Official Protocol Title:	A Phase 3 Randomized, Double-Blind, Placebo-Controlled Trial of Pembrolizumab (MK-3475) Plus Chemotherapy Versus Chemotherapy Plus Placebo for the First-Line Treatment of Persistent, Recurrent, or Metastatic Cervical Cancer (KEYNOTE-826)
NCT number:	NCT03635567
Document Date:	10 June 2022

Title Page

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Protocol Title: A Phase 3 Randomized, Double-Blind, Placebo-Controlled Trial of Pembrolizumab (MK-3475) Plus Chemotherapy Versus Chemotherapy Plus Placebo for the First-Line Treatment of Persistent, Recurrent, or Metastatic Cervical Cancer (KEYNOTE-826)

Protocol Number: 826-08

Compound Number: MK-3475

Sponsor Name:

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

Legal Registered Address:

126 East Lincoln Avenue

P.O. Box 2000

Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

IND	126191
EudraCT Number	2018-001440-53

Approval Date: 10 June 2022

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 8/ Global amendment	10-JUN-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 7/ Global amendment	05-JAN-2022	To state that the preplanned second interim analysis (IA2) will not be performed since the success criteria for the study hypotheses of progression-free survival (PFS) and overall survival (OS) for all the 3 groups (combined positive score [CPS] ≥1 group, all-comers, and CPS ≥10 group) were met at the first interim analysis (IA1).
Amendment 6/ Global amendment	29-JUN-2021	To update the dose modification and toxicity management guidelines for immune-related adverse events (irAEs).
Amendment 5/ Global amendment	30-OCT-2020	The objectives including primary efficacy endpoints were modified. The primary PFS endpoint per RECIST 1.1 will be assessed by the investigator.
Amendment 4/ Global amendment	02-APR-2020	Amendment 4 supersedes Amendment 3. The objectives and hypotheses were modified with an updated multiplicity strategy based on updated results from the KEYTRUDA program.
Amendment 3/ Global amendment	31-JAN-2020	The objectives and hypotheses were modified with an updated multiplicity strategy based on updated results from the KEYTRUDA program.

Document	Date of Issue	Overall Rationale
Amendment 2/ Global amendment	25-JUN-2019	Clarification of stratification factors and treatment duration.
Amendment 1/ Germany-specific amendment	13-NOV-2018	Insertion of the requirements to perform HIV, hepatitis B and C testing at Screening, monthly pregnancy testing, and urinalysis at every cycle during which bevacizumab is administered
Original Protocol	13-JUN-2018	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 08

Overall Rationale for the Amendments:

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.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
Title Page 10.1.1 Code of Conduct for Clinical Trials Throughout	Sponsor entity name and address change.	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.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3 Randomized, Double-Blind, Placebo-Controlled Trial of Pembrolizumab (MK-3475) Plus Chemotherapy Versus Chemotherapy Plus Placebo for the First-Line Treatment of Persistent, Recurrent, or Metastatic Cervical Cancer (KEYNOTE-826)

Short Title: Phase 3 Trial of 1L Pembrolizumab Plus Chemotherapy in Persistent, Recurrent, or Metastatic Cervical Cancer

Acronym: NA

Hypotheses, Objectives, and Endpoints:

In women with persistent, recurrent, or metastatic cervical cancer treated with pembrolizumab plus chemotherapy versus placebo plus chemotherapy:

The study will be considered positive if it is positive for either the PFS or OS hypothesis test for any of the 3 groups (CPS ≥1 group, all-comers, and CPS ≥10 group).

Primary Objectives	Primary Endpoints
- Objective: To compare progression-free survival (PFS) per Response Evaluation Criteria in Solid Tumors (RECIST 1.1) as assessed by investigator Hypothesis (H1): The combination of pembrolizumab plus chemotherapy is superior to placebo plus chemotherapy with respect to PFS per RECIST 1.1 as assessed by investigator for the Combined Positive Score (CPS) ≥1 group. Hypothesis (H2): The combination of pembrolizumab plus chemotherapy is superior to placebo plus chemotherapy with respect to PFS per RECIST 1.1 as assessed by investigator for all-comers. Hypothesis (H3): The combination of pembrolizumab plus chemotherapy is superior to placebo plus chemotherapy with respect to PFS per RECIST 1.1 as assessed by investigator for the CPS ≥10 group.	- PFS: The time from randomization to the first documented disease progression or death due to any cause, whichever occurs first

- Objective: To compare overall survival (OS) Hypothesis (H4): The combination of pembrolizumab plus chemotherapy is superior to placebo plus chemotherapy with respect to OS for the CPS ≥1 group. Hypothesis (H5): The combination of pembrolizumab plus chemotherapy is superior to placebo plus chemotherapy with respect to OS for all-comers. Hypothesis (H6): The combination of pembrolizumab plus chemotherapy is superior to placebo plus chemotherapy with respect to OS for the CPS ≥10 group.	- OS: The time from randomization to death due to any cause
Secondary Objectives	Secondary Endpoints
- Objective: To evaluate the objective response rate (ORR), duration of response (DOR), and 12-month PFS rate per RECIST 1.1 as assessed by investigator	- Objective Response (OR): Participants who have a best overall response of either confirmed complete response (CR) or partial response (PR) - DOR: The time from the first documented evidence of CR or PR until the first documented disease progression or death due to any cause, whichever occurs first - PFS-12: The proportion of participants that are PFS event-free at 12 months
- Objective: To evaluate PFS per RECIST 1.1 as assessed by BICR	- PFS: The time from randomization to the first documented disease progression or death due to any cause, whichever occurs first
- Objective: To compare the safety and tolerability by the proportion of adverse events (AEs)	- Participants experiencing adverse events (AEs), serious AEs, and immune-related AEs - Participants discontinuing study treatment due to AEs
- Objective: To evaluate changes in Health-Related Quality of Life (HRQoL) assessments using the global score of the European Organisation for the Research and Treatment of Cancer (EORTC) QLQ-C30	- The EORTC QLQ-C30 global score

Overall Design:

Study Phase	Phase 3
Primary Purpose	Treatment
Indication	Cervical cancer
Population	Women at least 18 years of age with persistent, recurrent, or metastatic cervical cancer who have not been treated with systemic chemotherapy.
Study Type	Interventional
Intervention Model	Parallel This is a multi-site study.
Type of Control	Placebo
Study Blinding	Double-blind
Masking	Participant Investigator Sponsor
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 48 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 600 participants will be randomized in this study.

Intervention Groups and Duration:

Intervention Groups	Arm 1: Pembrolizumab 200 mg intravenous (IV) infusion + Chemotherapy every 3 weeks (Q3W) Arm 2: Placebo + Chemotherapy Q3W Investigators may choose ANY 1 of 4 chemotherapy options prior to randomization: 1) Paclitaxel 175 mg/m^2 IV infusion + cisplatin 50 mg/m^2 IV infusion 2) Paclitaxel 175 mg/m^2 IV infusion + cisplatin 50 mg/m^2 IV infusion + bevacizumab 15 mg/kg IV infusion 3) Paclitaxel 175 mg/m^2 IV infusion + carboplatin AUC 5 IV infusion 4) Paclitaxel 175 mg/m^2 IV infusion + carboplatin AUC 5 IV infusion + bevacizumab 15 mg/kg IV infusion The option to use bevacizumab is permitted according to local practice, local label, and at the choice of the investigator.
Total Number	2 treatment groups
Duration of Participation	Each participant will participate in the study for approximately 28 months from the time the participant provides documented informed consent through the final contact. After the end of treatment, each participant will be followed for 90 days for serious AEs. After a screening phase of a maximum of 28 days, each participant will be assigned to receive study intervention until any of the following occurs: • Disease progression per RECIST 1.1 is detected locally and ideally verified by BICR (waiting to discontinue participant from study treatment until verification of PD by BICR is encouraged if the participant is clinically stable) • Disease progression is confirmed per iRECIST based on investigator assessment • Unacceptable adverse event(s) (AEs) • Intercurrent illness that prevents further administration of treatment • Investigator's decision to withdraw the participant • Administrative reasons requiring cessation of treatment

	• Until the participant has received a maximum number of cycles for each treatment component individually:
	  ○ Until the participant has received 35 administrations of pembrolizumab/placebo (approximately 2 years) and
	  ○ Until the participant has received 6 cycles of paclitaxel-platinum (cisplatin or carboplatin)
	  NOTE: Participants with on-going clinical benefit and who are tolerating combination chemotherapy may be allowed to continue chemotherapy beyond 6 cycles after Sponsor consultation.
	  ○ Bevacizumab may continue until disease progression or unacceptable AEs, per the local label or local practice.
	• Participants who stop study treatment after receiving 35 administrations of pembrolizumab for reasons other than disease progression or intolerability, or participants who attain a CR after having been treated for at least 8 cycles and receiving 2 doses of pembrolizumab beyond the date when the initial CR was declared, may be eligible for up to 17 additional administrations of pembrolizumab (approximately 1 year) upon experiencing disease progression (Section 6.6.2).
	After the end of treatment, each participant will be followed for the occurrence of AEs and spontaneously reported pregnancy as described under Section 8.4.
	Participants who discontinue for reasons other than radiographic disease progression will have post-treatment follow-up imaging for disease status until disease progression is documented radiographically per RECIST 1.1 and verified by BICR and only when clinically appropriate confirmed by the site per iRECIST (for participants treated with pembrolizumab/placebo), initiating a new anti-cancer treatment, withdrawing consent, becoming lost to follow-up, pregnancy, or death. All participants will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study.
	Upon study completion, participants are discontinued and may be enrolled in a pembrolizumab extension study.

Study Governance Committees:

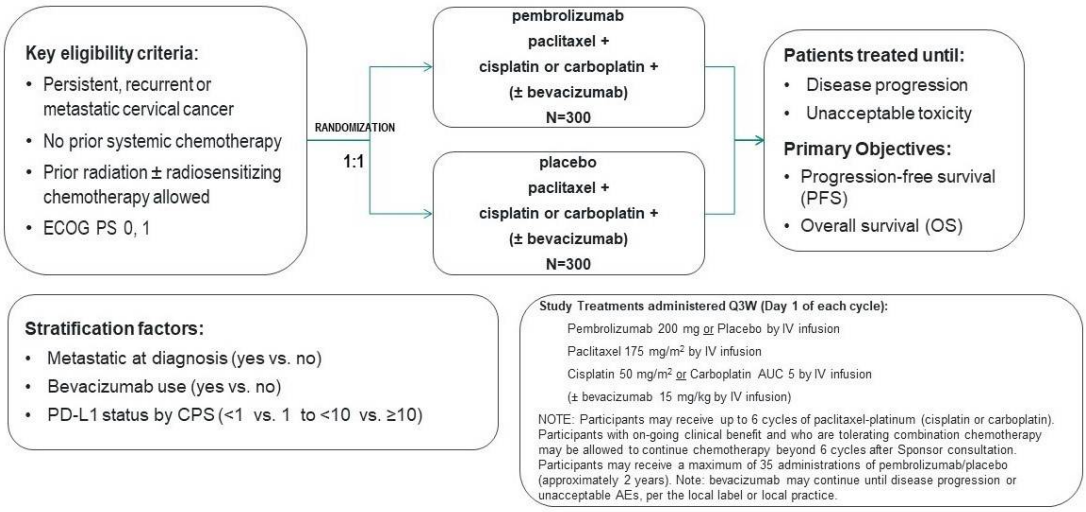
Steering Committee	No
Executive Oversight Committee	Yes
Data Monitoring Committee	Yes
Clinical Adjudication Committee	No
Study governance considerations are outlined in Appendix 1.	

Study Accepts Healthy Volunteers: No

A list of abbreviations used in this document can be found in Appendix 10.

1.2 Schema

The study diagram is outlined in Figure 1.



Abbreviations: AUC = area under concentration-time curve; CPS = combined positive score; ECOG = Eastern Cooperative Oncology Group; IV = intravenous; OS = overall survival; PD-L1 = programmed cell death ligand 1; PFS = progression-free survival; PS = performance score

Figure 1 Study Diagram

1.3 Schedule of Activities (SoA)

The SoAs for the Initial Treatment Phase and Second Course Retreatment Phase are outlined in Table 1 and Table 2, respectively.

1.3.1 Schedule of Activities – Initial Treatment Phase

Table 1 Study Schedule of Activities – Initial Treatment Phase

Study Period	Screening	Treatment						End of Treatment	Post-Treatment			Comments
Treatment Cycle	Screening	C1	C2	C3	C4	C5	C6-onward	EOT	Safety Follow-up	Efficacy Follow-up	Survival Follow-up	
Scheduled Days	-28 to -1		±3	±3	±3	±3	±3	At time of discon-tinuation	30 days from last dose[a] (+7d)	Q9W or Q12W[b] (±7d)	Q12W (±7d)	
Administrative Procedures												
Informed Consent	X											Documented informed consent form may be obtained at any time prior to any protocol-specific screening procedures being performed. Rescreened participants do not need to be reconsented if original consent was obtained greater than 28 days prior to Cycle 1. If the investigator plans to treat beyond initial investigator-assessed radiographic disease progression per RECIST 1.1, additional consent is required.
Informed Consent for Future Biomedical Research (FBR)	X											The participant may participate in the main study without participating in FBR.
Inclusion/Exclusion Criteria	X											
Participant ID Card Issued	X											Add randomization number at C1
Demographics	X											
Medical History	X											
Cervical Cancer History	X											All prior historical information must be reviewed (eg, prior surgeries, radiation, and other oncologic therapies)
Prior/Concomitant Therapy	X	X	X	X	X	X	X	X	X	X		

Study Period	Screening	Treatment						End of Treatment	Post-Treatment			Comments
Treatment Cycle	Screening	C1	C2	C3	C4	C5	C6-onward	EOT	Safety Follow-up	Efficacy Follow-up	Survival Follow-up	
Scheduled Days	-28 to -1		±3	±3	±3	±3	±3	At time of discon-tinuation	30 days from last dose[a] (+7d)	Q9W or Q12W[b] (±7d)	Q12W (±7d)	
Randomize Participant		X										Participant may be randomized up to 3 days prior to Cycle 1 Day 1
Review new anti-cancer therapy status								X	X	X	X	
Survival Status		←									→	All participants may be contacted for survival status at any time during the course of the study.
Clinical Procedures or Assessments												
Review Adverse Events	X	X	X	X	X	X	X	X	X	X		Report all AEs through 30 days following cessation of study intervention. Report SAEs through 90 days following cessation of study intervention or 30 days following cessation of study intervention if the participant initiates new anti-cancer therapy, whichever is earlier.
Full Physical Exam	X							X				
Directed Physical Exam		X	X	X	X	X	X		X			
Vital Signs	X	X	X	X	X	X	X	X	X			
12-Lead Electrocardiogram	X							X				
ECOG Performance Status	X	X	X	X	X	X	X	X				Assess within 14 days prior to randomization and prior to study intervention during treatment visits. Investigator or designee is to confirm that ECOG performance status is 0 or 1 prior to dosing at C1D1.

Study Period	Screening	Treatment						End of Treatment	Post-Treatment			Comments
Treatment Cycle	Screening	C1	C2	C3	C4	C5	C6-onward	EOT	Safety Follow-up	Efficacy Follow-up	Survival Follow-up	
Scheduled Days	-28 to -1		±3	±3	±3	±3	±3	At time of discon-tinuation	30 days from last dose[a] (+7d)	Q9W or Q12W[b] (±7d)	Q12W (±7d)	
Laboratory Procedures and Assessments												Laboratory results must be reviewed before study drug administration.
Pregnancy Test (urine or β-HCG)	X	←	—	—	—	—	→	X	X			WOCBP require negative test within 72 hours prior to randomization. In the event that more than 72 hours have elapsed between this pregnancy test and the first dose of study treatment, another pregnancy test must be performed and must be negative prior to receiving first dose of study treatment. A pregnancy test must be performed every month during study treatment. More frequent pregnancy testing may be performed if required by local regulations or if clinically indicated. Refer to Appendix 7 for country-specific requirements.
HIV Testing	X											Not required unless mandated by local health authority. Refer to Appendix 7 for country-specific requirements.
Hepatitis B and C Testing	X											Not required unless mandated by local health authority. Refer to Appendix 7 for country-specific requirements.
PT/INR and aPTT/PTT	X											Perform eligibility labs within 14 days prior to randomization. Participants receiving coumarin-based anticoagulants should have more frequent INR monitoring as clinically indicated.
CBC with Differential	X		X	X	X	X	X	X	X			Perform eligibility labs within 14 days prior to randomization. From Cycle 2 onwards, may perform up to 3 days prior to dosing.

Study Period	Screening	Treatment						End of Treatment	Post-Treatment			Comments
Treatment Cycle	Screening	C1	C2	C3	C4	C5	C6-onward	EOT	Safety Follow-up	Efficacy Follow-up	Survival Follow-up	
Scheduled Days	-28 to -1		±3	±3	±3	±3	±3	At time of discon-tinuation	30 days from last dose[a] (+7d)	Q9W or Q12W[b] (±7d)	Q12W (±7d)	
Chemistry Panel	X		X	X	X	X	X	X	X			Perform eligibility labs within 14 days prior to randomization. From Cycle 2 onwards, may perform up to 3 days prior to dosing.
T3/FT3, FT4, and TSH	X		X		X		X	X	X			At screening and every 2 cycles during treatment (C2, C4, C6,…). From Cycle 2 onwards, may perform up to 3 days prior to dosing. May perform centrally if unable to perform locally.
Urinalysis (for participants not receiving bevacizumab)	X		X		X		X	X	X			At screening, C2, C4, C6, and every 4 cycles thereafter (C10, C14, C18,…). From Cycle 2 onwards, may perform up to 3 days prior to dosing.
Urinalysis (for participants receiving bevacizumab)	X		X	X	X	X	X	X	X			At screening and at every cycle during which bevacizumab is administered from Cycle 2 onwards. From Cycle 2 onwards, may perform up to 3 days prior to dosing.
Sample Collection for Biomarkers												
Archival or Newly Obtained Tissue Collection	X											PD-L1 status must be determined prior to randomization.
Blood for Genetic Analysis		X										Collect predose for randomized participants only
Blood for RNA Analyses		X			X		X	X				Collect predose on Day 1 of C1, C4, C7, C10, C13, C16 (Q9W through C16), Day 1 of C20, C24, C28, C32 (Q12W up to C32), and at EOT.
Blood for Plasma Biomarker Analyses		X	X			X		X				Collect predose
Blood for Serum Biomarker Analyses		X	X			X		X				Collect predose

Study Period	Screening	Treatment						End of Treatment	Post-Treatment			Comments
Treatment Cycle	Screening	C1	C2	C3	C4	C5	C6-onward	EOT	Safety Follow-up	Efficacy Follow-up	Survival Follow-up	
Scheduled Days	-28 to -1		±3	±3	±3	±3	±3	At time of discon-tinuation	30 days from last dose[a] (+7d)	Q9W or Q12W[b] (±7d)	Q12W (±7d)	
Blood for ctDNA		X			X		X	X				Collect predose on Day 1 of C1, C4, C7, C10, C13, C16 (Q9W through C16), Day 1 of C20, C24, C28, C32 (Q12W after C16), and at EOT.
Efficacy Measurements												
CT – chest MRI – abdomen and pelvis	X	X						X		X[c]		Perform within 28 days prior to randomization. On treatment Q9W (±7 days) from randomization through Week 54, Q12W thereafter. If imaging was obtained within 28 days prior to EOT, scan at EOT is not mandatory. Schedule should be followed from date of randomization regardless of treatment delays.
Bone scan	X	X[c]										Perform within 28 days prior to randomization ONLY for participants with a history of bone metastases or who are clinically symptomatic. On study as clinically indicated. Perform at CR for participants who were positive at baseline or at any point during the study.
Brain scan	X	X[c]										Perform within 28 days prior to randomization ONLY for participants with brain metastases at baseline (to demonstrate stability) or who are clinically symptomatic. On study as clinically indicated. Perform at CR for participants who were positive at baseline or at any point during the study.

