucleic acid; SAE=serious adverse event; T3 = triiodothyronine; TSH = thyroid-stimulating hormone; WOCBP = women of childbearing potential; WONCBP = women of nonchild-bearing potential.

a. If the Discontinuation Visit (Section 8.11.3) occurs ≥30 days from the last dose of study intervention, the Safety Follow-up Visit does not need to be performed.

1.3.1 Imaging Assessments for Neoadjuvant/Adjuvant Treatment Period With Interval Debulking Surgery

Neoadjuvant / Adjuvant Treatment Period With Interval Debulking	
Imaging Visit	**Description**
Baseline	Perform imaging within 28 days prior to starting chemotherapy.
Peri-surgery	• Presurgery: Imaging performed a minimum of 21 days (+5 days) after C3D1 • Postsurgery: Imaging performed prior to resuming study intervention in C4D1 (-5 days) Note: If surgery is delayed, imaging should be delayed until prior to surgery (a minimum of 21 days after the last cycle of study intervention in the neoadjuvant phase) and then performed prior to the first dose of study intervention in the adjuvant phase. If cytoreduction is attempted but not performed (with or without biopsy collection) or deemed inappropriate, the next scheduled imaging assessment after C3D1 would occur at the EOT visit.
End-of-Treatment	Imaging performed at the time of treatment discontinuation (±4 weeks) and prior to starting a new anticancer treatment. If previous imaging was obtained within 4 weeks (28 days) before the date of discontinuation, then imaging at treatment discontinuation is not mandatory.
Abbreviations: C3D1 = Cycle 3, Day 1; C4D1 = Cycle 4, Day 1; EOT = end-of-treatment. NOTES: ▪ Chest, abdomen, and pelvis imaging – required at baseline and every timepoint according to the schedule above. ▪ Bone imaging – required at baseline for participants with a history of bone metastases or who are clinically symptomatic. If positive for bone metastases at baseline, perform bone imaging according to the schedule above. ▪ Brain imaging – required at baseline for participants with a history of brain metastases (to confirm stability) or who are clinically symptomatic (to rule out brain metastases). If positive for brain metastases, but eligible as noted in the eligibility criteria (Section 5.2, exclusion criterion No. 10) perform brain imaging according to the schedule above. ▪ Unscheduled imaging may be performed as clinically indicated.	

2 INTRODUCTION

MK-4830 is a novel CCI [redacted] that is an antagonist of ILT4. MK-4830 is under study for the treatment of solid tumors as monotherapy and as combination IO therapy with pembrolizumab.

2.1 Study Rationale

Treatment of newly diagnosed advanced OC is determined by the stage and risk of disease recurrence at diagnosis. Treatment options include either cytoreductive surgery followed by adjuvant chemotherapy (most likely platinum- and taxane-based) or chemotherapy alone. Alternatively, when the removal of all cancer during the initial surgery would be problematic due to tumor size, chemotherapy may be administered before surgery (neoadjuvant chemotherapy) to shrink the tumor, with additional chemotherapy after surgery (adjuvant chemotherapy). Clinically, complete remission is achieved in most newly diagnosed patients through a combination of cytoreductive surgery and chemotherapy; however, 10% of patients might not respond to first-line chemotherapeutic treatment and, of those who do respond,

between 55% and 75% will relapse within 2 years [du Bois, A., et al 2009] [Ledermann, J. A., et al 2013] [Edwards, S. J., et al 2015]. The overall 5-year survival rate for OC remains poor, ranging from 28% to 57% depending on age at diagnosis [Eisenhauer, E. L., et al 2012] [Edwards, S. J., et al 2015].

The anti-PD-1 antibody pembrolizumab has shown efficacy in combination with chemotherapy in patients with several advanced cancers and has a nonoverlapping toxicity profile with chemotherapy. The addition of pembrolizumab to carboplatin and pemetrexed improved efficacy and had a favorable benefit-to-risk profile in patients with chemotherapy-naïve, advanced nonsquamous NSCLC [Langer, C. J., et al 2016]. As neoadjuvant treatment, the addition of pembrolizumab to a carboplatin- and anthracycline-based neoadjuvant chemotherapy regimen for high-risk, early-stage TNBC provided a statistically significant improvement in the rate of pCR at the time of definitive surgery [Schmid, P., et al 2020] as well as a statistically significant and clinically meaningful improvement in EFS when continued as monotherapy in the adjuvant setting [Schmid, P., et al 2021]. These are the first published data to prospectively show a benefit of the addition of a PD-1 pathway inhibitor to chemotherapy for the neoadjuvant treatment of TNBC. Ongoing studies in several different tumor types are currently investigating the benefit of the addition of pembrolizumab to other front-line platinum-based chemotherapies, including OC (KEYLYNK-001).

While the advances in immunotherapy have improved treatment outcomes in cancer, tumors have several disparate mechanisms to limit immune responses and escape immunosurveillance. These resistance mechanisms vary by immune cell population, suggesting the need for combination therapy that inhibits multiple interacting pathways. Recent advances in targeting the PD-1/PD-L1 axis has demonstrated the potential for combination immunotherapy [Upadhaya, S., et al 2021].

One such approach centers on the modulation of immune-suppressive and tumor promoting myeloid populations [Chaib, M., et al 2020]. MDSCs in the tumor microenvironment represent a separate contributing feature of immune suppression and tumor promotion [Gao, X., et al 2021]. These MDSC populations contribute greatly to tumor immune evasion through multiple mechanisms including suppression of local T-cell activation and proliferation [Adah, D., et al 2016]. In OC, MDSCs are associated with immune suppression, tumor metastasis, shorter OS, a reduced disease-free interval, and poor prognosis [Singel, K. L., et al 2019] [Taki, M., et al 2018] [Banerjee, S., et al 2013], [Cui, T. X., et al 2013] [Huang, Q. T., et al 2017] [Mabuchi, S., et al 2021]. Therefore, relief of myeloid immune suppression in conjunction with T-cell activation through inhibition of the PD-1/PD-L1 axis, may improve antitumor efficacy in OC [Mabuchi, S., et al 2021].

MK-4830 is an antagonistic antibody directed toward ILT4, an inhibitory receptor that is highly expressed on myeloid cells and thought to be involved in immune tolerance and immunosuppression [Gao, A., et al 2018] [Gao, A., et al 2021]. Internal preclinical data demonstrate MK-4830 treatment results in tumor growth inhibition in CCI [redacted] supporting the scientific rationale underlying this study. The dose-escalation portion of the Phase 1 study (MK-4830-001) has recently been completed [Siu, L. L., et al 2020] [Siu, L. L., et al 2021]; based on safety and efficacy results, several expansion cohorts are planned, including an expansion cohort in OC.

CA-125 is the best-characterized blood-based biomarker in OC and has been widely studied. To improve its clinical utility [Berek, J. S., et al 2018], CA-125 has been used for both disease screening and monitoring [Rosenthal, A. N., et al 2017] [Berek, J. S., et al 2018] [Jacobs, I. J., et al 2016]. CA-125 levels do correlate with response to chemotherapy [Crawford, S. M. 2005], and levels of CA-125 prior to interval debulking surgery are associated with improved survival [Vasudev, N. S., et al 2011]. Although screening studies have demonstrated CA-125 increases the proportion of patients diagnosed with early-stage disease, the assay characteristics have prevented implementation of a screening program for OC. Use of CA-125 for disease monitoring during follow-up does not improve OS. Additionally, there are shortcomings of CA-125 monitoring that have resulted in the need to evaluate alternative technologies for blood-based biomarker development for both disease screening and monitoring tumor burden throughout treatment.

In recent years, the utility of interrogating genetic material released from tumor cells has provided the impetus for novel biomarker discovery and clinical utilization in OC [Thusgaard, C. F., et al 2021]. This led to the discovery and approach of liquid biopsies [Crowley, E., et al 2013] [Siravegna, G., et al 2017], which covers the approach of using tumor-derived circulating cfDNA and RNA, circulating tumor cells, and exosomes for the identification of disease. Of these technologies, ctDNA has proven to have the most utility due to stability and other technical considerations.

In OC, ctDNA has been used in an exploratory fashion for screening [Widschwendter, M., et al 2017], diagnosis [Vanderstichele, A., et al 2017], and prognosis [Thomsen, C. B., et al 2019]. More importantly, the ability of ctDNA to interrogate tumor genetics [Lin, K. K., et al 2019] [Dvorska, D., et al 2019] has provided a noninvasive mechanism for determination of tumor biology and potential treatment allocation. Furthermore, ctDNA has provided the opportunity to assess mechanisms of treatment response and resistance as shown by the identification and detection of reversion mutations to PARP inhibitors [Lin, K. K., et al 2019]. However, it is in disease monitoring where ctDNA offers much needed clinical utility, particularly as a replacement for CA-125. Two recent studies have demonstrated the ctDNA technology was better at monitoring treatment response than CA-125 [Widschwendter, M., et al 2017]. A recent study in OC using the Signatera assay from Natera Inc. demonstrated the ability to generate patient-specific ctDNA assays for disease monitoring. This data further highlighted the utility of ctDNA over that of CA-125 to monitor disease burden [Chapman, J. S., et al 2021]. More recently, ctDNA was investigated in the neoadjuvant OC setting in the CIDOC study (NCT03302884) [Mari, R., et al 2021]. This study demonstrated ctDNA may be a promising noninvasive marker to assess peritoneal cancer spreading and to predict surgical resection after neoadjuvant chemotherapy.

These data show the broad utility of ctDNA in OC and paths for future clinical development. In this translational study, we will investigate the clinical utility of ctDNA in OC as a blood-based technology to assess tumor biology and disease monitoring during neoadjuvant/adjuvant therapy with pembrolizumab and SOC chemotherapy with or without MK-4830. Furthermore, we will interrogate ctDNA as an early blood-based marker in relation to surgical outcomes [Siu, L. L., et al 2021]. It is envisaged that incorporation of

ctDNA technology will aid in the clinical development of promising agents like MK-4830 in addition to enhancing disease biology and mechanisms of drug action and resistance.

2.2 Background

Refer to the IB/approved labeling for detailed background information on MK-4830 and pembrolizumab.

2.2.1 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+ Tregs correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; HCC; malignant melanoma; and RCC. TILs can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [Dudley, M. E., et al 2005] [Hunder, N. N., et al 2008].

2.2.1.1 MK-4830 Background

MK-4830 is a novel, first-in-class, CCI [redacted] with high specificity of binding to the ILT4 receptor, thus inhibiting its interactions with MHC class I molecules including HLA-G. Based on in vitro data, MK-4830 has high affinity and potent receptor blocking activity to ILT4. MK-4830 has an acceptable preclinical safety profile and is in clinical development as an IV immunotherapy for advanced solid tumors. This mAb is being developed as a cancer immunotherapeutic with the potential to be used as an IO combination with KEYTRUDA® (pembrolizumab; a humanized anti-PD-1 receptor antibody), to increase anti-tumor efficacy in patients with various tumor indications.

ILT4, also known as LILRB2, is an inhibitory member of the LILR family that is expressed on myeloid and dendritic cells [Colonna, M., et al 1997] [Colonna, M,, et al 1998] [Fanger, N. A., et al 1998]. ILT4 binds MHC class I molecules including HLA-G [Allan, D. S., et al 1999] [Shiroishi, M., et al 2003] [Shiroishi, M., et al 2006]. HLA-G can directly inhibit immune cell function including cytolysis, proliferation, maturation, and chemotaxis [Lin, A. and Yan, W. H. 2015] [Morandi, F., et al 2014]. ILT4 and HLA-G are reported to have high expression in multiple tumor types [Liu, J., et al 2014] [Loumagne, L., et al 2014]. The interaction of ILT4 with HLA-G promotes signaling through immunoreceptor tyrosine-based inhibitory motifs via activation of SHP-1. This signaling can antagonize immunoreceptor tyrosine-based activation motif receptor-mediated activation of myeloid cells [Colonna, M,, et al 1998]. ILT4 signaling is also associated with induction of tolerogenic phenotypes in antigen presenting cells and was shown to promote HLA-G-dependent Type 1 regulatory T-cell development [Gregori, S., et al 2010].

In addition to HLA-G and other classical and non-classical MHC class I molecules (HLA-A, B, C, E, F, G), ILT4 has a range of additional ligands that include the ANGPTL family of

soluble signaling molecules and the MHC-like molecules CD1d [Zheng J, Umikawa M, Cui C, Li J, Chen X, Zhang C, et. al. 2012] [Li, D., et al 2009]. The range and variable immune functions of these ligands suggests a broader integrated immune biology of considerable complexity. ILT4 signaling may directly inhibit the function of monocytes, dendritic cells, and neutrophils, thus impairing the innate and adaptive immune anti-tumor response. Consequently, interrogating the breadth of ILT4 immunosuppressive activity has implications for ascertaining combination therapies and identifying cancer histologies for clinical investigation.

