Official Protocol Title:	A Phase 4, single-arm, open-label clinical study of pembrolizumab (MK-3475) to evaluate the efficacy and safety of MK-3475 plus carboplatin and paclitaxel as first-line treatment of recurrent/metastatic head and neck squamous cell carcinoma
NCT number:	NCT04489888
Document Date:	16 August 2022

Title Page

THIS PROTOCOL AMENDMENT AND ALL OF THE INFORMATION RELATING TO IT ARE CONFIDENTIAL AND PROPRIETARY PROPERTY OF MERCK SHARP & DOHME LLC, RAHWAY, NJ, USA (MSD).

Protocol Title: A Phase 4, single-arm, open-label clinical study of pembrolizumab (MK-3475) to evaluate the efficacy and safety of MK-3475 plus carboplatin and paclitaxel as first-line treatment of recurrent/metastatic head and neck squamous cell carcinoma (KEYNOTE-B10).

Protocol Number: B10-03

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	122325

Approval Date: 16 August 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 03	16-AUG-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. To update the chemotherapy dose modification guidance, to update the scan schedule for Second Course Phase, and to make minor protocol language clarifications.
Amendment 02	16-AUG-2021	To update imaging language to comply with Health Authority request. This includes clarification on the process to be followed after investigator-assessed disease progression and adding the definition of lack of clinical stability. To incorporate changes in the PCL (02-NOV-2020), which removed the allowance of radiation treatment as concomitant treatment during the study treatment phase. To make minor protocol language clarifications and to update the chemotherapy dose modification guidance.
Amendment 01	16-JUN-2021	To update the dose modification and toxicity management guidelines for irAEs.
Original Protocol	07-MAY-2020	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 03

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. To update the chemotherapy dose modification guidance, to update the scan schedule for Second Course Phase, and to make minor protocol language clarifications.

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.
6.6.2 Dose Modifications for Standard Treatment Chemotherapy	Updated carboplatin and paclitaxel contraindications, precautions, and dose modification guidance.	To align with the current Prescribing Information for paclitaxel and carboplatin.
1.3.2 Second Course Phase 8.2.1.4 Second Course (Retreatment) Tumor Scans	Updated the scan schedule during the Second Course Phase after Year 1 to every 9 weeks (63 days ±7 days), and added the option of a less frequent scan schedule of every 12 weeks after Sponsor consultation.	To align second course tumor scan schedule with the Initial Treatment Phase, and allow option of less frequent scans after Year 1, if appropriate, to align with clinical practice schedules.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis: Intervention Groups and Duration	In the intervention groups table, updated "Use" for all study interventions from "Experimental" to "Test Product".	To align with the EU CTR.
5 Study Population	Added a new paragraph stating that the collection and use of demographic data are to follow all local laws and participant confidentiality guidelines while supporting the study of the disease, its related factors, and the IMP under investigation.	To clarify the collection, use, and confidentiality of demographic data provided by the participants per the EU CTR.
6.1 Study Intervention(s) Administered	Made the following updates to Table 4: • Updated "Use" for all study interventions from "Experimental" to "Test Product" • Updated "NIMP" to "NIMP/AxMP" • Deleted drug-specific footnotes	To align with the EU CTR. To eliminate redundancy, as this information is included in Section 8.1.8.
1.1 Synopsis: Duration of Participation	Replaced specific reasons for the discontinuation of study intervention with "until one of the conditions for discontinuation of study intervention is met." Replaced specific reasons for the discontinuation of imaging with "until any of the conditions for discontinuation of imaging are met."	To maintain consistency with how the study intervention and tumor scan discontinuation criteria are defined throughout the protocol.

Section # and Name	Description of Change	Brief Rationale
1.3.1 Initial Treatment Phase 1.3.2 Second Course Phase	Added that information regarding poststudy anticancer treatment will be collected if new treatment is initiated, and all subsequent anticancer therapy given after study intervention discontinuation should be recorded in the eCRF in the notes column for Subsequent Anticancer Therapy Status.	To clarify when new anticancer therapy is given and recorded.
1.3.1 Initial Treatment Phase 1.3.2 Second Course Phase	Added a cross-reference to Appendix 2 in the notes column for hematology, chemistry, thyroid function tests, urinalysis, and coagulation factors.	To clarify the individual tests required in each laboratory panel.
4.1 Overall Design	Added that central Verification of Progression (VOP), or request for iCRO to verify PD, is not required.	To clarify that this study does not include VOP.
4.1 Overall Design 8.2.1.2 Tumor Scans During the Study 8.2.1.4 Second Course (Retreatment) Tumor Scans 8.2.1.5 RECIST 1.1 Assessment of Disease 8.11.4.2 Efficacy Follow-up Visits	Updated the list of reasons for discontinuing tumor scans/efficacy follow-up in each of these sections to align with Section 8.2.1.3.	To maintain consistency with how the tumor scan discontinuation criteria are defined throughout the protocol.

Section # and Name	Description of Change	Brief Rationale
6.1.2 Second Course	Simplified text describing conditions for Second Course retreatment, removed specific conditions of treatment during First Course, and clarified that an objective response or disease progression that occurs during the Second Course for a participant will not be counted as an event in the primary efficacy analyses.	To add flexibility, clarity, and consistency to the requirements for Second Course eligibility.
6.5 Concomitant Medications	Restructured section and added clarifications to make it clearer which concomitant treatments require discontinuation of study intervention before use, and which prohibited therapies would not necessarily require discontinuation of study intervention or may be permitted after Sponsor consultation. Stated that study intervention must first be discontinued if a participant will have oncologic surgery or radiation therapy for the disease under study. In the note regarding COVID-19 vaccines, added "replication-incompetent" before "adenoviral vaccines". Minor editorial clarifications to the permitted conditions of use for glucocorticoids. Clarified that the link provided for a list of strong/moderate inducers and inhibitors of CYP3A is not all-inclusive, and any inducers or inhibitors not approved in the US will not appear in the list, and that the investigator must review locally approved product labels and use best medical judgment.	To clarify which prohibited medications warrant the discontinuation of study intervention, and which require Sponsor consultation. To clarify that study intervention must be discontinued before surgery can be performed or radiotherapy can be administered. To clarify which COVID-19 vaccines are permitted. To clarify the permitted use of steroids. To ensure that investigators outside the US refer to locally approved product labels and use best medical judgment for any concomitant medications not included in the FDA list.

Section # and Name	Description of Change	Brief Rationale
6.6.1 Immune-Related Events and Dose Modification (Withhold, Treat, Discontinue)	In Table 5, replaced the term "Grade 1 myocarditis" with "Asymptomatic cardiac enzyme elevation with clinical suspicion of myocarditis (which was previously myocarditis Grade 1 using CTCAE v4.0)."	To update the pembrolizumab dose modification table to include elevated cardiac enzymes, suspected myocarditis, instead of Grade 1 myocarditis, based on updated CTCAE v5.0 toxicity grading.
6.6.2 Dose Modifications for Standard Treatment Chemotherapy	Added that dose modifications for hematologic AEs may also be based on hematology laboratory tests performed on or up to 3 days prior to Day 8 for paclitaxel 100 mg/m^2. After the statement that chemotherapy may be interrupted for a maximum of 6 weeks, clarified that this should be calculated from the omitted Day 1 dose to the next planned dose and must be within 9 weeks of the previously administered Day 1 dose. Added that Sponsor consultation is required to administer paclitaxel and/or carboplatin study intervention after a >6-week dose interruption of chemotherapy.	To clarify that dose modifications for hematologic AEs must also be followed for Day 8 if the participant is receiving paclitaxel 100 mg/m^2. To clarify that Sponsor consultation to continue chemotherapy is required after a >6-week dose interruption of paclitaxel and/or carboplatin.
7.1 Discontinuation of Study Intervention	Added new anticancer therapy to the list of reasons for discontinuation of study intervention.	To maintain consistency with how the study intervention discontinuation criteria are defined throughout the protocol.
8.1.8.1 Timing of Dose Administration	Updated premedication requirements for paclitaxel to refer to corticosteroids instead of steroids, and to include H_2-receptor antagonists.	To align with the current product Prescribing Information.

Section # and Name	Description of Change	Brief Rationale
8.2.1 Tumor Imaging and Assessment of Disease	In the last paragraph, clarified that Sponsor approval is required prior to continuing study intervention beyond progression, and that any confirmatory unscheduled scan following initial documentation of disease progression is not required.	Clarification regarding continuation of study intervention beyond progression and scan requirements.
8.2.1.2 Tumor Scans During the Study	Deleted sentence "Note: Response does not typically need to be verified in real time by the BICR."	This study does not require BICR verification of progression or any other tumor response (ie, CR, PR).
8.2.1.3 End of Treatment and Follow-up Tumor Scans	Clarified that disease progression as defined by RECIST 1.1 will be identified by the investigator. Cross-referenced Section 8.2.1.5 for alternative options available to the investigator.	To clarify that tumor scans are discontinued when disease progression is identified locally by the investigator, since there is no VOP in this study. To refer to details of the process to be followed after disease progression is established by the investigator.
8.2.1.5 RECIST 1.1 Assessment of Disease	Clarified process to be followed if disease progression is established by the investigator.	To clarify scan schedule.
8.3.4.2 Pregnancy Test	Deleted sentence "Repeated pregnancy test (such as monthly testing) may be conducted if required by local regulation." Added sentence "Pregnancy testing requirements during study treatment and in post-treatment are described in Appendix 2."	Repeated pregnancy testing is not optional, but is required during study treatment and in post-treatment as described in Appendix 2.

Section # and Name	Description of Change	Brief Rationale
8.8 Biomarkers	Changed "Newly Obtained or Archival Tumor Tissue Collection" to "Tumor Tissue".	To reduce ambiguity and eliminate a source of confusion. "Tumor tissue" represents all tumor collections (archival tissue, newly obtained/biopsies, etc.).
8.8.1 Planned Genetic Analysis Sample Collection	Added that the planned genetic analysis sample should be obtained predose on Day 1, but may be collected at the next scheduled blood draw, if needed.	To clarify biomarker sample collection.
8.9 Future Biomedical Research Sample Collection	Deleted list of samples and replaced with "Leftover samples listed in Section 8.8".	To reduce ambiguity and eliminate a source of confusion.
8.11.3 Participants Discontinued From Study Intervention but Continuing to Be Monitored in the Study	Updated section heading to clarify that the section applies for participants who have discontinued from study treatment, but are continuing to be monitored in the study. Added that the Discontinuation Visit may either occur within 21 days after the last dose of study intervention, or approximately 30 days after the last dose of study intervention if combined with the 30-Day Safety Follow Visit, and that study procedures for both visits (notably laboratory tests) should be performed before initiation of new anticancer therapy.	To improve clarity on the information included in this section. To clarify when the Discontinuation Visit should be performed and that study procedures for the Discontinuation and 30-Day Safety Follow-Up Visits should be performed before initiation of new anticancer therapy.
8.11.4.3 Survival Follow-up Contacts	Added that information regarding poststudy anticancer treatment will be collected and recorded in the eCRF if a new anticancer treatment is initiated.	To align with clarifications made in the Schedule of Activities in Sections 1.3.1 and 1.3.2.