Study Period	Screening	Treatment						End of Treatment	Post-Treatment			Comments
Treatment Cycle	Screening	C1	C2	C3	C4	C5	C6-onward	EOT	Safety Follow-up	Efficacy Follow-up	Survival Follow-up	
Scheduled Days	-28 to -1		±3	±3	±3	±3	±3	At time of discon-tinuation	30 days from last dose[a] (+7d)	Q9W or Q12W[b] (±7d)	Q12W (±7d)	
Health-Related Quality of Life (HRQoL)												
ePROs (perform in this order) 1) EQ-5D-5L 2) EORTC QLQ-C30 3) EORTC QLQ-CX24		X	X	X	X	X	X	X	X			Perform on Day 1 of Cycles 1 to 14, every other cycle thereafter up to Cycle 44, EOT, and Safety Follow-up. If the participant does not complete the HRQoL survey(s), the MISS_MODE form must be completed to capture the reason the assessment(s) was not performed.
Study Drug Administration												
Treatment eligibility assessment		X										Document rationale for participant eligibility for treatment with: 1) bevacizumab and 2) the combination of cisplatin + paclitaxel + bevacizumab.
MK-3475 or placebo + Chemotherapy		X	X	X	X	X	X					Order of study intervention administration: 1) pembrolizumab or placebo, 2) paclitaxel, 3) cisplatin or carboplatin, 4) bevacizumab. Participants should receive up to 6 cycles of paclitaxel-platinum (cisplatin or carboplatin) treatment. Participants with ongoing clinical benefit and who are tolerating combination chemotherapy may be allowed to continue chemotherapy beyond 6 cycles with Sponsor consultation. Subjects should continue biologic treatment (pembrolizumab/placebo and/or bevacizumab) until disease progression or prohibitive toxicity. Participants may receive a maximum of 35 administrations of pembrolizumab/placebo.

Study Period	Screening	Treatment						End of Treatment	Post-Treatment			Comments
Treatment Cycle	Screening	C1	C2	C3	C4	C5	C6-onward	EOT	Safety Follow-up	Efficacy Follow-up	Survival Follow-up	
Scheduled Days	-28 to -1		±3	±3	±3	±3	±3	At time of discon-tinuation	30 days from last dose[a] (+7d)	Q9W or Q12W[b] (±7d)	Q12W (±7d)	

AE = adverse event; aPTT = activated partial thromboplastin time; β-HCG = beta-human chorionic gonadotropin; BICR = blinded independent central review ; CBC = complete blood count; CR = complete response; CT = computed tomography; ctDNA = circulating tumor DNA; CX = Cycle X; ECOG = Eastern Cooperative Oncology Group; EORTC = European Organisation for the Research and Treatment of Cancer, EOT = End of treatment; ePRO = electronic patient-reported outcome; EQ-5D-5L = EuroQoL-5D-5L; FBR = Future biomedical research; FT3 = free triiodothyronine; FT4 = free thyroxine; HIV = human immunodeficiency virus; HRQoL = health-related Quality of Life; ID = identification; INR = international normalized ratio; iRECIST = modified RECIST 1.1 for immune-based therapeutics; MRI = magnetic resonance imaging; PD-L1 = programmed cell death ligand 1; PT = prothrombin time; PTT = partial prothrombin time; Q9W = every 9 weeks; Q12W = every 12 weeks; QLQ-C30 = Quality of Life Questionnaire Core 30; QLQ-CX24 = Quality of Life Questionnaire Cervical Cancer Module; RECIST = Response Evaluation Criteria in Solid Tumors; RNA = ribonucleic acid; SAE=serious adverse event; T3 = triiodothyronine; TSH = thyroid-stimulating hormone; WOCBP = woman/women of child bearing potential.

a. If the End of Treatment Visit occurs ≥30 days from last dose of study treatment, a Safety Follow-up Visit is not required. All procedures for both visits will be performed at the End of Treatment Visit.
b. Efficacy Follow-Up visits to be scheduled to coincide with Follow-Up imaging.
c. Participants who discontinue study treatment for reasons other than radiographic disease progression will have post-treatment efficacy follow-up imaging for disease status until disease progression is documented radiographically per RECIST 1.1 by the investigator, and verified by BICR, and confirmed by the site per iRECIST when clinically appropriate (for participants treated with pembrolizumab/placebo), or upon initiating a new anti-cancer treatment, withdrawing consent, becoming lost to follow-up, pregnancy or death, whichever comes first.

1.3.2 Schedule of Activities – Second Course Retreatment Phase

Table 2 Study Schedule of Activities – Second Course Retreatment Phase

Study Period	Treatment						End of Treatment	Post-Treatment			Comments
Treatment Cycle	C1	C2	C3	C4	C5	C6-C17	EOT	Safety Follow-up	Efficacy Follow-up	Survival Follow-up	
Scheduled Days		±3	±3	±3	±3	±3	At time of discon-tinuation	30 days from last dose[a] (+7d)	Q12W[b] (±7d)	Q12W (±7d)	
Administrative Procedures											
Eligibility Criteria	X										
Concomitant Therapy	X	X	X	X	X	X	X	X	X		
Review new anti-cancer therapy status							X	X	X	X	
Survival Status	←								→	X	All participants may be contacted for survival status at any time during the course of the study.
Clinical Procedures or Assessments											
Review Adverse Events	X	X	X	X	X	X	X	X	X		Report all AEs through 30 days following cessation of study intervention. Report SAEs through 90 days following cessation of study intervention or 30 days following cessation of study intervention if the participant initiates new anti-cancer therapy, whichever is earlier.
Full Physical Exam	X						X				
Directed Physical Exam		X	X	X	X	X		X			
Vital Signs	X	X	X	X	X	X	X	X			
12-Lead Electrocardiogram	X						X				
ECOG Performance Status	X	X	X	X	X	X	X				Assess within 3 days prior to second course C1 and prior to treatment during treatment visits.

Study Period	Treatment						End of Treatment	Post-Treatment			Comments
Treatment Cycle	C1	C2	C3	C4	C5	C6-C17	EOT	Safety Follow-up	Efficacy Follow-up	Survival Follow-up	
Scheduled Days		±3	±3	±3	±3	±3	At time of discon-tinuation	30 days from last dose[a] (+7d)	Q12W[b] (±7d)	Q12W (±7d)	
Laboratory Procedures and Assessments											
Pregnancy Test (urine or β-HCG)	X	←	—	—	—	→	X	X			WOCBP require negative test within 72 hours prior to second course C1. A pregnancy test must be performed every month during study treatment. More frequent pregnancy testing may be performed if required by local regulations or if clinically indicated. Refer to Appendix 7 for country-specific requirements.
PT/INR and aPTT/PTT	X										Perform within 3 days prior to second course C1. Participants receiving coumarin-based anticoagulants should have more frequent INR monitoring as clinically indicated.
CBC with Differential	X	X	X	X	X	X	X	X			Perform within 3 days prior to second course C1. From C2 onwards, may perform up to 3 days prior to dosing.
Chemistry Panel	X	X	X	X	X	X	X	X			Perform within 3 days prior to second course C1. From C2 onwards, may perform up to 3 days prior to dosing.
T3/FT3, FT4, and TSH	X		X		X	X	X	X			Perform within 3 days prior to second course C1 and every 2 cycles during treatment (C3, C5, C7,…). May perform centrally if unable to perform locally.
Urinalysis	X		X		X	X	X	X			Perform within 3 days prior to second course C1. Perform at C3, C5 and every 4 cycles thereafter (C9, C13, C17).

Study Period	Treatment						End of Treatment	Post-Treatment			Comments
Treatment Cycle	C1	C2	C3	C4	C5	C6-C17	EOT	Safety Follow-up	Efficacy Follow-up	Survival Follow-up	
Scheduled Days		±3	±3	±3	±3	±3	At time of discon-tinuation	30 days from last dose[a] (+7d)	Q12W[b] (±7d)	Q12W (±7d)	
Efficacy Measurements											
CT – chest MRI – abdomen and pelvis	X[c]										Perform within 28 days prior to second course C1. On treatment Q12W or more frequently if clinically indicated.
Bone scan	X[c]										Perform within 28 days prior to second course C1 for those participants with a history of bone metastases or clinically symptomatic. On treatment as clinically indicated.
Brain scan	X[c]										Perform within 28 days prior to second course C1 for those participants with a history of brain metastases or clinically symptomatic. On treatment as clinically indicated.
Study Drug Administration											
MK-3475	X	X	X	X	X	X					

AE = adverse event; aPTT = activated partial thromboplastin time; β-HCG = beta-human chorionic gonadotropin; CBC = complete blood count; CT = computed tomography; CX = Cycle X; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FT3 = free triiodothyronine; FT4 = free thyroxine; INR = international normalized ratio; iRECIST = modified RECIST 1.1 for immune-based therapeutics; MRI = magnetic resonance imaging; PT = prothrombin time; PTT = partial prothrombin time; Q12W = every 12 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; T3 = triiodothyronine; TSH = thyroid-stimulating hormone; WOCBP = woman/women of child bearing potential.

a. If the second course End of Treatment Visit occurs ≥30 days from last dose of study treatment, a second Safety Follow-up Visit is not required. All procedures for both visits will be performed at the second End of Treatment Visit.
b. Second course Efficacy Follow-Up visits to be scheduled to coincide with second course Follow-Up imaging.
c. Participants who discontinue the second course for reasons other than radiographic disease progression will have post-treatment efficacy follow-up imaging for disease status until disease progression (or until progression is confirmed per iRECIST if the participant is clinically stable), initiating a nonstudy cancer treatment, withdrawing consent, or becoming lost to follow-up.

2 INTRODUCTION

Globally, cervical cancer is the fourth most common cancer in women, with an estimated 528,000 new cases in 2012, representing 12% of all female cancers [International Agency for Research on Cancer 2012]. Approximately 90% of the ~270,000 deaths from cervical cancer in 2015 occurred in low- and middle-income countries [International Agency for Research on Cancer 2012].

Cervical cancer occurs at much lower rates in the United States (US), ranking 21st among all new cancer cases, accounting for approximately 0.8% of the new cases [National Cancer Institute. 2014]. Due to current screening procedures used in Western countries for the early detection of cervical intraepithelial neoplasia (CIN) and cervical cancer, almost half of the newly diagnosed adult cervical cancer patients (46%) have Stage I (localized) cancer, with a 5-year survival rate of 91.5% [National Cancer Institute. 2014]. It is estimated that in 2017, there will be 12,820 new cases of cervical cancer and an estimated 4,210 women will die of this disease [National Cancer Institute. 2014]. The median age at the diagnosis of cervical cancer is 49 years. Five-year survival rates decrease with stage at diagnosis, from 91.5% for localized disease to 17.3% for metastatic disease [National Cancer Institute. 2014]. Patients with distant metastases and/or recurrent disease have a poor prognosis, with a median OS between 6.4 and 9.4 months [National Comprehensive Cancer Network 2017].

Treatment options for cervical cancer in adults include surgery (conization and hysterectomy), radiation, and chemotherapy alone or in combination, depending on the stage of the disease [National Comprehensive Cancer Network 2017]. Patients with advanced (persistent, recurrent, or metastatic) cervical cancer have limited, mainly palliative, treatment options. Standard first-line chemotherapy for advanced cervical cancer consists of paclitaxel combined with cisplatin or carboplatin [Moore, D. H., et al 2004] [Kitagawa, R., et al 2015] [Tewari, K. S. 2017]. However, the National Comprehensive Cancer Network (NCCN) guidelines recommend consideration of clinical trials as a treatment option even in the first-line setting, highlighting the unmet medical need for adult women with advanced cervical cancer [National Comprehensive Cancer Network 2017].

2.1 Study Rationale

Women with persistent, recurrent, or metastatic cervical cancer face a grim prognosis with survival dependent on stage at diagnosis [Landy, R., et al 2016]. Once cervical cancer becomes advanced, surgery and radiation are no longer treatment options and systemic chemotherapy is provided for palliation. Both the NCCN and European Society for Medical Oncology (ESMO) cervical cancer treatment guidelines offer limited options. For example, ESMO recommends the following [Marth, C., et al 2017]:

- Palliative chemotherapy with the aim of relieving symptoms and improving quality of life if the patient has a performance score (PS) <2 and no formal contraindications.
- Cisplatin-based doublets with topotecan or paclitaxel have demonstrated superiority to cisplatin monotherapy in terms of response rate and PFS.

- Paclitaxel and cisplatin combined with bevacizumab is considered the preferred first-line regimen in metastatic or recurrent cervical cancer based on a balance between the efficacy and toxicity profile.

- The combination of paclitaxel and carboplatin could be considered an alternative for patients who are not candidates for cisplatin.

Similarly, the NCCN recommends various combinations of cisplatin, paclitaxel, bevacizumab, topotecan, and gemcitabine as first-line combination therapy. Cisplatin, carboplatin, and paclitaxel are possibilities as first-line monotherapy, and there are various regimens of similar chemotherapies for second-line treatment [National Comprehensive Cancer Network 2017].

Both NCCN and ESMO rely on the results from the Gynecologic Oncology Group (GOG) 204 and 240 clinical trials. The GOG 240 trial compared cisplatin (50 mg/m^2 on Day 1 or 2) plus paclitaxel (135 mg/m^2 or 175 mg/m^2 on Day 1) in 21-day cycles with and without IV bevacizumab (15 mg/kg on Day 1) [Tewari, K. S., et al 2017]. The GOG 204 study, which investigated 4 cisplatin-containing doublet chemotherapy regimens for the treatment of patients with recurrent or metastatic cervical carcinoma, showed that the ORR was 29.1%, PFS was 5.8 months, and OS was 12.9 months for the cisplatin plus paclitaxel combination [Monk, B. J., et al 2009].

The current study will evaluate paclitaxel plus cisplatin or carboplatin with or without bevacizumab plus pembrolizumab or placebo. KEYNOTE-158 served as the proof of concept to demonstrate efficacy of pembrolizumab monotherapy in second and later lines of treatment for participants with cervical cancer. The ORR for participants treated with pembrolizumab in the cervical cancer cohort of KEYNOTE-158 was 17.0% (95% CI: 8%, 31%), with 3 confirmed and 5 unconfirmed responses [Schellens, J. H. M., et al 2017]. The observed ORR appeared to increase with longer follow-up, suggesting that immunotherapy may offer long-term responses in a heavily pretreated population with considerable unmet medical need.

2.2 Background

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD 1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD 1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. KEYTRUDA® (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the Investigator's Brochure.

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+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [Dudley, M. E., et al 2005] [Hunder, N. N., et al 2008].

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

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

2.2.2 Preclinical and Clinical Studies

Therapeutic studies in mouse models have shown that administration of antibodies blocking the PD-1/PD-L1 interaction enhances infiltration of tumors by CD8+ T-cells and leads ultimately to tumor rejection. Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated anti-tumor responses as a monotherapy in murine models of squamous cell carcinoma, pancreatic carcinoma, melanoma and colorectal cancer (CRC). Blockade of the PD-1 pathway effectively promoted CD8+ T-cell infiltration into the tumor and the presence

of IFN-γ, granzyme B and perforin, indicating that the mechanism of action involved local infiltration and activation of effector T-cell function *in vivo* [Nomi, T., et al 2007] [Cai, G., et al 2004] [Blank, C. and Mackensen, A. 2007] [Iwai, Y., et al 2002] [Tsushima, F., et al 2006] [Korman, A., et al 2007]. Experiments have confirmed the *in vivo* efficacy of PD-1 blockade as a monotherapy as well as in combination with chemotherapy in syngeneic mouse tumor models (refer to the IB).

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

2.2.3 Ongoing Clinical Studies

Refer to the IB for ongoing clinical study data for pembrolizumab.

2.2.4 Information on Other Study-related Therapy

Cisplatin is generally regarded as the most active agent and is recommended as a first-line single-agent chemotherapy option for recurrent or metastatic cervical cancer; reported response rates are approximately 20% to 30%, with an occasional complete response [National Comprehensive Cancer Network 2016]. Overall survival with cisplatin is approximately 6 to 9 months. Both carboplatin and paclitaxel have each been reported to be tolerable and efficacious and are possibilities as first-line single-agent chemotherapy. Therefore, palliation with single agents cisplatin, carboplatin, or paclitaxel is a reasonable approach in patients with recurrent disease not amenable to surgical or radio therapeutic approaches.

Cisplatin-based combination chemotherapy regimens, such as cisplatin/paclitaxel/bevacizumab (category 1), cisplatin/paclitaxel (category 1), and cisplatin/topotecan (category 2A), have been extensively investigated in clinical studies [National Comprehensive Cancer Network 2016]. A randomized Phase 3 study (GOG 169) in 264 patients compared cisplatin/paclitaxel versus cisplatin alone for metastatic, recurrent, or persistent cervical cancer. Patients receiving the 2-drug combination had a higher response rate (36% vs. 19%) and improved PFS (4.8 months vs. 2.8 months; $p>0.001$) compared to single-agent cisplatin, although no improvement was seen in median survival. Patients who responded to cisplatin/paclitaxel had a significant improvement in quality of life.

Recently published data from a Phase 3 randomized trial (JCOG0505) suggested that carboplatin/paclitaxel is noninferior to cisplatin/paclitaxel in 253 women with metastatic or recurrent cervical cancer [Kitagawa, R., et al 2015]. Many physicians use carboplatin/paclitaxel because of ease of administration and tolerability. Results from JCOG0505 showed that the carboplatin/paclitaxel (TC) regimen was noninferior to cisplatin/paclitaxel (TP) in terms of median overall survival (18.3 months for TP vs. 17.5 months for TC; HR=0.994 (90% CI, 0.79 to 1.25); $p=0.032$) and non-hospitalization periods were significantly longer for patients receiving TC. However, among patients who had not received prior cisplatin, the OS for TC and TP was 13.0 and 23.2 months, respectively (HR=1.571; 95% CI, 1.06 to 2.32). Based on these data, the panel recommends carboplatin/paclitaxel as a category 1 option for patients who have received prior cisplatin

therapy. Carboplatin/paclitaxel is a category 2A recommendation for other indications (ie, for patients who have not received prior platinum-based therapy).

A recent systematic review of the data on cisplatin/paclitaxel and carboplatin/paclitaxel regimens also suggested that lower toxicity carboplatin-based regimens appear to be an equally effective alternative to cisplatin-based regimens for treating recurrent or metastatic cervical cancer [Skarlos, D. V., et al 1994]. Based on the collective findings from GOG 240 and JGOG0505, the panel has opted to include carboplatin/paclitaxel/bevacizumab as an additional treatment option for recurrent or metastatic cervical cancer (category 2A). Based on the previous studies, cisplatin/paclitaxel and carboplatin/paclitaxel have become the most widely used systemic regimens for metastatic or recurrent cervical cancer.