In OC, expression of the ILT4 ligand, HLA-G, is associated with advanced stage disease, high-grade histology, and worse prognosis [Sheu, J. J. C. 2007] [Song, M. J., et al 2021] [Andersson, E., et al 2016]. HLA-G is more frequently expressed in advanced serous metastatic cells than in primary tumor lesions and inversely correlated with the frequency of tumor-infiltrating immune cells [Andersson, E., et al 2016]. HLA-G is also associated with direct immune evasion [Menier, C., et al 2009].

MK-4830 is a CCI anti-ILT4 antagonistic mAb on an CCI /Lambda framework. MK-4830 was selected based on its specificity to ILT4, its ability to block HLA-G binding to ILT4 and its ability to rescue ILT4-related inhibitory function. The CCI isotype was chosen to minimize effector function and framework-mediated cross-linking ability leading to agonist activity.

CCI [redacted].

In addition, MDSCs promote immunosuppression in the tumor microenvironment via inhibition of local T-cell activation and proliferation. Therefore, relief of myeloid immunosuppression may potentiate T-cell activation and improve the efficacy of T-cell targeted therapies such as pembrolizumab, even in tumors that do not normally respond to PD-1 antagonism alone. This would suggest that removal of immune suppression, induced by ILT4 blockade using MK-4830, combined with the T-cell check point inhibitor, pembrolizumab, will offer substantially augmented anti-tumor efficacy compared with either treatment alone. This scientific rationale provides justification to pursue MK-4830 and pembrolizumab as combination therapy.

For more details refer to the MK-4830 IB.

2.2.1.2 Pembrolizumab Background

Pembrolizumab is a potent CCI [redacted] 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.

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.

For more details on specific indications refer to the pembrolizumab IB.

2.2.1.3 Overview of Ovarian Cancer

OC is one of the leading causes of cancer death among women [Sung, H., et al 2021]. In 2021, the estimated number of new cases and deaths from OC in the US is 21,410 and 13,770, respectively [Siegel, R. L., et al 2021]. Worldwide, OC represents one of the 10 most common cancer diagnoses and one of the leading causes of cancer-related deaths in women [Sung, H., et al 2021]. Due to lack of tumor-specific signs and symptoms and effective screening tests for early detection, over 75% of OC patients are first diagnosed at advanced stages. Based on the US data from 2010 to 2016, at initial diagnosis, 58% had distant metastasis, 21% had regional disease and only 16% had localized disease [Siegel, R. L., et al 2021]. The overall 5-year survival rate of OC is approximately 49% counting all stages of

disease, whereas, the 5-year survival rate for patients with distant metastasis is only 30% [Siegel, R. L., et al 2021].

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

2.2.1.4 Current Standard of Care and Unmet Medical Need

The current SOC for advanced epithelial OC (FIGO Stage II to Stage IV) includes primary cytoreductive/debulking surgery followed by postoperative front-line (ie, adjuvant) systemic treatment with IV carboplatin and paclitaxel administered Q3W for 6 cycles; however, weekly paclitaxel has also been frequently used to replace Q3W paclitaxel. In addition, where locally approved for front-line treatment, IV bevacizumab can be added to IV carboplatin and paclitaxel for up to 6 cycles in the adjuvant setting and then continued as a single agent in the maintenance setting. The utilization of bevacizumab in the first-line and maintenance settings is variable based on local guidelines and patient characteristics [Hall, J. P., et al 2020]. This leads to a heterogeneous population that has implications for clinical study design, efficacy assessment of agents in early development, and the contribution of anti-angiogenesis pathways for translational data analyses. In a recent analysis of real-world data on OC treatment obtained from 340 physicians from the US and select European countries, only 26% of patients received a bevacizumab-containing regimen in the first-line setting [Hall, J. P., et al 2020]. In suitable cases, postoperative chemotherapy, usually cisplatin plus paclitaxel, can be delivered via the intraperitoneal route. Finally, in cases with bulky disease that is initially unresectable, 3 cycles of standard platinum/taxane-based chemotherapy can be administered as neoadjuvant therapy prior to cytoreductive/debulking surgery (ie, interval cytoreductive/debulking surgery) followed by an additional 3 cycles of standard platinum/taxane-based chemotherapy [Morgan, R. J ., et al 2016] [Ledermann, J. A., et al 2013].

The goal of cytoreductive/debulking surgery is to achieve resection of all macroscopically visible tumors, while the goals of postoperative first-line chemotherapy are: 1) to help achieve complete remission in those with residual disease, and 2) to prevent disease recurrence for those with complete tumor resection. However, after these primary treatments, only a small proportion of patients will achieve long-term disease-free and survival status. A meta-analysis on data from 3 randomized studies following the standard primary treatment with surgery and platinum/taxane-based chemotherapy (N=3126), showed that only 24% of

patients were recurrence-free after a median follow-up time of 53.9 months. The remaining 76% had recurrent disease (17.2%) or had died (58.8%) [du Bois, A., et al 2009].

Maintenance treatment for adult ovarian cancer patients follows first-line platinum-based chemotherapy and is composed of bevacizumab and/or PARPi-based regimens. The specific maintenance regimen will depend upon patient characteristics, homologous recombination deficiency status, and the response to first-line therapy among others [Mirza, M. R., et al 2021] [Advani, S. H., et al 2021] [Hall, J. P., et al 2020], [Gupta, S., et al 2019]. Consequently, the maintenance setting treatment in an unselected population is heterogeneous with respect to therapy utilization and clinical outcomes. Due to lack of baseline clinical or safety datasets on the efficacy of MK-4830 with selected first-line OC patient populations, coupled with the design considerations of treatment heterogeneity in the maintenance setting, this study will complete after platinum-based therapy. Participants will discontinue study intervention and undertake maintenance therapy as per local treatment guidelines.

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

2.2.2 ctDNA

ctDNA is the release of genomic DNA from tumor cells mainly via apoptosis, necrosis, and secretion [Chen, Q., et al 2019]. ctDNA can be readily detected in plasma and other fluids like the cerebrospinal fluid, saliva, and urine. However, blood is becoming the predominant sample for ctDNA interrogation. Blood-based interrogation of ctDNA offers many patient and logistical advantages over tissue-based methods. Constantly improving technology and assay development has meant that the ability of ctDNA to be used as an analyte for translational and biomarker cancer research has expanded significantly.

The US FDA has already approved several single-gene assays or multigene panels to detect tumor genetic alterations in plasma ctDNA for use as companion diagnostics that is then matched to specific molecularly-targeted therapies. Proposed uses of ctDNA in OC range from early detection through to identification of tumor genetics and biology [Sharbatoghli, M., et al 2020] [Yu, M., et al 2021] [Chen, Q., et al 2019], [Cheng, X., et al 2017] [Elias, K. M., et al 2018]. Recent data has also demonstrated ctDNA as a predictor of neoadjuvant therapy and surgical outcomes [Mari, R., et al 2021]. This is of particular interest in the neoadjuvant setting as it potentially enables a rapid determination of clinical activity for new therapeutics and may enhance criteria for predicting surgical outcomes like CRS.

The next technical advances for clinical applications likely include early cancer detection and, in the adjuvant or maintenance setting, making treatment decisions based upon detection of ctDNA as a surrogate for disease burden in patients that is indicative of early relapse prior

to image detection. Detection of minimal residual disease using flow cytometry or PCR-based methods has been well-established within hematological malignancies like AML [Voso, M. T., et al 2019] or lymphoma [Jung, D., et al 2020]. However, similar technologies with high levels of specificity and sensitivity have been lacking for solid tumors. Some technologies like circulating tumor cells [Wu, C. Y., et al 2020] or exosomes [Garcia-Silva, S., et al 2021] have shown promise but will be technically difficult to implement or develop routine clinical assays. ctDNA represents a readily executable analyte with an expanding array of assay technologies for MRD detection from bespoke personalized assays [Bratman, S. V., et al 2020] to tumor-specific methylation-based patterning [Luo, H., et al 2021]. The use of ctDNA as a surrogate for disease burden in OC may prove more informative than CA-125 in disease monitoring [Chapman, J. S., et al 2021].

2.2.3 Microsampling

Smaller collection volumes are critical in vulnerable populations such as pediatrics and oncology due to blood volume collection restrictions. To meet this demand, microsampling technologies are being developed and have been approved for collecting biological samples for clinical use. These approaches reduce sample volume, reduce pain associated with collection, and may enable collection outside of planned clinical visits. Providing opportunities to collect samples remotely can reduce patient burden and enable patients to enroll in clinical studies without being geographically colocated with clinical sites [Dockendorf, M. F., et al 2019] [Dockendorf, M. F., et al 2021]. The need to develop remote sampling capabilities was highlighted during the disruption in clinical studies from the COVID-19 pandemic [Brown, L., et al 2021]. Finally, the ability to collect samples outside the traditional clinic visit allows interrogation of biological changes that occur outside the logistical constraint of clinical site visits. Historically, new sampling technology has been successfully implemented across the pharmaceutical industry in multiple clinical studies for PK analysis [Kothare, P. A., et al 2016] [Li, C. C., et al 2018]. DBS microsampling applications for drug quantitation are well accepted and specific considerations for validation of DBS assays are included in the FDA bioanalytical method validation guidance released in May 2018 [Food and Drug Administration 2018]. New devices such as the CCI and CCI provide high sample quality without the pain associated with fingerstick based collection methods. MSD has experience implementing these new approaches across several clinical studies in infectious disease for drug level measurements. It is desirable to assess these novel technologies to determine the utility of these approaches for applications beyond PK.

2.2.4 Preclinical and Clinical Studies

Refer to the respective IBs for a summary of preclinical and clinical study data for MK-4830 and pembrolizumab.

2.2.5 Ongoing Clinical Studies

Refer to the respective IBs for a summary of ongoing clinical studies for MK-4830 and pembrolizumab.

2.2.6 Information on Other Study-related Therapy

For additional information on carboplatin, paclitaxel (or docetaxel, if applicable), and Avastin (or biosimilar), refer to the respective approved product labels.

2.3 Benefit/Risk Assessment

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

As discussed in Section 2.2.1.4, the chemotherapy backbone carboplatin and paclitaxel represent one of the preferred treatment options for the first-line treatment of advanced OC [Dewdney, S. B., et al 2010] [Machida, H., et al 2020] [Patel, A., et al 2021]. Given the high rate of relapse following initial treatment for OC [Ledermann, J. A., et al 2013], there is an unmet medical need for an effective and tolerable first-line treatment regimen. Furthermore, there is a need for the identification of biomarkers that will quickly predict response to treatment. The use of ctDNA as a surrogate for disease burden in OC may prove more informative than CA-125 in disease monitoring [Chapman, J. S., et al 2021].

OC is thought to be an immune responsive disease. Furthermore, in OC, the expression of the ILT4 ligand, HLA-G, is associated with advanced stage disease, high-grade histology, and worse prognosis [Sheu, J. J. C. 2007] [Song, M. J., et al 2021] [Andersson, E., et al 2016]. HLA-G was more frequently expressed in advanced serous metastatic cells than in primary tumor lesions and inversely correlated with the frequency of tumor-infiltrating immune cells [Andersson, E., et al 2016]. HLA-G was also associated with direct immune evasion [Menier, C., et al 2009]. Finally, the therapeutic benefit of adding pembrolizumab to chemotherapy, including in combination with platinum agents, has been shown in several indications (eg, NSCLC, HNSCC, TNBC; refer to the pembrolizumab IB).

Data from KEYNOTE-100, in participants with recurrent OC, suggest improved efficacy for pembrolizumab monotherapy in those participants whose tumors express PD-L1 with the cutoff of CPS ≥10. KEYLYNK-001 is currently investigating the clinical activity of pembrolizumab in combination with platinum-based chemotherapy with or without olaparib. The combination of pembrolizumab and chemotherapy has been clinically established in several tumor types including TNBC in the neoadjuvant setting as demonstrated by KEYNOTE-522 [Schmid, P., et al 2020]. A recent study demonstrated that pembrolizumab may be safely added to preoperative treatment in neoadjuvant OC and worthy of additional investigation [Ray-Coquard, I. L., et al 2021] [Matulonis, U. A., et al 2020].

The MK-4830 Phase 1 study has demonstrated clinical activity in OC [Siu, L. L., et al 2021] and acceptable safety when combined with pembrolizumab. In the 84 participants with multiple tumor types treated with MK-4830 (cutoff data was 10-JUL-2020), no DLTs were observed, and an MTD was not reached in either the monotherapy or the pembrolizumab combination therapy group.

Therefore, targeting the ILT4 and PD-1/PD-L1 pathway in addition to one of the preferred chemotherapy regimens for OC is an attractive target for therapeutic intervention. The benefit-risk for this study is considered to be favorable.