Section # and Name	Description of Change	Brief Rationale
10.2 Appendix 2: Clinical Laboratory Tests	Updated the required duration of pregnancy testing for WOCBP during post-treatment from at 30 days/4 weeks after the last dose of study intervention, to until 120 days after the last dose of pembrolizumab, 30 days after the last dose of paclitaxel, and 6 months after the last dose of carboplatin.	To ensure that pregnancy testing is continued for the time required to eliminate systemic exposure after the last dose of study interventions, as noted in Section 5.1.
Throughout Document	Minor administrative, formatting, grammatical, and/or typographical changes were made throughout the document.	To ensure clarity and accurate interpretation of the intent of the protocol.

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LIST OF TABLES

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 4, single-arm, open-label clinical study of pembrolizumab (MK-3475) to evaluate the efficacy and safety of MK-3475 plus carboplatin and paclitaxel as first-line treatment of recurrent/metastatic head and neck squamous cell carcinoma (KEYNOTE-B10).

Short Title: MK-3475 Taxane Combo Single-Arm Phase 4

Acronym: KEYNOTE-B10

Hypotheses, Objectives, and Endpoints:

Adult participants with a histologically or cytologically-confirmed R/M HNSCC that is considered incurable by local therapies will be enrolled in this study.

Throughout this protocol, the term RECIST 1.1 refers to the adjustment of RECIST 1.1 to include a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Refer to Section 4.2.1.1 for further details.

Primary Objectives	Primary Endpoints
Objective: To evaluate the efficacy of pembrolizumab + carboplatin + paclitaxel with respect to objective response rate (ORR) per RECIST 1.1 as assessed by blinded independent central review (BICR).	Objective Response: Complete response (CR) or Partial response (PR)
Secondary Objectives	Secondary Endpoints
Key Objective: To evaluate the efficacy of pembrolizumab + carboplatin + paclitaxel with respect to duration of response (DOR) per RECIST 1.1 as assessed by blinded independent central review (BICR).	DOR: For participants who demonstrate confirmed 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.
Objective: To evaluate the efficacy of pembrolizumab + carboplatin + paclitaxel with respect to progression-free survival (PFS) per RECIST 1.1 as assessed by blinded independent central review (BICR).	PFS: The time from first dose to the first documented disease progression or death due to any cause, whichever occurs first.
Objective: To evaluate the efficacy of pembrolizumab + carboplatin + paclitaxel with respect to overall survival (OS).	OS: The time from first dose to death due to any cause.

Objective: To assess the safety and tolerability of study intervention with pembrolizumab + carboplatin + paclitaxel.	- AEs. - Study intervention discontinuation due to AEs.

Overall Design:

Study Phase	Phase 4
Primary Purpose	Treatment
Indication	Treatment of participants with R/M HNSCC
Population	Participants with R/M HNSCC who are eligible for 1L treatment
Study Type	Interventional
Intervention Model	Single Group This is a multi-site study.
Type of Control	No Treatment Control
Study Blinding	Unblinded Open-label
Blinding Roles	No Blinding
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 100 participants will be treated. All allocated participants who are treated will be included in the APaT analysis as described in Section 9.0.

Intervention Groups and Duration:

Intervention Groups

Drug	Dosage Level(s)	Dose Frequency	Route of Administration	Regimen/ Treatment Period/	Use
Pembrolizumab[a]	200 mg	Q3W	IV infusion	Day 1 of each cycle (35 cycles)	Test Product
Carboplatin	AUC 5 mg/mL/min	Q3W	IV infusion	Day 1 of each cycle (6 cycles)	Test Product
Paclitaxel[b]	100 mg/m^2	Q1W	IV infusion	Day 1 and Day 8 of each cycle (6 cycles)	Test Product
Paclitaxel[b]	175 mg/m^2	Q3W	IV infusion	Day 1 of each cycle (6 cycles)	Test Product

Abbreviations: AUC = area under the curve; IV = intravenous; Q1W = weekly; Q3W = every 3 weeks.
[a] Pembrolizumab must be administered prior to chemotherapy.
[b] Paclitaxel 100 mg/m^2 Q1W or paclitaxel 175 mg/m^2 Q3W.

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

Total Number of Intervention Groups/ Arms

1 Arm

Duration of Participation

Each participant will participate in the study from the time that the participant provides documented informed consent through the final protocol-specified contact.

After a screening phase of 28 days, each participant will be assigned to receive study intervention until one of the conditions for discontinuation of study intervention is met.

Participants who complete study intervention after receiving 35 administrations of pembrolizumab, and participants who attain a complete response and stop study intervention may be eligible for up to 17 additional administrations of pembrolizumab (approximately 1 year) upon experiencing disease progression.

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

Participants who discontinue for reasons other than radiographic disease progression will have post-treatment follow-up imaging for disease status until any of the conditions for discontinuation of imaging are met.

All participants will be followed for overall survival until death, withdrawal of consent, or the end of the study.

Study Governance Committees:

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

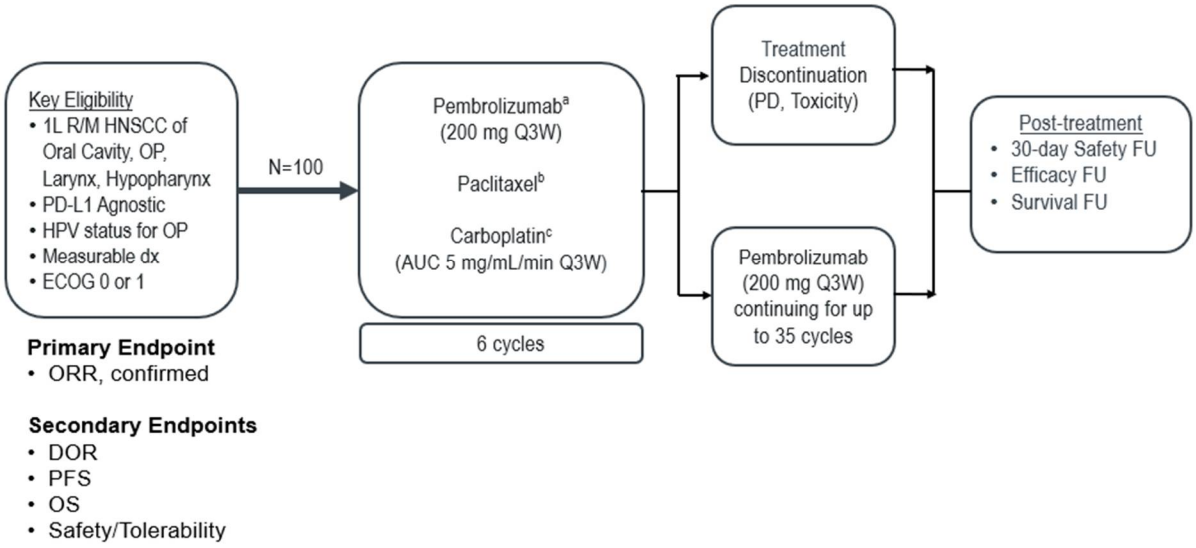
Study Accepts Healthy Volunteers: No

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

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Initial Treatment Phase



1L=first-line; AUC=area under the curve; CR=complete response; dx=disease DOR=duration of response; ECOG=Eastern Cooperative Oncology Group; FU=Follow-up; HNSCC=head and neck squamous cell carcinoma; HPV=Human papillomavirus; OP=oropharynx; ORR=objective response rate; OS=overall survival; PD=progressive disease; PD-L1=programmed cell death ligand-1; PFS=progression-free survival; PR=partial response; Q1W=weekly; Q3W=every 3 weeks; R/M=recurrent/metastatic SD=stable disease.

[a] Participants who complete 35 cycles of pembrolizumab study intervention after achieving SD/PR/CR may be eligible to receive an additional 17 cycles of pembrolizumab if disease progression occurs.

[b] Paclitaxel, per Investigator's choice of:

- 100 mg/m^2 Q1W on Day 1 and Day 8 (6 cycles), **OR**
- 175 mg/m^2 Q3W on Day 1 (6 cycles).

[c] Carboplatin AUC 5 mg/mL/min Q3W on Day 1 (6 cycles).

1.3 Schedule of Activities

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

1.3.1 Initial Treatment Phase

Details regarding procedures listed in this table are outlined in Section 8.0.

Table 1 Initial Treatment Phase

Study Period:	Screening	Intervention (21-Day Cycles)									End of Treatment	Post-treatment Visits			Notes
Visit Number/Title:	Screening	C1			C2 to C4			C5 to C6		C7 to C35		Safety FU	Efficacy FU	Survival FU	
Cycle Day		1	8	15	1	8	15	1	8	1					
Scheduling Window (days)	-28 to -1	+3	±3	±3	±3	±3	±3	±3	±3	±3	At time of treatment discon	30d after last dose (+7d)	Q6W (Y1) or Q9W (Y2+) (± 7d)	Q12W (± 14d)	
Administrative Procedures															
Informed Consent	X														If the investigator plans to treat beyond disease progression, additional consent is required.
Informed Consent for Future Biomedical Research	X														This is optional for the participant.
Inclusion/Exclusion Criteria	X														
Participant Identification Card	X	X[a]													[a] Add the allocation number at the time of treatment/ allocation.
Medical History	X														Includes demographics, smoking, alcohol and tobacco use.
Prior Treatment for HNSCC	X														

Study Period:	Screening	Intervention (21-Day Cycles)									End of Treatment	Post-treatment Visits			Notes
Visit Number/Title:	Screening	C1			C2 to C4			C5 to C6		C7 to C35		Safety FU	Efficacy FU	Survival FU	
Cycle Day		1	8	15	1	8	15	1	8	1					
Scheduling Window (days)	-28 to -1	+3	±3	±3	±3	±3	±3	±3	±3	±3	At time of treatment discon	30d after last dose (+7d)	Q6W (Y1) or Q9W (Y2+) (± 7d)	Q12W (± 14d)	
Prior/Concomitant Medication Review[a]	X	X			X			X		X	X	X			[a] All prior/concomitant medications received within 28 d prior to the first dose of study intervention and up to 30 d after the last dose of study intervention should be recorded. All concomitant medications received for SAEs and ECIs should be recorded.
Contact IRT	X	X	X[a]		X	X[a]		X	X[a]	X	X				When participant provides documented informed consent, contact IRT to obtain screening number. On C1D1, contact IRT to obtain allocation number. At subsequent visits, contact IRT to ensure visits are captured in the IRT system (for centrally sourced study intervention). [a] Visit D8 only applies to participants receiving paclitaxel 100 mg/m^2 Q1W.