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.

The analysis of data from 47 subjects in Group E from KEYNOTE-158 showed that pembrolizumab is an effective and generally well tolerated treatment for cervical cancer in subjects who received prior treatments. Treatment with pembrolizumab 200 mg Q3W provided a clinically meaningful ORR of 17.0%, with 3 confirmed and 5 unconfirmed responses [Schellens, J. H. M., et al 2017]. No new safety signals associated with pembrolizumab were identified. The nature, frequency, and severity of AEs were either generally consistent with the established safety profile of pembrolizumab or with the underlying disease or anticipated in patients who received prior treatments including pelvic irradiation.

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

3 HYPOTHESIS, OBJECTIVES, AND ENDPOINTS

In women with persistent, recurrent, or metastatic cervical cancer treated with pembrolizumab plus chemotherapy versus placebo plus chemotherapy:

The study will be considered positive if it is positive for either the PFS or OS hypothesis test for any of the 3 groups (CPS ≥1 group, all-comers, and CPS ≥10 group).

Objectives	Endpoints
Primary	
• Objective: To compare progression-free survival (PFS) per Response Evaluation Criteria in Solid Tumors (RECIST 1.1) as assessed by investigator Hypothesis (H1): The combination of pembrolizumab plus chemotherapy is superior to placebo plus chemotherapy with respect to PFS per RECIST 1.1 as assessed by investigator for the Combined Positive Score (CPS) ≥1 group. Hypothesis (H2): The combination of pembrolizumab plus chemotherapy is superior to placebo plus chemotherapy with respect to PFS per RECIST 1.1 as assessed by investigator for all-comers. Hypothesis (H3): The combination of pembrolizumab plus chemotherapy is superior to placebo plus chemotherapy with respect to PFS per RECIST 1.1 as assessed by investigator for the CPS ≥10 group.	• PFS: The time from randomization to the first documented disease progression or death due to any cause, whichever occurs first
• Objective: To compare overall survival (OS) Hypothesis (H4): The combination of pembrolizumab plus chemotherapy is superior to placebo plus chemotherapy with respect to OS for the CPS ≥1 group. Hypothesis (H5): The combination of pembrolizumab plus chemotherapy is superior to placebo plus chemotherapy with respect to OS for all-comers. Hypothesis (H6): The combination of pembrolizumab plus chemotherapy is superior to placebo plus chemotherapy with respect to OS for the CPS ≥10 group.	• OS: The time from randomization to death due to any cause

Objectives	Endpoints
Secondary	
• Objective: To evaluate the objective response rate (ORR), duration of response (DOR), and 12-month PFS rate per RECIST 1.1 as assessed by investigator	• Objective Response (OR): Participants who have a best overall response of either confirmed complete response (CR) or partial response (PR) • DOR: The time from the first documented evidence of CR or PR until the first documented disease progression or death due to any cause, whichever occurs first • PFS-12: The proportion of participants that are PFS event-free at 12 months
• Objective: To evaluate PFS per RECIST 1.1 as assessed by BICR	• PFS: The time from randomization to the first documented disease progression or death due to any cause, whichever occurs first
• Objective: To compare the safety and tolerability by the proportion of adverse events (AEs)	• Participants experiencing adverse events (AEs), serious AEs, and immune-related AEs • Participants discontinuing study treatment due to AEs
• Objective: To evaluate changes in Health-Related Quality of Life (HRQoL) assessments using the global score of the European Organisation for the Research and Treatment of Cancer (EORTC) QLQ-C30	• The EORTC QLQ-C30 global score

Objectives	Endpoints
Tertiary/Exploratory	
• Objective: To evaluate the objective response rate (ORR), duration of response (DOR), and 12-month PFS rate per RECIST 1.1 as assessed by BICR	• Objective Response (OR): Participants who have a best overall response of either confirmed complete response (CR) or partial response (PR) • DOR: The time from the first documented evidence of CR or PR until the first documented disease progression or death due to any cause, whichever occurs first • PFS-12: The proportion of participants that are PFS event-free at 12 months
• Objective: To evaluate PFS using modified RECIST 1.1 for immune-based therapeutics (iRECIST), as assessed by investigator	• PFS per iRECIST is defined as time from the date of randomization to the date of the first documentation of confirmed immune-related progressive disease (iPD) or death (whichever occurs first)
• Objective: To identify molecular (genomic, metabolic, and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of pembrolizumab and other treatments	• Germline genetic variation, genetic (DNA) mutations from tumor, tumor and blood RNA variation, proteomics and IHC, and other biomarkers
• To evaluate changes in HRQoL assessments using the EORTC QLQ-C30, EORTC QLQ-CX24, and European Quality of Life EQ-5D-5L instruments	• HRQoL will be assessed using the EORTC QLQ-C30 (scores other than global score), EORTC QLQ CX24, and EQ-5D-5L
• To characterize utilities using the EQ-5D-5L	• Utilities will be assessed using the EQ-5D-5L

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 3 randomized, double-blind, placebo-controlled trial of pembrolizumab plus chemotherapy versus chemotherapy alone in women at least 18 years of age with a histologically confirmed diagnosis of persistent, recurrent, or metastatic cervical cancer who are not eligible for treatment with curative intent (such as with surgery and/or radiation) and who have not previously been treated with systemic chemotherapy, with the exception of chemotherapy used as a radiosensitizing agent.

Approximately 600 participants will be enrolled into the study. Participants must have measurable disease per RECIST 1.1 as assessed by the local site investigator/radiology and must provide an adequate archival or newly obtained tumor tissue sample for determination of PD-L1 expression status in order to be eligible. A complete list of study inclusion/exclusion criteria is found in Section 5. The study includes dual-primary efficacy endpoints: 1) PFS per RECIST 1.1 as assessed by investigator and 2) OS.

After a screening period of a maximum of 28 days, eligible participants will first be stratified by metastatic (FIGO 2009 Stage IVB) at initial diagnosis (yes vs. no), investigator decision to use bevacizumab (yes vs. no), and PD-L1 status (CPS <1 vs. CPS 1 to <10 vs. CPS ≥10), then randomized centrally to one of the 2 treatment groups below. NOTE: The 2009 version of FIGO included para-aortic lymph node involvement as Stage IVB disease while the 2018 version of FIGO does not include para-aortic lymph node involvement as Stage IVB disease. Para-aortic lymph node involvement will be considered evidence of metastatic disease for purposes of stratification of all participants at the time of randomization.

Arm 1: Pembrolizumab 200 mg by IV infusion plus chemotherapy Q3W

Arm 2: Placebo by IV infusion plus chemotherapy Q3W

In Arms 1 and 2, the investigator may select any one of the following four treatment regimens prior to randomization:

1) Paclitaxel 175 mg/m^2 IV infusion + cisplatin 50 mg/m^2 IV infusion

2) Paclitaxel 175 mg/m^2 IV infusion + cisplatin 50 mg/m^2 IV infusion + bevacizumab 15 mg/kg IV infusion

3) Paclitaxel 175 mg/m^2 IV infusion + carboplatin AUC 5 IV infusion

4) Paclitaxel 175 mg/m^2 IV infusion + carboplatin AUC 5 IV infusion + bevacizumab 15 mg/kg IV infusion

All study treatments should be administered on Day 1 of each 3-week treatment cycle. Cisplatin may be administered on Day 2 of each 3-week treatment cycle if per local practice.

The option to use bevacizumab is permitted according to local practice and at the choice of the investigator; however, the decision to use or not use bevacizumab must be decided prior to randomization, as this is a stratification factor.

A participant may switch from cisplatin to carboplatin during the course of the study if required for clinical factors (eg, impairment of renal function).

During the treatment period, participants will have routine clinic visits for administration of study treatment, monitoring safety and well-being, and assessing changes in disease status. Key safety assessments include physical examinations, vital signs, electrocardiography (ECG), hematology and chemistry laboratories, thyroid function testing and urinalysis. At each visit, AEs and SAEs will be evaluated and graded per the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. The doses of study treatment may be interrupted, reduced (only applicable for chemotherapy), or discontinued upon experiencing severe AEs in accordance with the dose modification guidelines for each study treatment (refer to Section 6.6 for details).

Scheduled on-study imaging assessments for disease status include computed tomography (CT) of the chest and magnetic resonance imaging (MRI) of the abdomen and pelvis. The first on study imaging assessment will be performed at 9 weeks (63 days ±7 days) from the date of randomization. Subsequent tumor imaging should be performed every 9 weeks (Q9W) (63 days ±7 days) through Week 54 and every 12 weeks (Q12W) (84 days ±7 days) thereafter. Bone scans and brain scans should be performed on study as clinically indicated and again at CR if the participant was positive for bone or brain metastases at baseline or at any point during the study. When a participant is first identified by the local site investigator/radiology as having radiographic disease progression (PD), the site will submit all imaging for PD to be verified by BICR. Participants who are clinically stable may continue study treatment while waiting for BICR verification of PD. Progressive disease may be further confirmed by subsequent imaging at the site. Refer to Section 8.2.1 for details about tumor imaging and assessments.

Participants may interrupt or discontinue pembrolizumab/placebo and continue other study treatment(s). Similarly, participants may interrupt or discontinue chemotherapy and/or bevacizumab and continue pembrolizumab/placebo.

Participants will receive study treatments until disease progression per RECIST 1.1 is detected locally and ideally verified by BICR (waiting to discontinue participant from study treatment until verification of PD by BICR is encouraged if the participant is clinically stable), disease progression is confirmed per iRECIST based on investigator assessment, unacceptable AEs, intercurrent illness that prevents further administration of treatment, investigator decision to withdraw the participant from treatment, or administrative reasons requiring cessation of treatment.

Participants may receive up to 6 cycles of paclitaxel-platinum (cisplatin or carboplatin). Participants with ongoing clinical benefit and who are tolerating combination chemotherapy may be allowed to continue chemotherapy beyond 6 cycles after Sponsor consultation.

Participants may receive a maximum of 35 administrations of pembrolizumab/placebo (approximately 2 years). Note: Bevacizumab may continue after discontinuation of all other study drugs until disease progression or unacceptable AEs, per the local label or local practice.

In the event that a CR has been observed in a participant, study treatment may be discontinued at the discretion of the investigator after the CR has been confirmed by radiographic imaging and the participant has received at least 2 treatments with pembrolizumab/placebo beyond the date when the initial CR was declared and after completing a minimum of 8 total cycles of treatment (~24 weeks). Participants who discontinue study treatment after receiving 35 administrations of pembrolizumab for reasons other than disease progression or intolerability, or participants who attain a CR and stop study treatment may be eligible for up to 17 additional administrations of pembrolizumab (approximately 1 year) upon experiencing disease progression (refer to Section 6.6.2 for second course retreatment with pembrolizumab).

Participants who discontinue study treatment for reasons other than radiographic disease progression will have post-treatment efficacy follow-up imaging for disease status until disease progression is documented radiographically per RECIST 1.1 by the Investigator, and verified by BICR per RECIST 1.1, and when clinically appropriate, confirmed by the site per iRECIST, or upon initiating a new anti-cancer treatment, withdrawing consent, becoming lost to follow-up, pregnancy or death, whichever occurs first.

After discontinuation of study treatment, participants may initiate subsequent anti-cancer treatment at the discretion of the treating physician and the participant per local standard of care. After verification of progression by BICR per RECIST 1.1 and/or initiation of a subsequent anti-cancer treatment, all participants will be followed for survival (by phone contact or clinic visit) until death, withdrawal of consent, loss to follow-up, or until the study is concluded or terminated early, whichever comes first.

This protocol does not allow participants to cross over to the pembrolizumab plus chemotherapy arm if they experience progression with placebo plus chemotherapy.

Two interim efficacy analyses (at approximately 22 months and 30 months from first participant randomized) and one final analysis (at approximately 40 months from first patient randomized) were planned, but IA2 will not be performed. Following Amendment 7, the preplanned IA2 is no longer required because the success criteria for the study hypotheses of PFS and OS were met at IA1. Study assumptions, sample size calculations, details and timing of the interim and final analyses for the CPS ≥1 group, all-comers, and CPS ≥10 group are described in detail in Section 9.7.2.

The study will have an external Data Monitoring Committee (eDMC) to monitor safety during the course of the study, to evaluate efficacy at the interim analyses, and to provide recommendations for the study in accordance with the eDMC charter and the sSAP (Section 10.1.4).

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

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

This is a pivotal Phase 3 randomized, double-blind study to evaluate the efficacy and safety of the combination of pembrolizumab plus chemotherapy compared with placebo plus chemotherapy. The study includes dual-primary efficacy endpoints: 1) PFS per RECIST 1.1 as assessed by investigator and 2) OS.

Progression-free survival has been used as an acceptable primary endpoint in randomized Phase 3 trials to support regulatory approval for new treatments in advanced solid tumors in both the first-line setting and in participants who have failed prior treatments. Therefore, PFS by investigator is included as a primary endpoint for the study.

Overall survival is considered the gold standard endpoint to demonstrate superiority of anti-cancer therapy.

RECIST 1.1 will be used by the investigator and BICR when assessing images for efficacy measures and by the investigator for determining eligibility (Section 8.2.3.3). Although traditional RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, this protocol has implemented a modification to RECIST 1.1 to allow a maximum of 10 target lesions in total and 5 per organ.

RECIST 1.1 will be adapted to account for the unique tumor response characteristics seen following treatment with pembrolizumab (Section 8.2.3.3). Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and patients treated with pembrolizumab may manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Thus, standard RECIST 1.1, may not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab. Based on an analysis of participants with melanoma enrolled in KEYNOTE-001 (KN001), 7% of evaluable participants experienced delayed or early tumor pseudo-progression. Of note, participants who had progressive disease (PD) by RECIST 1.1 but not by the immune-related response criteria [Wolchok, J. D., et al 2009] had longer overall survival than participants with PD by both criteria [Hodi, F. S., et al 2014]. Additionally, the data suggest that RECIST 1.1 may underestimate the benefit of pembrolizumab in approximately 15% of participants. These findings support the need to apply a modification to RECIST 1.1 that takes into account the unique patterns of atypical responses in immunotherapy and enables treatment beyond initial radiographic progression, if the participant is clinically stable.

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

4.2.1.2 Safety Endpoints

Safety parameters frequently used for evaluating investigational systemic anticancer treatments are included as safety endpoints including, but not limited to, the incidence of, causality, and outcome of AEs/SAEs; and changes in vital signs and laboratory values. AEs will be assessed as defined by CTCAE, Version 4.0.

4.2.1.3 Patient-reported Outcomes

Symptomatic improvement is considered a clinical benefit and accepted by health authorities. As part of the analyses for this study, participants will provide information regarding their HRQoL via the following questionnaires: EQ-5D-5L, EORTC QLQ-C30, and EORTC QLQ-CX24 (performed in this order). These measures are not pure efficacy or safety endpoints because they are affected by both disease progression and treatment tolerability.

4.2.1.3.1 EQ-5D-5L

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

4.2.1.3.2 EORTC QLQ-C30

The EORTC QLQ-C30 is the most widely used cancer-specific HRQoL instrument, which contains 30 items and measures five functioning dimensions (physical, role, cognitive, emotional, and social), three symptom items (fatigue, nausea/vomiting, pain), six single items (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact), and a global health and quality of life scale. This instrument has been translated and validated into 81 languages and used in more than 3,000 studies worldwide.

4.2.1.3.3 EORTC QLQ-CX24

The EORTC QLQ-CX24 is a disease-specific questionnaire developed and validated to address measurements specific to cervical cancer. It is one of multiple disease-specific modules developed by the EORTC QLG (Quality of Life Group) designed for use in clinical trials, to be administered in addition to the EORTC QLQ-C30 to assess disease-specific treatment measurements.

4.2.1.4 Planned Exploratory Biomarker Research

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

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

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

Genetic (DNA) analyses from tumor

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

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

Proteomics and immunohistochemistry (IHC) using blood or tumor

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

Other 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 enzyme-linked immunoassay (ELISA) measure such proteins in serum. Correlation of expression with response to pembrolizumab therapy may identify new approaches for predictive biomarkers in blood, representing a major advance from today's reliance on assessing tumor biomarkers. This research would serve to develop such assays for future clinical use.

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

4.2.1.5 Future Biomedical Research

The Sponsor will conduct future biomedical research on specimens for which consent was provided during this study. This research may include genetic analyses (DNA), gene expression profiling (ribonucleic acid [RNA]), proteomics, metabolomics (serum, plasma)

and/or the measurement of other analytes, depending on which specimens are consented for future biomedical research.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main study) and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for future biomedical research 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 future biomedical research are presented in Appendix 6.

4.2.2 Rationale for the Use of Comparator/Placebo

The use of placebo in combination with standard chemotherapy will ensure the objectivity of investigator-assessed progression as well as any decisions to interrupt/discontinue therapy. Cross over will not be allowed at time of documented disease progression. Chemotherapy is standard of care as recommended by the NCCN and ESMO guidelines.

4.3 Justification for Dose

The planned dose of pembrolizumab for this study is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the KEYTRUDA development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W),
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications, and
- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically based PK [PBPK] analysis) at 200 mg Q3W.

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and nonsmall cell lung cancer (NSCLC), covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q3W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2, and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200-mg fixed dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-

response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer, and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other participant covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight-based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics, and given that fixed dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

4.3.1 Pembrolizumab

4.3.1.1 Planned Dose for this Study

The planned dose of pembrolizumab for this trial is 200 mg Q3W. The initial dose approved by the Food and Drug Administration (FDA) for treatment of melanoma subjects was 2 mg/kg Q3W. Currently, clinical trials evaluating pembrolizumab are using a fixed dose of 200 mg Q3W. The use of a fixed dose is based on PK findings summarized below.

4.3.1.2 Maximum Dose/Exposure for this Study

The PK profile of pembrolizumab is consistent with that of other humanized mAbs, which typically have a low clearance and a limited volume of distribution. A population PK model, which characterized the influence of body weight and other subject covariates on exposure using available data from 1139 subjects (from KN001 and KN002) has been performed. The majority of these subjects (1077; 94.6%) had advanced melanoma. The distribution of exposures from the 200 mg fixed dose were predicted to considerably overlap those obtained with the 2 mg/kg dose, and importantly, maintained individual subject exposures within the exposure range established in melanoma as associated with maximal clinical response. This comparison also demonstrated that the 200 mg Q3W regimen provided no substantive differences in PK variability (range of the distribution of individual exposures) as seen with weight-based dosing.

In translating to other solid tumor indications, similarly flat exposure-response relationships for efficacy and safety as observed in subjects with melanoma can be expected, as the

antitumor effect of pembrolizumab is driven through immune system activation rather than through a direct interaction with tumor cells, rendering it independent of the specific tumor type. In addition, available PK results in subjects with melanoma, NSCLC, and other solid tumor types support a lack of meaningful difference in PK exposures obtained at tested doses among tumor types.

4.3.1.3 Rationale for Dose Interval and Study Design

A fixed-dose regimen is expected to simplify the dosing regimen (potentially reducing dosing errors), as well as be more convenient for physicians. A fixed-dosing scheme will also reduce complexity in the logistical chain at treatment facilities, as well as reducing waste.