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

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

In participants with high-grade serous ovarian cancer:

Objectives	Endpoints
Primary	
Objective: Among patients with detectable ctDNA at baseline, to evaluate whether the reduction from baseline in circulating tumor DNA at Cycle 3 (ΔctDNA) is larger in participants receiving MK-4830 + pembrolizumab in combination with standard of care (SOC) therapy than in those receiving pembrolizumab + SOC therapy.	ctDNA, the continuous mean mutant/tumor molecules per mL.
Secondary	
Objective: Among patients with detectable ctDNA at baseline, to evaluate the association between neoadjuvant ΔctDNA at Cycle 3 from baseline and surgical outcomes.	ctDNA pCR, all surgical specimens collected during the interval debulking surgery are microscopically negative for residual tumor. CRS, tiered response score based omental assessment of residual disease.
Objective: To estimate the difference in pCR and CRS following neoadjuvant treatment between arms.	pCR CRS
Objective: To evaluate the safety and tolerability of the study intervention administered.	Adverse events (AEs) Study intervention discontinuation due to AEs

Objectives	Endpoints
Tertiary/Exploratory	
Objective: To identify molecular (genomic, metabolic, and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of MK-4830 in combination with pembrolizumab and SOC.	Molecular (genomic, metabolic and/or proteomic) determinants of response or resistance to treatments, using blood and/or tumor tissue.
Objective: To evaluate the ability of molecular (genomic, metabolic, and/or proteomic) data from microsampling, collected in the clinic and at home, to replicate molecular data obtained from traditional blood collection.	Genetic (DNA) mutations from tumor, tumor and blood RNA variation, proteomics and metabolomics, and other blood-derived biomarkers (eg, cfDNA) using traditional blood collection and microsampling.
Objective: To evaluate microsampling device use, feasibility of collection, and accuracy of collecting microsamples both at the clinic and at home.	Compliance in use of device Device performance Quality of samples collected Sample volumes collected
Objective: To evaluate whether baseline ctDNA levels are associated with neoadjuvant chemotherapy and surgical outcomes.	Mean mutant/tumor molecules per mL pCR CRS
Objective: To evaluate ctDNA and CA-125 as markers for disease monitoring.	ctDNA CA-125 Measures of clinical response (eg, complete response [CR] and partial response [PR]) and surgical outcome
Objective: To evaluate additional measures of clinical response, such as objective response rate as assessed by the investigator according to RECIST 1.1 in participants with measurable disease in each arm separately.	Measures of clinical response (eg, CR and PR)

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 2, randomized, active-controlled, parallel-group, multisite, open-label, neoadjuvant and adjuvant study of pembrolizumab and SOC therapy with MK-4830 versus pembrolizumab and SOC therapy in participants with high-grade serous OC.

Approximately 160 participants will be randomly assigned in a 1:1 ratio to 1 of 2 treatment arms:

Arm 1:
Neoadjuvant phase: 3 cycles of carboplatin/paclitaxel* plus pembrolizumab (200 mg Q3W) plus MK-4830 (800 mg Q3W) prior to surgery
Adjuvant phase: 3 cycles of carboplatin/paclitaxel* plus pembrolizumab (200 mg Q3W) plus MK-4830 (800 mg Q3W) ± Avastin (or biosimilar) after surgery

Arm 2:
Neoadjuvant phase: 3 cycles of carboplatin/paclitaxel* plus pembrolizumab (200 mg Q3W)
Adjuvant phase: 3 cycles of carboplatin/paclitaxel* plus pembrolizumab (200 mg Q3W) ± Avastin (or biosimilar) after surgery

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

Carboplatin AUC 5 or AUC 6 Q3W plus paclitaxel 175 mg/m^2 Q3W

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

Docetaxel 75 mg/m^2 Q3W plus carboplatin AUC 5 or AUC 6 Q3W

Participants will receive 3 cycles of study intervention prior to interval debulking surgery (neoadjuvant treatment) and another 3 cycles of study intervention after interval debulking surgery (adjuvant treatment) Figure 1. Interval debulking surgery should be completed no more than 6 weeks after last dose of neoadjuvant treatment. Participants should resume study intervention when clinically appropriate but no more than 7 weeks following interval debulking surgery. Sponsor consultation and approval is required for surgeries delayed >6 weeks after Day 1 of Cycle 3.

Participants for whom interval debulking is either attempted and not performed or deemed inappropriate may continue on-study intervention for up to 6 cycles following Sponsor

consultation and approval. Such participants should resume study intervention as planned at the next treatment cycle (ie, no more than 3 weeks after Day 1 of Cycle 3).

The optional use of Avastin (or biosimilar) in the adjuvant phase (ie, Cycles 4 to 6) is permitted according to local practice and at the choice of the investigator; however, the investigator must decide on the use of Avastin (or biosimilar) after surgery and it must be selected in IRT prior to starting treatment in the adjuvant phase. If surgery is delayed (following Sponsor consultation and approval), Avastin (or biosimilar) cannot be started until after surgery. *Note: Use of Avastin (or biosimilar) is not permitted in the neoadjuvant phase (ie, prior to surgery in Cycles 1 to 3).*

For participants who will receive Avastin (or biosimilar) in the adjuvant phase, there is a Safety Lead-in to demonstrate a tolerable safety profile for Arm 1 when Avastin (or biosimilar) is added. Participants treated with pembrolizumab + MK-4830 + carboplatin/paclitaxel + Avastin (or biosimilar) will be closely followed for DLTs for the first cycle after the first dose of study intervention in the adjuvant phase (the DLT evaluation period). The number of participants with DLTs (Section 6.6.3) will be monitored according to the mTPI [Ji, Y., et al 2007] table as outlined in Table 9 (Appendix 9) with a target DLT rate of 30%. If a DU is reached or a D is indicated Table 9, the use of Avastin (or biosimilar) will be prohibited for the remainder of the study.

This study will use an siDMC to monitor safety (Appendix 1). The siDMC will review safety data from all participants on a frequent basis throughout the study as outlined in the siDMC charter. The siDMC may meet on an ad hoc basis to review additional safety data as needed.

After Cycle 6, participants will have completed study intervention and may begin maintenance therapy at the discretion of the investigator, per institutional guidelines and local regulatory approvals. Participants who have completed study intervention or who discontinue study intervention for a reason other than disease progression will begin Long-term Follow-up as outlined in Section 8.11.4.2.

Tumor marker data (ie, CA-125) will not be used for defining PD to evaluate progression-related study objectives; however, CA-125 may be used to make clinical decisions, including the decision to discontinue a participant from study intervention (Section 7.1). Clinical criteria such as the Gynecologic Cancer Intergroup criteria [Rustin, G. J., et al 2011] will also be considered for the management of clinical events (eg, bowel obstruction) without radiographic disease progression. Participants who discontinue due to CA-125 increase and concurrent malignant bowel obstruction will have post-treatment follow-up imaging to evaluate disease status until disease progression is radiographically documented per RECIST 1.1 by the investigator as outlined in Section 8.2.1.4.

Participants will be followed for 30 days after the last dose of study intervention in Cycle 6 (Section 8.11.4.1). AE monitoring will be ongoing throughout the study and graded in severity according to the guidelines outlined in the NCI CTCAE v5.0. AEs and SAEs will be reported by the investigator or delegate as outlined in Section 8.4.1.

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

Patients with advanced OC have a poor 5-year survival rate (30%), which represents an area of unmet medical need that may benefit from novel IO and chemotherapy options, improved patient treatment selection, and more advanced monitoring while on-treatment. Determining patient selection criteria and treatment combinations requires the development of translational datasets and establishment of key technology to achieve those goals.

The neoadjuvant/adjuvant setting with interval debulking surgery is a recognized SOC treatment algorithm for first-line advanced OC. The neoadjuvant setting allows for rapid assessment of translational and clinical objectives through sample collection and determination of pathological responses at surgery. Three cycles of neoadjuvant standard platinum/taxane-based chemotherapy prior to cytoreductive/debulking surgery (ie, interval cytoreductive/debulking surgery) followed by an additional 3 cycles of standard platinum/taxane-based chemotherapy is an accepted clinical design [Morgan, R. J ., et al 2016] [Ledermann, J. A., et al 2013]. Three cycles of neoadjuvant therapy are a suitable number of treatment cycles to evaluate treatment-related-related changes in the tumor microenvironment and immune system generated by checkpoint inhibition.

This clinical study will test the utility of ctDNA as a measure of clinical response and minimal residual disease (in conjunction with other exploratory immune markers) in treatment-naïve HGSOC treated with a combination of SOC therapy and a novel immunotherapy combination of PD-1 and ILT4 inhibitors.

Cancer cells shed ctDNA, which represents an increasingly important blood-based analyte for interrogation of tumor presence, tumor biology, genetics, and disease burden. Clinical evidence has demonstrated that ctDNA provides a blood-based mechanism to detect minimal residual disease and serve as a predictor for both response, treatment resistance, and disease progression months prior to RECIST 1.1 assessment or surgery [Ignatiadis, M., et al 2021]. Furthermore, ctDNA has the potential to complement other established blood-based markers like CA-125 [Soletormos, G., et al 2016]. Analysis of ctDNA has a potential regulatory role as a surrogate biomarker for clinical and surgical outcomes, and disease progression. It is envisaged that by exploring ctDNA in the neoadjuvant and surgical OC setting will help define criteria for rapid appraisal of treatment outcomes.

The advent of targeting immune checkpoints such as CTLA-4 and PD-1 has led to several treatment advances in oncology [Marin-Acevedo, J. A., et al 2021]. Inhibitors against additional checkpoints such as TIGIT and LAG3 [Rodriguez-Abreu, D., et al 2020] have shown initial clinical activity. These targets are predominantly T-cell targets with some expression in other immune cell types.

The myeloid ILT4 pathway has more recently been defined as a new checkpoint target for therapeutic intervention [Gao, A., et al 2021]. Unlike the aforementioned targets, there is

little known about the functionality of this pathway in the broader oncology space, particularly mechanisms of response and resistance. Unlike PD-1 which has 2 identified ligands, PD-L1 and PD-L2, ILT4 has considerably more complexity with several ligands identified [Gao, A., et al 2018]. Thus, delineating pathway biology is paramount for understanding mechanisms or response and resistance. MK-4830 has demonstrated clinical activity in a Phase 1 study [Siu, L. L., et al 2021] and is currently being investigated in several expansion cohorts, including late-stage OC.

The complexity by which tumors escape immune surveillance suggests that multiple checkpoints may need to be targeted. Clinical evidence has demonstrated, in a wide range of tumor types, that many patients fail to respond to PD-1 inhibitors [Chen, S., et al 2021]. The combination of anti-PD-1 and anti-ILT4 agents is consistent with the hypothesis that removing multiple inhibitory signals of immune evasion could potentially result in an added benefit [Siu, L. L., et al 2021].

As with many oncology pathways under interrogation, early determination of clinical activity is usually performed in the advanced setting beyond first-line therapy in heavily treated patients. This has implications for immune system status and tumor biology. This study design enables a rapid read on activity and a treatment naïve population in which to study the immunology of the ILT4 pathway.

The SOC treatment paradigm for OC of interval debulking surgery along with neoadjuvant therapy is an appropriate clinical space for the above mentioned translational of investigations [Elies, A., et al 2018] [Machida, H., et al 2020] [Melamed, A., et al 2016], [Qin, M., et al 2018]. Neoadjuvant chemotherapy offers the opportunity to test upfront chemosensitivity and response to new agents to identify early clinical activity and patients at higher risk of relapse. The advent of newer and effective treatment options targeting different tumor biologies (eg, PARP inhibitors) has opened the way to clinical trials investigating these agents as a substitute or in addition to chemotherapy in the neoadjuvant setting in all comers or molecularly selected OC patients. Thus, neoadjuvant treatment before debulking surgery could also represent an optimal approach for testing new and effective treatments and biomarkers, with the potential to accelerate drug development due to availability of pre- and post-treatment tumor tissue [Cowan, R., et al 2016]. The latter point is of particular importance for agents like MK-4830 that are new classes of agents early in clinical development.

This study will also evaluate the potential of microsampling to obtain low volume and low risk blood samples to conduct multi-omic disease analyses. Reduction of collected blood volumes and the ability to have “at home” collection using this approach may allow incorporation of new translational and biomarker technologies into clinical care in the future. The recent advent of the COVID-19 pandemic has highlighted the need for reliable at home blood collection approaches such as the microsampling device that is incorporated into this study.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

Surgical outcomes will be measured using pCR criteria and CRS [Ivantsov, A. O. 2018] [Bohm, S., et al 2015]. CRS is an acceptable exploratory surgical criterion for assessing the completeness of neoadjuvant treatment followed by interval debulking surgery. It is a 3-tiered scoring system (CRS1-3) based on the pathological analysis of surgically removed omental masses, with CRS3 (complete or near-complete response) characterized by the lack of residual tumor cells in the omentum or presence of tumor foci up to 2 mm maximum size. CRS3 is found after neoadjuvant chemotherapy in approximately 30% to 40% patients with high-grade serous OC and is reproducibly related with the improvement of the disease prognosis. In addition to CRS, complete pathological responses will be recorded [Bohm, S., et al 2015] and will be defined as all surgical specimens collected during interval debulking surgery are microscopically negative for residual tumor.