Study Period:	Screening	Intervention (21-Day Cycles)									End of Treatment	Post-treatment Visits			Notes
Visit Number/Title:	Screening	C1			C2 to C4			C5 to C6		C7 to C35		Safety FU	Efficacy FU	Survival FU	
Cycle Day		1	8	15	1	8	15	1	8	1					
Scheduling Window (days)	-28 to -1	+3	±3	±3	±3	±3	±3	±3	±3	±3	At time of treatment discon	30d after last dose (+7d)	Q6W (Y1) or Q9W (Y2+) (± 7d)	Q12W (± 14d)	
Assignment of Treatment/ Randomization (Allocation) Number		X													It is strongly preferred that participants receive first dose of study intervention on day of allocation. Study intervention should begin within 3 d of allocation.
Subsequent Anticancer Therapy Status											X	X	X	X	Information regarding poststudy anticancer treatment will be collected if new treatment is initiated. All subsequent anticancer therapy given after study intervention discontinuation should be recorded in the eCRF.
Survival Status		←								→				X	On Sponsor request, participants may be contacted for survival status at any time during the course of the study.
Study Intervention Administration															
Pembrolizumab		X			X			X		X					Pembrolizumab given on D1 (up to 35 cycles). Pembrolizumab should be given first, when given on the same day as other study intervention.
Paclitaxel Administration (Investigator choice of one of the following doses) Note: Paclitaxel should be given after pembrolizumab															
• Paclitaxel (100 mg/m^2 Q1W)		X	X		X	X		X	X						Paclitaxel 100 mg/m^2 given on D1 and D8 (6 cycles) (Dose Modification Table 9).

Study Period:	Screening	Intervention (21-Day Cycles)									End of Treatment	Post-treatment Visits			Notes
Visit Number/Title:	Screening	C1			C2 to C4			C5 to C6		C7 to C35		Safety FU	Efficacy FU	Survival FU	
Cycle Day		1	8	15	1	8	15	1	8	1					
Scheduling Window (days)	-28 to -1	+3	±3	±3	±3	±3	±3	±3	±3	±3	At time of treatment discon	30d after last dose (+7d)	Q6W (Y1) or Q9W (Y2+) (± 7d)	Q12W (± 14d)	
• Paclitaxel (175 mg/m^2 Q3W)		X			X			X							Paclitaxel 175 mg/m^2 given on D1 (6 cycles) (Dose Modificaton Table 9).
Carboplatin		X			X			X							Carboplatin given on D1 (6 cycles). Carboplatin should be given last, when given on the same day as other study intervention (Dose Modification Table 7 and Table 8).
Efficacy Procedures															
Tumor Scans (head and neck, chest, abdomen) and RECIST 1.1 Assessment Note: Scans of the brain and pelvis are optional (if clinically indicated).	X				X[a]			X[a]		X[a]	X		X		BICR confirmation of measurable disease is required at Screening. Timing of tumor scans will be calculated from the date of allocation. [a] Scans are performed at Screening, Wk 6 (+ 7 d, no earlier than Day 42) and every 6 wk (± 7 d) during Y1. After Y1, scans are performed every 9 wk (± 7 d). This schedule will be maintained regardless of treatment delays (Section 8.2.1.2).

Study Period:	Screening	Intervention (21-Day Cycles)									End of Treatment	Post-treatment Visits			Notes
Visit Number/Title:	Screening	C1			C2 to C4			C5 to C6		C7 to C35		Safety FU	Efficacy FU	Survival FU	
Cycle Day		1	8	15	1	8	15	1	8	1					
Scheduling Window (days)	-28 to -1	+3	±3	±3	±3	±3	±3	±3	±3	±3	At time of treatment discon	30d after last dose (+7d)	Q6W (Y1) or Q9W (Y2+) (± 7d)	Q12W (± 14d)	
Safety Procedures															
Full Physical Examination	X [a]										X				[a] Tumor staging needs to be completed per AJCC Cancer Staging Manual, eighth Edition [American Joint Committee on Cancer 2018].
Height	X														
Directed Physical Examination		X	X	X	X	X	X	X		X		X			
Vital Signs (temperature, heart rate, respiratory rate, resting blood pressure, and weight)	X	X	X	X	X	X	X	X	X[a]	X	X	X			[a] For C5 and C6, Visit D8 procedures only apply to participants receiving paclitaxel 100 mg/m^2 Q1W.
12-lead ECG (Local)	X[a]														[a] Required at Screening only. ECG should be performed at subsequent visits only if clinically indicated.
ECOG Performance Status	X[a]	X			X			X		X	X	X			[a] Screening ECOG within 7 d before initiation of study intervention.

Study Period:	Screening	Intervention (21-Day Cycles)									End of Treatment	Post-treatment Visits			Notes
Visit Number/Title:	Screening	C1			C2 to C4			C5 to C6		C7 to C35		Safety FU	Efficacy FU	Survival FU	
Cycle Day		1	8	15	1	8	15	1	8	1					
Scheduling Window (days)	-28 to -1	+3	±3	±3	±3	±3	±3	±3	±3	±3	At time of treatment discon	30d after last dose (+7d)	Q6W (Y1) or Q9W (Y2+) (± 7d)	Q12W (± 14d)	
AE/SAE Review		X	X	X	X	X	X	X	X[a]	X	X	X	X		Report AEs occurring within 30 d after the last dose of study intervention. Report SAEs occurring within 90 d after the last dose of study intervention, or 30 d after the last dose of study intervention if a new anticancer therapy is initiated, whichever is first. [a] For C5 and C6, Visit D8 procedures only apply to participants receiving paclitaxel 100 mg/m^2 Q1W.
Laboratory Procedures/Assessments (Local Laboratory)															
Highly sensitive serum or Urine hCG Pregnancy Test (WOCBP only)	X[a]				X			X		X	X	X			[a] WOCBP require a negative test within 24 h before the first dose of study intervention. If a urine test cannot be confirmed as negative, a serum pregnancy test is required to be confirmed as negative. Serum or urine pregnancy tests will be performed during the study per Appendix 2.

Study Period:	Screening	Intervention (21-Day Cycles)									End of Treatment	Post-treatment Visits			Notes
Visit Number/Title:	Screening	C1			C2 to C4			C5 to C6		C7 to C35		Safety FU	Efficacy FU	Survival FU	
Cycle Day		1	8	15	1	8	15	1	8	1					
Scheduling Window (days)	-28 to -1	+3	±3	±3	±3	±3	±3	±3	±3	±3	At time of treatment discon	30d after last dose (+7d)	Q6W (Y1) or Q9W (Y2+) (± 7d)	Q12W (± 14d)	
HIV, Hepatitis B, and Hepatitis C	X [a]														[a] Required at Screening only if mandated by local health authority.
Hematology	X		X	X	X	X	X	X	X[a]	X	X	X			Perform screening laboratory tests within 7 d prior to the first dose. After C1, laboratory samples can be collected up to 3 d prior to D1 of subsequent cycles. Refer to Appendix 2. [a] For C5 and C6, Visit D8 procedures only apply to participants receiving paclitaxel 100 mg/m^2 Q1W.
Chemistry	X		X	X	X	X	X	X	X[a]	X	X	X			Perform screening laboratory tests within 7 d prior to the first dose. After C1, laboratory samples can be collected up to 3 d prior to D1 of subsequent cycles. Refer to Appendix 2. [a] For C5 and C6, Visit D8 procedures only apply to participants receiving paclitaxel 100 mg/m^2 Q1W.

Study Period:	Screening	Intervention (21-Day Cycles)									End of Treatment	Post-treatment Visits			Notes
Visit Number/Title:	Screening	C1			C2 to C4			C5 to C6		C7 to C35		Safety FU	Efficacy FU	Survival FU	
Cycle Day		1	8	15	1	8	15	1	8	1					
Scheduling Window (days)	-28 to -1	+3	±3	±3	±3	±3	±3	±3	±3	±3	At time of treatment discon	30d after last dose (+7d)	Q6W (Y1) or Q9W (Y2+) (± 7d)	Q12W (± 14d)	
Thyroid Function Tests (T3 or FT3, T4 or FT4, and TSH)	X [a]				X[a]			X[a]		X[a]		X			[a] Perform screening laboratory tests within 7 d prior to the first dose, then at C2 and every 2 cycles thereafter (C4, C6, C8, etc.). After Screening, laboratory samples can be collected up to 3 d prior to D1 of subsequent cycles. The central laboratory may be used only if the local laboratory cannot perform these tests. Refer to Appendix 2.
Urinalysis	X				X			X[a]		X[a]		X			Perform screening laboratory tests within 7 d prior to the first dose. Refer to Appendix 2. [a] Collect on D1 for first 6 cycles (when chemo is given), and then every 6 cycles after C6 (C6, C12, C18, etc.). After Screening, laboratory samples can be collected up to 3 d prior to D1 of subsequent cycles.

Study Period:	Screening	Intervention (21-Day Cycles)									End of Treatment	Post-treatment Visits			Notes
Visit Number/Title:	Screening	C1			C2 to C4			C5 to C6		C7 to C35		Safety FU	Efficacy FU	Survival FU	
Cycle Day		1	8	15	1	8	15	1	8	1					
Scheduling Window (days)	-28 to -1	+3	±3	±3	±3	±3	±3	±3	±3	±3	At time of treatment discon	30d after last dose (+7d)	Q6W (Y1) or Q9W (Y2+) (± 7d)	Q12W (± 14d)	
Coagulation Factors (PT/INR and aPTT/PTT)	X[a]														[a] Perform screening laboratory tests within 7 d prior to the first dose. Additional testing is to be performed as clinically indicated for participants taking anticoagulants. Refer to Appendix 2.
HPV status using CINtec® p16 Histology assay (oropharynx participants only)	X														Historical result may be used. If historical p16 testing result is not available or cannot be performed locally, a new or archival tumor tissue sample must be submitted to the central laboratory, and results must be received prior to allocation.
Biomarkers (Central Laboratory)															
Newly Obtained or Archival Tumor Tissue Collection	X														New or archival tumor tissue sample <5 years of age at time of sample submission must be provided for PD-L1 biomarker analysis prior to allocation (Section 5.1, inclusion criterion #7 and Section 8.1.13).
Blood for Genetic Analysis		X													Collect predose on C1D1. See Section 8.8.