4.3.2 Chemotherapy and Bevacizumab

Further monitoring/assessments should be performed in accordance with the local label and/or local practice for cisplatin, carboplatin, paclitaxel, and bevacizumab.

4.3.2.1 Paclitaxel

Paclitaxel 175 mg/m^2 will be administered as an IV infusion on Day 1 of each 3-week treatment cycle according to the local label and/or per local practice.

All participants should receive premedication to prevent severe hypersensitivity reactions according to the local label and/or per local practice. It is highly recommended that the premedication be administered after pembrolizumab/placebo and before chemotherapy.

4.3.2.2 Cisplatin

Cisplatin 50 mg/m^2 will be administered as an IV infusion on Day 1 of each 3-week treatment cycle immediately after paclitaxel according to the local label and/or per local practice.

Cisplatin may be administered on Day 2 of each 3-week treatment cycle if per local practice.

A participant may switch from cisplatin to carboplatin during the course of the study if required for clinical factors (eg, impairment of renal function).

4.3.2.3 Carboplatin

Carboplatin AUC 5 will be administered as an IV infusion on Day 1 of each 3-week treatment cycle immediately after paclitaxel according to the local label and/or per local practice.

A participant may switch from cisplatin to carboplatin during the course of the study if required for clinical factors (eg, impairment of renal function).

4.3.2.4 Bevacizumab

Bevacizumab 15 mg/kg will be administered as an IV infusion on Day 1 of each 3-week treatment cycle immediately after cisplatin or carboplatin according to the local label and/or per local practice.

The option to use bevacizumab is permitted according to local practice and at the choice of the investigator.

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).

On study completion, participants are discontinued and may be enrolled in a pembrolizumab extension study.

4.4.1 Clinical Criteria for Early Study Termination

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

5 STUDY POPULATION

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

5.1 Inclusion Criteria

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

1. Female participants who are at least 18 years of age on the day of providing informed consent.

2. Have persistent, recurrent, or metastatic squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix which has not been treated with systemic chemotherapy and is not amenable to curative treatment (such as with surgery and/or radiation).

NOTE: Prior chemotherapy utilized as a radiosensitizing agent and completed at least 2 weeks prior to randomization with resolution of all treatment-related toxicities is allowed. AEs due to previous treatments should be resolved to ≤ Grade 1 or baseline. Participants with ≤ Grade 2 neuropathy or ≤ Grade 2 alopecia are eligible.

Female Participants

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

- Is not a WOCBP

  OR

- Is a WOCBP and:

  - Uses a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5 during the intervention period and for at least the time needed to eliminate each study intervention after the last dose of study intervention and agrees not to donate eggs (ova, oocytes) to others or freeze/store for her own use for the purpose of reproduction during this period. The length of time required to continue contraception for each study intervention is as follows:

    - Pembrolizumab/placebo 120 days
    - Chemotherapy 210 days
    - Bevacizumab 210 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 72 hours 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 8.3.4.2.

- 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

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

Additional Categories

5. Have measurable disease per RECIST 1.1 as assessed by the local site investigator/radiology. Lesions situated in a previously irradiated area are considered measurable only if progression has been demonstrated in such lesions.

6. Have provided archival tumor tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated for prospective determination of PD-L1 status prior to randomization.

   Note: Formalin-fixed, paraffin embedded (FFPE) tissue blocks are preferred to slides. Newly obtained biopsies are preferred to archived tissue. If submitting unstained cut slides, newly cut slides should be submitted to the testing laboratory within 14 days from the date slides are cut (details pertaining to tumor tissue submission can be found in the Laboratory Manual).

7. Have an Eastern Cooperative Oncology Group (ECOG) PS of 0 to 1 within 14 days prior to randomization.

8. Have adequate organ function as indicated by the following laboratory values (Table 3) within 14 days prior to randomization:

Table 3 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500/mcL
Platelets	≥100,000/mcL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[a]
Renal	
Creatinine OR calculated or measured creatinine clearance (CrCl)[b] (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for participants with creatinine levels >1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤1.5xULN OR Direct bilirubin ≤ULN for participants with total bilirubin levels >1.5xULN
AST (SGOT) and ALT (SGPT)	≤2.5xULN OR ≤5xULN for participants with liver metastases
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT) or Partial Thromboplastin Time (PTT)[c]	≤1.5 X ULN unless the participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants
a. Criterion 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. c. PTT may be performed if the local laboratory is unable to perform aPTT.	

5.2 Exclusion Criteria

Refer to Appendix 7 for country-specific requirements.

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

Medical Conditions

1. A WOCBP who has a positive urine pregnancy test within 72 hours prior to randomization (see Appendix 5). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

   Note: In the event that 72 hours have elapsed between the pregnancy test and the first dose of study treatment, another pregnancy test (urine or serum) must be performed and must be negative in order for participant to start receiving study medication.

2. Has known active CNS metastases and/or carcinomatous meningitis. Participants with known brain metastases may participate provided that the brain metastases have been previously treated (except with chemotherapy) and are radiographically stable. To

demonstrate radiographic stability of previously treated brain metastases, a minimum of 2 post-treatment brain imaging assessments are required: 1) The first brain imaging must be acquired after treatment of brain metastases has been completed 2) The second brain imaging must be obtained during screening (ie, within 28 days prior to randomization) and >4 weeks after the previous post-treatment brain imaging.

Note: Known brain metastases are considered active, if any of the following criteria are applicable:

a. Brain imaging during screening demonstrates progression of existing metastases and/or appearance of new lesions compared to brain imaging performed at least 4 weeks earlier.

   Radiographic stability of previously treated brain metastases is based on local radiology/investigator review, but dated reports of 2 imaging studies (the most recent performed during screening) documenting stability of brain metastasis(es) over ≥4 weeks must be available at the site for submission to the central imaging vendor, if later needed.

b. Neurological symptoms attributed to brain metastases have not returned to baseline.

c. Steroids were used for management of symptoms related to brain metastases within 28 days prior to randomization.

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

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

4. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in doses exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to randomization.

5. 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.

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

7. Has an active infection requiring systemic therapy.

8. Has a known history of human immunodeficiency virus (HIV) infection.

   Note: No testing for HIV is required unless mandated by local health authority.

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

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

10. Has a known history of active tuberculosis (TB; *Bacillus* tuberculosis).

Prior/Concomitant Therapy

11. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (eg, CTLA-4, OX 40, CD137).

12. Has received prior systemic chemotherapy for treatment of cervical cancer (chemotherapy used as a radiosensitizing agent and completed at least 2 weeks prior to randomization is permitted).

13. Has not recovered adequately from toxicity and/or complications from major surgery prior to randomization.

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

15. Has received a live vaccine within 30 days prior to randomization. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

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

17. Has a contraindication or hypersensitivity to any component of cisplatin, carboplatin, paclitaxel, or bevacizumab. NOTE: Investigators must use the local label for contraindications, prohibited medications, and precautions for use.

Prior/Concurrent Clinical Study Experience

18. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to randomization.

    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.

Other Exclusions

19. Is pregnant or breastfeeding or expecting to conceive within the projected duration of the study, starting with the screening visit through 120 days following last dose of pembrolizumab/placebo and 210 days following last dose of chemotherapy or bevacizumab (if applicable).

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

21. Has a known psychiatric or substance abuse disorder that would interfere with cooperating with the requirements of the study.

22. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the participant's participation for the full duration of the study, or is not in the best interest of the participant to participate, in the opinion of the treating investigator.

5.3 Lifestyle Considerations

Not applicable.

5.3.1 Meals and Dietary Restrictions

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

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

None.

5.3.3 Activity Restrictions

None.

5.3.4 Contraception

Study intervention may have adverse effects on a fetus in utero. Refer to Appendix 5 for approved methods of contraception.

Participants should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study, participants of childbearing potential must adhere to the contraception requirement (Appendix 5) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of pembrolizumab/placebo and 210 days after the last dose of chemotherapy/bevacizumab. If there is any question that a participant of childbearing potential will not reliably comply with the requirements for contraception, that participant should not be entered into the study.

5.3.5 Pregnancy

If a participant inadvertently becomes pregnant while on treatment with study intervention, the participant will be immediately discontinued from study intervention. The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor without delay and within 24 hours if the outcome is a serious adverse experience (eg, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study Investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor.

5.3.6 Use in Nursing Women

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

5.4 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 Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines.

5.5 Participant Replacement Strategy

A participant who discontinues from study intervention OR withdraws 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.

6.1 Study Intervention(s) Administered

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

Table 4 Study Interventions

Arm Name	Arm Type	Intervention Name	Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP/ NIMP	Sourcing
Pembrolizumab	Experimental	Active	Drug	Vial	25 mg/mL (100 mg/4 mL)	200 mg	IV Infusion	Day 1 of each 3-week treatment cycle	Combination agent	IMP	Centrally by Sponsor
Placebo	Placebo Comparator	Placebo	Drug	Solution for infusion	Normal Saline or Dextrose	0 mg	IV Infusion	Day 1 of each 3-week treatment cycle	Placebo	IMP	Provided locally by the trial site, subsidiary, or designee
Paclitaxel	Other	Chemotherapy	Drug	Vial	6 mg/mL (16.7 mL)[a]	175 mg/m^2	IV Infusion	Day 1 of each 3-week treatment cycle	Combination agent	NIMP	Provided centrally by the Sponsor or locally by the trial site, subsidiary, or designee
Carboplatin	Other	Chemotherapy	Drug	Vial	10 mg/mL (60 mL)[a]	AUC 5	IV Infusion	Day 1 of each 3-week treatment cycle	Combination agent	NIMP	Provided centrally by the Sponsor or locally by the trial site, subsidiary, or designee

Arm Name	Arm Type	Intervention Name	Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP/ NIMP	Sourcing
Cisplatin	Other	Chemotherapy	Drug	Vial	1 mg/mL (50 mL)[a]	50 mg/m^2	IV Infusion	Day 1 of each 3-week treatment cycle[b]	Combination agent	NIMP	Provided centrally by the Sponsor or locally by the trial site, subsidiary, or designee
Bevacizumab	Other	Chemotherapy	Drug	Vial	20 mg/mL (4 mL)[a]	15 mg/kg	IV Infusion	Day 1 of each 3-week treatment cycle	Combination agent	NIMP	Provided locally by the trial site, subsidiary, or designee

AUC = area under concentration-time curve; IMP = investigational medicinal product; IV = intravenous; NIMP = noninvestigational medicinal product.

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

b. Cisplatin may be administered on Day 2 of each 3-week treatment cycle if per local practice.

All study interventions will be administered on an outpatient basis.

All products indicated in Table 4 will be provided centrally by the Sponsor or locally by the study site, subsidiary or designee, depending on local country operational or regulatory requirements with the exception of bevacizumab, which will be supplied locally and reimbursed by the Sponsor at sites that do not have other funding for bevacizumab purchase or reimbursement. Participants must continue with the same form of bevacizumab throughout the duration of the study.

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

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

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Details on preparation and administration of pembrolizumab are provided in the Pharmacy Manual. Paclitaxel, cisplatin, carboplatin, and bevacizumab will be prepared and administered as per the approved product label(s).

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

Randomization will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). There are 2 treatment arms. Participants will be assigned randomly in a 1:1 ratio to pembrolizumab plus chemotherapy or placebo plus chemotherapy, respectively. The choice of chemotherapy will be determined prior to randomization and documented in the IVRS/IWRS.

6.3.2 Stratification

Treatment randomization will be stratified based on the following criteria:

1) Metastatic (FIGO [2009] Stage IVB) at initial diagnosis (yes vs. no)

2) Investigator decision to use bevacizumab (yes vs. no), and

3) PD-L1 status (CPS <1, CPS 1 to <10, CPS ≥10).

A total of 12 strata will be utilized in this study.

NOTE: The 2009 version of FIGO included para-aortic lymph node involvement as Stage IVB disease while the 2018 version of FIGO does not include para-aortic lymph node involvement as Stage IVB disease. Para-aortic lymph node involvement will be considered evidence of metastatic disease for purposes of stratification of all participants at the time of randomization.

6.3.3 Blinding

A double-blinding technique with in-house blinding will be used. Pembrolizumab and placebo will be prepared and/or dispensed in a blinded fashion by an unblinded pharmacist or other qualified site personnel. The participant, the investigator, and Sponsor personnel or delegate(s) who are involved in the study treatment administration or clinical evaluation of the participants are unaware of treatment group assignments.

6.4 Study Intervention Compliance

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

Participants are prohibited from receiving the following therapies during the Screening and Treatment Phases of this study:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy

  Note: Palliative radiation therapy to a symptomatic, nontarget lesion may be allowed after consultation with the Sponsor. On-study nonpalliative radiation and radiation to a target lesion per RECIST 1.1 is not permitted.

  Note: Palliative radiation during the screening phase (≤2 weeks of radiotherapy) to non-CNS disease is allowed.

- Live vaccines within 30 days prior to randomization and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

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

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

- 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
    - Intra-articular joint use
    - For inhalation in the management of asthma or chronic obstructive pulmonary disease

Participants who, in the assessment of the Investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study.

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

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. Concomitant medications administered 30 days after the last dose of study intervention should be recorded for SAEs and events of clinical interest (ECIs) as defined in Section 8.4.7.

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, Table 5. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab/placebo.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab/placebo, the investigator does not need to follow the treatment guidance. Refer to Table 5 in Section 6.6.1 for guidelines regarding dose modification and supportive care.

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

6.5.1.1 Hematopoietic Growth Factors

Primary prophylactic use of granulocyte colony stimulating factors (G-CSF) may be used to treat treatment emergent neutropenia as indicated by the current American Society of Clinical Oncology guidelines [National Comprehensive Cancer Network 2010]. The use of hematopoietic growth factors is at the discretion of the treating physician in line with local guidelines.

6.6 Dose Modification (Escalation/Titration/Other)

Pembrolizumab/placebo may be interrupted or discontinued. Cisplatin, carboplatin, paclitaxel, and bevacizumab may be reduced, interrupted or discontinued; dose modifications should be performed according to the local label and/or local practice.

Any component of the combination therapy may be interrupted or discontinued independently. It is allowed for participants to interrupt or discontinue chemotherapy or bevacizumab and continue pembrolizumab/placebo. Similarly, it is allowed for participants to interrupt or discontinue pembrolizumab/placebo and continue chemotherapy or bevacizumab.

The investigator may attribute toxicity to one or more components of the combination. Reduction, interruption or discontinuation of an individual component is appropriate if, in the opinion of the investigator, the toxicity is clearly related to that component of the combination. If, in the opinion of the investigator, the toxicity is related to the combination itself, all components should be reduced, interrupted or discontinued appropriately.

Pembrolizumab/placebo may be interrupted due to toxicity for a maximum of 12 weeks. Prior to restarting pembrolizumab/placebo after an interruption of more than 12 weeks, the investigator must discuss this with the Sponsor.

Cisplatin, carboplatin, paclitaxel, and bevacizumab may be interrupted due to toxicity for a maximum of 6 weeks. Restarting these treatments after an interruption of more than 6 weeks will require a signed Sponsor Consultation Form. To ensure that subjects receive adequate standard of care chemotherapy, supportive care measures (eg, erythrocyte infusion, thrombocyte infusion, G-CSF, and erythropoietin) should be utilized before dose modification unless other reasons to modify standard of care dosing for chemotherapy agents occur. For example, when it is appropriate, supportive care measures should be initiated for resolution of Grade 2 or Grade 3 chemotherapy-related AEs of anemia or leukopenia instead of immediately proceeding with a dose reduction or dose interruption.

Any requests for nonemergency unblinding will be considered on an individual participant basis and only after consultation with the Sponsor.

6.6.1 Dose Modification (Escalation/Titration/Other)

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

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

Dose Modification and Toxicity Management Guidelines for irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations are provided in Table 5.

Table 5 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab Monotherapy, Coformulations or IO Combinations

General instructions:

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

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

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

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

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

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

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

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

Dose Modification and Toxicity Management of Infusion Reactions Related to Pembrolizumab

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

Table 6 Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

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

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

Other Allowed Dose Interruption for Pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to study therapy. Participants should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the participant's study record.

6.6.2 Second Course

Participants who stop treatment with stable disease (SD) or better who then experience radiographic disease progression may be eligible for up to 17 additional administrations (second course) of pembrolizumab, if unblinding reveals that the participant had received pembrolizumab during the first course. Second course is available on an individual basis and only after consultation with the Sponsor. This retreatment is termed the Second Course Phase of this study and is only available if the study remains open and the participant meets the following conditions.

Participant must meet the criteria under either 1 or 2 below:

1. Stopped initial treatment with study treatment after attaining an investigator-determined confirmed CR based on RECIST 1.1, and

    - Was treated with at least 8 infusions of pembrolizumab before discontinuing treatment, and

    - Received at least 2 infusions of pembrolizumab beyond the date when the initial CR was declared

    OR

2. Had SD, PR, or CR and stopped pembrolizumab after receiving 35 infusions (approximately 2 years) of pembrolizumab for reasons other than disease progression or intolerability

After meeting criteria under 1 or 2 above, participant must also meet all of the following:

- Experienced investigator-determined radiographic disease progression by RECIST 1.1 after stopping initial treatment, and

- Upon unblinding was found to have received pembrolizumab, and

- No new anti-cancer treatment was administered after the last dose of study treatment, and

- The participant meets all of the safety parameters listed in the inclusion criteria and none of the safety parameters listed in the exclusion criteria, and

- The study is ongoing.

An objective response or disease progression that occurs during the Second Course Phase for a participant will not be counted as an event in the primary efficacy analyses in this study.

6.7 Intervention After the End of the Study

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

6.8 Clinical Supplies Disclosure

The emergency unblinding call center will use the randomization schedule for the study to unblind participants and to unmask study intervention identity. The emergency unblinding call center should only be used in cases of emergency (see Section 8.1.10). In the event that the emergency unblinding call center is not available for a given site in this study, the central electronic intervention randomization system (IRT) should be used to unblind participants

and to unmask study intervention identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

See Section 8.1.10 for a description of the method of unblinding a participant during the study, should such action be warranted.

6.9 Standard Policies

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

"You have participated in a study conducted by the Sponsor. This letter is to advise you that you were among those who received a look-alike drug. You did not receive the active drug as manufactured by MSD."

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

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

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention prior to completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 1.3 and Section 8.12.3.

Participants may discontinue study intervention at any time for any reason or be dropped from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study intervention discontinuation are provided in Section 8.1.9.

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.

- The participant's treatment assignment has been unblinded. Participants unblinded due to AEs suspected to be related to blinded treatment should be discontinued from blinded treatment but may continue with chemotherapy. Note: this applies only to first-course treatment.

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

- The participant has a confirmed positive serum pregnancy test.

- Confirmed radiographic disease progression (iCPD) outlined in Section 8.2.3.4 (exception if the Sponsor approves treatment continuation).

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

- The study is terminated by the Sponsor.

- The study is terminated by the local health authority, IRB, or IEC.

- Any prolonged interruption of study intervention beyond the permitted periods, for irAE management or other allowed dose interruptions, as noted in Section 6.6 require Sponsor consultation prior to restarting treatment. If treatment will be discontinued, 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 meets a pembrolizumab/placebo discontinuation criteria specified in the dose modification in Table 5 and Table 6.