RECIST 1.1 will be used when assessing images for efficacy measures (Section 8.2.1.4). This study will use objective response based on RECIST 1.1 criteria as assessed by the investigator as an exploratory endpoint. Objective response is defined as a confirmed CR or confirmed PR per RECIST 1.1 as assessed by investigator recorded between the start of and end-of-treatment, or disease progression or death due to any cause within that period, whichever occurs first.

4.2.1.1.1 RECIST 1.1

RECIST 1.1 will be used by the investigator when assessing images for primary efficacy (Section 8.2.1.4). Although traditional RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, this protocol has implemented an adjustment to RECIST 1.1 to allow a maximum of 10 target lesions in total and 5 per organ.

4.2.1.2 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 v5.0.

4.2.1.3 Pharmacokinetic Endpoints

PK endpoints will not be evaluated in this study.

4.2.1.4 Pharmacodynamic Endpoints

The primary objective of this study will be to measure changes in ctDNA as a translational primary endpoint to establish the clinical validity of ctDNA kinetics in the neoadjuvant and adjuvant setting. The aim is to determine if quantification of ctDNA can perform as a surrogate for clinical and surgical response to the neoadjuvant combination therapies. ctDNA

is rapidly becoming an experimental surrogate measure of tumor burden and clinical responses in a range of clinical spaces across many tumor types.

4.2.1.5 Planned Exploratory Biomarker Research

The mechanism of action of many antitumor agents 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 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 antineoplastic drugs. To identify novel biomarkers, biospecimens (ie, blood components, tumor material) will be collected to support analyses of cellular components (eg, protein, DNA, RNA, metabolites) and other circulating molecules. Investigations may include, but are not limited to:

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

This research may evaluate whether genetic variation within a clinical study population correlates with response to the treatment(s) under evaluation. If genetic variation is found to predict efficacy or AEs, the data might inform optimal use of therapies in the patient population. Furthermore, it is important to evaluate germline DNA variation across the genome to interpret tumor-specific DNA mutations. In addition to studying variation across the human genome, BRCA and homologous repair deficiency status will specifically be investigated as these are common in patients with HGSOC. 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 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 antitumor therapies. Specific gene sets (ie, those capturing interferon-gamma transcriptional pathways) may be evaluated and new signatures may be identified. Individual genes may also be evaluated (eg, IL-10). MicroRNA profiling may also be pursued as well as exosomal profiling.

Proteomics and IHC using blood or tumor

Tumor and blood samples from this study may undergo proteomic analyses (eg, PD-L1 IHC). PD-L1 protein level in tumor sections, assessed by IHC, has been shown to correlate with response to pembrolizumab in patients with NSCLC, for example. 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 antitumor 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 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.

4.2.1.5.1 Translational Oncology Research

The tumor microenvironment plays a fundamental role to dictate the efficacy of cancer immunotherapy. Multiple cell types are present and cross-talk with each other in the tumor milieu. To better understand how different cell types and their interactions affect patient responses, as well as to better understand molecular mechanisms of cancer, patient-derived ex-vivo and in vivo models will be generated using fresh tumor material from consenting patients at select sites in this study. Investigations may include, but are not limited to:

Primary cell line generation, including organoids

Fresh tumor specimens will be digested either mechanically or enzymatically. When applicable, different cell populations may be separated by either flow cytometry or mass cytometry based sorting. Primary tumor cells will be amplificated by organoid culture or adherent 2D culture with tumor type-specific protocols. Cancer associated fibroblast may be isolated and cultured on gelatin-coated surface in fibroblast growth medium, or other similar reagents. In addition, TILs can be stimulated and amplified through a combination of factors, such as CD3/CD2/CD28 activation beads, cytokines and antibodies. Further isolation of

tumor-specific T-cell clones may also be performed by stimulation of TILs with matched primary tumor cells.

Pharmacological perturbation of single or coculture of primary cells

Various 2-dimensional and 3-dimensional coculture may be performed under applicable pharmacological perturbations with applicable biological readouts including, but not limited to, cytokine secretion, flow cytometry or other protein-based assays, imaging, microscopy, gene expression or other genomic assays.

Different reagents may be applied, including possible future drugs, to evaluate the effect on tumor cells.

Patient-derived xenograft murine tumor model

Primary tumor cells may be implanted into either immunosuppressed or humanized murine host to facilitate in vivo studies. Animals may be treated with different combinations of pharmacological perturbations to better understand the mechanism of action of possible patient responses.

Genetic and transcriptomic analysis

This research may evaluate whether genetic or transcriptomic variations within the collection of primary cell lines or murine tumor models correlates with response to the treatment(s) under evaluation. If genetic variation is found to predict efficacy the data might inform optimal use of therapies in the patient population.

4.2.1.6 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

Carboplatin and paclitaxel represent one of the preferred treatment options for the first-line treatment of advanced OC. Docetaxel may be considered for participants who either experience a severe hypersensitivity reaction or an AE that requires discontinuation of

paclitaxel only after Sponsor consultation and approval. This study will use pembrolizumab added to SOC chemotherapy as the comparator arm consistent with the KEYLYNK-001 study. This will enable delineation of contributing immune effects of inhibiting PD-1 alone versus the combination of PD-1 and ILT4 inhibition. Furthermore, our knowledge of PD-1 inhibition and biology within ovarian cancer itself is limited and the comparator arm will aid in understanding that immune and tumor biology. Based upon the MK-4830 Phase 1 study data [Siu, L. L., et al 2021] and relationship between the PD-1 and ILT4 pathways, this combination checkpoint therapy is a potential backbone in several tumor types. Delineating the PD-1 and ILT4 biology will contribute to clinical development in those tumors where pembrolizumab has established clinical efficacy.

4.3 Justification for Dose

4.3.1 Starting Dose for This Study

4.3.1.1 MK-4830

The planned dose of MK-4830 in this study is 800 mg Q3W. Based on safety and efficacy data in Study MK-4830-001, 800 mg demonstrated promising anticancer activity, was generally well tolerated, and was determined to be the RP2D [Siu, L. L., et al 2020].

4.3.1.2 Rationale for Chemotherapy Dosing Regimen

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

4.3.1.3 Pembrolizumab

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

Clinical data from 8 randomized studies in melanoma and NSCLC indications demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg Q2W representing an approximate 5- to 7.5-fold exposure range (refer to IB, Section 5.2.2)

Population PK analysis showing that both fixed dosing and weight-based dosing provides similar control of PK variability with considerable overlap in the distributions of exposures, supporting suitability of 200 mg Q3W

Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications

Pharmacology data showing full target saturation in both systemic circulation (inferred from PK data) and tumor (inferred from PBPK analysis) at 200 mg Q3W

4.3.2 Maximum Dose/Exposure for This Study

The maximum dose/exposure of study intervention (pembrolizumab, MK-4830, and chemotherapy) in this study is 6 treatment cycles: 3 cycles prior to interval debulking surgery (neoadjuvant treatment) and 3 cycles after interval debulking surgery (adjuvant treatment).

The maximum dose/exposure of Avastin (or biosimilar) in this study is 3 treatment cycles: 3 cycles after interval debulking surgery (adjuvant treatment).

4.4 Beginning and End-of-Study Definition

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

For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory test result or at the time of final contact with the last participant, whichever comes last.

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

The Sponsor estimates that the maximum duration of the study from first participant entered through long-term follow-up will be 3 years (~2.5 years after study intervention has been completed) to attain the final assessment of the study (eg, to evaluate safety and/or long-term efficacy) for all evaluable participants. Refer to the Synopsis, Section 1.1, for the duration of participation of participants.

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), 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.

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

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

5.1 Inclusion Criteria

A participant will be eligible for inclusion in the study if the participant:

Type of Participant and Disease Characteristics

1. Has histologically-confirmed FIGO Stage III or Stage IV HGSOC, primary peritoneal cancer, or fallopian tube cancer [Prat, J. and FIGO Committee on Gynecologic Oncology 2014].

2. Is a candidate for carboplatin and paclitaxel chemotherapy, to be administered in the neoadjuvant and adjuvant setting.

3. Is a candidate for interval debulking surgery.

4. Has either a CA-125 (kilounits/L):CEA (ng/mL) ratio ≥25 [Vergote, I., et al 2010] or, if the CA-125:CEA ratio is <25, then a workup should be negative for the presence of a non-OC tumor (eg, breast or GI cancers including CRC).

5. Is able to provide archival tissue or newly obtained core, incisional, or excisional biopsy of a tumor lesion. Details pertaining to tumor tissue submission requirements can be found in the laboratory manual.

   Note: Prior to randomization, archival or newly obtained tissue at Screening must be confirmed to be of sufficient quality and quantity to analyze the primary endpoint (which requires tissue for analysis) by the designated laboratory. Participants will not be eligible for the study if it is not of sufficient quality and quantity, and they cannot provide an additional sample that meets the above criteria.

Demographics

6. Is female and at least 18 years of age on the day of providing documented informed consent.

7. Has an ECOG PS of 0 or 1, as assessed within 7 days prior to the first dose of study intervention on Day 1 of Cycle 1.

Female Participants

8. A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 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:

  - MK-4830: 180 days
  - Pembrolizumab: 120 days
  - Chemotherapy: 180 days (refer to Appendix 7 for country-specific requirements)
  - Avastin (or biosimilar 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.

- Has a negative highly sensitive pregnancy test (urine or serum) as required by local regulations) within either 24 hours (urine) or 72 hours (serum) before the first dose of study 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.

- 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

9. 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

10. Has an adequate organ function as defined in Table 1; all screening laboratory tests should be performed within 7 days prior to the first dose of study intervention on Day 1 of Cycle 1.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/µL
Platelets	≥100 000/µL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[a]
Renal	
Creatinine OR Measured or calculated[b] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN OR ≥30 mL/min for participant with creatinine levels >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	≤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 and without packed red blood cell (pRBC) transfusion within last 2 weeks.

[b]Creatinine clearance (CrCl) should be calculated per institutional standard.

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

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

Medical Conditions

1. Has a non-HGSOC histology.

2. Has a history of (noninfectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease.

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

   Note: The time requirement does not apply to participants who underwent successful definitive resection of basal cell carcinoma of the skin, squamous-cell carcinoma of the skin, superficial bladder cancer, in-situ cervical cancer, or other in-situ cancers.

   Note: Participants with synchronous primary endometrial cancer or a past history of primary endometrial cancer that meet the following conditions are not excluded: Stage not greater than IA; no more than superficial myometrial invasion, without vascular or lymphatic invasion; no poorly differentiated subtypes, including papillary serous, clear cell or other FIGO Grade 3 lesions.

Prior/Concomitant Therapy

4. Has received prior treatment for any stage of OC, including radiation or systemic anticancer therapy (eg, chemotherapy, hormonal therapy, immunotherapy, investigational therapy).

5. Is a participant for whom intraperitoneal chemotherapy is planned or has been administered as first-line therapy.

6. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-ILT4, or anti-HLA-G agent or with an agent directed to another stimulatory or coinhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137) or MDSC-directed therapy.

7. Has received a live or live-attenuated vaccine within 30 days before the first dose of study intervention. Administration of killed vaccines is allowed. Refer to Section 6.5 for information on COVID-19 vaccines.

Prior/Concurrent Clinical Study Experience

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

   Note: Participants who have entered the follow-up phase of an investigational study may participate as long as it has been 4 weeks after the last dose of the previous investigational agent.

Diagnostic Assessments

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

   Note: Participants that require intermittent use of non-systemic steroids such as ocular, inhaled, intranasal, topical steroids, or local steroid injections are not excluded from the study.

10. 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 imaging of the brain as a site of disease as specified in the SoA.

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

12. Has severe hypersensitivity (≥Grade 3) to pembrolizumab, carboplatin, paclitaxel (or docetaxel, if applicable), Avastin or biosimilar (if using) and/or any of their excipients.

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

14. Has an active infection, requiring systemic therapy.

15. 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.

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

    Refer to Appendix 7 for country-specific requirements.

17. Has received colony-stimulating factors (eg, G-CSF, GM-CSF, or recombinant erythropoietin) within 4 weeks (28 days) prior to receiving study intervention on Day 1 of Cycle 1.

18. Has had surgery <6 months prior to Screening to treat borderline ovarian tumors, early-stage OC, or early-stage fallopian tube cancer.

19. 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.

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

21. Has current, clinically relevant bowel obstruction (including subocclusive disease), abdominal fistula, or GI perforation, related to underlying epithelial OC.

    Note: This applies only to participants who will receive Avastin (or biosimilar) during Cycles 4 to 6 and should be confirmed prior to the first dose of Avastin (or biosimilar).

22. Has a history of hemorrhage, hemoptysis, or active GI bleeding within 6 months prior to randomization.

    Note: This applies only to participants who will receive Avastin (or biosimilar) during Cycles 4 to 6 and should be confirmed prior to the first dose of Avastin (or biosimilar).

23. Has uncontrolled hypertension.

    Note: This applies only to participants who will receive Avastin (or biosimilar) during Cycles 4 to 6 and should be confirmed prior to the first dose of Avastin (or biosimilar). Use of antihypertensive medications to control blood pressure is permitted.