Study Period:	Screening	Intervention (21-Day Cycles)									End of Treatment	Post-treatment Visits			Notes
Visit Number/Title:	Screening	C1			C2 to C4			C5 to C6		C7 to C35		Safety FU	Efficacy FU	Survival FU	
Cycle Day		1	8	15	1	8	15	1	8	1					
Scheduling Window (days)	-28 to -1	+3	±3	±3	±3	±3	±3	±3	±3	±3	At time of treatment discon	30d after last dose (+7d)	Q6W (Y1) or Q9W (Y2+) (± 7d)	Q12W (± 14d)	
Blood for RNA Analysis		X			X			X[a]			X				[a] Collect predose on C1D1, C2D1, C5D1 and at EOT.
Blood for ctDNA Analysis		X			X[a]			X[a]		X[a]	X				Collect predose on C1D1, C2D1, C3D1. [a] After C3D1 collection, the ctDNA samples should be collected within ±7 d of all subsequent scan visits (actual scan date) and at EOT. Collection of ctDNA samples is not required after EOT. After Wk 6, scan visits are every 6 wk (±7 d) during Y1. After Y1, scan visits will occur every 9 wk (±7 d).

AE=adverse event; aPTT=activated partial thromboplastin time; BICR=blinded independent central review; BP=blood pressure; C=cycle; ctDNA=circulating tumor deoxyribonucleic acid; CXDY=Cycle X Day Y; d=day; discon=discontinuation; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; eCRF=electronic case report form; EOT=end of treatment; FT3=free triiodothyronine; FT4=free thyroxine; FU=follow-up; hCG=human chorionic gonadotropin; HIV=human immunodeficiency virus; HNSCC=head and neck squamous cell carcinoma; HPV=Human papillomavirus; INR=international normalized ratio; IRT=interactive response technology; PT=prothrombin time; PTT=partial thromboplastin time; Q1W=weekly; Q6W=every 6 weeks; Q9W=every 9 weeks; Q12W=every 12 weeks; RECIST 1.1=Response evaluation criteria in solid tumors; RNA=ribonucleic acid; SAE=serious adverse event; SoA=schedule of activities; T3=triiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone; Wk(s)=weeks; WOCBP=women of childbearing potential; Y1=Year 1; Y2=Year 2.

1.3.2 Second Course Phase

Further details on Second Course (Retreatment) Phase are outlined in Section 6.1.2 and 8.2.1.4. Second Course retreatment participants may receive up to 17 cycles (approximately 1 year) of pembrolizumab study intervention.

Table 2 Second Course Phase

Study Period:	Intervention (21-Day Cycles)						End of Treatment	Post-treatment Visits			Notes
Visit / Cycle Number	C1	C2	C3	C4	C5	C6 to C17		Safety Follow-up	Second Course Efficacy FU	Survival FU	
Cycle Day	1	1	1	1	1	1					
Scheduling Window (days)	+3	±3	±3	±3	±3	±3	At time of treatment discon	30d after last dose (+7d)	Q6W (Y1) or Q9W (Y2+) (± 7d)	Q12W (± 14d)	
Administrative Procedures											
Informed Consent	X										Reconsent is required at the time of progression if study intervention will continue and/or restart.
Second Course Inclusion/Exclusion Criteria	X										
Contact IRT	X	X	X	X	X	X	X				On C1D1, contact IRT to register the participant in Second Course. At subsequent visits, contact IRT to ensure visits are captured in the IRT system.
Prior/Concomitant Medication Review[a]	X	X	X	X	X	X	X	X			[a] All prior/concomitant medications received within 28 d prior to the first dose of second course study intervention and up to 30 d after the last dose of study intervention should be recorded. All concomitant medications received for SAEs and ECIs should be recorded.

Study Period:	Intervention (21-Day Cycles)						End of Treatment	Post-treatment Visits			Notes
Visit / Cycle Number	C1	C2	C3	C4	C5	C6 to C17		Safety Follow-up	Second Course Efficacy FU	Survival FU	
Cycle Day	1	1	1	1	1	1					
Scheduling Window (days)	+3	±3	±3	±3	±3	±3	At time of treatment discon	30d after last dose (+7d)	Q6W (Y1) or Q9W (Y2+) (± 7d)	Q12W (± 14d)	
Subsequent Anticancer Therapy Status							X	X	X	X	Information regarding poststudy anticancer treatment will be collected if new treatment is initiated. All subsequent anticancer therapy given after study intervention discontinuation should be recorded in the eCRF.
Survival Status	←					→				X	On Sponsor request, participants may be contacted for survival status at any time during the course of the study.
Study Intervention Administration											
Pembrolizumab Administration IV Q3W	X	X	X	X	X	X					
Efficacy Procedures											
Tumor Scans (head and neck, chest, abdomen) and RECIST 1.1 Assessment **Note:** Scans of the brain and pelvis are optional (if clinically indicated).	X[a]		X		X	X	X		X		[a] Baseline scan is the CT or MRI showing PD. Baseline tumor scans must be performed within 28 d before C1. First on-study scan at Wk 6 (+ 7 d, no earlier than 42 d after Cycle 1 Day 1 of Second Course), every 6 wk (± 7 d) during Y1, and every 9 wk (± 7 d) thereafter (a 12-weekly scan schedule may be implemented after Y1 following consultation with the Sponsor). This schedule will be followed regardless of delays in study intervention (see Section 8.2.1.4).
Safety Procedures											
Full Physical Examination	X						X				
Directed Physical Examination		X	X	X	X	X		X			

Study Period:	Intervention (21-Day Cycles)						End of Treatment	Post-treatment Visits			Notes
Visit / Cycle Number	C1	C2	C3	C4	C5	C6 to C17		Safety Follow-up	Second Course Efficacy FU	Survival FU	
Cycle Day	1	1	1	1	1	1					
Scheduling Window (days)	+3	±3	±3	±3	±3	±3	At time of treatment discon	30d after last dose (+7d)	Q6W (Y1) or Q9W (Y2+) (± 7d)	Q12W (± 14d)	
Vital Signs (temperature, heart rate, respiratory rate, resting blood pressure, and weight)	X	X	X	X	X	X	X	X			
12-lead ECG	X [a]										[a] Perform within 7 d prior to first dose in C1. ECG should be performed at subsequent visits only if clinically indicated.
ECOG Performance Status	X [a]	X	X	X	X	X	X	X			[a] Perform within 7 d prior to first dose in C1.
AE/SAE Review	X	X	X	X	X	X	X	X	X		Report AEs occurring within 30 d after the last dose of study intervention. Report SAEs occurring within 90 d after the last dose of study intervention, or 30 d after the last dose of study intervention if a new anticancer therapy is initiated, whichever is first.
Laboratory Procedures/Assessments (Local Laboratory)											
Highly sensitive serum or urine hCG pregnancy test (WOCBP only)	X [a]										[a] Obtain a urine pregnancy test within 72 h before the first dose for WOCBP participants. If a urine pregnancy test cannot be confirmed as negative, a serum pregnancy test is required. Additional urine/serum testing may be performed if clinically warranted, and/or as defined by local regulations.

Study Period:	Intervention (21-Day Cycles)						End of Treatment	Post-treatment Visits			Notes
Visit / Cycle Number	C1	C2	C3	C4	C5	C6 to C17		Safety Follow-up	Second Course Efficacy FU	Survival FU	
Cycle Day	1	1	1	1	1	1					
Scheduling Window (days)	+3	±3	±3	±3	±3	±3	At time of treatment discon	30d after last dose (+7d)	Q6W (Y1) or Q9W (Y2+) (± 7d)	Q12W (± 14d)	
Hematology	X [a]	X	X	X	X	X	X	X			[a] Perform within 7 d prior to first dose in C1 to confirm Second Course eligibility. After Cycle 1, laboratory samples can be collected up to 3 d prior to the scheduled visit. Refer to Appendix 2.
Chemistry	X [a]	X	X	X	X	X	X	X			[a] Perform within 7 d prior to first dose in C1 to confirm Second Course eligibility. After C1, laboratory samples can be collected up to 3 d prior to the scheduled visit. Refer to Appendix 2.
Thyroid Function Tests (T3 or FT3, T4 or FT4, TSH)	X [a]		X		X	X [a]		X			[a] Perform within 7 d prior to first dose in C1, then every 2 cycles thereafter (C3, C5, C7, etc.). After Cycle 1, laboratory samples can be collected up to 3 d prior to the scheduled visit. Refer to Appendix 2.
Urinalysis	X[a]										[a] Perform within 7 d prior to first dose in C1 to confirm Second Course eligibility. Additional testing to be conducted as clinically indicated. Refer to Appendix 2.
Coagulation Factors (PT/INR and aPTT/PTT)	X[a]										[a] Perform within 7 d prior to first dose in C1. Additional testing to be conducted as clinically indicated for participants taking anticoagulants. Refer to Appendix 2.

AE=adverse event; aPTT=activated partial thromboplastin time; C=cycle; CT=computed tomography; CXDY=Cycle X Day Y; d = day; discon = discontinuation; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FT3=free triiodothyronine; FT4= free thyroxine; FU=follow-up; hCG=human chorionic gonadotropin; INR=international normalized ratio; IRT=interactive response technology; IV=intravenous; MRI=magnetic resonance imaging; PD=progressive disease; PT=prothrombin time; PTT=partial thromboplastin time; Q9W=every 9 weeks; Q12W=every 12 weeks; RECIST 1.1=Response evaluation criteria in solid tumors; SAE=serious adverse event; T3=triiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone; Wk(s)=Weeks; WOCBP=women of childbearing potential.

2 INTRODUCTION

Pembrolizumab, in combination with carboplatin and paclitaxel, rather than 5-FU, is being investigated for participants eligible for 1L treatment of R/M HNSCC in this open-label Phase 4 study.

2.1 Study Rationale

Head and neck cancers describe an anatomically heterogeneous group of cancers that arise most often from the oral cavity, the oropharynx, hypopharynx, and the larynx [Dorsey, K. 2013]. More than 90% of head and neck cancers are squamous cell carcinomas, originating from the epithelium of the mucosal lining of the upper aerodigestive tract [Gupta, B., et al 2016]. Head and neck cancers are the ninth most common malignancy in the world, with high mortality rates in developing countries (age-standardized mortality rates of 7.9 and 2.2 per 100,000 in males and females, respectively) [Gupta, B., et al 2016].