- The participant has received a maximum number of cycles for each treatment component individually:

    - The participant has received 35 administrations of pembrolizumab/placebo (approximately 2 years) and

    - The participant has received 6 cycles of paclitaxel-platinum (cisplatin or carboplatin)

    NOTE: Participants with ongoing clinical benefit and who are tolerating combination chemotherapy may be allowed to continue chemotherapy beyond 6 cycles after Sponsor consultation.

    NOTE: Bevacizumab may continue until disease progression or unacceptable AEs, per the local label or local practice.

    NOTE: The number of treatments is calculated starting with the first dose. Participants who stop the combination or pembrolizumab after receiving 35 doses may be eligible for retreatment if they progress after stopping study intervention provided they meet the requirements detailed in Section 6.6.2. Participants may be retreated in the Second Course Phase (Retreatment) for up to an additional 17 cycles (approximately 1 year).

7.2 Participant Withdrawal From the Study

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

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

Specific details regarding procedures to be performed at the time of withdrawal from the study,as well as specific details regarding withdrawal from future biomedical research, are outlined in Section 8.1.9. 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 or trained staff. Delegation of study site personnel responsibilities will be documented in the Investigator Study File Binder (or equivalent).

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

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

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

8.1 Administrative and General Procedures

8.1.1 Informed Consent

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

8.1.1.1 General Informed Consent

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

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

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

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

8.1.2 Inclusion/Exclusion Criteria

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

8.1.3 Participant Identification Card

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

The participant identification card also contains contact information for the emergency unblinding call center so that a healthcare 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 significant.

Comprehensive details regarding the participant's cervical cancer history will be recorded separately and not listed as medical history. These details include but are not limited to FIGO stage at diagnosis, histopathology, location(s) of tumor burden, and all prior treatment (including prior radiation, prior radiosensitizing chemotherapy, and prior surgery).

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

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

8.1.5.2 Concomitant Medications

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

8.1.6 Assignment of Screening Number

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

8.1.6.1 Treatment Eligibility Assessment (TEA and TEAA) Forms

A TEA form is included in this study to document the investigators' choice of treatment among the options within the control arm and the rationale. These data may be required to support reimbursement efforts for pembrolizumab.

The investigator must document the rationale for participant eligibility for treatment with: 1) bevacizumab [TEAA form] and 2) combination of cisplatin + paclitaxel + bevacizumab [TEA form].

8.1.7 Assignment of Treatment/Randomization Number

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

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

8.1.8 Study Intervention Administration

Study intervention(s) will be administered by the investigator and/or study staff according to the specifications within the pharmacy manual. Study treatment should begin within 3 days of randomization.

Further monitoring/assessments should be performed in accordance with the local label and/or local practice for cisplatin, carboplatin, paclitaxel, and bevacizumab.

8.1.8.1 Timing of Dose Administration

The order of treatment administration is recommended to be as follows:
1) pembrolizumab/placebo, 2) paclitaxel, 3) cisplatin or carboplatin and then
4) bevacizumab. It is highly recommended that the premedication be administered after pembrolizumab/placebo and before chemotherapy.

Pembrolizumab/placebo will be administered on Day 1 of each 21-day cycle (± 3 days) starting on C1D1. Pembrolizumab/placebo should be administered after all predose study procedures and assessments have been completed. Pembrolizumab/placebo should be administered as a 30-minute IV infusion. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of –5 min and +10 min is permitted (ie, infusion time is 30 minutes: -5 min/+10 min). The Pharmacy Manual contains specific instructions for the preparation and administration of pembrolizumab/placebo.

Paclitaxel 175 mg/m^2 will be administered as an IV infusion on Day 1 of each 3-week treatment cycle after the administration of pembrolizumab/placebo according to the local label and/or per local practice. All participants should receive premedication to prevent severe hypersensitivity reactions according to the local label and/or per local practice.

Cisplatin 50 mg/m^2 will be administered as an IV infusion on Day 1 of each 3-week treatment cycle immediately after paclitaxel according to the local label and/or per local practice. Cisplatin may be administered on Day 2 of each 3-week treatment cycle per local practice.

Alternately carboplatin AUC 5 will be administered as an IV infusion on Day 1 of each 3-week treatment cycle immediately after paclitaxel according to the local label and/or per local practice.

Bevacizumab 15 mg/kg will be administered as an IV infusion, preferably following paclitaxel and cisplatin or carboplatin. It is best to have all medications given within a single study visit on the same day, if possible. Bevacizumab use should follow the local label and/or local practice.

8.1.9 Discontinuation and Withdrawal

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

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

8.1.9.1 Withdrawal From Future Biomedical Research

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

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

8.1.10 Participant Blinding/Unblinding

This is a double-blind trial; therefore, the Sponsor, investigator and participant will not know the treatment administered.

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

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

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

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

Nonemergency unblinding will only be permitted after consultation and approval from the Sponsor.

8.1.11 Calibration of Equipment

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

8.2 Efficacy Assessments

8.2.1 Tumor Imaging and Assessment of Disease

The process for image collection and transmission to the central imaging vendor is in the SIM.

Submit all of the following to the central imaging vendor:

- All screening and on-study scheduled imaging per the SoA
- Supplemental imaging performed to support a positive or negative bone scan, such as plain X-rays that may be acquired for correlation
- Images obtained at an unscheduled time point, even via other modalities, to determine disease progression
- Imaging performed for other reasons but captures radiologic disease progression based on investigator assessment

Tumor imaging of the chest is to be acquired by CT. MRI is preferred for the abdomen and pelvis, unless MRI is contraindicated or local practice standards dictate otherwise. The SIM provides alternative options for tumor imaging if MRI or the use of contrast is medically contraindicated. MRI is the strongly preferred modality for imaging the brain.

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

8.2.2 Initial Tumor Imaging During Screening

Initial tumor imaging at screening must be performed within 28 days prior to the date of randomization. Scans performed as part of routine clinical management are acceptable for use as screening tumor imaging if they are of diagnostic quality, were performed within 28 days prior to the date of randomization, and can be assessed by the central imaging vendor.

Participant eligibility, confirmation of measurable disease, will be determined using local (investigator/site radiologist) assessment based on RECIST 1.1.

Required imaging at screening includes:

- CT of the chest
- MRI of the abdomen and pelvis
- A bone scan for participants with a history of bone metastases or who are clinically symptomatic
- MRI of the brain for participants with brain metastases at baseline (to demonstrate stability prior to enrollment) or who are clinically symptomatic

8.2.3 Tumor Imaging During the Study

The first on-study imaging assessment should be performed at 9 weeks (63 days ±7 days) from the date of randomization. Subsequent tumor imaging should be performed Q9W (63 days ±7 days) through Week 54 or more frequently if clinically indicated. After Week 54, participants who remain on treatment will have imaging performed Q12W (84 days ±7 days). Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts.

Participants who discontinue study treatment for reasons other than radiographic disease progression will have post-treatment efficacy follow-up imaging for disease status until disease progression is documented radiographically per RECIST 1.1 by the investigator, and verified by BICR per RECIST 1.1, and when clinically appropriate, confirmed by the site per iRECIST, or upon initiating a new anti-cancer treatment, withdrawing consent, pregnancy, or death, whichever occurs first. All supplemental imaging must be submitted to the central imaging vendor.

Objective response should be confirmed by a repeat imaging assessment. Tumor imaging to confirm PR or CR should be performed at least 4 weeks after the first indication of a response is observed. Participants will then return to regular scheduled imaging, starting with the next scheduled imaging time point. Participants who receive additional imaging for confirmation do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point.

Per iRECIST (Section 8.2.3.4), disease progression in participants treated with pembrolizumab/placebo should be confirmed by the site 4 to 8 weeks after site-assessed first radiologic evidence of PD in clinically stable participants. Participants who have unconfirmed disease progression may continue on treatment at the discretion of the site investigator until progression is confirmed by the site, provided they have met the conditions detailed in Section 8.2.3.4. Participants who obtain a confirmation scan do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point if clinically stable. Participants who

have confirmed disease progression, as assessed by the site, will discontinue study treatment. Exceptions are detailed in Section 8.2.3.4.

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

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

For participants who discontinue study intervention without documented disease progression, every effort should be made to continue monitoring their disease status by tumor imaging using the same imaging schedule used while on treatment (every 9 weeks through Week 54 or 12 weeks after Week 54) until disease progression per RECIST 1.1 is verified by BICR, the start of a new anti-cancer treatment, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first.

8.2.3.2 Second Course (Retreatment) Tumor Imaging

Tumor imaging must be performed within 28 days prior to restarting treatment with pembrolizumab. Investigator-determined progression will be used to determine eligibility. A second course imaging should be submitted to the central imaging vendor for quality control, storage, and possible retrospective review.

The first on-study imaging assessment should be performed at 12 weeks (84 days ±7 days) after the restart of treatment. Subsequent tumor imaging should be performed every 12 weeks (84 days ±7 days) or more frequently if clinically indicated.

Per iRECIST (Section 8.2.3.4), if tumor imaging shows initial PD, tumor assessment should be repeated 4 to 8 weeks later in order to confirm PD with the option of continuing treatment while awaiting radiologic confirmation of progression. Participants who obtain confirmatory imaging do not need to undergo scheduled tumor imaging if it is less than 4 weeks later and may wait until the next scheduled imaging time point, if clinically stable.

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

For participants who discontinue Second Course study intervention, tumor imaging should be performed at the time of treatment discontinuation (±4 week window). If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory. For participants who discontinue study intervention due to documented disease progression, this is the final required tumor imaging.

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

8.2.3.3 RECIST 1.1 Assessment of Disease

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

Initial tumor imaging showing site-assessed PD should be submitted immediately for BICR verification of PD. The site will be notified if the BICR verifies PD using RECIST 1.1.

Figure 2 illustrates the imaging flow involving verification of PD for clinically stable participants.

8.2.3.4 iRECIST Assessment of Disease

iRECIST is based on RECIST 1.1, but adapted to account for the unique tumor response seen with immunotherapeutic drugs. iRECIST will be used by the investigator to assess tumor response and progression, and make treatment decisions. When clinically stable, participants should not be discontinued until progression is confirmed by the investigator, working with local radiology, according to the rules outlined in Appendix 8. This allowance to continue treatment despite initial radiologic PD takes into account the observation that some participants can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. This data will be captured in the clinical database.

Clinical stability is defined as the following:

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

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

If the investigator decides to continue treatment, the participant may continue to receive study treatment and the tumor assessment should be repeated 4 to 8 weeks later to confirm

PD by iRECIST, per investigator assessment. Images should continue to be sent in to the central imaging vendor for potential retrospective BICR.

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

If a participant has confirmed radiographic progression (iCPD) as defined in Appendix 8, study treatment should be discontinued; however, if the participant is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered following consultation with the Sponsor. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 1.3 and submitted to the central imaging vendor.

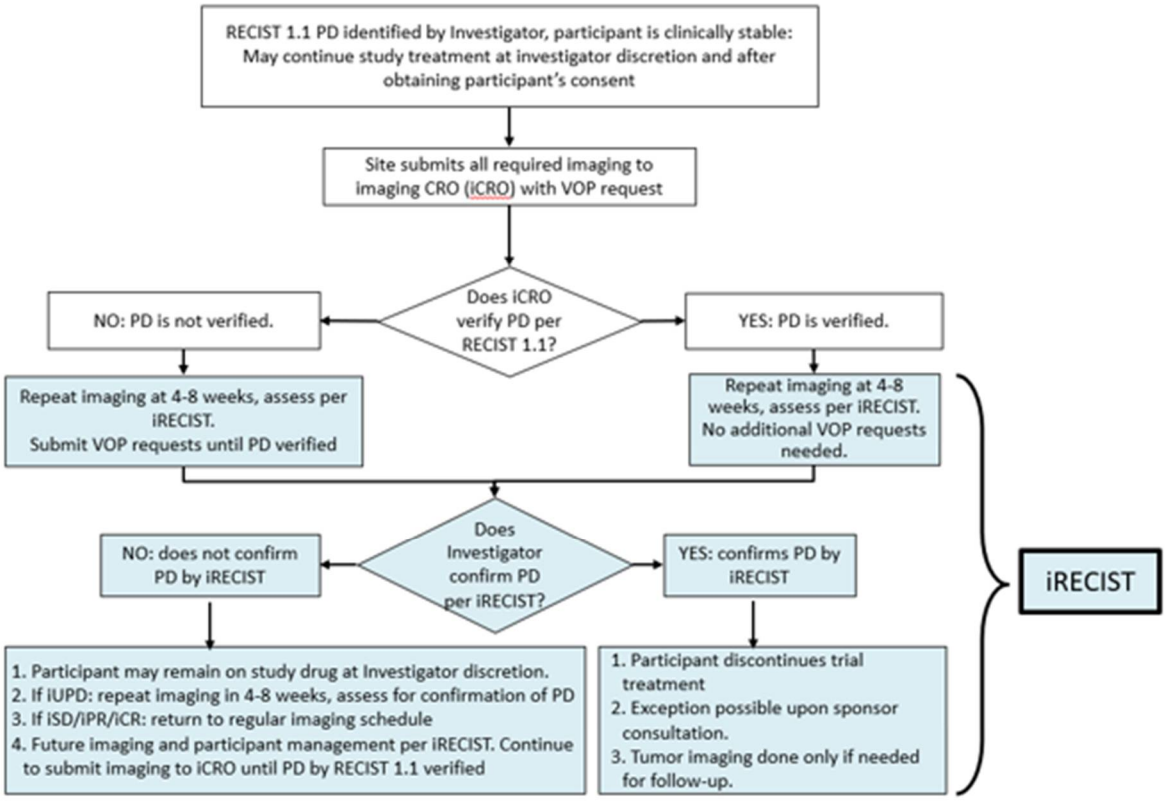
A description of the adaptations and iRECIST process is provided in Appendix 8, with additional details in the iRECIST publication [Seymour, L., et al 2017]. A summary of imaging and treatment requirements after first radiologic evidence of progression is provided in Table 7 and illustrated as a flowchart in Figure 2.

Table 7 Imaging and Treatment After First Radiologic Evidence of Progressive Disease

	Clinically Stable		**Clinically Unstable**	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD by RECIST 1.1 per investigator assessment	Submit the imaging to BICR for verification of progression and repeat imaging at 4 to 8 weeks to confirm PD per iRECIST.	Should continue study treatment at the investigator's discretion while awaiting confirmatory tumor imaging by site by iRECIST and BICR verification of progression.	Submit the imaging to BICR for verification of progression and repeat imaging at 4 to 8 weeks to confirm PD per investigator's discretion.	Discontinue treatment
Repeat tumor imaging confirms PD (iCPD) by iRECIST per investigator assessment	No additional imaging required (continue imaging if Sponsor grants exception to continue treatment)	Discontinue treatment (exception is possible upon consultation with Sponsor).	No additional imaging required.	Not applicable

	Clinically Stable		**Clinically Unstable**	
	Imaging	**Treatment**	**Imaging**	**Treatment**
Repeat tumor imaging shows iUPD by iRECIST per investigator assessment	Repeat imaging at 4 to 8 weeks to confirm PD. May occur at next regularly scheduled imaging visit. Submit the imaging to BICR for verification of progression.	Continue study treatment at the investigator's discretion.	Repeat imaging at 4 to 8 weeks to confirm PD per investigator's discretion only. Submit the imaging to BICR for verification of progression.	Discontinue treatment
Repeat tumor imaging shows iSD, iPR, or iCR by iRECIST per investigator assessment.	Continue regularly scheduled imaging assessments.	Continue study treatment at the investigator's discretion.	Continue regularly scheduled imaging assessments.	May restart study treatment if condition has improved and/or clinically stable per investigator's discretion. Next tumor imaging should occur according to the regular imaging schedule.

BICR=blinded independent central review; iCPD=iRECIST confirmed progressive disease; iCR=iRECIST complete response; iPR=iRECIST partial response; iRECIST=modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; iSD=iRECIST stable disease; iUPD=iRECIST unconfirmed progressive disease; PD=progressive disease; RECIST 1.1=Response Evaluation Criteria in Solid Tumors 1.1; VOP=verification of progression.
Note: If progression has been centrally verified, further management is by the site, based on iRECIST. Any further imaging should still be submitted to the central imaging vendor, but no rapid review will occur. If RECIST 1.1 disease progression has not been centrally verified, ideally the site should continue treatment. Whether or not treatment continues, imaging should be collected and submitted to the central imaging vendor with VOP request until RECIST 1.1 progression is verified by BICR.)



Abbreviations: CRO=contract research organization; iCR=iRECIST complete response; iCRO=imaging contract research organization; iPR=iRECIST partial response; iRECIST=modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; iSD=iRECIST stable disease; iUPD=iRECIST unconfirmed progressive disease; PD=progressive disease; RECIST=Response Evaluation Criteria in Solid Tumors; VOP=verification of progression.

Figure 2 Imaging and Treatment for Clinically Stable Participants Treated With Pembrolizumab After First Radiologic Evidence of PD Assessed by the Investigator

8.2.4 Patient-reported Outcomes

The EQ-5D-5L, EORTC QLQ-C30, and EORTC QLQ-CX24 questionnaires will be administered by trained site personnel and completed electronically by participants in the following order: EQ-5D-5L first, then EORTC QLQ-C30, and then EORTC QLQ-CX24. The questionnaires should be administered prior to dosing on Day 1 of Cycles 1 to 14, every other cycle thereafter up to Cycle 44, EOT, and Safety Follow-up.

The translated version of the EORTC QLQ-CX24 may not be available at the time a site opens for enrollment. If the local language translation is not available at the time for a participant's Cycle 1 Day 1 visit, then the EORTC QLQ-CX24 will not be required for this participant at any point during the study. All other PRO measures must be completed per the SoA. The translated EORTC QLQ-CX24 may become available after a site begins enrolling participants. Any participant who is enrolled after the local language translation becomes available must complete all PRO measures, including the EORTC QLQ- CX24 according to

the SoA from Cycle 1 Day 1 onwards. For some sites, the EORTC QLQ-CX24 translation might not be available for the entire duration of the study.

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

8.3 Safety Assessments

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

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

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

8.3.1 Physical Examinations

A complete or directed physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) as per institutional standards. Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.1.1 Full Physical Examination

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

8.3.1.2 Directed Physical Examination

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

8.3.2 Vital Signs

Blood pressure, temperature, pulse, respiratory rate, and weight will be assessed according to the SoA (Section 1.3). Height will be measured at screening only. It is highly recommended that abnormal blood pressure measurements be confirmed.

8.3.3 Electrocardiograms

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

8.3.4 Clinical Safety Laboratory Assessments

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

The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the case report form (CRF). The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the Laboratory Manual and the SoA (Section 1.3).

If laboratory values from nonprotocol specified laboratory assessments performed at the institution’s local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).

For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

8.3.4.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

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

8.3.4.2 Pregnancy Test

All women who are being considered for participation in the study, and who are not surgically sterilized or postmenopausal, must be tested for pregnancy within 72 hours prior to randomization. In the event that more than 72 hours have elapsed between this pregnancy test and the first dose of study treatment, another pregnancy test must be performed and must be negative prior to receiving first dose of study treatment. If a urine test is positive or not evaluable, a serum test will be required. Participants must be excluded/discontinued from the study in the event of a positive test result.