Other Exclusions

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

25. Has either had major surgery within 3 weeks of randomization or has not recovered from any effects of any major surgery.

26. In the judgment of the investigator, is unlikely to comply with the study procedures, restrictions, and requirements of the study.

5.3 Lifestyle Considerations

There are no lifestyle considerations for this study.

5.3.1 Meals and Dietary Restrictions

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

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

No restrictions are required.

5.3.3 Activity 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 (study interventions provided by the Sponsor) will be packaged to support enrollment. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

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

Table 2 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Admini-stration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Arm 1	Experi-mental	Carboplatin	Drug	Solution for Infusion	10 mg/mL	AUC5-AUC6	IV Infusion	Q3W; Day 1 of each 3-week cycle	Background Treatment	NIMP/ AxMP	Local or Central
Arm 1	Experi-mental	Paclitaxel	Drug	Solution for Infusion	6 mg/mL	175 mg/m2	IV Infusion	Q3W; Day 1 of each 3-week cycle	Background Treatment	NIMP/ AxMP	Local or Central
Arm 1	Experi-mental	Pembro-lizumab	Biological/ Vaccine	Solution for Infusion	25 mg/mL	200 mg	IV Infusion	Q3W; Day 1 of each 3-week cycle	Test product	IMP	Central
Arm 1	Experi-mental	MK-4830	Biological/ Vaccine	Solution for Infusion	100 mg/vial	800 mg	IV Infusion	Q3W Day 1 of each 3-week cycle	Test product	IMP	Central
Arm 1	Experi-mental	Avastin (or biosimilar)	Biological/ Vaccine	Solution for Infusion	25 mg/mL	Variable	IV Infusion	Q3W; Day 1 of each 3-week cycle of Cycles 4 to 6	Background Treatment	NIMP/ AxMP	Local or Central
Arm 2	Experi-mental	Carboplatin	Drug	Solution for Infusion	10 mg/mL	AUC5-AUC6	IV Infusion	Q3W; Day 1 of each 3-week cycle	Background Treatment	NIMP/ AxMP	Local or Central
Arm 2	Experi-mental	Paclitaxel	Drug	Solution for Infusion	6 mg/mL	175 mg/m2	IV Infusion	Q3W; Day 1 of each 3-week cycle	Background Treatment	NIMP/ AxMP	Local or Central
Arm 2	Experi-mental	Pembro-lizumab	Biological/ Vaccine	Solution for Infusion	25 mg/mL	200 mg	IV Infusion	Q3W; Day 1 of each 3 week cycle	Test product	IMP	Central

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Admini-stration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Arm 2	Experi-mental	Avastin or biosimilar	Biological/ Vaccine	Solution for Infusion	25 mg/mL	Variable	IV Infusion	Q3W; Day 1 of each 3 week cycle of Cycles 4 to 6	Background Treatment	NIMP/ AxMP	Local or Central

Abbreviations: AUC = area under the concentration-time curve; EEA = European Economic Area; IMP = investigational medicinal product; IV = intravenous; NIMP/AxMP = noninvestigational/auxiliary medicinal product; Q3W = every 3 weeks.

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.

All supplies indicated in Table 2 will be provided per the "Sourcing" column depending on local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number where possible (eg, not applicable in the case where multiple lots or batches may be required due to the length of the study, etc).

Refer to Section 8.1.9 and the pharmacy manual for details regarding administration of the study intervention.

6.1.1 Treatment

In this study, the treatment course for MK-4830 Q3W and/or pembrolizumab Q3W consists of 6 treatment cycles. Note: The number of treatment cycles is calculated starting with the first dose.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

There are no specific calculations or evaluations required to be performed to administer the proper dose to each participant. The rationale for selection of doses to be used in this study is in Section 4.3. Carboplatin, paclitaxel (and potentially docetaxel), and Avastin (or biosimilar) will be prepared and administered as per the approved product label and per the pharmacy manual.

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 and Arm 2, respectively.

6.3.2 Stratification

No stratification based on age, sex, or other characteristics will be used in this study.

6.3.3 Blinding

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

6.4 Study Intervention Compliance

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

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 for irAEs associated with either pembrolizumab or MK-4830 and for other allowed dose interruptions of pembrolizumab and MK-4830.

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 identification 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 time periods specified by this protocol for that medication or vaccination. 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.
- Anticancer hormonal therapy (eg, anti-estrogens).

  Note: Hormonal replacement therapy is allowed.
- Investigational agents other than pembrolizumab and MK-4830.
- Radiation therapy.

  Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator’s discretion.
- Live or live-attenuated vaccines within 30 days before the first dose of study intervention and while participating in the study.

  Note: Killed vaccines are allowed.

  Note: Any licensed COVID-19 vaccine (including for Emergency Use) in a particular country is allowed as long as they are mRNA vaccines, adenoviral vaccines, or inactivated vaccines. These vaccines will be treated as 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 to have an immunologic etiology.
  - For the prevention of emesis.

- To premedicate for IV contrast allergies.
- To treat 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 chronic obstructive pulmonary disease.
- Strong and moderate inducers or inhibitors of either CYP3A4 or CYP2C8.

  Note: Refer to the local approved product label of each of the chemotherapy agents used in this study for specific guidance. A current list of strong/moderate inducers/inhibitors of CYP3A4 can be found at the following website:

  https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling

  Note: the use of aprepitant as an antiemetic is allowed during the study (Section 8.1.9.1.6).

In addition to the medications listed here, site staff should refer to the local approved product label for permitted and prohibited medications, as well as drug-drug interactions for each chemotherapy agent used in this study.

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

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medications will be recorded on the eCRF, including all 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 ECI are to be recorded. SAEs and ECI are defined in Section 8.4.

6.5.1 Rescue Medications and Supportive Care

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

Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 6.6.

6.6 Dose Modification (Escalation/Titration/Other)

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

Dose Modification and Toxicity Management for Immune-related AEs Associated with Pembrolizumab Monotherapy, Coformulations or IO Combinations

AEs associated with pembrolizumab monotherapy, coformulation, or IO combination 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 monotherapy, coformulation, or IO combination 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 monotherapy, coformulation, or IO combination 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.

Attribution of Toxicity:

When study interventions are administered in combination, attribution of an AE to a single component is likely to be difficult. Therefore, while the investigator may attribute a toxicity event to pembrolizumab monotherapy, coformulations, or IO combinations, pembrolizumab monotherapy, coformulations, or IO combinations must be held according to the criteria in the Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events.

Holding Study Interventions:

When study interventions are administered in combination and if the AE is considered immune-related, pembrolizumab monotherapy, coformulations, or IO combinations should be held according to recommended Dose Modification criteria.

If the toxicity does not resolve or the criteria for resuming treatment are not met, the participant must be discontinued from pembrolizumab monotherapy, coformulations, or IO combinations.

Restarting Study Interventions:

Participants may restart pembrolizumab monotherapy, coformulations, or IO combinations as described below:

If the toxicities do resolve and conditions are aligned with what is defined in the Dose Modification and Toxicity Management Guidelines for irAEs, pembrolizumab monotherapy, coformulations, or IO combinations may be restarted at the discretion of the investigator.

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

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

General instructions:

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

irAEs	Toxicity Grade (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 (previously CTCAE v4.0 Grade 1)	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
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		
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 (MK-4830 + Pembrolizumab)

Pembrolizumab monotherapy, coformulations or IO combinations (MK-4830 + pembrolizumab) may cause severe or life-threatening infusion reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab monotherapy, coformulations or IO combinations (MK-4830 + pembrolizumab) associated infusion reactions are provided in Table 4.

Table 4 Pembrolizumab Monotherapy, Coformulations or IO Combinations (MK-4830) 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.	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
	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.	
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

h=hour; IV=intravenous; CTCAE=Common Terminology Criteria for Adverse Events; IV=intravenous; NCI=National Cancer Institute; NSAIDs=nonsteroidal anti-inflammatory drugs; PO=orally.

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 3 weeks for Q3W (21 days) of the originally scheduled dose and within 42 days of the previously administered dose, unless otherwise discussed with the Sponsor. The reason for study intervention interruption is to be documented in the participant's study record.

6.6.2 Chemotherapy Dose Modifications

Carboplatin and/or paclitaxel (or docetaxel) may be reduced, interrupted, or discontinued at the investigator's discretion per the approved product labels, local regulations, and/or institutional standards. If chemotherapy (either carboplatin or paclitaxel [or docetaxel] or both) is interrupted or discontinued, pembrolizumab, and/or MK-4830 should be continued. If pembrolizumab or MK-4830 is interrupted or discontinued, chemotherapy should be continued.

Avastin (or biosimilar), if using, may be interrupted, or discontinued at the investigator's discretion per the approved product label and local regulations. If Avastin (or biosimilar) is interrupted or discontinued, chemotherapy, pembrolizumab, and/or MK-4830 should be continued. If pembrolizumab or MK-4830 is interrupted or discontinued, Avastin (or biosimilar) should be continued as per the approved product label, local regulations, and/or institutional standards for a maximum of 3 cycles following surgery.

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

Supportive care measures (eg. G-CSF, erythropoietin, blood transfusion) should be used according to local standards to manage chemotherapy-induced myelosuppression 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 Definition of Dose-limiting Toxicity

All toxicities will be graded using NCI CTCAE v5.0 based on the investigator assessment. The DLT window of observation will be during the first cycle of Avastin (or biosimilar) administration (ie, the first cycle after surgery [Cycle 4]) following surgery.

The occurrence of any of the following toxicities during the DLT observation period will be considered a DLT, if assessed by the investigator to be possibly, probably, or definitely related to study intervention administration:

- Grade 4 nonhematologic toxicity (not laboratory).
- Grade 4 hematologic toxicity lasting ≥7 days, except thrombocytopenia:
  - Grade 4 thrombocytopenia of any duration
  - Grade 3 thrombocytopenia associated with clinically significant bleeding
- Any nonhematologic AE ≥Grade 3 in severity should be considered a DLT, with the following exceptions: Grade 3 fatigue lasting ≤3 days; Grade 3 diarrhea, nausea, or vomiting without use of antiemetics or antidiarrheals per SOC; Grade 3 rash without use of corticosteroids or anti-inflammatory agents per SOC.
- Any Grade 3 or Grade 4 nonhematologic laboratory value if:
  - Clinically significant medical intervention is required to treat the participant, or
  - The abnormality leads to hospitalization, or
  - The abnormality persists for >1 week
  - The abnormality results in a DILI (see Section 8.4.7 for criteria)

  Exceptions: Clinically nonsignificant, treatable, or reversible laboratory abnormalities including liver function tests, uric acid, etc.
- Febrile neutropenia Grade 3 or Grade 4:
  - Grade 3 is defined as ANC <1000/mm^3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than 1 hour.
  - Grade 4 is defined as ANC <1000/mm^3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than 1 hour, with life-threatening consequences and urgent intervention indicated.
- Prolonged delay (>2 weeks) in initiating Cycle 2 due to intervention-related toxicity.
- Any intervention-related toxicity that causes the participant to discontinue intervention during Cycle 1.
- Grade 5 toxicity.

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

This study is open-label; therefore, the participant, the study-site personnel, the Sponsor, and/or designee are not blinded. Study intervention (name, strength, or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

6.9 Standard Policies

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

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/vaccination regimen will still continue to be monitored in the 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 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.

Clinical progression without radiographic disease progression defined by elevated CA-125 [Rustin, G. J., et al 2011] in conjunction with any of the following criteria for malignant bowel obstruction:

Any of the following: new or worsening abdominal pain, nausea, or vomiting

Abdominal distension, constipation, and/or diarrhea

No evidence of metabolic or electrolyte abnormalities leading to impaired intestinal motility

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

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 and 6.6.2, require Sponsor consultation and approval 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 8.2.1.4 (after obtaining informed consent addendum and Sponsor communication, the investigator may elect to continue treatment beyond disease progression).

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

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

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.

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

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA.

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

The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study-site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).

All study-related medical decisions must be made by an investigator who is a qualified physician .

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before documented ICF may be used for screening or baseline purposes

provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.

Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

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

8.1 Administrative and General Procedures

8.1.1 Informed Consent

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

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 qualifies for the study.

8.1.3 Participant Identification Card

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

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

8.1.4 Medical History

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

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

8.1.4.1 Ovarian Cancer History

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

8.1.5 Debulking Surgery

All eligible participants will undergo interval debulking surgery per the local SOC. Interval debulking surgery should be performed between 3 to 6 weeks following Day 1 of Cycle 3; any delay to interval debulking surgery (eg, due to an AE) requires approval from the Sponsor. The last dose of study intervention of the neoadjuvant phase should be administered no less than 3 weeks before surgery. Participants should resume study intervention when clinically appropriate but no longer than 7 weeks following surgery. Details regarding the date of surgery, surgical findings, residual tumor postsurgery, surgical pathology, etc. will be recorded in the appropriate eCRF. Surgical resection sample will be reviewed as per standard guidelines by the local pathologist to confirm pathological CR and omentum for CRS following interval debulking surgery. Debulking surgery may be performed at a hospital/surgical unit separate from the investigator site.