More than 90% of patients with HNSCC initially present with disease confined to the head and neck mucosa and/or to the regional cervical lymph nodes [Machiels, J. P. 2011]. Surgery and radiation therapy are markedly effective for patients with Stage I and II disease. However, despite intensive multimodal treatment, approximately 50% of patients with locally advanced Stage III or Stage IV HNSCC recur initially with locoregional disease. However, a significant proportion of these patients ultimately have incurable disease recurrence requiring palliative systemic treatment. The prognosis for patients with R/M HNSCC is dismal and OS is less than 1 year [Argiris, A., et al 2017].

Patients with R/M HNSCC present a therapeutic challenge. Historically, first-line treatment has generally included the combination of either cetuximab or docetaxel with a platinum-based chemotherapy with or without 5-FU, as shown with the OS advantage of the EXTREME regimen. More recently, the KEYNOTE-048 study showed an OS advantage compared with the EXTREME regimen and has replaced it as the new standard of care. KEYNOTE-048, an ongoing Phase 3, open-label study to compare the efficacy and safety of pembrolizumab as monotherapy or in combination with chemotherapy (platinum plus 5-FU) in first-line treatment versus the standard EXTREME chemotherapy regimen (cetuximab in combination with platinum plus 5-FU) is provided in Section 2.2.3. In the population of all participants regardless of PD-L1 expression status, there was a clinically meaningful difference in OS when comparing pembrolizumab plus chemotherapy with standard treatment. The pembrolizumab plus chemotherapy group had a longer DOR than the EXTREME regimen and the safety profile was comparable. There was a clinically meaningful difference in OS when comparing pembrolizumab monotherapy group with standard treatment for participants whose tumors expressed PD-L1 (CPS ≥1). The pembrolizumab monotherapy group had more responders who achieved a CR and a more durable DOR. The safety profile for pembrolizumab monotherapy was favorable. Based on this data, pembrolizumab is now approved in the US and EU as monotherapy and in combination with chemotherapy for 1L R/M HNSCC treatment.

Patients who are asymptomatic usually are treated with monotherapy to balance the side-effects associated with combination regimens. Options for first-line single-agent treatment

include platinum, 5-FU, paclitaxel, docetaxel, methotrexate, cetuximab, gemcitabine, or capecitabine [National Comprehensive Cancer Network 2018].

The available evidence from several exploratory and preclinical studies on the interaction between taxanes and platinum agents is of high interest and suggests that inhibition of microtubule assembly by taxanes [Abal, M., et al 2003] and the formation of DNA adducts by platinum agents together lead to apoptosis of the tumor cell. [Siddik, Z. H. 2003] [Chao, S. Y., et al 2011]. Adding anti-PD-1 to this combination may further potentiate tumor cell death by increasing T-cell mediated immune response.

The idea of combining paclitaxel and anti-PD-1 has been shown in a recent in vitro study. In this study, paclitaxel increased MMP-13 expression in R/M HNSCC cells and suggested that paclitaxel is a strong candidate for use in combination with anti-PD-1 therapy. MMP-13 may play a critical role in the shedding/cleavage of PD-L1 and therefore this may be an important factor of combining paclitaxel with anti-PD-1 [Hira-Miyazawa, M., et al 2018].

Based on the preclinical rationale and emerging clinical data, treatment guidelines also note the use of taxanes combination with platinum as an alternative treatment option.

Taxanes can help expand the treatment options available in the first line, where they can replace 5-FU in the both Pembrolizumab + Platinum + 5-FU regimen per KEYNOTE-048 and EXTREME regimen, as well as in second- or later-line settings and in settings where cisplatin/carboplatin treatment is unsuitable [Iglesias Docampo, L. C., et al 2018].

The combination of taxanes with checkpoint inhibitors is currently being evaluated, such as in the single-arm, Phase 1/2 PemDoc II study of pembrolizumab plus docetaxel [National Library of Medicine 2020]. Furthermore, the following studies are investigating the efficacy and safety of combining taxanes with platinum and cetuximab [National Library of Medicine 2020] [National Library of Medicine 2020] [National Library of Medicine 2020] [National Library of Medicine 2020] [Guigay, J., et al 2019].

Based on the KEYNOTE-048 results, pembrolizumab became the first-line treatment of R/M HNSCC for the majority of patients. Taxanes can help expand the available treatment options in the first line, where they can be used instead of 5-FU. Encouraging early results from preclinical and small clinical studies on the combination of taxanes suggest that taxanes can have additive immunogenic effects with other immuno-oncology based anticancer therapies. The combination of taxanes with checkpoint inhibitors is also currently being evaluated in Phase 1/2 studies. Therefore, there is a strong biological and mechanistic rationale behind combining pembrolizumab with a platinum and a taxane agent when treating patients with R/M SCCHN. In this proposed study, carboplatin was selected over cisplatin as the platinum agent due to the potentially less toxic side effect profile. Based on KEYNOTE-048 approvals, carboplatin and cisplatin were shown to be effective platinum agents for patients with R/M HNSCC [Burtness, B., et al 2019]. In addition, the 2020 NCCN HNSCC guidelines [National Comprehensive Cancer Network 2020], state that either cisplatin or carboplatin can be used as 1L R/M HNSCC systemic therapy component and the guidelines do not favor one platinum agent to another in this situation. Such combination regimens can

take advantage of adding pembrolizumab to further potentiate antitumor activity of platinum and taxane combination, as shown in preclinical and early clinical studies.

The intended population of this Phase 4 study represents patients with a high unmet medical need considering such patients with incurable disease and combination therapy of pembrolizumab with taxanes may provide additional 1L treatment options for R/M HNSCC patients, where they can replace 5-FU in the pembrolizumab + chemotherapy regimen per KEYNOTE-048 study.

2.2 Background

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

2.2.1 Pharmaceutical and Therapeutic Background

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

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

PD-1 and its family members are type I transmembrane glycoproteins containing an IgV–type domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. 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 CD3ζ, PKCθ, and ZAP70, which are involved in the CD3 T-cell signaling cascade [Okazaki, T., et al 2001] [Chemnitz, J. M., et al 2004] [Sheppard, K-A, et al 2004] [Riley, J. L. 2009]. The mechanism

by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [Parry, R. V., et al 2005] [Francisco, L. M., et al 2010]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in R/M HNSCC.

2.2.2 Preclinical and Clinical Studies

2.2.2.1 Completed Studies with Pembrolizumab in Head and Neck Cancer

Refer to the pembrolizumab IB for preclinical and clinical study data for pembrolizumab [IB Edition 18 2020].

2.2.3 Ongoing Clinical Studies

There is an expansive ongoing research program of clinical studies evaluating pembrolizumab in patients with a number of hematological and solid malignancies, including HNSCC. The clinical program for HNSCC consists of the completed and ongoing studies for recurrent/metastatic disease: KEYNOTE-012, KEYNOTE-055, KEYNOTE-040, KEYNOTE-048, LEAP-009, LEAP-010, as well as this study, KEYNOTE-B10.

Completed/Active Clinical Studies of Pembrolizumab in HNSCC

KEYNOTE-012

KEYNOTE-012 is a Phase 1B multicohort study of MK-3475 in participants with advanced solid tumors, including 2 cohorts of participants with R/M HNSCC.

Efficacy was evaluated for a subgroup of 174 participants with recurrent and/or metastatic HNSCC who progressed on or after treatment with platinum containing chemotherapy and cetuximab (n=110) or platinum containing chemotherapy without previous cetuximab (n=64). Participants received 10 mg/kg pembrolizumab Q2W (n=53) or 200 mg Q3W (n=121).

The major efficacy outcome measures were ORR and DOR; secondary outcome measures included PFS and OS. Outcome measures were assessed by BICR using RECIST 1.1. Efficacy results for the 2 subgroups of participants (previously treated with platinum containing chemotherapy with cetuximab versus without cetuximab) were ORR of 14% compared with 20% and similar DOR ≥6 months of 86% and 85%.

The ORR and DOR were similar, irrespective of dosage regimen (10 mg/kg Q2W or 200 mg Q3W) or HPV tumor status. For the combined population (n=174) who progressed after platinum based chemotherapy regardless of cetuximab, the ORR was 16% (95% CI: 11, 22) with a complete response rate of 5%.

The results of KEYNOTE-012, supported by the results of KEYNOTE-055, demonstrate consistent and clinically meaningful activity of pembrolizumab 200 mg Q3W in heavily pretreated participants with HNSCC. The clinically meaningful response rate, coupled with

the durability of response, demonstrates the benefit of pembrolizumab in the treatment of platinum-progressed HNSCC [IB Edition 18 2020].

KEYNOTE-055

KEYNOTE-055 is a Phase 2, nonrandomized, single cohort study of pembrolizumab (200 mg Q3W) monotherapy in a heavily pretreated population of patients with recurrent/metastatic HNSCC who have progressed on prior platinum and cetuximab therapy. Results from 171 participants treated with pembrolizumab were presented by Bauml et al [Bauml, J., et al 2017]. When confirmed responses were evaluated, the ORR was 16% (CR, n=1; PR, n=27; 95% CI: 11% to 23%) with a median DOR of 8 months (range, 2+ to 12+ months); the stable disease rate was 19% (n=33; 95% CI: 14% to 26%). Response rates were slightly higher in participants that were PD-L1 positive; 18% of participants with CPS ≥1% PD-L1 expression responded to pembrolizumab compared with 12% of participants with CPS <1% expression. Nonetheless, PD-L1–negative participants responded to pembrolizumab at a rate that is clinically meaningful; 6- and 12-month PFS and OS rates were relatively similar between PD-L1–negative and PD-L1–positive participants. The results presented by Bauml et al [Bauml, J., et al 2017], confirm findings from KEYNOTE-012 in the recurrent/metastatic HNSCC population; pembrolizumab monotherapy (200 mg Q3W) demonstrates consistent and clinically meaningful activity in heavily pretreated participants with HNSCC.

KEYNOTE-040

KEYNOTE-040 is an ongoing Phase 3, randomized, active-controlled, open-label study of pembrolizumab versus the choice of 3 different SOC therapies in participants with R/M HNSCC. Four hundred and ninety-five participants with R/M HNSCC were randomized 1:1 to receive pembrolizumab 200 mg Q3W or the investigator's choice of one of the following therapies chosen prior to randomization: single-agent methotrexate, single-agent docetaxel, or single-agent cetuximab. Randomization was stratified by ECOG performance status (0 vs. 1), HPV status (oropharynx – p16 positive vs. oropharynx – p16 negative or larynx/hypopharynx/oral cavity HNSCC), and PD-L1 status (strong positive or not; strong positive was defined as TPS ≥50% PD-L1 testing by IHC). The primary objective of the study was to evaluate OS in participants with R/M HNSCC treated with pembrolizumab compared with SOC treatment. Enrollment is closed, but participants are ongoing in the study.