Pregnancy testing (urine or serum as required by local regulations) should be conducted at monthly intervals during intervention. Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study. Refer to Appendix 7 for country-specific requirements.

8.3.5 Performance Assessments

8.3.5.1 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Appendix 9) at screening (within 14 days prior to randomization), prior to the administration of each dose of study intervention and during the efficacy follow-up period as specified in the SoA, Section 1.3.

8.4 Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Reportable Safety Events

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

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

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AE, SAEs, and other reportable safety events for outcome according to Section 8.4.3.

The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity and causality.

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 randomization, must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event causes the participant to be excluded from the study, or is the result of a protocol-specified intervention, including, but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

All AEs from the time of randomization through 30 days following cessation of study intervention must be reported by the investigator.

All AEs meeting serious criteria, from the time of randomization through 90 days following cessation of study intervention or 30 days following cessation of study intervention if the participant initiates new anti-cancer therapy, whichever is earlier, must be reported by the investigator.

All pregnancies and exposure during breastfeeding, from the time of randomization through 120 days following last dose of pembrolizumab/placebo and 210 days following last dose of chemotherapy or bevacizumab (if applicable), or 30 days following cessation of study intervention if the participant initiates new anti-cancer therapy must be reported by the investigator.

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

Investigators are not obligated to actively seek AE or SAE or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study 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 8.

Table 8 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Time Period: Consent to Randomization**	**Reporting Time Period: Randomization through Protocol-Specified Follow-up Period**	**Reporting Time Period: After the Protocol-Specified Follow-up Period**	**Timeframe to Report Event and Follow-up Information to SPONSOR**
Nonserious Adverse Event (NSAE)	Report if: - Due to protocol-specified intervention - Causes exclusion - Participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
Serious Adverse Event (SAE) including Cancer and Overdose	Report if: - Due to protocol-specified intervention - Causes exclusion - Participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - Drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/ Lactation Exposure	Report if: - Due to intervention - Causes exclusion	Report all	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event
Event of Clinical Interest (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
Event of Clinical Interest (Do not require regulatory reporting)	Report if: - Due to intervention - Causes exclusion	Report - Non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event

ECI = event of clinical interest; DILI = drug-induced liver injury; 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 AE and/or SAE and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AE, SAE, and other reportable safety events including pregnancy and exposure during breastfeeding, events of clinical interest (ECI), 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. All AEs will be reported to regulatory authorities, IRB/IECs, and investigators in accordance with all applicable global laws and regulations (ie, per ICH Topic E6 (R2) Guidelines for Good Clinical Practice [GCP]).

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

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

8.4.5 Pregnancy and Exposure During Breastfeeding

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

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

Progression of the cancer under study is not considered a reportable event.

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

8.4.7 Events of Clinical Interest (ECIs)

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

Events of clinical interest for this study include:

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

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

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

8.5 Treatment of Overdose

For this study, an overdose of pembrolizumab will be defined as any dose of 1000 mg or greater (≥5 times the indicated dose).

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

8.6 Pharmacokinetics

There is no pharmacokinetic evaluation in this trial.

8.7 Pharmacodynamics

There is no pharmacodynamic evaluation in this trial.

8.8 Future Biomedical Research Sample Collection

If the participant provides documented informed consent for future biomedical research, the leftover specimens listed in Section 8.10 Biomarkers will be retained as part of future biomedical research.

8.9 Planned Genetic Analysis Sample Collection

Samples should be collected for planned analysis of associations between genetic variants in germline/tumor DNA and drug response. If a documented law or regulation prohibits (or local IRB/Independent Ethics Committee [IEC] does not approve) sample collection for these purposes, then such samples should not be collected at the corresponding sites. Leftover DNA extracted from planned genetic analysis samples will be stored for future biomedical research only if the participant provides documented informed consent for Future Biomedical Research.

8.10 Biomarkers

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

- Blood for genetic analysis
- Blood for RNA analysis
- Blood for plasma biomarker analysis
- Blood for serum biomarker analysis
- Blood for ctDNA
- New or archival tumor tissue

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

8.10.1 Tumor Tissue Collection for Biomarker Analyses

Characterization of PD-L1 expression will be evaluated by a central laboratory for all participants as part of screening. Archival tumor tissue sample or newly obtained core or excisional biopsy of a tumor lesion (not previously irradiated) must be provided to the central laboratory for testing, and be deemed adequate for evaluation, prior to randomization. Newly obtained biopsies are preferred to archived tissue. FFPE tissue blocks are preferred to slides.

If submitting unstained slides, the slides should be freshly cut and submitted to the testing laboratory within 14 days from the site slide section date. If the sample is determined to be nonevaluable prior to testing by the central laboratory, a new sample should be submitted if available. Individual subject PD-L1 status will not be disclosed to investigative sites or study participants.

Detailed instructions for tissue collection, processing, and shipment are provided in the Laboratory Manual.

8.11 Health Economics Medical Resource Utilization

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

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

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

8.12 Visit Requirements

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

8.12.1 Screening

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

- Eligibility laboratory tests are to be performed within 14 days prior to randomization.
- Evaluation of ECOG is to be performed within 14 days prior to randomization.
- For women of reproductive potential, a urine or serum pregnancy test will be performed within 72 hours prior to randomization. If pregnancy test is done more than 72 hours prior to first dose of study intervention, another negative pregnancy test is required prior to starting study medication. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site 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.

8.12.2 Treatment Period Visit

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

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

Participants who discontinue from study treatment should continue to be monitored according to the requirements in the SoA (Section 1.3).

8.12.4 Post-treatment Visit

8.12.4.1 Safety Follow-up Visit

The mandatory Safety Follow-up Visit should be conducted 30 days (+7 days) after the last dose of study intervention or before the initiation of a new anti-cancer treatment, whichever comes first. Reasonable efforts should be made to have the participant return for the Safety Follow-up Visit and report any AEs that may occur prior to initiating new anti-cancer therapy. If the participant has an End of Treatment visit ≥30 days after the last dose of study treatment, the Safety Follow-up Visit is not required; all procedures for both visits will be performed at the End of Treatment Visit.

Participants who are eligible for second course retreatment with pembrolizumab may have up to 2 safety follow-up visits, 1 after the Initial Treatment Period and 1 after the Second Course Retreatment Phase.

8.12.4.2 Efficacy Follow-up Visits

Participants who complete the protocol-required cycles of study intervention or who discontinue study intervention for a reason other than disease progression will begin the Efficacy Follow-up Phase and should be assessed according to the on-treatment imaging schedule [Q9W (63 days ±7 days) from randomization through Week 54 and Q12W (84 days ±7 days) thereafter] to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anti-cancer therapy, BICR-verified disease progression, withdrawal of consent, pregnancy, death, and end of the study.

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

Participants who are eligible to receive retreatment with pembrolizumab according to the criteria in Section 6.6.2 will move from the Efficacy Follow-up Phase to the Second Course Phase when they experience disease progression. Details are provided in the SoA (Section 1.3.2) for retreatment with pembrolizumab.

8.12.4.3 Survival Follow-up Contacts

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

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

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

- For participants who entered but are no longer being assessed during the Efficacy Follow-up Phase, the first survival follow-up contact will be scheduled 12 weeks after the last efficacy assessment follow-up visit has been performed.

8.12.5 Survival Status

To ensure current and complete survival data is available at the time of database locks, updated survival status may be requested during the course of the study by the Sponsor. For example, updated survival status may be requested prior to but not limited to an external Data Monitoring Committee (eDMC) review, interim and/or final analysis. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding participants that have a previously recorded death event in the collection tool).

9 STATISTICAL ANALYSIS PLAN

9.1 Statistical Analysis Plan Summary

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

Key elements of the statistical analysis plan (SAP) are summarized below. The comprehensive plan is provided in Sections 9.2 through 9.12.

Study Design Overview	A Phase 3 Randomized, Double-Blind, Placebo-Controlled Trial of Pembrolizumab (MK-3475) Plus Chemotherapy Versus Chemotherapy Plus Placebo for the First-Line Treatment of Persistent, Recurrent, or Metastatic Cervical Cancer (KEYNOTE-826)
Treatment Assignment	Approximately 600 participants will be randomized in a 1:1 ratio between 2 treatment arms: • Arm 1: Pembrolizumab plus paclitaxel and cisplatin or carboplatin • Arm 2: Placebo plus paclitaxel and cisplatin or carboplatin Stratification factors are as follows: • Metastatic (FIGO [2009] Stage IVB) at initial diagnosis (yes vs. no) • Bevacizumab use (yes vs. no) • PD-L1 status (CPS <1 vs. CPS 1 to <10 vs. CPS ≥ 10)
Analysis Populations	• Efficacy: Intention-to-Treat (ITT) • Safety: All Participants as Treated (APaT)
Primary Endpoints	• Progression-free survival (PFS) based on RECIST 1.1 as assessed by investigator • Overall survival (OS)
Secondary Endpoints	• Objective response rate (ORR) by investigator using RECIST 1.1 • Duration of response (DOR) by investigator using RECIST1.1 • PFS rate at 12 months by investigator using RECIST 1.1 • PFS by BICR using RECIST 1.1 • Patient-reported quality of life by EORTC QLQ-C30 global score • Safety and tolerability of the two treatment arms
Statistical Methods for Key Efficacy Analyses	The primary hypotheses will be evaluated by comparing PFS and OS using a stratified Log-rank test. The hazard ratio will be estimated using a stratified Cox regression model. Event rates over time will be estimated within each treatment group using the Kaplan-Meier method.
Statistical Methods for Key Safety Analyses	The analysis of safety results will follow a tiered approach. The tiers differ with respect to the analyses that will be performed. There are no events of interest that warrant elevation to Tier 1 events in this study. Tier 2 parameters will be assessed via point estimates with 95% confidence intervals (CIs) provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters. The 95% CIs for the between-treatment differences in percentages will be provided using the Miettinen and Nurminen method.

Interim Analyses	Two interim analyses (IAs) and 1 final analysis (FA) are planned in this study. Comparisons between two treatment arms will be conducted at the IAs and final analysis. Results of the IAs will be reviewed by the eDMC. Details are provided in Section 9.7 – Interim Analyses. • IA1: PFS and OS analysis approximately 22 months after the first participant is randomized. The analysis will be triggered when approximately 370 PFS events for CPS ≥1 group have been observed. • IA2: PFS and OS analysis approximately 30 months after the first participant is randomized. The analysis will be triggered when at least 435 PFS events for CPS ≥1 group have been observed. • FA: Final OS analysis approximately 40 months after the first participant is randomized. The analysis will be triggered when at least 378 OS events for CPS ≥1 group have been observed.
Multiplicity	The overall Type I error rate over the multiple endpoints will be controlled at 2.5% (one-sided). A total of 0.5% Type I error rate is initially allocated to test PFS superiority between two arms for CPS ≥10 group, CPS ≥1 group and all-comers; a total of 2% Type I error rate is initially allocated to test OS superiority between two arms for CPS≥10 group, CPS ≥1 group and all-comers. The graphical approach of Maurer and Bretz [Maurer, W. 2013] will be applied to reallocate alpha among the hypotheses of PFS and OS. Lan-DeMets O'Brien-Fleming group sequential methods will be used to allocate alpha among the interim and final analyses for the PFS and OS endpoints. The study will be considered positive if it is positive for either PFS or OS hypothesis test for any of the three groups (CPS ≥10 group, CPS ≥1 group, and all-comers).
Sample Size and Power	The planned sample size is approximately 600 participants (510 participants for CPS ≥1 group; 300 participants for CPS ≥10 group) with 300 participants in each arm. The study is event-driven and completes after accumulation of sufficient events to determine efficacy for PFS and for OS. For all-comers (N=600), with approximately 432 and 508 events between 2 arms at the planned PFS analyses, the study will have 91% power to detect a hazard ratio of 0.70 at the 0.004 significance level. With 289, 378, and 445 events between 2 arms at the planned OS interim and final analyses, the study will have 90% power to detect a hazard ratio of 0.72 at the 0.016 significance level. Details are provided in section 9.9 – Sample Size and Power Calculations.

Following Amendment 7, the preplanned second interim analysis (IA2) is no longer required for formal hypothesis testing and will not be performed. This is because the success criteria for the study hypotheses of PFS and OS for all 3 groups (CPS ≥1 group, all-comers, and CPS ≥10 group) were met at the first interim analysis (IA1). The prespecified final analysis will be performed without multiplicity adjustment when approximately 378 OS events for CPS ≥1 group have been observed. Updated analyses may be performed during the study at any time point to provide additional estimates with longer follow-up.

9.2 Responsibility for Analyses/In-house Blinding

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

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

The Clinical Biostatistics department will generate the randomized allocation schedule(s) for study treatment assignment.

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

9.3 Hypotheses/Estimation

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

9.4 Analysis Endpoints

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

Primary

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

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

Secondary

ORR: The proportion of participants who have a best overall response of either confirmed CR or PR per RECIST 1.1 as assessed by investigator.

DOR: For participants who demonstrate CR or PR, the time from the first documented evidence of CR or PR until the first documented disease progression assessed per RECIST 1.1 by investigator or death due to any cause, whichever occurs first.

PFS-12: PFS rate as assessed at 12 months: The proportion of participants that are PFS event-free at 12 months per RECIST 1.1 as assessed by investigator.

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

PRO: PRO endpoints will be assessed by EORTC QLQ-C30 global score. Details will be provided in the sSAP.

Exploratory

Objective response rate (ORR), duration of response (DOR), and 12-month PFS rate are assessed by BICR per RECIST 1.1. PFS per iRECIST is defined as specified for the respective endpoints using RECIST 1.1 above, with the exception that: 1) a confirmation assessment of PD (at least 4 weeks after the initial PD assessment) is required for participants who remain on study treatment following a documented PD per RECIST 1.1, and 2) responses of iSD, iPR, and iCR are permitted as a best overall response after iUPD. Participants who discontinue study treatment following a documented PD assessment per RECIST 1.1 will be counted as having disease progression on the date of the documented PD assessment. Responses will be based on investigator assessment. PRO endpoints will be assessed by EQ-5D-5L, EORTC QLQ-C30 (scores other than global score), and EORTC QLQ-CX24.

9.5 Analysis Populations

9.5.1 Efficacy Analysis Populations

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

9.5.2 Safety Analysis Populations

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

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

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

9.5.3 PRO Analysis Population

The PRO analyses are based on the PRO full analysis set (FAS) population, defined as participants who have at least 1 PRO assessment available and have received at least 1 dose of study medication.

9.6 Statistical Methods

9.6.1 Statistical Methods for Efficacy Analyses

Statistical testing and inference for safety analyses are described in Section 9.6.2. Efficacy results that will be deemed to be statistically significant after consideration of the Type I error control strategy are described in Section 9.8. Nominal p-values will be computed for other efficacy analyses but should be interpreted with caution due to potential issues of multiplicity.

9.6.1.1 Progression-free Survival

The non-parametric Kaplan-Meier method will be used to estimate the PFS curve in each treatment group. The treatment difference in PFS will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, the HR) between the treatment arms. The HR and its 95% CI from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate will be reported. The stratification factors used for randomization (Section 6.3.2) will be applied to both the stratified log-rank test and the stratified Cox model. Median PFS and its 95% CIs will be updated post the second interim analysis; however, no formal statistical test will be performed.

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

In order to evaluate the robustness of the PFS endpoint, one primary and two sensitivity analyses with a different set of censoring rules will be performed. For the primary analysis, if the events (PD or death) are immediately after more than one missed disease assessment, the data are censored at the last disease assessment prior to missing visits. Also, data after new anti-cancer therapy are censored at the last disease assessment prior to the initiation of new anti-cancer therapy. The first sensitivity analysis follows the complete follow-up intention-to-treat principle. That is, PDs/deaths are counted as events regardless of missed study visits or initiation of new anti-cancer therapy. The second sensitivity analysis considers discontinuation of treatment or initiation of an anti-cancer treatment subsequent to discontinuation of study-specified treatments, whichever occurs later, to be a PD event for participants without documented PD or death. If a participant meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied. The censoring rules for primary and sensitivity analyses are summarized in Table 9.

Table 9 Censoring Rules for Primary and Sensitivity Analyses of Progression-Free Survival

Situation	Primary Analysis	Sensitivity Analysis 1	Sensitivity Analysis 2
PD or death documented after ≤1 missed disease assessment and before new anti-cancer therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death	Progressed at date of documented PD or death
Death or progression after ≥ 2 consecutive missed disease assessments without further valid non-PD disease assessments, or after new anti-cancer therapy	Censored at last disease assessment prior to the earlier date of ≥2 consecutive missed disease assessment and new anti-cancer therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death
No PD and no death and new anti-cancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment	Progressed at treatment discontinuation due to reasons other than complete response; otherwise censored at last disease assessment if still on study or completed study treatment
No PD and no death; new anti-cancer treatment is initiated	Censored at last disease assessment before new anti-cancer treatment	Censored at last disease assessment	Progressed at date of new anti-cancer treatment

PD=progressive disease

Median PFS and CIs will be updated at final OS analysis; however, there will be no formal statistical testing for the PFS endpoint.

9.6.1.2 Overall Survival

The non-parametric Kaplan-Meier method will be used to estimate the survival curves. The treatment difference in survival will be assessed by the stratified log-rank test (based on the stratification factors defined in Section 6.3.2). A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, the HR). The HR and its 95% CI from the stratified Cox model with a single treatment covariate will be reported. The stratification factors used for randomization (Section 6.3.2) will be applied to both the stratified log-rank test and the stratified Cox model. Participants without documented death at the time of analysis will be censored at the date of last known contact. Restricted Mean Survival Time (RMST) method may be conducted for OS to account for the possible non-proportional hazards effect.

A summary of the primary analysis strategy for the key efficacy endpoints is provided in Table 10.

Table 10 Efficacy Analysis Methods for Key Efficacy Endpoints

Endpoint/Variable	Statistical Method	Analysis Population	Missing Data Approach
Primary Analyses:			
PFS (RECIST 1.1) by investigator	Testing: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored according to rules in Table 9
OS	Testing: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored at last known alive date
Secondary Analyses:			
ORR (RECIST 1.1) by investigator	Estimation: Stratified Miettinen and Nurminen method	ITT	Participants with missing data are considered non-responders
DOR (RECIST 1.1) by investigator	Summary statistics using Kaplan-Meier method	All responders in ITT	Non-responders are excluded from the analysis
PFS rate at 12 months (RECIST 1.1) by investigator	Kaplan-Meier estimation with CI	ITT	Censored according to rules in Table 9
PFS (RECIST 1.1) by BICR	Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored according to rules in Table 9

BICR = blinded independent central review; CI = confidence interval; DOR = duration of response; ITT = Intention-to-Treat; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors 1.1.

9.6.1.3 Objective Response Rate (ORR)

Stratified Miettinen and Nurminen's method will be used for comparison of the ORR between two treatment groups. The difference in ORR and its 95% confidence interval from the stratified Miettinen and Nurminen's method with strata weighting by sample size will be reported. The stratification factors used for randomization (See Section 6.3.2) will be applied to the analysis.