Surgery may be performed earlier than Cycle 3 for clinical reasons for participant care in accordance with local SOC for disease management. Similarly, surgery may be delayed after Cycle 3 for clinical reasons in accordance with local SOC for disease management or due to AEs. In these instances, Sponsor consultation and approval are required prior to any change in the protocol-defined timing of surgery.

If the investigator determines that a participant has unresectable disease following the 3 neoadjuvant treatment cycles, the participant may continue treatment in the study without undergoing the interval debulking surgery and receive up to 6 cycles of treatment following Sponsor consultation and approval. For these participants, a tumor biopsy should be collected, if possible (Section 8.1.5.1). Participants should resume study intervention when clinically appropriate but no longer than 6 weeks following the last dose of study intervention of the neoadjuvant phase.

8.1.5.1 Tumor Tissue Biopsy and Sample Collection

Participants are required to submit archival or newly obtained core, incisional, or excisional biopsy of a tumor lesion during the screening period for local confirmation of HGSOC histology, baseline biomarker assessment, and for generation of the ctDNA assay. The surgical resection sample collected during interval debulking will be sent for detailed pathological assessment (site pathologist is required to take participants' samples not only from the ovaries/ tube or omentum but also from other organs resected as part of the debulking to confirm pCR). This study may also conduct exploratory histological confirmation of high-grade serous carcinoma of tumor samples from enrolled participants.

For those participants who were randomized as eligible for interval debulking surgery but failed to undergo surgery and are continuing on-study intervention, a core or excisional biopsy should be collected, if possible, prior to resuming study intervention in Cycle 4.

All biopsies should be obtained and prepared according to the instructions outlined in the Laboratory Manual for this study.

8.1.6 Prior and Concomitant Medications Review

8.1.6.1 Prior Medications

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

8.1.6.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study including at the time of surgery and through the Safety Follow-up Visit. Additionally, the investigator or qualified designee will record medication, if any, taken by the participant following PD.

8.1.7 Assignment of Screening Number

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

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

8.1.8 Assignment of Treatment/Randomization Number

All eligible participants will be randomly allocated and will receive a treatment/randomization number. The treatment/randomization number identifies the participant for all procedures occurring after treatment 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.

8.1.9 Study Intervention Administration

Study interventions will be administered by the investigator and/or study staff according to the specifications within the pharmacy manual.

Study intervention should begin within 3 days of randomization.

8.1.9.1 Timing of Dose Administration

Administer study intervention in the following order:

1. Pembrolizumab
2. MK-4830 (Arm 1 only)
3. Paclitaxel (or docetaxel)
4. Carboplatin
5. Avastin (or biosimilar), if using, in Cycles 4 to 6

NOTE: Local practices for the sequence of drug administration for chemotherapies (excluding Avastin or biosimilar) can be followed if preferred. The date and time of administration must be captured in the eCRF.

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

The reason for any variability in administration of study intervention outside of the protocol-specified window should be documented in the participant's chart and recorded on the eCRFs.

8.1.9.1.1 Pembrolizumab

Pembrolizumab (200 mg) will be administered as a 30-minute IV infusion Q3W for 6 cycles. 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).

8.1.9.1.2 MK-4830

MK-4830 (800 mg) will be administered as a 30-minute IV infusion Q3W for 6 cycles. MK-4830 will be administered 30 minutes after completion of pembrolizumab 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).

8.1.9.1.3 Paclitaxel (or Docetaxel)

Paclitaxel (175 mg/m^2 Q3W) will be administered as an IV infusion for 6 treatment cycles as per local practice and labels. The infusion time should follow local practice and labels. All participants should be premedicated with oral or IV steroid and antihistamines according to the approved product label and/or standard practice. Additional premedications should be administered as per standard practice.

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

8.1.9.1.4 Carboplatin

Carboplatin (AUC 5 or 6 mg/mL•min Q3W) will be administered as an IV infusion for 6 treatment cycles as per local practice and labels. The infusion time of carboplatin should follow local practice and labels. The carboplatin dose should be calculated using Calvert formula (see below) and should not exceed 900 mg.

Calvert Formula:

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

The estimated GFR used in the Calvert's formula should not exceed 125 mL/min to calculate the maximum carboplatin dose (mg). An example calculation for AUC 6 for a participant with a GFR of 125 mg/mL is as follows:

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

8.1.9.1.5 Avastin (or Biosimilar)

If Avastin (or biosimilar) is used, it should be administered, as per local practice and label, starting on Day 1 of the first cycle following surgery (ie, Cycle 4), after carboplatin. The local practice for the sequence of drug administration can be followed if preferred. The date and dose of Avastin (or biosimilar) administered will be recorded in the eCRF.

Note: Use of Avastin (or biosimilar) is not permitted in the neoadjuvant phase (ie, prior to surgery in Cycles 1 to 3).

8.1.9.1.6 Antiemetic Therapy

The use of antiemetic therapy should follow Multinational Association of Supportive Care in Cancer guidelines [Roila, F., et al 2016] and should include a 5-HT_3 receptor antagonist, dexamethasone (or equivalent), and/or aprepitant.

8.1.10 Discontinuation and Withdrawal

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

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

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

8.1.10.1 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.

8.1.11 Participant Blinding/Unblinding

This is an open-label study; there is no blinding for this study. The emergency unblinding call center will be available so that a health care provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.12 Calibration of Equipment

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

8.1.13 Microsampling Device

Two CCI devices will be used to obtain capillary blood samples from participants' arms. Additionally, at select participating investigational sites, one CCI device will be used to obtain capillary blood samples from participants' arms. The CCI device collects a dried blood sample on an absorptive material and the CCI collects a liquid blood sample that can be further processed to plasma or serum. Both devices adhere to the skin of participant's upper arm and use lancets to pierce the skin and a delicate vacuum to flow blood into the tool. Further instructions on the use of both devices will be provided in the laboratory manual.

Device failures (ie, lancet does not pierce skin, or device does not collect blood) or AEs directly related to both devices should be communicated to the Sponsor by the investigator. Additionally, AEs involving the devices should be recorded on the appropriate eCRF. Refer to the laboratory manual for additional details.

Timepoints for the collection of these samples can be found in the SoA. Please refer to the laboratory manual for detailed instructions on sample collection, storage, and shipment.

8.2 Efficacy/Immunogenicity 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 the study or goes into safety follow-up. The process for scan collection and transmission to the iCRO can be found in the SIM. Tumor scans by CT are strongly preferred. For the abdomen and pelvis, contrast-enhanced MRI may be used when CT with iodinated contrast is contraindicated, or when mandated by local practice. 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.

8.2.1.1 Initial Tumor Scans

Initial tumor scans at Screening must be performed within 28 days prior to the date of randomization. Any scans obtained after Cycle 1 Day 1 cannot be included in the screening assessment. The site must review screening scans to confirm the participant has measurable disease per RECIST 1.1.

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 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 imaging assessment should be performed at least 21 days (+5 days) after Day 1 of Cycle 3 and prior to the debulking surgery. The next on-study imaging assessment should be performed after surgery prior to resuming study intervention in Cycle 4 (-5 days; Section 1.3).

Note: If surgery is delayed, imaging should be delayed until prior to surgery (a minimum of 21 days after the last cycle of study intervention in the neoadjuvant phase) and then performed prior to the first dose of study intervention in the adjuvant phase. If cytoreduction is attempted but not performed (with or without biopsy collection) or deemed inappropriate, the next scheduled imaging assessment after Cycle 3 Day 1 would be performed a minimum of 21 days after Cycle 6 Day 1 (ie, the EOT visit; Section 8.2.1.3).

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

8.2.1.3 End-of-Treatment Tumor Scans

Imaging should be performed at the time of treatment discontinuation (±4 weeks) and prior to starting a new anticancer treatment. If previous imaging was obtained within 4 weeks (28 days) before the date of discontinuation, then imaging at treatment discontinuation is not mandatory.

8.2.1.4 RECIST 1.1 Assessment of Disease

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

Following surgery, tumor response will be assessed using a more limited application of RECIST 1.1 to evaluate participants as either showing progression, or not showing progression. In participants who have residual disease, progression is defined as growth of residual disease (following RECIST 1.1 methods of measurement) or appearance of new lesions. In participants without residual disease, progression is defined as the detection of new lesions on subsequent scans.

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

- Investigator judgment will determine action
- 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

8.3 Safety Assessments

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

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

8.3.1 Physical Examinations

A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard at the timepoints specified in the SoA. Height and weight will also be measured and recorded.

For cycles that do not require a complete physical examination, a brief directed physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard as clinically indicated before study intervention administration.

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

8.3.2 Vital Signs

The investigator or qualified designee will assess vital signs at Screening and as specified in the SoA. Vital signs will include, temperature, systolic and diastolic blood pressure, pulse rate, and respiratory rate.

For participants who will start Avastin (or biosimilar) in the adjuvant phase (ie, after surgery in Cycle 4), blood pressure must be measured prior to the first administration of Avastin (or biosimilar) to ensure the participants do not have uncontrolled hypertension.

8.3.3 Electrocardiograms

A standard 12-lead ECG will be obtained and reviewed by an investigator or medically qualified designee (consistent with local requirements) as outlined in the SoA using an ECG machine that automatically calculates the HR and measures PR, QRS, QT, and QTc intervals. Additional ECGs may be performed 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.

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(s) as noted in Section 5.1. The length of time required to continue pregnancy testing for each study intervention is as follows:
    - MK-4830: 180 days
    - Pembrolizumab: 120 days
    - Chemotherapy: 180 days
    - Avastin (or biosimilar if used): 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 participant's participation in the study.

8.3.6 Eastern Cooperative Oncology Group Performance Status

The investigator or qualified designee will assess ECOG status at screening, prior to the administration of each cycle of study treatment as specified in the SoA (Section 1.3).

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

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in Appendix 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 he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 5.

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

Table 5 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
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 towards the safety of participants and the safety of a study intervention under clinical investigation are met.

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

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

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

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

8.4.5 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding 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:

1. An overdose of Sponsor's product, as defined in Section 8.5.

2. 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 the purposes of this study, an overdose will be defined as follows:

- Pembrolizumab: ≥5 times the protocol-specified dose
- MK-4830: ≥3 times the protocol-specified dose
- Paclitaxel (or docetaxel), carboplatin, and Avastin (or biosimilar): any dose ≥20% over the protocol-specified dose

No specific information is available on the treatment of overdose of MK-4830, pembrolizumab, chemotherapy, or Avastin (or biosimilar). In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

8.6 Pharmacokinetics

PK parameters will not be evaluated in this study.

8.7 Pharmacodynamics

Sample collection, storage, and shipment instructions for pharmacodynamic samples will be in the laboratory manual.

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 biomarker analysis

Blood for plasma biomarker analysis

Blood for RNA analyses

Blood for ctDNA analyses

Dried whole blood from CCI device

Liquid whole blood from CCI device

Archival or newly obtained tissue collection

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

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.

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 samples as outlined 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

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

Documented informed consent must be obtained prior to performing any protocol-specific procedure. Results of a test performed prior to documented consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 28-day Screening Period, except for the following:

- Laboratory tests are to be performed within 7 days prior to the first dose of study intervention on Day 1 of Cycle 1. An exception is HIV and hepatitis testing which may be performed up to 28 days prior to randomization if required by the local health authority. Refer to Appendix 7 for country-specific requirements.

- Evaluation of ECOG PS is to be performed within 7 days prior to the first dose of study intervention on Day 1 of Cycle 1.

- For WOCBP, a pregnancy test (urine or serum) will be performed within either 24 hours (urine) or 72 hours (serum) prior to the first dose of study intervention on Day 1 of Cycle 1. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory). Refer to Appendix 7 for country-specific requirements.

- Archival or newly obtained tissue obtained at screening must be confirmed to be of sufficient quality and quantity by the designated laboratory.

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

8.11.2 Treatment Period

Visit requirements are outlined in the SoA. Specific procedure-related details are provided in Section 8.1.

8.11.3 Discontinued Participants Continuing to be Monitored in the Study

Participants who discontinue study intervention due to disease progression/recurrence or start of a new anticancer therapy will have Safety Follow-up (Section 8.11.4.1).

The Discontinuation Visit (end-of-treatment) should occur at the time study intervention is discontinued for any reason. If the Discontinuation Visit occurs 30 days from the last dose of study intervention, at the time of the mandatory Safety Follow-up Visit, the Discontinuation Visit procedures and any additional Safety Follow-up procedures should be performed. If the Discontinuation Visit occurs ≥30 days from the last dose of study intervention, the Safety Follow-up Visit does not need to be performed.

8.11.4 Post-treatment Visits

8.11.4.1 Safety Follow-up

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.

8.11.4.2 Long-term Follow-up

Participants who complete the protocol-required cycles of study intervention or who discontinue study intervention for a reason other than disease progression will begin Long-term Follow-up and should be assessed every 4 weeks by telephone contact for up to 24 weeks after the last dose of study intervention to monitor pregnancy status. Every effort should be made to collect information regarding pregnancy status until the start of new anticancer therapy, disease progression, death, end of study. Information regarding poststudy anticancer treatment will be collected if new treatment is initiated.