The efficacy and safety data from the final analysis were reported, and at the time of the final analysis, 181 (73%) of 247 patients in the pembrolizumab group and 207 (83%) of 248 patients in the SOC group had died. The median OS in the ITT population was 8.4 months (95% CI 6.4-9.4) with pembrolizumab and 6.9 months (5.9-8.0) with SOC (HR = 0.8, 0.65-0.98; nominal p=0.0161). In the ITT population, the median DOR was 18.4 months in the pembrolizumab group compared with only 5 months for SOC [Cohen, E. E. W., et al 2019].

For participants with a PD-L1 CPS≥1 tumor score, the HR for OS was 0.74 (95% CI 0.58-0.93; nominal p= 0.0049), with a median survival of 8.7 months (95% CI 6.9-11.4) for pembrolizumab versus 7.1 months (5.7-8.3) with SOC. In participants whose tumor had

PD-L1 TPS ≥50% expression, the HR for death was 0.53 (95% CI 0.35-0.81; nominal *p*=0.0014), and median OS was 11.6 months (95% CI 8.3-19.5) compared with 6.6 months (4.8-9.2) for pembrolizumab and SOC, respectively.

Fewer patients treated with pembrolizumab than with SOC had treatment-related AEs (63% vs. 84%), as well as higher toxicity AEs (Grade ≥3 treatment-related AEs 13% vs. 36%).

KEYNOTE-048

KEYNOTE-048 is an ongoing Phase 3, randomized, active-controlled, open-label study of pembrolizumab, or pembrolizumab plus platinum plus 5-FU chemotherapies versus platinum plus 5-FU plus cetuximab (EXTREME regimen) in participants with 1L R/M HNSCC. A total of 882 participants with 1L R/M HNSCC were randomized worldwide 1:1:1 between the 3 arms of the study to examine the efficacy and safety of pembrolizumab (n= 301 participants), or pembrolizumab plus chemotherapy (n= 281 participants) versus SOC with cetuximab and chemotherapy (n= 300 participants) [Burtness, B., et al 2018] [CSR P048V01MK3475 2018]. The primary endpoints of the study are PFS per RECIST 1.1 as assessed by BICR, and OS [CSR P048V01MK3475 2018].

Data from the second interim analysis for KEYNOTE-048 were presented at the 2018 ESMO Congress [Burtness, B., et al 2018]. The cutoff date for this final PFS/interim OS analysis was 13-JUN-2018, with a minimum follow-up of approximately 17 months. For OS, pembrolizumab monotherapy was superior to the EXTREME regimen in participants with a CPS ≥20, HR = 0.61 (95% CI 0.45-0.83, *p*=0.0007), and yielded a median OS that was longer with pembrolizumab (14.9 months) than the EXTREME regimen (10.7 months). Statistical significance was also achieved for pembrolizumab monotherapy in participants whose tumors had PD-L1 expression of CPS ≥1 with HR = 0.78 (95% CI 0.64-0.96, *p*=0.0086) and a median OS of 12.3 months versus 10.3 months in participants receiving the EXTREME regimen [Burtness, B., et al 2018].

Confirmed ORR for pembrolizumab versus EXTREME was 23% versus 36% for CPS ≥20 with a more durable DOR of 20.9 versus 4.2 months, and 19% versus 35% for CPS ≥1 with a median DOR of 20.9 versus 4.5 months for CPS ≥1 [Burtness, B., et al 2018].

Pembrolizumab monotherapy had a more favorable toxicity profile compared with the EXTREME regimen with few treatment-related AEs (58.3% vs. 96.9%), fewer treatment-related Grade 3 to 5 AEs (16.7% vs. 69.0%), and fewer treatment-related AEs that led to treatment discontinuation (4.7% vs. 19.9%) [CSR P048V01MK3475 2018].

Data cutoff of the final analysis was 25-FEB-2019 (approximately 25 months after the last participant was randomized) [CSR P048 2020]. In participants whose tumors had PD-L1 expression, OS results further confirmed the statistically and clinically meaningful results observed at the second interim analysis, with an OS HR = 0.74 [95% CI: 0.61, 0.90] for CPS ≥1 and HR = 0.58 [95% CI: 0.44, 0.78] for CPS ≥20 [CSR P048 2020]. In the population of all participants, there was a clinically meaningful difference in OS when comparing pembrolizumab plus chemotherapy with standard treatment. The pembrolizumab monotherapy group had more responders who achieved a CR and a more durable DOR (22.6

vs. 4.5 months) [Rischin, D., et al 2019]. The safety results at the final analysis were similar to those observed at the second interim analysis.

At the second interim analysis, pembrolizumab + chemotherapy significantly improved OS in the total population (HR = 0.77 [95% CI 0.63-0.93]; *p*=0.00335 [CSR P048V01MK3475 2018]. Additionally, the safety profiles for pembrolizumab + chemotherapy and the EXTREME regimen were comparable (95.3% vs. 96.9% treatment-related AEs; 71.0% vs 69.0% treatment-related Grade 3 to 5 AEs; and 22.8% vs 19.9% treatment-related AEs that led to treatment discontinuation) [CSR P048V01MK3475 2018].

At the final analysis, pembrolizumab + chemotherapy OS results (HR = 0.72 [95% CI: 0.60 0.87] [CSR P048 2020]), further confirmed the statistically significant and clinically meaningful OS observed at the second interim analysis. In the population of participants who tumors express PD-L1, OS was statistically significant and clinically meaningful in PD-L1 CPS ≥1 (HR = 0.65 [95% CI: 0.53, 0.80], *p*=0.00002) and in CPS ≥20 (HR = 0.60 [95% CI: 0.45, 0.82], *p*=0.00044) [CSR P048 2020]. Furthermore, in participants whose tumors had PD-L1 expression, ORR and median time to response were similar, but the pembrolizumab + chemotherapy group had more durable DOR of 6.7 versus 4.3 months for CPS ≥1 and 7.1 versus 4.2 months for CPS ≥20 [Rischin, D., et al 2019]. The safety results at the final analysis were similar to those observed at the second interim analysis.

In summary, for 1L R/M HNSCC, pembrolizumab monotherapy significantly improved OS over the EXTREME regimen in both the CPS ≥20 and CPS ≥1 populations. Responses to pembrolizumab were durable with a more favorable toxicity profile compared with the EXTREME regimen. Pembrolizumab plus chemotherapy improved OS in the total population and in participants whose tumors had PD-1 expression, with a comparable safety profile. Therefore, pembrolizumab-based treatment may be considered a new 1L standard of care for R/M HNSCC.

2.2.4 Information on Other Study-related Therapy

A variety of chemotherapies are used for patients with 1L R/M HNSCC. Early studies showed small survival benefits after treatment with cisplatin or methotrexate or chemotherapy combinations. In next 2 decades, following this early report from the Liverpool consortium, cisplatin, carboplatin, methotrexate, paclitaxel, 5-FU, and their various combinations have been evaluated in several Phase 3 studies [Liverpool Head and Neck Oncology Group 1990] [Forastiere, A. A., et al 2001] [Forastiere, A. A., et al 1992] [Gibson, M. K., et al 2005] [Jacobs, C., et al 1992] [Schornagel, J. H., et al 1995].

The proposed choice of the taxane, paclitaxel, as single-agent SOC chemotherapy is based on the 2020 HNSCC NCCN guidelines [National Comprehensive Cancer Network 2020] recognizing these agents as appropriate treatment options in the first-line setting, input from key opinion leaders, and prior precedence in 1L registration trials. In consideration of institutional preferences and per NCCN recommendations, paclitaxel will be offered in 2 different doses and dosing schedule: 100 mg/m^2 Q1W and 175 mg/m^2 Q3W in this study.

Paclitaxel has been shown in several clinical trials to show clinical efficacy for the treatment of R/M HNSCC. The majority of these studies are in mixed populations of 1L and 2L R/M HNSCC. In the BERIL-1 study, paclitaxel plus buparlisib was compared versus paclitaxel plus placebo for participants with second line R/M HNSCC. Approximately 78 participants with second line R/M HNSCC were enrolled in this study and received paclitaxel 80 mg/m^2 weekly. ORR was observed to be 14% for the paclitaxel plus placebo arm. For this treatment arm, median OS was 6.5 months (5.3-8.8) and median PFS was 3.5 months (2.2-3.7).

Furthermore, there are number of studies investigating the efficacy and safety of taxane plus platinum regimens in 1L R/M HNSCC setting [National Library of Medicine 2020] [National Library of Medicine 2020] [National Library of Medicine 2020] [National Library of Medicine 2020] [Guigay, J., et al 2019].

The combination of taxanes with checkpoint inhibitors is also currently being evaluated, such as in the single-arm, Phase 1/2 PemDoc II study of pembrolizumab plus docetaxel [National Library of Medicine 2020].

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.

With the results of the KEYNOTE-048 clinical study demonstrating survival benefit with pembrolizumab for 1L R/M HNSCC, and considering that the intended population of this Phase 4 study represent patients with a high unmet medical need and incurable disease, combination therapy of pembrolizumab with carboplatin and taxanes may provide additional 1L treatment options for R/M HNSCC patients, where they can replace 5-FU in the pembrolizumab + chemotherapy regimen per KEYNOTE-048 study.

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

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

Adult participants with a histologically or cytologically-confirmed R/M HNSCC that is considered incurable by local therapies will be enrolled in this study.

Throughout this protocol, the term RECIST 1.1 refers to the adjustment of RECIST 1.1 to include a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Refer to Section 4.2.1.1 for further details.

Objectives	Endpoints
Primary	
Objective: To evaluate the efficacy of pembrolizumab + carboplatin + paclitaxel with respect to objective response rate (ORR) per RECIST 1.1 as assessed by blinded independent central review (BICR).	Objective Response: Complete response (CR) or Partial response (PR)
Secondary	
Key Objective: To evaluate the efficacy of pembrolizumab + carboplatin + paclitaxel with respect to duration of response (DOR) per RECIST 1.1 as assessed by blinded independent central review (BICR).	DOR: For participants who demonstrate confirmed 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.
Objective: To evaluate the efficacy of pembrolizumab + carboplatin + paclitaxel with respect to progression-free survival (PFS) per RECIST 1.1 as assessed by blinded independent central review (BICR).	PFS: The time from first dose to the first documented disease progression or death due to any cause, whichever occurs first.
Objective: To evaluate the efficacy of pembrolizumab + carboplatin + paclitaxel with respect to overall survival (OS).	OS: The time from first dose to death due to any cause.
Objective: To assess the safety and tolerability of study intervention with pembrolizumab + carboplatin + paclitaxel.	• AEs. • Study intervention discontinuation due to AEs.
Tertiary/Exploratory	
Objective: To identify molecular (genomic, metabolic, and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of pembrolizumab + carboplatin + paclitaxel and other treatments.	Molecular (genomic, metabolic and/or proteomic) determinants of response or resistance to treatments, using blood and/or tumor tissue.