9.6.1.4 Duration of Response (DOR)

For participants who demonstrate CR or PR, DOR is defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first. Censoring rules for DOR are summarized in Table 11. DOR will be assessed using RECIST 1.1 by investigator and BICR, respectively. For each DOR analysis, a corresponding summary of the censoring reasons for responding participant will also be provided. Responding participants who are alive, have not progressed, have not initiated new anti-cancer treatment, have not been determined to be lost to follow-up, and have had a disease assessment within ~5 months of the data cutoff date are considered ongoing responders at the time of analysis. If a participant meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied.

Table 11 Censoring Rules for DOR

Situation	Date of Progression or Censoring	Outcome
No progression nor death, no new anti-cancer therapy initiated	Last adequate disease assessment	Censor (non-event)
No progression nor death, new anti-cancer therapy initiated	Last adequate disease assessment before new anti-cancer therapy initiated	Censor (non-event)
Death or progression after ≥2 consecutive missed disease assessments	Last adequate disease assessment prior to the ≥2 missed adequate disease assessments	Censor (non-event)
Death or progression after ≤1 missed adequate disease assessments	PD or death	End of response (Event)
PD = progressive disease A missed disease assessment includes any assessment that is not obtained or is considered inadequate for evaluation of response.		

9.6.1.5 Progression-Free Survival Rate at 12 months

Kaplan-Meier estimates of the survival function for PFS at 12 months will be provided by treatment group. Confidence intervals for the difference between the treatment groups will be constructed using standard methods.

9.6.2 Statistical Methods for Safety Analyses

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

The analysis of safety results will follow a tiered approach (Table 12). The tiers differ with respect to the analyses that will be performed. Adverse events (specific terms as well as system organ class terms) and events that meet predefined limits of change (PDLCs) in laboratory values, vital signs, and ECG parameters are either prespecified as "Tier 1" endpoints, or will be classified as belonging to "Tier 2" or "Tier 3" based on the observed proportions of participants with an event.

Tier 1 Events

Safety parameters or AEOSIs that are identified *a prior* constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance. AEOSIs that are immune-mediated or potentially immune-mediated are well documented and will be evaluated separately; however, these events have been characterized consistently throughout the pembrolizumab clinical development program and determination of statistical

significance is not expected to add value to the safety evaluation. Further, the addition of pembrolizumab to chemotherapy treatments included in this study has not been found to impact safety. Additionally, there are no known AEs associated with participants for which determination of a p-value is expected to impact the safety assessment. Therefore, there are no Tier 1 events in this study.

Tier 2 Events

Tier 2 parameters will be assessed via point estimates with 95% confidence intervals provided for differences in the proportion of participants with events (also via the Miettinen and Nurminen method [1985]).

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

Tier 3 Events

Safety endpoints that are not Tier 1 or 2 events are considered Tier 3 events. The broad AE categories consisting of the proportion of participants with any AE, a drug-related AE, a serious AE, an AE which is both drug-related and serious, a Grade 3-5 AE, a drug-related Grade 3-5 AE, and discontinuation due to an AE will be considered Tier 3 endpoints. Only point estimates by treatment group are provided for Tier 3 safety parameters.

Continuous Safety Measures

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

Table 12 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	p-Value	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	Grade 3-5 AE (incidence ≥5% of participants in one of the treatment groups)		X	X
	Serious AE (incidence ≥5% of participants in one of the treatment groups)		X	X
	AEs (incidence ≥10% of participants in one of the treatment groups)		X	X
Tier 3	Any AE			X
	Any Grade 3-5 AE			X
	Any Serious AE			X
	Any Drug-Related AE			X
	Any Serious and Drug-Related AE			X
	Any Grade 3-5 and Drug-Related AE			X
	Discontinuation due to AE			X
	Death			X
	Specific AEs, SOCs (incidence <10% of participants in all of the treatment groups)			X
	Change from Baseline Results (lab toxicity shift, vital signs)			X
Abbreviations: AE = adverse event; CI = confidence interval; SOC = system organ class.				

9.6.3 Statistical Methods for PRO Analyses:

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

A 10-point change in PRO score is perceived to be clinically meaningful to participants according to previous research. Correspondingly, a participant's post-baseline PRO score will be classified as "improvement", "stable", or "deterioration" according to a 10 point or greater change for EORTC QLQ-C30 global score. The number and proportion of participants with "improved", "stable", or "deteriorated" symptoms/scales will be summarized by treatment arm.

Time-to-deterioration is defined as the time from the first PRO assessment to deterioration or death, whichever occurs first [Yang, J. C., et al 2013]. The Kaplan-Meier method will be used to estimate times to deterioration survival curve for each treatment arm, and the Cox proportional hazards regression model will be used to estimate the magnitude of treatment difference.

Details of PRO analyses will be described in the sSAP.

9.6.4 Summaries of Baseline Characteristics and Demographics

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

9.7 Interim Analyses

An external Data Monitoring Committee (eDMC) will serve as the primary reviewer of the results of the interim analyses of the study and will make recommendations for discontinuation of the study or protocol modifications to an Executive Oversight Committee (EOC) of the SPONSOR. If the eDMC recommends modifications to the design of the protocol or discontinuation of the study, this executive committee (and potentially other limited SPONSOR personnel) may be unblinded to results at the treatment level in order to act on these recommendations. The extent to which individuals are unblinded with respect to results of interim analyses will be documented by the unblinded statistician. Additional logistical details will be provided in the eDMC Charter. Key aspects of the interim analyses are described in Section 9.7.

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

9.7.1 Safety Interim Analyses

A safety assessment by the eDMC will take place after 20 participants in the experimental arm have completed 2 cycles of treatment. Adverse events and dose modifications will be compared between arms. If a substantial majority of the enrolled participants (ie, more than 80%) in the experimental arm require a dose modification by the end of the Cycle 2, and taking into consideration the background rate of AEs and dose modifications for control-arm participants, the Sponsor may consider amending the protocol to reduce chemotherapy dose(s) for the remainder of the trial.

The eDMC will conduct regular safety interim analyses. The timing of these safety interim analyses will be specified in the eDMC charter.

9.7.2 Efficacy Interim Analyses

Two interim analyses are planned in addition to the final analysis for this study. Results of the interim analyses will be reviewed by the eDMC. There is no expectation to stop the trial

before superiority hypotheses for OS have been adequately evaluated. However, earlier positive findings may form the basis for earlier regulatory submission based on the recommendation of eDMC.

The first interim analysis (interim analysis for PFS and OS) will be conducted when approximately 370 PFS events have been observed for CPS ≥1 group. The second interim analysis (final PFS analysis and interim OS analysis) may be conducted when at least 435 PFS events for CPS ≥1 group have been observed. It is estimated that approximately 508 PFS events for all-comers and approximately 247 PFS events for CPS ≥10 group will be observed by then. The final analysis (final OS analysis) may be conducted when at least 378 OS events for CPS ≥1 group have been observed. It is estimated that approximately 445 OS events for all-comers and approximately 196 OS events for CPS ≥10 group will be observed by then. The Sponsor will closely monitor the PFS and OS events for each hypothesis test. If the number of PFS or OS events for CPS ≥10 group or all-comers is significantly lower than the required events for final analysis, then the timing of the final analysis for that hypothesis test may be re-evaluated.

The analyses planned, endpoints evaluated, and drivers of the timing are summarized in Table 13.

Table 13 Summary of Interim and Final Analyses Strategy

Analyses	Key Endpoints	Events Required for the Analysis	Estimated Time After First Participant Randomized	Primary Purpose of Analysis
IA1 (interim analysis for PFS and OS)	PFS	Timing of analysis will be triggered when ~ 370 PFS events for CPS ≥1 group has been observed. It is estimated that ~210 PFS events for CPS ≥10 group and ~432 PFS events for all-comers will be observed at the same time.	~22 months	• Demonstrate PFS superiority at interim analysis for CPS ≥1 group, CPS ≥10 group, and all-comers
	OS	OS interim analysis will be performed at the same time. It is estimated ~246 OS events for CPS ≥1 group, ~127 OS events for CPS ≥10 group and ~289 OS events for all-comers will be observed.		• Demonstrate OS superiority at interim analysis for CPS ≥1 group, CPS ≥10 group, and all-comers

Analyses	Key Endpoints	Events Required for the Analysis	Estimated Time After First Participant Randomized	Primary Purpose of Analysis
IA2 (final analysis for PFS/interim analysis for OS)	PFS	Timing of analysis will be triggered when at least 435 PFS events for CPS ≥1 group have been observed. It is estimated that ~247 PFS events for CPS ≥10 group and ~508 PFS events for all-comers will be observed by then.	~30 months	• Demonstrate PFS superiority for CPS ≥1 group, CPS ≥10 group and all-comers
	OS	OS interim analysis will be performed at the same time. It is estimated ~321 OS events for CPS ≥1 group, ~167 OS events for CPS ≥10 group and ~378 OS events for all-comers will be observed.		• Demonstrate OS superiority at interim analysis for CPS ≥1 group, CPS ≥10 group and all-comers
Final analysis	OS	Timing of analysis will be triggered when at least 378 OS events for CPS ≥1 group has been observed. It is estimated that ~196 OS events for CPS ≥10 group and 445 OS events for all-comers will be observed by then.	~40 months	• Demonstrate OS superiority for CPS ≥1 group, CPS ≥10 group and all-comers

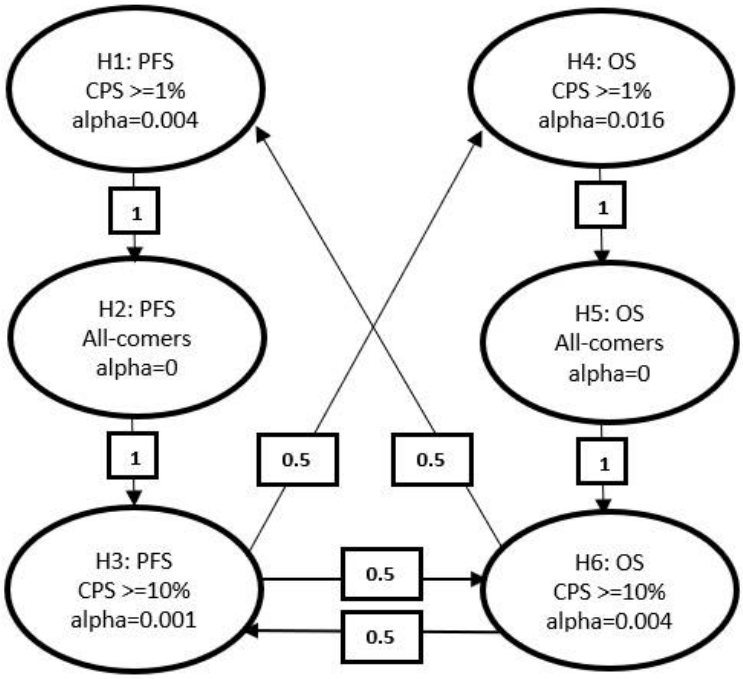
CPS = combined positive score; IAX= interim analysis X; OS = overall survival; PFS = progression-free survival.

Following Amendment 7, the preplanned IA2 is no longer required and will not be performed, as described in Section 9.1.

9.8 Multiplicity

The study uses the graphical method of Maurer and Bretz [Maurer, W. 2013] to provide strong multiplicity control across the 2 primary efficacy hypotheses regarding PFS and OS for CPS ≥1 group, all-comers, and CPS ≥10 group.

Figure 3 shows the initial 1-sided α allocation for each hypothesis in the ellipse representing the hypothesis. The weights for reallocation from each hypothesis to the others are represented in the boxes on the lines connecting hypotheses. This is further explained below.



CPS = combined positive score; PFS= progression-free survival; OS = overall survival.

Figure 3 Multiplicity Graph for Type I Error Control of Study Hypotheses

9.8.1 Efficacy Analyses

9.8.1.1 PFS

The study initially allocates one-sided α=0.005 to test PFS between two treatment groups for CPS ≥1 group, all-comers, and CPS ≥10 group. If the null hypothesis of PFS for CPS ≥1 group is rejected, as shown in Figure 3, its α=0.004 will be reallocated to the PFS analysis for all-comers, and if the null hypothesis of PFS for all-comers is rejected, its α=0.004 will be reallocated to the PFS analysis for CPS ≥10 group. Table 14 below shows the bounds and boundary properties for PFS testing which were derived using a Lan-DeMets O'Brien-Fleming *α*-spending function. If the actual number of events at the PFS analyses differ from those specified in the table, the bounds will be adjusted using the Lan-DeMets O'Brien-Fleming spending function accordingly.

Table 14 Efficacy Boundaries and Properties for PFS Analyses

Population	Analysis[a]	Value	α=0.004	
CPS ≥1	IA1: 85%	Z	2.911	
	N: 510	p (1-sided)	0.002	
	Events:370	~HR at bound	0.739	
	Month: 22	P(Cross) if HR=1	0.002	
		P(Cross) if HR=0.68	0.788	
	IA2: 100%	Z	2.700	
	N: 510	p (1-sided)	0.003	
	Events: 435	~HR at bound	0.772	
	Month: 30	P(Cross) if HR=1	0.004	
		P(Cross) if HR=0.68	0.911	
Population	Analysis[a]	Value	α=0.004	
All-comers	IA1: 85%	Z	2.911	
	N: 600	p (1-sided)	0.002	
	Events: 432	~HR at bound	0.756	
	Month: 22	P(Cross) if HR=1	0.002	
		P(Cross) if HR=0.70	0.787	
	IA2: 100%	Z	2.700	
	N: 600	p (1-sided)	0.003	
	Events: 508	~HR at bound	0.787	
	Month: 30	P(Cross) if HR=1	0.004	
		P(Cross) if HR=0.70	0.910	
Population	Analysis[a]	Value	α=0.005	α=0.001
CPS ≥10	IA1: 85%	Z	2.829	3.383
	N: 300	p (1-sided)	0.002	0.0004
	Events: 210	~HR at bound	0.677	0.627
	Month: 22	P(Cross) if HR=1	0.002	0.0004
		P(Cross) if HR=0.60	0.808	0.625
	IA2: 100%	Z	2.627	3.125
	N: 300	p (1-sided)	0.004	0.001
	Events: 247	~HR at bound	0.716	0.672
	Month: 30	P(Cross) if HR=1	0.005	0.001
		P(Cross) if HR=0.60	0.921	0.817

CPS = combined positive score; HR = hazard ratio; IAX = interim analysis X; PFS = progression-free survival.

a. This column displays the number (Events) and percentage (%) of needed PFS events, the expected sample size (N) and the estimated months (Month) after first participant is randomized for each analysis.

p (1-sided): the nominal α for testing.

~HR at bound: the approximate hazard ratio required to reach an efficacy bound.

P (Cross if HR=1): the probability of crossing a bound at or before each analysis under the null hypothesis

P (Cross if HR=0.68 or 0.70 or 0.60): the probability of crossing a bound at or before each analysis under the alternative hypothesis.

9.8.1.2 OS

The study initially allocates one-sided α=0.020 to test OS between two treatment groups for CPS ≥1 group, all-comers, and CPS ≥10 group. The OS hypothesis for CPS ≥1 group may be tested at one-sided α=0.016 (initially allocated) or higher if one or more null hypothesis for PFS test are rejected. If the null hypothesis of OS for CPS ≥1 group is rejected, as shown in Figure 3, its α will be allocated to the OS analysis for all-comers, and if the null hypothesis of OS for all-comers is rejected, its α will be reallocated to the OS analysis for CPS ≥10 group. Table 15 below shows the bounds and boundary properties for OS testing which were derived using a Lan-DeMets O'Brien-Fleming *α*-spending function. If the actual number of events at the OS analyses differ from those specified in the table, the bounds will be adjusted using the Lan-DeMets O'Brien-Fleming spending function accordingly.

Table 15 Efficacy Boundaries and Properties for OS Analysis

Population	Analysis[a]	Parameter	α=0.016	
CPS ≥1	IA1: 65%	Z	2.767	
	N: 510	p (1-sided)	0.003	
	Events: 246	~HR at bound	0.703	
	Month: 22	P(Cross) if HR=1	0.003	
		P(Cross) if HR=0.70	0.512	
	IA2: 85%	Z	2.405	
	N: 510	p (1-sided)	0.008	
	Events: 321	~HR at bound	0.765	
	Month: 30	P(Cross) if HR=1	0.009	
		P(Cross) if HR=0.70	0.791	
	Final: 100%	Z	2.221	
	N: 510	p (1-sided)	0.013	
	Events: 378	~HR at bound	0.796	
	Month: 40	P(Cross) if HR=1	0.016	
		P(Cross) if HR=0.70	0.901	
Population	Analysis[a]	Parameter	α=0.016	
All-comers	IA1: 65%	Z	2.771	
	N: 600	p (1-sided)	0.003	
	Events: 289	~HR at bound	0.722	
	Month: 22	P(Cross) if HR=1	0.003	
		P(Cross) if HR=0.72	0.509	
	IA2: 85%	Z	2.404	
	N: 600	p (1-sided)	0.008	
	Events: 378	~HR at bound	0.781	
	Month: 30	P(Cross) if HR=1	0.009	
		P(Cross) if HR=0.72	0.790	
	Final: 100%	Z	2.221	
	N: 600	p (1-sided)	0.013	
	Events: 445	~HR at bound	0.810	
	Month: 40	P(Cross) if HR=1	0.016	
		P(Cross) if HR=0.72	0.901	

Population	Analysis[a]	Parameter	α=0.020	α=0.004
CPS ≥10	IA1: 65%	Z	2.665	3.339
	N: 300	p (1-sided)	0.004	0.0004
	Events: 127	~HR at bound	0.623	0.548
	Month: 22	P(Cross) if HR=1	0.004	0.0004
		P(Cross) if HR=0.60	0.585	0.304
	IA2: 85%	Z	2.306	2.928
	N: 300	p (1-sided)	0.011	0.002
	Events: 167	~HR at bound	0.700	0.636
	Month: 30	P(Cross) if HR=1	0.012	0.002
		P(Cross) if HR=0.60	0.845	0.648
	Final : 100%	Z	2.137	2.704
	N: 300	p (1-sided)	0.016	0.003
	Events: 196	~HR at bound	0.737	0.680
	Month: 40	P(Cross) if HR=1	0.020	0.004
		P(Cross) if HR=0.60	0.931	0.815

CPS = combined positive score; HR = hazard ratio; IAX = interim analysis X; OS = overall survival.
a. This column displays the number (Events) and percentage (%) of needed PFS events, the expected sample size (N) and the estimated months (Month) after first participant is randomized for each analysis.
p (1-sided): the nominal α for testing.
~HR at bound: the approximate hazard ratio required to reach an efficacy bound.
P(Cross if HR=1): the probability of crossing a bound at or before each analysis under the null hypothesis
P(Cross if HR=0.70 or 0.72 or 0.60): the probability of crossing a bound at or before each analysis under the alternative hypothesis.

Following Amendment 7, the preplanned IA2 is no longer required and will not be performed, as described in Section 9.1.

9.8.2 Safety Analyses

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

9.9 Sample Size and Power Calculations

This study is well-powered for both primary endpoints.

Enrollment of 600 participants (all-comers) is assumed to occur over 16 months. Approximately 510 participants are expected to be CPS ≥1 and 300 participants are expected to be CPS ≥10.