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. Changes to analyses made after the protocol has been finalized, but prior to final database lock, will be documented in a sSAP and referenced in the Clinical Study Report for the study. Details around the analysis approach for biomarker endpoints related to the exploratory objectives are deemed out of scope for this SAP but may be the subject of sSAPs.

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 to 9.12.

Study Design Overview	A Randomized, Phase 2 Study of Pembrolizumab And Chemotherapy With or Without MK-4830 as Neoadjuvant Treatment for High-Grade Serous Ovarian Cancer. The primary objective is to evaluate whether the reduction from baseline in ctDNA at Cycle 3 is larger in participants receiving MK-4830 + pembrolizumab in combination with SOC therapy arm than in those receiving pembrolizumab + SOC arm among treated participants with detectable ctDNA at baseline.
Treatment Assignment	Approximately 160 participants will be randomized in a 1:1 ratio between 2 treatment groups: (1) Arm 1 and (2) Arm 2. This is an open-label study.
Primary Endpoint	1. ctDNA, mean mutant/tumor molecules per mL (continuous).
Secondary Endpoints	1. pCR, all surgical specimens collected during the interval debulking surgery are microscopically negative for residual tumor (binary; pCR vs. not). 2. CRS, tiered response score based omental assessment of residual disease (binary; CRS3 vs. non-CRS3).
Statistical Methods for Key Efficacy Analyses	For the primary objective, the posterior probability that the coefficient for treatment assignment is less than zero in a cLDA model, where ctDNA values at baseline and Cycle 3 will be modeled as the response vector and treatment assignment (MK-4830 containing vs. not) is included as the independent variable with the constraint that the mean ctDNA value at baseline is the same for both treatment groups, will be used to evaluate whether the reduction in ctDNA from baseline is larger amongst the MK-4830 containing arm.
Statistical Methods for Key Safety Analyses	Safety will be evaluated using descriptive statistics by treatment group.
Interim Analyses	A preliminary analysis of the primary objective will be conducted at 50% enrollment. Final analysis will occur approximately 4 months after LPLV.
Multiplicity	No multiplicity adjustment.
Sample Size and Power	The planned sample size is approximately 160 participants.

9.2 Responsibility for Analyses/In-house Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Early Clinical Development Statistics Department of the Sponsor.

This study is being conducted as an unblinded, open-label study; ie, participants, investigators, and Sponsor personnel will be aware of participant treatment assignments after each participant is randomized and treatment is assigned.

Biomarker assays used to assess the primary, secondary, and tertiary/exploratory objectives in this study will be performed by personnel blinded to participants' treatment and clinical outcome data.

9.3 Hypotheses/Estimation

Objectives of the study are stated in Section 3. There are no hypotheses to be tested.

9.4 Analysis Endpoints

9.4.1 Efficacy Endpoints

Secondary Efficacy Endpoints

pCR: all surgical specimens collected during the interval debulking surgery are microscopically negative for residual tumor (binary; pCR vs. not).

CRS: tiered response score based omental assessment of residual disease (to be analyzed as binary; CRS3 score vs. non-CRS3).

Exploratory Efficacy Endpoints

Exploratory efficacy endpoints may include measures of clinical outcome and surgical response, which are deemed out of scope for this SAP but may be the subject of sSAPs.

9.4.2 Biomarker Endpoints

Primary and Secondary Biomarker Endpoints

The primary and secondary biomarker endpoint is the change in the mean mutant/tumor molecules per mL (MTM/mL) at Cycle 3 from baseline (continuous) detailed in Section 4.2.1.1.

Exploratory Biomarker Endpoints

Details around other biomarker-related endpoints associated with the exploratory objectives, including additional molecular (eg, CA-125, genomic, metabolic, proteomic) endpoints, as well as details for the processing and normalization of these complex data sources, are deemed out of scope for this SAP, but may be the subject of sSAPs.

9.4.3 Safety Endpoints

Refer to Section 4.2.1.2 for a description of safety measures.

9.5 Analysis Populations

9.5.1 Efficacy and Safety Analysis Population

The APaT population will be used for the analysis of safety in this study. The APaT population consists of all randomized participants who received at least one dose of study intervention. Participants will be included in the treatment group corresponding to the study intervention they actually received. For most participants this will be the treatment group to which they are randomized. Participants who take incorrect study intervention for the entire treatment period will be included in the treatment group corresponding to the study intervention actually received. Inclusion of participants who take incorrect study intervention for a portion of the time in which treatment group will be described in the CSR.

The APaT population that underwent surgery (ie, that has a surgical outcome) will be used for the analysis of efficacy in this study, as efficacy endpoints are surgical outcomes. Efficacy analyses associated with change in ctDNA will use the biomarker analysis population described in Section 9.5.2.

9.5.2 Biomarker Analysis Population

The subset of the APaT with detectable ctDNA at baseline will be used for the analysis of ctDNA.

9.6 Statistical Methods

9.6.1 Statistical Methods for Biomarker/Efficacy Analyses

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

Those generating the biomarker data will remain blinded to a participant's treatment and clinical status in order to preserve an objective evaluation of the study objectives.

9.6.1.1 Primary Objective

cLDA will be used to evaluate whether the reduction in ctDNA from baseline is larger in the MK-4830-containing arm. The cLDA model will include ctDNA values at baseline and post-treatment as part of the dependent response vector and treatment assignment (MK-4830 containing vs. not) as the independent variable with the constraint that the mean ctDNA value at baseline is the same for both treatment groups. The cLDA model will be parameterized in a Bayesian framework, assuming noninformative priors, and the posterior probability that the coefficient for treatment assignment is less than zero in the cLDA model will be reported. ctDNA may be transformed. Descriptive and visual summaries (ie, spider plots and/or boxplots) of the change in ctDNA (MTM/mL) will be provided by treatment group.

9.6.1.2 Secondary Objectives

Logistic regression modeling of pCR (or CRS) will be used to evaluate whether the reduction in ctDNA from baseline is associated with improved pCR in each treatment group. The logistic regression model will include binary surgical response endpoint pCR (or CRS) as the dependent variable and change in ctDNA (MTM/mL) at Cycle 3 from baseline and treatment assignment as the independent variables. The posterior probabilities that the coefficient for change in ctDNA is less than zero and that the coefficient for treatment assignment (MK-4830 containing vs. not) is greater than zero in the multivariable logistic regression model will be reported. The logistic regression model will also include a term for baseline ctDNA value. ctDNA may be transformed. The association of change in ctDNA with pCR (or CRS) will also be evaluated using the AUROC in each treatment group pooled and separately. Descriptive and visual summaries (ie, spider plots and/or boxplots) of ΔctDNA (MTM/mL) will be provided pooled and/or by treatment group.

pCR (or CRS) rate is estimated as the proportion of participants with pCR (or CRS) in each group separately and will be reported with the 95% CI using the exact method based on the binomial distribution (Clopper-Pearson). Miettinen and Nurminen's method will be used to estimate the treatment difference between the 2 treatment arms and the associated 95% CI will be reported.

9.6.1.3 Exploratory Objectives

Details around the analysis approach for biomarker endpoints related to the exploratory objectives are deemed out of scope for this SAP but will be the subject of sSAPs.

Table 6 summarizes the estimation strategy for the primary and secondary objectives detailed above.

Table 6 Analysis Strategy for Primary Objectives

Endpoint/Variable (Description, Time Point)	**Primary vs. Supportive Approach**	**Statistical Method**	**Analysis Population**
Primary Objective			
Change in ctDNA from baseline at Cycle 3 (continuous; Mean Mutant/Tumor Molecules per mL [MTM/mL])	P	Bayesian parameterization of cLDA	Study participants must have baseline and on-treatment ctDNA assessment; study participants must have detectable ctDNA at baseline.
	S	Summary statistics, visual representations	
Secondary Objectives			
Change in ctDNA from baseline at Cycle 3 (continuous; MTM/mL); pCR/CRS (binary)	P	Bayesian parameterization of logistic regression	Study participants must have baseline and on-treatment ctDNA assessment; study participants must have detectable ctDNA at baseline; study participants must have surgical outcome.
	S	AUROC, summary statistics, visual representations	
pCR/CRS (binary)	P	Miettinen and Nurminen's method	APaT; Study participants must have surgical outcome.
Abbreviations: APaT = all-participants-as-treated; AUROC = area under the ROC curve; cLDA = constrained longitudinal data analysis; CRS = chemotherapy response score; ctDNA = circulating tumor DNA; MTM=mean mutant/tumor molecules; P = Primary approach; pCR = pathological complete response; S = Supportive approach.			

9.6.2 Statistical Methods for Safety Analyses

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

Descriptive summary statistics will be provided by treatment group for safety endpoints. For continuous measures such as changes from baseline in laboratory tests and vital signs, summary statistics for baseline, on-treatment, and change from baseline values will be provided in table format. Additional safety endpoints may also be summarized as deemed clinically appropriate.

9.7 Interim Analyses

A preliminary analysis of the primary objective will be conducted at 50% enrollment to serve as a first look at the data and a feasibility assessment of the ctDNA assay. Final analysis will occur approximately 4 months after LPLV.

9.8 Multiplicity

No multiplicity adjustment.

9.9 Sample Size and Power Calculations

The study will enroll approximately 160 participants; of which approximately 80% (N~128) are expected to be included in the primary analysis population (ie, have detectable ctDNA at baseline). Participants with nondetectable ctDNA at baseline will be excluded from the primary objective analysis. No formal hypotheses are being tested.

Table 7 illustrates the relationship between post-treatment ctDNA values and treatment assignment in a cLDA model, such that the mean ctDNA value is the same between the 2 treatment groups based on results from 10,000 simulated datasets of expected sample size. Simulations assume ctDNA at baseline is normally distributed on the $\log_{10}$ scale with mean 1.5 and standard deviation 1.15 and assume various fold changes in the mean ctDNA at post-treatment timepoint. At the expected sample size and under distributional assumptions from limited presurgical ctDNA data in ovarian cancer [Chapman, J. S., et al 2021], dramatic differences in the post-treatment mean between treatment groups provide the highest probability of detecting a statistically significant difference (Table 7).

Table 7 Illustrative Simulation of the Relationship Between Post-treatment ctDNA Values and Treatment Assignment in cLDA Model for Varied Fold Change in the Mean ctDNA for MK-4830 Containing Arm Versus Not

Sample Size of Analysis Population	Mean Fold Change in Mean ctDNA at Post-treatment Timepoint for MK-4830 Containing Arm vs. Not[a]	Probability Reduction in Mean ctDNA Differs Significantly in MK-4830 Containing Arm vs. Not[b]
128	1.02	5.2%
	0.87	10.2%
	0.73	23.4%
	0.51	58.9%
	0.33	83.5%

cLDA=constrained longitudinal data analysis; ctDNA = circulating tumor deoxyribonucleic acid; MTM=mean mutant/tumor molecules.

a. Mean fold change (mean ctDNA [MTM/mL] at post-treatment timepoint for MK-4830 containing arm/mean ctDNA at post-treatment timepoint for other arm) of 10,000 simulated datasets

b. Proportion of 10,000 simulations such that the change in mean ctDNA over time (at post-treatment timepoint) differs significantly by nominal α=0.05 using cLDA model such that mean ctDNA at baseline is the same among MK-4830 containing arm vs. not

9.10 Subgroup Analyses

Not applicable.

9.11 Compliance (Medication Adherence)

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

9.12 Extent of Exposure

Extent of exposure for a participant is defined as the number of cycles in which the participant receives the study medication infusion. Summary statistics will be provided on the extent of exposure.

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), Regulation (EU) 536/2014, 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.

The Sponsor has EU-approved Binding Corporate Rules since 2017, covering all aspects of its Global Privacy Program (Corporate Policy 20), and is self-certified pursuant to the EU-US Data Privacy Framework.

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

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

10.1.3.3 Confidentiality of IRB/IEC Information

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

10.1.4 Committees Structure

10.1.4.1 Standing Internal Data Monitoring Committee

To supplement the routine monitoring outlined in this protocol, a separate siDMC will monitor the interim data from this study. The siDMC is comprised of members of Sponsor Senior Management, none of whom are directly associated with the conduct of this study. The siDMC will monitor the study at an appropriate frequency (as detailed in the charter) for evidence of adverse effects of study intervention, as described in the detailed monitoring guidelines. The siDMC will determine whether the study should continue (or other modifications, prespecified or otherwise, should be made) according to the protocol, considering the overall risk and benefit to study participants. The siDMC will also make recommendations to the Sponsor protocol team regarding steps to ensure both participant safety and the continued ethical integrity of the study. Specific details regarding responsibilities of the siDMC will be described in a separate charter that is reviewed and approved by the siDMC.