Objectives	Endpoints
Objective: To investigate the relationship between treatment and PD-L1 as assessed per CPS≥1, CPS≥20, CPS≥50 and TPS≥50%, using tumor tissue samples.	Objective Response

4 STUDY DESIGN

4.1 Overall Design

This is a nonrandomized, single-arm, multisite, open-label study of intravenous pembrolizumab (also known as MK-3475) combined with carboplatin and paclitaxel in participants with R/M HNSCC who have not previously received systemic therapy in the R/M setting (1L intervention). This Phase 4 study will be conducted in participants who have measurable disease per RECIST 1.1 as assessed by BICR, an ECOG performance status of 0 or 1, and have a tumor that is considered incurable by local therapies.

Approximately 100 participants will be allocated to receive pembrolizumab combined with carboplatin and paclitaxel. The study design is shown in Figure 1.

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.

Participation in this study will be dependent on supplying tumor tissue for PD-L1 testing and p16 IHC testing (if HPV status is not already known). The specimen will be evaluated at a central laboratory facility for expression status of PD-L1 in a retrospective manner. In addition, participation will be dependent on confirmation of measurable disease by BICR at baseline.

After allocation, participants will be evaluated with tumor scans to assess response to study intervention every 6 weeks from allocation through Year 1, and every 9 weeks after Year 1. All scans obtained during the study will be submitted to the iCRO for BICR, which will assess the scans using RECIST 1.1 (Section 4.2.1.1) for determination of ORR, DOR, and PFS. Central Verification of Progression (VOP), or request for iCRO to verify PD, is not required.

AE monitoring will be ongoing throughout the study. AEs will be graded in severity according to the guidelines outlined in the NCI CTCAE v5.0.

Participants will receive combined treatment with pembrolizumab, carboplatin, and the investigator's choice of paclitaxel dose (paclitaxel 100 mg/m^2 Q1W or paclitaxel 175 mg/m^2 Q3W) for 6 cycles or until a discontinuation criterion is met. Treatment with pembrolizumab will continue for up to 35 cycles, or until a discontinuation criterion (Section 7.1) is met.

Participants who meet the criteria outlined in Section 6.1.2 may be considered for Second Course treatment with up to 17 cycles of pembrolizumab. Carboplatin and paclitaxel will not be given in the Second Course (Retreatment) Phase.

After the end of treatment, each participant will be followed for a minimum of 30 days for AE monitoring. SAEs will be collected for up to 90 days after the end of treatment or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier. Participants will have post-treatment follow-up for disease status until initiating new anticancer treatment, experiencing disease progression, pregnancy, death, withdrawing consent, or becoming lost to follow-up.

Survival follow-up will begin following PD or the start of new anticancer treatment, whichever occurs first. On Sponsor request, participants may be contacted for survival status at any time during the study.

4.2 Scientific Rationale for Study Design

If the safety profile is acceptable and this combination improves ORR, this study could support the combination of pembrolizumab with carboplatin and paclitaxel and provide additional treatment options for participants with 1L R/M HNSCC.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

This study will use ORR as the sole primary endpoint, and DOR, OS, and PFS as secondary endpoints. OS has been recognized as the gold standard for demonstration of superiority of a new antineoplastic therapy in randomized clinical trials. ORR, DOR and PFS are based on RECIST 1.1 criteria as assessed by BICR. ORR, DOR and PFS are acceptable measures of clinical benefit for a late stage study that demonstrates superiority of a new antineoplastic therapy, especially if the magnitude of the effect is large and the therapy has an acceptable risk/benefit profile. The use of BICR and RECIST 1.1 to assess ORR, DOR and PFS is typically considered acceptable by regulatory authorities. Scans will be submitted to an iCRO and read by independent central review. The final determination of radiologic progression for treatment decisions will be based on the local site investigator/radiology assessment, rather than central assessment of progression.

RECIST 1.1

RECIST 1.1 will be used when assessing images for efficacy measures. Although the original RECIST 1.1 publication recommends a maximum of 5 target lesions in total and 2 per organ, this protocol has implemented an adjustment to RECIST 1.1 to allow a maximum of 10 target lesions in total and 5 per organ, if a larger number of target lesions is needed to adequately represent the tumor burden. Refer to Section 8.2.1.5 for additional detail.

4.2.1.2 Safety Endpoints

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

4.2.1.3 Pharmacokinetic Endpoints

No PK endpoints are planned for this study.

4.2.1.4 Pharmacodynamic Endpoints

No pharmacodynamic endpoints are planned for this study.

4.2.1.5 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, 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/or blood RNA analyses

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

Proteomics and IHC using blood and/or tumor

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

Other blood-derived biomarkers

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

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

4.2.1.6 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 (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

Not applicable.

4.3 Justification for Dose

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

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

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

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

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

4.3.1 Starting Dose for This Study

All participants will receive:

- Pembrolizumab 200 mg IV Q3W. Pembrolizumab dose reductions are not permitted.

- Carboplatin AUC 5 mg/mL/min IV Q3W.
- Paclitaxel 100 mg/m^2 IV Q1W or paclitaxel 175 mg/m^2 Q3W per investigator's choice.

Dose reductions of carboplatin or paclitaxel are permitted per protocol guidelines (see Section 6.6.2).

4.3.2 Maximum Dose/Exposure for This Study

The maximum dose/exposure of pembrolizumab allowed in this study is 200 mg Q3W for approximately 2 years (35 cycles). Participants meeting criteria for Second Course treatment with pembrolizumab (Section 6.1.2) may receive an additional 200 mg IV Q3W for approximately 1 year (17 cycles).

The maximum dose/exposure of carboplatin allowed in this study is AUC 5 mg/mL/min Q3W for 6 cycles. The maximum dose/exposure of the investigator's choice of paclitaxel is paclitaxel 100 mg/m^2 Q1W on Day 1 and Day 8 (6 cycles) or paclitaxel 175 mg/m^2 Q3W on Day 1 (6 cycles).

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).

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

4.4.1 Clinical Criteria for Early Study Termination

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

5 STUDY POPULATION

As stated in the Code of Conduct for Clinical Trials (Appendix 10.1.1), this study includes participants of varying age, race, ethnicity, and sex. The collection and use of these demographic data will follow all local laws and participant confidentiality guidelines while supporting the study of the disease, its related factors, and the IMP under investigation.

Male or female participants with R/M HNSCC that is not suitable for curative treatment with local therapies who are at least 18 years of age will be enrolled in this study.

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

5.1 Inclusion Criteria

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

Type of Participant and Disease Characteristics

1. Has histologically or cytologically-confirmed diagnosis of R/M HNSCC that is considered incurable by local therapies.

    - Has not had prior systemic therapy administered in the recurrent or metastatic setting. Systemic therapy, which was completed more than 6 months prior to providing documented informed consent for this study, if given as part of multimodal treatment for locally advanced disease, is allowed.

    - Has a primary tumor location of oropharynx, oral cavity, hypopharynx, or larynx.

    - Does not have a primary tumor site of nasopharynx (any histology).

    - Does not have an unknown primary tumor.

    - Has M1 or Stage IVC disease (presence of distant metastases) if newly-diagnosed with HNSCC.

Demographics

2. Is male or female, and at least 18 years of age, at the time of providing documented informed consent.

Male Participants

3. Male participants are eligible to participate if they agree to the following during the intervention period and for at least 95 days after carboplatin/paclitaxel.

    - Refrain from donating sperm

- PLUS either:

    - Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

- OR

    - Must agree to use contraception unless confirmed to be azoospermic (vasectomized or secondary to medical cause [Appendix 5]) as detailed below:

- Agree to use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant. Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile-vaginal penetration.

- Male participants must also agree to use male condom when engaging in any activity that allows for passage of ejaculate to another person of any sex.

Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions are more stringent than the requirements above, the local label requirements are to be followed.

Please note that 95 days after carboplatin/paclitaxel is stopped, if the participant is on pembrolizumab only, no male contraception measures are needed.

Female Participants

4. 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 using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis), as described in Appendix 5 during the intervention period and for at least 120 days post pembrolizumab or 30 days post paclitaxel, or 6 months post carboplatin whichever occurs last, and agrees not to donate eggs (ova, oocytes) to others or freeze/store for her own use for the purpose of reproduction during this period. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention.

- A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 24 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 located in Appendix 2.

- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

- Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions are more stringent than the requirements above, the local label requirements are to be followed.

Informed Consent

5. The participant (or legally acceptable representative) has provided documented informed consent/assent for the study. The participant may also provide consent/assent for future biomedical research. However, the participant may participate in the main study without participating in future biomedical research.

Additional Categories

6. Has measurable disease per RECIST 1.1 as assessed by BICR.

   Note: Lesions situated in a previously irradiated area are considered measurable if progression has been shown in such lesions.

7. Has provided tumor tissue for PD-L1 biomarker analysis from a core or excisional biopsy (FNA is not adequate) of a tumor lesion not previously irradiated. Repeat samples may be required if adequate tissue is not provided. FFPE tissue blocks are preferred to slides. A newly obtained biopsy (within 90 days prior to start of study treatment) is strongly preferred, but an archival sample is acceptable.

   Note: Details pertaining to tumor tissue submission can be found in the procedures manual or laboratory manual.

8. Participants with oropharyngeal cancer must have results from testing of HPV status defined as p16 IHC testing using CINtec® p16 Histology assay and a 70% cutoff point. If HPV status was previously tested using this method, no additional testing is required.

   Note: If local p16 IHC testing results are not available or cannot be assessed using this method, a tumor tissue sample must be submitted for p16 IHC testing at the designated central laboratory, and results must be received prior to allocation.

   Note: Oral cavity, hypopharynx, and larynx cancer are not required to undergo HPV testing by p16 IHC, as by convention these tumor locations are assumed to be HPV-negative.

9. Has an ECOG performance status of 0 or 1 assessed within 7 days before initiation of study intervention.

10. Has adequate organ function as defined in the following table (Table 3). Specimens must be collected within 7 days prior to the start of study intervention.