The duration of PFS in the control arm is assumed to follow an exponential distribution with a median of 7.1 months based on historical data. The PFS hypothesis testing was designed as below:

H1: CPS ≥1 group (N=510): At one-sided α = 0.004 and power of 91% to detect a hazard ratio of 0.68 with approximately 370 and 435 events between 2 arms at the planned PFS analyses.

H2: All-comers (N=600): At one-sided α = 0.004 and power of 91% to detect a hazard ratio of 0.70 with approximately 432 and 508 events between 2 arms at the planned PFS analyses (when H1 is rejected).

H3: CPS ≥10 group (N=300): At one-sided α = 0.005 and power of 92% to detect a hazard ratio of 0.60 with approximately 210 and 247 events between 2 arms at the planned PFS analyses (when H1 and H2 are rejected).

The duration of OS in the control arm is assumed to follow an exponential distribution with a median of 15.1 months based on historical data. The OS hypothesis testing was designed as follows:

H4: CPS ≥1 group (N=510): At one-sided α = 0.016 and power of 90% to detect a hazard ratio of 0.70 with approximately 246, 321, and 378 events between 2 arms at the planned OS analyses.

H5: All-comers (N=600): At one-sided α = 0.016 and power of 90% to detect a hazard ratio of 0.72 with approximately 289, 378, and 445 events between 2 arms at the planned OS analyses (when H4 is rejected).

H6: CPS ≥10 group (N=300): At one-sided α = 0.020 and power of 93% to detect a hazard ratio of 0.60 with approximately 127, 167, and 196 events between 2 arms at the planned OS analyses (when H4 and H5 are rejected).

Power and interim analysis calculations were performed using EAST 6.4.

Following Amendment 7, the preplanned IA2 is no longer required and will not be performed, as described in Section 9.1.

9.10 Subgroup Analyses

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

- Stratification factors
    - Metastatic (FIGO [2009] Stage IVB) at diagnosis (Yes vs. No)
    - Bevacizumab use (Yes vs. No)
    - PD-L1 status (CPS <1 vs. CPS 1 to <10 vs. CPS ≥10)

- Age group (<65 years vs. ≥65 years)
- Race (white, non-white)
- ECOG performance status (0, 1)

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

9.11 Compliance (Medication Adherence)

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

9.12 Extent of Exposure

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

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Code of Conduct for Clinical Trials

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

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

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

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

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if potential fraud, scientific/research misconduct, privacy incidents/breaches or Clinical Trial-related Significant Quality Issues are reported, such matters are investigated. When necessary, appropriate corrective and/or preventative actions are defined and regulatory authorities and/or ethics review committees are notified.

B. Publication and Authorship

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

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

III. Participant Protection

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

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

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

B. Safety

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

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

C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible, as well as all applicable data protection rights. Unless required by law, only the investigator, Sponsor (or individuals acting on behalf of MSD), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

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

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

10.1.3 Data Protection

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

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

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

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

10.1.3.3 Confidentiality of IRB/IEC Information

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

10.1.4 Committees Structure

10.1.4.1 Executive Oversight Committee

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

10.1.4.2 External Data Monitoring Committee

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

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

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

10.1.5 Publication Policy

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

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

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

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007 and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor of the study is solely responsible for determining whether the study and its results are subject

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

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

10.1.7 Compliance with Law, Audit, and Debarmen

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP (eg, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use GCP: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical study. The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in this appendix under the Code of Conduct for Clinical Studies.

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

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

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

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

10.1.8 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator

or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

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

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

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

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

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

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

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

10.1.9 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

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

10.1.10 Study and Site Closure

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

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

10.2 Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 16 will be performed by the local laboratory.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations. Refer to Appendix 7 for country-specific requirements.

Table 16 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential[a]: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Chemistry	Blood Urea Nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the upper limit of normal)
	Albumin	Carbon dioxide (CO_2 or Bicarbonate)[c]	Chloride	Phosphorous
	Creatinine[d]	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose (nonfasting)	Calcium	Alkaline phosphatase	Triiodothyronine (T3/FT3)[e]
	Free Thyroxine (FT4)[e]	Thyroid-stimulating hormone (TSH)[e]	Urea[b]	Uric acid
Routine Urinalysis[f]	Specific gravity pH, glucose, protein, blood, ketones, by dipstick Microscopic examination (if blood or protein is abnormal)			

Laboratory Assessments	Parameters
Other Screening Tests	• PT/INR and aPTT[g] Serum or urine β human chorionic gonadotropin (β hCG) pregnancy test (as needed for WOCBP)[h] Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody) if mandated by local health authority

Abbreviations: aPTT = activated partial thromboplastin time; HIV = human immunodeficiency virus; INR = international normalized ratio; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; PT = Prothrombin Time; RBC = red blood cell; WBC = white blood cell; WOCBP = woman/women of child bearing potential.

NOTES:

a- Reporting results as absolute values is preferable.

b- Blood urea nitrogen is preferred; if not available, urea may be tested.

c- Performed only if considered local standard of care.

d- Creatinine clearance should be calculated per institutional standard. GFR (measured or calculated) or creatinine clearance can be used in place of creatinine.

e- Free T4, T3, and TSH levels will be performed at screening and every 2 cycles during treatment (C2, C4, C6,…), at the time of discontinuation (End of Treatment), and at the Safety-Follow- up visit. May perform centrally if unable to perform locally. Free T3 is acceptable where T3 cannot be determined. There may be instances when sites are unable to obtain the thyroid function testing results prior to scheduled dosing. After Cycle 1, review of thyroid function test results after dosing is acceptable.

f- Performed at every cycle during which bevacizumab is administered.

g- Performed as part of the screening assessment and as clinically indicated.

h- Perform on women of childbearing potential only. Urine pregnancy test is preferred. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. For women of childbearing potential, pregnancy testing should be conducted every month during study intervention, or more frequently if required by local regulations or if clinically indicated.

Investigators must document their review of each laboratory safety report.

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

10.3.1 Definition of AE

AE definition

An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

NOTE: For purposes of AE definition, study intervention (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, device, diagnostic agent, or protocol specified procedure whether investigational (including placebo or active comparator product) or marketed, manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.

Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.

Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.

For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

Events NOT meeting the AE definition

Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.

Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.

Refer to Section 8.4.7 for protocol-specific exceptions.

10.3.2 Definition of SAE

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

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

a. **Results in death**

b. **Is life-threatening**

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

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

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

10.3.3 Additional Events Reported in the Same Manner as SAE

Additional events that require reporting in the same manner as SAE

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

Is a new cancer (that is not a condition of the study)

Is associated with an overdose

10.3.4 Recording AE and SAE

AE and SAE recording

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

The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.

It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.

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

Assessment of intensity

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.

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

- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

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

    - Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).

    - Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or 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 adverse event?

    - The determination of the likelihood that the Sponsor's product caused the adverse event 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 adverse event 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 adverse event:

  - **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 trials with investigational medicinal product)?

  - **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors?

  - **Dechallenge:** Was the Sponsor's product discontinued or dose/exposure/frequency reduced?

    - If yes, did the AE resolve or improve?

      - If yes, this is a positive dechallenge.

    - If no, this is a negative dechallenge.

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

  - **Rechallenge:** Was the participant re-exposed to the Sponsor's product in this trial?

    - 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 trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH 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 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.

- **Consistency with Study treatment 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 one of the criteria used when determining regulatory reporting requirements.

- For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each adverse event 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 adverse event to the single agent.

Follow-up of AE and SAE

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

New or updated information will be recorded in the CRF.

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

10.3.5 Reporting of AE, SAE, and Other Reportable Safety Events to the Sponsor

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

The primary mechanism for reporting to the Sponsor will be the electronic data collection (EDC) tool.

Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).

If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.

Reference Section 8.4.1 for reporting time requirements.

The site will enter the SAE data into the electronic system as soon as it becomes available.

After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.

If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).

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

SAE reporting to the Sponsor via paper CRF

If the EDC tool is not operational, facsimile transmission or secure 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 Incidents: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

N/A

10.5 Appendix 5: Contraceptive Guidance and Pregnancy Testing

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP:

Premenarchal

Premenopausal female with 1 of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

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

Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.

- Females on HRT and whose menopausal status is in doubt will be required to use 1 of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraception Requirements

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

10.5.3 Pregnancy Testing

WOCBP may only be randomized after a negative highly sensitive urine or serum pregnancy test within 72 hours prior to randomization. In the event that more than 72 hours have elapsed between this pregnancy test and the first dose of study treatment, another pregnancy test must be performed and must be negative prior to receiving the first dose of study treatment.

Pregnancy testing (urine or serum as required by local regulations) should be conducted at monthly intervals during intervention. Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study. Refer to Appendix 7 for country-specific requirements.

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.

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

The specimens consented and/or collected in this study as outlined in Section 8.10 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 drugs/vaccines may interact with
- 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.

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

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

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

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

5. Biorepository Specimen Usage

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

6. Withdrawal From Future Biomedical Research

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

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

7. Retention of Specimens

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

Specimens from the study site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not utilized in a particular study, the study site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which

operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

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

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

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

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

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

12. Questions

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

13. References

1. National Cancer Institute [Internet]: Available from https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45618

2. International Conference on Harmonization [Internet]: E15: Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. Available from http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html

3. Industry Pharmacogenomics Working Group [Internet]: Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

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

10.7 Appendix 7: Country-specific Requirements

Germany-specific Information

1. Section 1.3.1 Schedule of Activities – Initial Treatment Phase

    - Monthly urine or serum pregnancy testing is required until 120 days after the last dose of pembrolizumab/placebo and 210 days after the last dose of chemotherapy/bevacizumab.

    - Testing for HIV is required at Screening.

    - Testing for Hepatitis B and Hepatitis C is required at Screening.

2. Section 1.3.2 Schedule of Activities – Second Course Treatment Phase

    - Monthly urine or serum pregnancy testing is required until 120 days after the last dose of pembrolizumab.

3. Section 5.2 Exclusion Criteria

    - Exclusion Criterion 8: Testing for HIV is required at Screening.

    - Exclusion Criterion 9: Testing for Hepatitis B and Hepatitis C is required at Screening.

4. Section 8.3.4.2 Pregnancy Test

    - Monthly urine or serum pregnancy testing is required until 120 days after the last dose of pembrolizumab/placebo and 210 days after the last dose of chemotherapy/bevacizumab.

5. Section 10.2 Appendix 2: Clinical Laboratory Tests

    - Monthly urine or serum pregnancy testing is required until 120 days after the last dose of pembrolizumab/placebo and 210 days after the last dose of chemotherapy/bevacizumab.

    - Testing for HIV is required at Screening.

    - Testing for Hepatitis B and Hepatitis C is required at Screening.

6. Section 10.5 Appendix 5: Contraceptive Guidance and Pregnancy Testing

    - Monthly urine or serum pregnancy testing is required until 120 days after the last dose of pembrolizumab/placebo and 210 days after the last dose of chemotherapy/bevacizumab.

France-specific Information

1. Section 5.2 Exclusion Criteria

    - Exclusion Criterion 9: Hepatitis B and Hepatitis C testing must be performed during the screening period and prior to enrollment.

2. Section 1.3.1 Schedule of Activities – Initial Treatment Phase

    - Monthly urine or serum pregnancy testing is required for all participants through 6 months following the last dose of study intervention.

3. Section 1.3.2 Schedule of Activities – Second Course Treatment Phase

    - Monthly urine or serum pregnancy testing is required for all participants through 6 months following the last dose of study intervention.

4. Section 8.3.4.2 Pregnancy Test

    - Monthly urine or serum pregnancy testing is required for all participants through 6 months following the last dose of study intervention.

5. Section 10.2 Appendix 2: Clinical Laboratory Tests

    - Monthly urine or serum pregnancy testing is required for all participants through 6 months following the last dose of study intervention.

6. Section 10.5 Appendix 5: Contraceptive Guidance and Pregnancy Testing

    - Monthly urine or serum pregnancy testing is required for all participants through 6 months following the last dose of study intervention.

7. Section 6.6.1 Dose Modification, Table 5 Pembrolizumab/Placebo Dose Modification and Toxicity Management Guidelines for Immune-related AEs

    - Discontinuation is required for confirmed cases of Stevens-Johnson (SJS) and toxic epidermal necrolysis (TEN).

Argentina-specific Information

1. Section 1.3 Schedule of Activities - Screening and Treatment Phase

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

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

Assessment at Screening and Prior to RECIST 1.1 Progression

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

Assessment and Decision at RECIST 1.1 Progression

For participants who show evidence of radiological PD by RECIST 1.1 as determined by the investigator, the investigator will decide whether to continue a participant on study intervention until repeat imaging is obtained (using iRECIST for participant management) (see Table 7 and Figure 2). This decision by the investigator should be based on the participant's overall clinical condition.

Clinical stability is defined as the following:

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

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

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

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

- Increase in the sum of diameters of target lesion(s) identified at baseline to ≥20% and ≥5 mm from nadir
  Note: The iRECIST publication uses the terminology "sum of measurements," but "sum of diameters" will be used in this protocol, consistent with the original RECIST 1.1 terminology.
- Unequivocal progression of nontarget lesion(s) identified at baseline
- Development of new lesion(s)

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

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

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

Assessment at the Confirmatory Imaging

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

Confirmation of Progression

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

Any of the factors that were the basis for the iUPD at the previous visit show worsening

- For target lesions, worsening is a further increase in the sum of diameters of ≥5 mm, compared to any prior iUPD time point
- For nontarget lesions, worsening is any significant growth in lesions overall, compared to a prior iUPD time point; this does not have to meet the “unequivocal” standard of RECIST 1.1
- For new lesions, worsening is any of these:
    - An increase in the new lesion sum of diameters by ≥5 mm from a prior iUPD time point
    - Visible growth of new nontarget lesions
    - The appearance of additional new lesions

Any new factor appears that would have triggered PD by RECIST 1.1

Persistent iUPD

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

None of the progression-confirming factors identified above occurs AND

The target lesion sum of diameters (initial target lesions) remains above the initial PD threshold (by RECIST 1.1)

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

Resolution of iUPD

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

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

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

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

Management Following the Confirmatory Imaging

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

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

Detection of Progression at Visits After Pseudo-progression Resolves

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

Target lesions

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

Nontarget lesions

- If nontarget lesions have never shown unequivocal progression, their doing so for the first time results in iUPD.

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

New lesions

- New lesions appear for the first time

- Additional new lesions appear

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

- Previously identified nontarget lesions show any significant growth

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

The decision process is identical to the iUPD confirmation process for the initial PD, with one exception: If new lesions occurred at a prior instance of iUPD, and at the confirmatory imaging the burden of new lesions has increased from its smallest value (for new target lesions, the sum of diameters is ≥5 mm increased from its nadir), then iUPD cannot resolve to iSD or iPR. It will remain iUPD until either a decrease in the new lesion burden allows resolution to iSD or iPR, or until a confirmatory factor causes iCPD.

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

10.9 Appendix 9: Eastern Cooperative Oncology Group (ECOG) Performance Status

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

10.10 Appendix 10: Abbreviations

Abbreviation	Expanded Term
1L	first line
AE	adverse event
AEOSI	adverse events of special interest
ALT	alanine transaminase
APaT	All Participants as Treated
aPTT	activated partial thromboplastin time
AST	aspartate transaminase
AUC	area under concentration-time curve
BCG	*Bacillus* Calmette–Guérin
β-HCG	beta-human chorionic gonadotropin
BICR	blinded independent central review
CBC	complete blood count
CD28	cluster of differentiation 28
CI	confidence interval
CIN	cervical intraepithelial neoplasia
cLDA	constrained longitudinal data analysis
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease caused by severe acute respiratory syndrome coronavirus 2
CPS	combined positive score
CR	complete response
CRF	Case Report Form
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
CTFG	Clinical Trial Facilitation Group
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
CX	Cycle X
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data collection
eDMC	external Data Monitoring Committee
EMA	European Medicines Agency
ePRO	electronic patient-reported outcome
EQ-5D-5L	EuroQoL-5D-5L
EOC	Executive Oversight Committee
EORTC	European Organisation for the Research and Treatment of Cancer
EOT	end of treatment
ESMO	European Society for Medical Oncology
FAS	Full Analysis Set
FBR	Future Biomedical Research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act

Abbreviation	Expanded Term
FFPE	Formalin-fixed, paraffin embedded
FIGO	International Federation of Gynecology and Obstetrics (Fédération Internationale de Gynécologie et d'Obstétrique)
FSH	Follicle stimulating hormone
FT3	Free triiodothyronine
FT4	Free thyroxine
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factors
GFR	glomerular filtration rate
GI	gastrointestinal
GOG	Gynecologic Oncology Group
HIV	human immunodeficiency virus
HR	hazard ratio
HRQoL	health-related quality of life
HRT	hormone replacement therapy
IB	Investigator's Brochure
IA	interim analysis
ICF	Informed Consent Form
ICH	International Council on Harmonisation
iCPD	Confirmed radiographic disease progression
iCR	iRECIST complete response
iCRO	imaging contract research organization
IEC	Independent Ethics Committee
Ig	immunoglobulin
IgG4	immunoglobulin G4
IHC	immunohistochemistry
IMP	Investigational Medicinal Product
IND	Investigational New Drug
INR	international normalized ratio
iPD	immune-related progressive disease
iPR	immune-related partial response
irAE	immune-related AE
IRB	Institutional Review Board
iRECIST	modified RECIST 1.1 for immune-based therapeutics
IRT	intervention randomization system
iSD	iRECIST stable disease
ITT	Intention-to-Treat
IUD	intrauterine device
iUPD	iRECIST unconfirmed progressive disease
IUS	intrauterine hormone-releasing system
IV	intravenous
IVRS/IWRS	interactive voice response system / integrated web response system
mAb	monoclonal antibody
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NDA	New Drug Application
NIMP	Non-Investigational Medicinal Product
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	nonsmall cell lung cancer
NYHA	New York Heart Association

Abbreviation	Expanded Term
OR	objective response
ORR	objective response rate
OS	overall survival
OTC	over-the-counter
PBPK	physiologically based PK
PD	progressive disease
PD 1	programmed cell death 1
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PDLC	predefined limit of change
PFS	progression-free survival
PK	pharmacokinetic
PKCθ	protein kinase C-theta
po	orally
PR	partial responses
PRO	patient-reported outcomes
PS	performance score
PT	prothrombin time
PTT	partial thromboplastin time
Q2W	every 2 weeks
Q3W	every 3 weeks
Q9W	every 9 weeks
Q12W	every 12 weeks
QLQ-C30	Quality of Life Questionnaire Core 30
QLQ-CX24	Quality of Life Questionnaire Cervical Cancer Module
RECIST	Response Evaluation Criteria in Solid Tumors
RMST	restricted mean survival time
RNA	ribonucleic acid
SAC	Scientific Advisory Committee
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SIM	Site Imaging Manual
SoA	schedule of activities
SOC	System Organ Class
sSAP	supplemental SAP
SUSAR	suspected unexpected serious adverse reaction
T1DM	type 1 diabetes mellitus
T3	triiodothyronine
T4	thyroxine
TB	tuberculosis
TC	carboplatin/paclitaxel
TEA	treatment eligibility assessment
TMDD	target-mediated drug disposition
TP	cisplatin/paclitaxel
T-regs	regulatory T-cells
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
US	United States

Abbreviation	Expanded Term
VOP	verification of progression
WOCBP	woman/women of childbearing potential
ZAP70	zeta-chain-associated protein kinase

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