10.1.5 Publication Policy

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

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

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

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical trials Regulation 536/2014, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu, https://euclinicaltrials.eu, or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfil

these requirements. MSD entries are not limited to FDAAA or the EMA clinical trials Regulation 536/2014 mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study-site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials Regulation 536/2014, or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this study or its results to those registries.

10.1.7 Compliance with Law, Audit, and Debarment

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

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

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

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

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

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

For investigators located in countries with serious breach reporting requirements, investigator will promptly report to the Sponsor any serious breach or suspected serious breach that occurs in compliance with those requirements. Unless more specifically defined in the applicable requirements, a serious breach is any breach of the applicable clinical trial regulation or of the clinical trial protocol which is likely to affect to a significant degree: (i)

the safety or rights of a trial participant, or (ii) the reliability and robustness of the data generated in the clinical trial.

10.1.8 Data Quality Assurance

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

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

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

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

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

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

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

Records and documents, including participants' documented informed consent, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period (eg, EU CTR: 25 years after the end of the study). No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.9 Source Documents

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

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

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

10.1.10 Study and Site Closure

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

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

10.2 Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 8 will be performed by the local laboratory. If the local laboratory is unable to perform these tests, the site should submit the sample to the central laboratory for testing. Details are provided in the Laboratory Manual.

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 8 Protocol-required Safety Laboratory Assessments

<table>
<tr><th>Laboratory Assessments</th><th colspan="4">Parameters</th></tr>
<tr><td>Hematology</td><td>Platelet Count
RBC Count
Hemoglobin
Hematocrit</td><td colspan="2">RBC Indices:
MCV
MCH
MCHC
Reticulocytes[a]</td><td>WBC count with Differential:
Neutrophils[a]
Lymphocytes[a]
Monocytes
Eosinophils
Basophils</td></tr>
<tr><td rowspan="7">Chemistry</td><td>BUN[b]
Blood Urea[b]</td><td>Potassium</td><td>AST/SGOT</td><td>Total bilirubin (and direct bilirubin if total bilirubin is above the ULN)</td></tr>
<tr><td>Albumin</td><td>Bicarbonate or CO_2[c]</td><td>Chloride</td><td>Phosphorous</td></tr>
<tr><td>Creatinine</td><td>Sodium</td><td>ALT/SGPT</td><td>Total Protein</td></tr>
<tr><td>Glucose (fasting or nonfasting)</td><td>Calcium</td><td>Alkaline phosphatase</td><td>GGT</td></tr>
<tr><td>LDH</td><td>Magnesium</td><td>Uric acid</td><td>TSH[d]</td></tr>
<tr><td>T3 (FT3 is acceptable)</td><td>FT4</td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td></tr>
<tr><td>Routine Urinalysis</td><td colspan="4">Specific gravity
pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick
Microscopic examination (if blood or protein is abnormal)</td></tr>
<tr><td>Pregnancy Testing</td><td colspan="4">Highly sensitive serum or urine hCG pregnancy test (as needed for WOCBP)</td></tr>
</table>

Laboratory Assessments	Parameters
Other Screening Tests	FSH (as needed in WONCBP only) PT/INR and aPTT/PTT[e] Serology (HIV antibody, HBsAg, and HCV RNA). NOTE: Certain ex-US sites require testing for HIV, HBV, and HCV during Screening. Consult with regional health authorities and institutional standards to confirm if such testing is applicable. Cortisol to be determined at Screening, and the morning of surgery, and on Day 1 of Cycles 4 and 5. Cortisol measurements should be obtained in the morning. CEA and CA-125 may be analyzed by the local laboratory to verify eligibility at Screening. A confirmatory sample must be submitted to the central laboratory. CA-125 will be assessed centrally at all imaging visits.

Abbreviations: ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; C1D1 = Cycle 1, Day 1; CA-125 = cancer antigen 125; CEA = carcinoembryonic antigen; CO_2 = carbon dioxide; FSH = follicle-stimulating hormone; FT3 = free triiodothyronine; FT4 = free thyroxine; GGT = gamma-glutamyl transferase; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; HIV = human immunodeficiency virus; INR = International Normalized Ratio; LDH = lactate dehydrogenase; MCH = mean corpuscular hemoglobin; MCHC = mean cell hemoglobin concentration; MCV = mean corpuscular volume; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell; RNA = ribonucleic acid; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; T3 = triiodothyronine; T4 = thyroxine; TFTs = thyroid function tests; TSH = thyroid-stimulating hormone; ULN = upper limit of normal; WBC = white blood cell; WOCBP = women of childbearing potential; WONCBP = women of nonchildbearing potential.

a. Percentage (%) is preferred but absolute results can be reported per local standard of practice. Report the results in the same manner throughout the study.
b. Urea is acceptable if BUN is not available as per standard of practice. Only 1 specified test should be reported.
c. Test only if either it is the local standard of care or if clinically indicated.
d. Participants may be dosed in subsequent cycles after C1D1 while TFTs are pending.
e. Performed as part of the screening assessments and as clinically indicated for participants taking anticoagulants.

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

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

10.3.1 Definition of 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 non-therapeutic 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 (also referred to as Sponsor's product) 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 Sponsor's product cause the AE?

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

The following components are to be used to assess the relationship between the Sponsor's product and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the AE:

- **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?

- **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with 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 Sponsor's product discontinued or dose/exposure/frequency reduced?
    - If yes, did the AE resolve or improve?
    - If yes, this is a positive dechallenge.
    - If no, this is a negative dechallenge.

  (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the study is a single-dose drug study; or (4) Sponsor's product(s) is/are only used 1 time.)

- **Rechallenge:** Was the participant re-exposed to the Sponsor's product in this study?
    - If yes, did the AE recur or worsen?
    - If yes, this is a positive rechallenge.
    - If no, this is a negative rechallenge.

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

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

Consistency with study intervention profile: Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?

The assessment of relationship will be reported on the case report forms/worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.

Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).

- Yes, there is a reasonable possibility of Sponsor's product relationship:
    - There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.
- No, there is not a reasonable possibility of Sponsor's product relationship:
    - Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)

For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.

The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each AE causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (ie, to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the investigator's opinion, there is sufficient data to support full attribution of the AE to the single agent.

Follow-up of AE and SAE

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

New or updated information will be recorded in the CRF.

The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.6 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 e-mail of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.

In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.

Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.

Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

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

Not applicable

10.5 Appendix 5: Contraceptive Guidance

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

10.6 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 are critical to understanding clinical context of analytical results.

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

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

5. Biorepository Specimen Usage[3, 4]

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses 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 utilized in a particular study, the study site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security[3, 4]

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

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

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

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

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

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

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

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

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

12. Questions

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

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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/

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10.7 Appendix 7: Country-specific Requirements

10.7.1 France

5.1 Inclusion Criteria

WOCBP are required to continue using contraception for 210 days (7 months) after discontinuation of chemotherapy.

10.7.2 Italy

1.3 Schedule of Activities and 5.2 Exclusion Criteria

HIV, hepatitis B, and hepatitis C testing are required at baseline.

10.8 Appendix 8: Abbreviations

Abbreviation	Expanded Term
5-HT3	5-hydroxytryptomine
ADL	activities of daily living
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myelogenous leukemia
ANC	absolute neutrophil count
ANGPTL	angiopoietin-like proteins
APaT	All-Participants-as-Treated
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the concentration-time curve
AUROC	area under the ROC curve
AxMP	Auxiliary Medicinal Product
BRCA	breast cancer susceptibility gene
CA-125	cancer antigen-125
CD28	cluster of differentiation 28
CD3	cluster of differentiation 3
CD3ζ	cluster of differentiation 3 zeta
CD8	cluster of differentiation 8
CEA	carcinoembryonic antigen
cfDNA	cell-free DNA
CI	confidence interval
CIDOC	circulating tumor DNA as an early marker of recurrence and treatment efficacy in ovarian carcinoma
cLDA	constrained longitudinal data analysis
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COPD	chronic obstructive pulmonary disease
COVID-19	corona virus disease of 2019
CL	clearance
CPS	combined positive score
CR	complete response
CRC	colorectal cancer
CRF	Case Report Form
CRS	chemotherapy response score
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTCAE v5.0	Common Terminology Criteria for Adverse Events, Version 5.0
ctDNA	circulating tumor DNA
CTFG	Clinical Trial Facilitation Group

Abbreviation	Expanded Term
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
CYP	cytochrome P450
D	de-escalate to the next lower dose
DBS	dried blood spot
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DU	the current dose is unacceptably toxic
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data collection
EEA	European Economic Area
EFS	event-free survival
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
E-R	exposure response
EU	European Union
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
FoxP3	Forkhead box protein 3
FSH	follicle-stimulating hormone
FSR	first site ready
GCIG	Gynecologic Cancer Intergroup
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GI	gastrointestinal
GM-CSF	granulocyte macrophage colony-stimulating factor
HBsAg	hepatitis B surface antigen
HCC	hepatocellular carcinoma
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HGSOC	high-grade serous ovarian carcinoma
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HR	heart rate
HRD	homologous repair deficiency
HRT	hormone replacement therapy
IB	Investigator's Brochure

Abbreviation	Expanded Term
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
ICSR	Individual Case Safety Report
IEC	Independent Ethics Committee
Ig	immunoglobulin
CCI	[redacted]
IgV	immunoglobulin-variable
IHC	immunohistochemistry
IL-10	interleukin-10
ILT4	immunoglobulin-like transcript 4
IMP	Investigational Medicinal Product
IND	investigational new drug
IO	immune-oncology
irAEs	immune-related AEs
IRB	Institutional Review Board
IRT	interactive response technology
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous(ly)
IVD	in vitro diagnostic
LAG3	lymphocyte-activation gene 3
LILR	leukocyte immunoglobulin-like receptor
LILRB2	leukocyte immunoglobulin-like receptor B2
LPLV	last patient last visit
mAb	monoclonal antibody
MDSC	myeloid-derived suppressor cells
MHC	major histocompatibility complex
MRD	measurable residual disease
MRI	magnetic resonance imaging
mRNA	messenger RNA
MSI	microsatellite instability
MTD	maximum tolerated dose
mTPI	modified Toxicity Probability Interval
NCI	National Cancer Institute
NIMP	Noninvestigational Medicinal Product
NSCLC	non–small cell lung cancer
OC	ovarian cancer
OS	overall survival
OTC	over-the-counter
PARP	poly (ADP-ribose) polymerase

Abbreviation	Expanded Term
PBMC	peripheral blood mononuclear cells
PBPK	physiologically-based PK
pCR	pathologic complete response
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed cell death 1 protein
PD-L1	programmed cell death 1 ligand 1
PD-L2	programmed cell death 1 ligand 2
PK	pharmacokinetic
PKCθ	protein kinase C-theta
PMBC	peripheral blood mononuclear cells
po	orally
PR	partial response
Q2W	every 2 weeks
Q3W	every 3 weeks
RCC	renal cell carcinoma
RECIST 1.1	Response Evaluation Criteria In Solid Tumors version 1.1
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SGCTG	Scottish Gynaecological Cancer Trials Group
SHP-1	Src-homology 2 domain containing phosphatase-1
SHP-2	Src-homology 2 domain containing phosphatase-2
siDMC	Standing Internal Data Monitoring Committee
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
TIGIT	T-cell immunoreceptor with Ig and ITIM domains
TIL	tumor-infiltrating lymphocyte
TNBC	triple-negative breast cancer
WOCBP	woman/women of childbearing potential
WONCBP	woman/women of nonchildbearing potential
ZAP70	zeta-chain-associated protein kinase

10.9 Appendix 9: mTPI Table

The first 10 participants treated with pembrolizumab + MK-4830 + carboplatin/paclitaxel + Avastin (or biosimilar) will be closely followed for DLTs for the first cycle after the first dose of study intervention in the adjuvant phase (the DLT evaluation period). The number of participants with DLTs (Section 6.6.3) will be monitored according to the mTPI [Ji, Y., et al 2007] table as outlined in Table 9 with a target DLT rate of 30%.

Table 9 Dose-finding Rules per mTPI Design

Number of Participants with at Least 1 DLT	**Number of Participants Evaluable for DLT at Current Dose**							
	3	**4**	**5**	**6**	**7**	**8**	**9**	**10**
0	E	E	E	E	E	E	E	E
1	S	S	S	E	E	E	E	E
2	D	S	S	S	S	S	S	S
3	DU	DU	D	S	S	S	S	S
4		DU	DU	DU	D	D	S	S
5			DU	DU	DU	DU	DU	D
6				DU	DU	DU	DU	DU
7					DU	DU	DU	DU
8						DU	DU	DU
9							DU	DU
10								DU

D = De-escalate to the next lower dose; DLT = dose-limiting toxicity; DU = The current dose is unacceptably toxic; E = Escalate to the next higher dose; mTPI = modified toxicity probability interval; S = Stay at the current dose.

Note: Target toxicity rate=30%. Flat noninformative prior Beta (1,1) is used as a prior and ε1=ε2=0.03 [Ji, Y., et al 2007] [Ji, Y. and Wang, S.-J. 2013] [Ji, Y., et al 2010].

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