Table 3 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/µL
Platelets	≥100 000/µL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[a]
Renal	
Creatinine OR Measured or calculated[b] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN OR ≥30 mL/min for participant with creatinine levels >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)[c]	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

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

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

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

[c]PTT may be performed if the local lab is unable to perform aPTT.

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

5.2 Exclusion Criteria

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

Medical Conditions

1. Has disease that is suitable for local therapy administered with curative intent.

2. Has PD within 6 months of completion of curatively intended systemic treatment for locoregionally advanced HNSCC.

3. Has a life expectancy of less than 3 months and/or has rapidly progressing disease (eg, tumor bleeding, uncontrolled tumor pain) in the opinion of the treating investigator.

4. Has a diagnosed and/or treated additional malignancy within 5 years prior to allocation with the exception of: curatively treated basal cell carcinoma of the skin, squamous cell carcinoma of the skin, curatively resected in situ cervical cancer, and curatively resected in situ breast cancer. Other exceptions may be considered with Sponsor consultation.

   Note: The time requirement for no malignancy for 5 years does not apply to the cancer for which a participant is enrolled in the study.

Prior/Concomitant Therapy

5. Has had radiation therapy (or other nonsystemic therapy) within 2 weeks prior to allocation or participant has not fully recovered (ie, ≤Grade 1 or at baseline) from adverse events due to a previously administered treatment.

   Note: Participants with ≤Grade 2 neuropathy, ≤Grade 2 alopecia, or laboratory values in Table 3 are an exception to this criterion and may qualify for the study.

   Note: If the participant had a major operation, the participant must have recovered adequately from the procedures and/or any complications from the operation before starting study intervention.

6. 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 coinhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137).

7. Has received a live or live-attenuated vaccine within 30 days prior to the first dose of study intervention. Administration of killed vaccines are allowed.

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

Prior/Concurrent Clinical Study Experience

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

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

Diagnostic Assessments

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

    - Corticosteroid use as premedication for allergic reactions (eg, IV contrast), or as a prophylactic management of AEs related to the chemotherapies specified in the protocol is allowed. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

10. Has known active CNS metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable, (ie, without evidence of progression) for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable and without requirement of steroid treatment for at least 7 days prior to first dose of study intervention.

11. Has a history of any contraindication or has a severe hypersensitivity to any components of pembrolizumab (≥Grade 3) or SOC chemotherapy.

12. 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.

13. Has a history of (non-infectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease.

14. Has an active infection requiring systemic therapy.

15. Has a known history of HIV infection. No HIV testing is required unless mandated by local health authority.

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

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

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

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

Other Exclusions

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

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

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

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study, but are not subsequently allocated in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines.

Participants who fail screening may be re-screened for eligibility following consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

5.5 Participant Replacement Strategy

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

6 STUDY INTERVENTION

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

Clinical supplies (pembrolizumab, carboplatin, and paclitaxel) will be packaged to support enrollment as required. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

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

Table 4 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Arm 1	Experimental	Pembrolizumab	Drug	Solution for Infusion	25 mg/mL	200 mg	IV Infusion	Day 1 of each cycle (35 cycles)	Test Product	IMP	Central
Arm 1	Experimental	Carboplatin	Drug	Solution for Infusion	10 mg/mL	AUC 5 mg/mL/min	IV Infusion	Day 1 of each cycle (6 cycles)	Test Product	IMP	Provided centrally by the Sponsor or locally by the study site
Arm 1	Experimental	Paclitaxel	Drug	Solution for Infusion	6 mg/mL	100 mg/m^2	IV Infusion	Day 1 and Day 8 of each cycle (6 cycles)	Test Product	IMP	Provided centrally by the Sponsor or locally by the study site
Arm 1	Experimental	Paclitaxel	Drug	Solution for Infusion	6 mg/mL	175 mg/m^2	IV Infusion	Day 1 of each cycle (6 cycles)	Test Product	IMP	Provided centrally by the Sponsor or locally by the study site

AUC = area under the curve; IV = intravenous; Q3W = every 3 weeks

The classification of Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product/Auxiliary Medicinal Product (NIMP/AxMP) in this table is based on guidance issued by the European Commission and applies to countries in the European Economic Area (EEA). Country differences with respect to the definition/classification of IMP and NIMP/AxMP may exist. In these circumstances, local legislation is followed.

All study interventions will be administered on an outpatient basis.

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

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

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

6.1.1 Treatment

The initial treatment or first course of pembrolizumab consists of up to 35 treatments, and chemotherapy (paclitaxel and carboplatin) consists of up to 6 treatments.

Note: The number of treatments is calculated starting with the first dose.

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

6.1.2 Second Course

All participants who have completed the first course (or stopped for confirmed CR) may be eligible for up to an additional 17 cycles of pembrolizumab if there is an investigator-determined progressive disease (by RECIST 1.1) after initial treatment. This retreatment is the Second Course of this study.

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

- The participant received pembrolizumab
- No new anticancer treatment was administered after the last dose of study intervention
- The participant meets all of the inclusion criteria and none of the exclusion criteria
- The study is ongoing

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

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Dose Preparation for Pembrolizumab

The dose amount required to prepare the pembrolizumab infusion solution will be based on a fixed-dose of 200 mg. Details on preparation and administration of pembrolizumab are provided in the Pharmacy Manual.

Dose Preparation for Carboplatin

Carboplatin AUC 5 mg/mL/min is administered as an IV infusion over 15-60 minutes Q3W (Day 1 only) for 6 cycles immediately after paclitaxel or per local treatment guidelines and product label. The carboplatin dose should be calculated using Calvert formula (see below). Carboplatin dose should not exceed 750 mg.

Calvert Formula: Total Dose (mg) = (target AUC) x (CrCl + 25)

The estimated GFR used in the Calvert formula should not exceed 125 mL/min

Maximum carboplatin dose (mg) = target AUC 5 (mg•min/mL) x (125 + 25) = 5 x

150 mL/min = 750 mg

Dose Preparation for Paclitaxel

Refer to Section 8.1.8.1. Paclitaxel may be administered per local treatment guidelines and product label.

6.2.2 Handling, Storage, and Accountability

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

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

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

For all study sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard

and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Intervention allocation will occur centrally using IRT. There is one study intervention arm. Participants will be allocated to pembrolizumab, carboplatin, and an investigator's choice of paclitaxel dose (paclitaxel 100 mg/m^2 Q1W or paclitaxel 175 mg/m^2 Q3W). The investigator's choice of paclitaxel dose will be determined prior to allocation and documented in the IRT system.

6.3.2 Stratification

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

6.3.3 Blinding

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

Although there is no treatment blinding in this study, sites and participants are blinded/masked to central testing results for PD-L1 status and biomarker testing.

6.4 Study Intervention Compliance

If there are interruptions in the study intervention schedule, the details of and reason for any interruption of study intervention will be documented in the participant's medical record. Refer to Section 6.6.1 for dose modification and toxicity management for irAEs associated with pembrolizumab and for other allowed dose interruptions of pembrolizumab.

Administration of pembrolizumab, carboplatin, and paclitaxel will be monitored by the investigator or study staff. The total volume of study intervention infused will be compared with the total volume prepared to determine compliance with each dose administered.

6.5 Concomitant Therapy

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

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

- If a participant enters the Second Course, all concomitant medications received within 30 days before the first dose of Second Course treatment should be recorded. After the Second Course Safety Follow-up visit, record all concomitant medications received for SAEs and ECIs as defined in Section 8.4.

All diagnostic, therapeutic, or surgical procedures relating to malignancy should be recorded. Palliative and supportive care is permitted during the course of the study for underlying medical conditions and management of symptoms. Surgery or radiotherapy for tumor control is not permitted during the study; study intervention must first be discontinued if the participant will have oncologic surgery or radiation therapy for the disease under study.

If participants receive additional anticancer therapies, this will be judged to represent evidence of disease progression, and study medication will be discontinued. These participants should complete all end of treatment assessments and continue to be followed for survival in the follow-up period.

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

- Systemic antineoplastic chemotherapy or biological therapy not specified in this protocol.

- Immunotherapy not specified in this protocol (with the exception of denosumab).

  Note: Bisphosphonate or denosumab therapy is allowed as long as it is begun at least 2 weeks prior to allocation. If started after allocation and used for reasons other than for the prevention of skeletal-related events, it will be determined to be consistent with symptomatic progression of disease and clinical progression will be declared at the time followed by discontinuation of study intervention, because bisphosphonate/denosumab is used in the treatment of bone metastases.

- Investigational agents other than those specified in the protocol.

- Radiation therapy, for the disease under study or for any reason in the anatomical sites of the disease under study.

  Note: Discussion with the Sponsor's Clinical Director is required to permit continuation of study intervention in specific circumstances where radiation treatment will not impact the study endpoints assessment during the study.

- Oncologic surgery, to the disease under study.

  Note: Discussion with the Sponsor's Clinical Director is required, to continue with study treatment, if surgery is done for palliative relief of symptoms and does not impact study endpoints assessment, during study.

The following treatments/vaccines are prohibited during the study, but would not necessarily require study intervention discontinuation:

- Live or live-attenuated vaccines within 30 days prior to the first dose of study intervention and while participating in the study.

  Note: Killed vaccines are allowed.

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

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

If the investigator determines that a participant requires systemic glucocorticoids in doses >10 mg/day prednisone (or its equivalent) for any reason that is not an exception in the list below, this is prohibited during the study treatment phase. The investigator must consult the Sponsor's Clinical Director to determine if study intervention may be permitted for cases of glucocorticosteroid use that do not fall in the exceptions list below:

- Systemic glucocorticoids are prohibited, except when used for the following purposes:
  - For inhaled and/or oral steroids as part of a stable regimen for the treatment of asthma/COPD or for an asthma/COPD exacerbation (only short-term oral or IV use in doses >10 mg/day prednisone equivalent).
  - To modulate symptoms from an AE that is suspected to have an immunologic etiology.
  - For treatment of potential irAEs, as indicated in Table 5.
  - For the prevention of drug-related emesis.

- For use as premedication for chemotherapeutic agents specified in the protocol.
- To avoid allergic reactions (eg, IV contrast dye).
- For use as premedication or postmedication to prevent allergic reactions (eg, IV contrast dye in CT scans).
- Brief, limited use (≤7 days) of systemic corticosteroids is permitted when considered SOC (eg, for exacerbation of asthma or chronic obstructive pulmonary disease).
- For chronic systemic replacement doses of steroids (eg, not more than prednisone 10 mg daily or its equivalent) are permitted during the study, as are local steroid injections and topical steroids.
- Topical or ocular steroid administration, intra-articular joint use, oral steroids less than or equal to 10 mg prednisone daily (or its equivalent), or for any other non-parenteral steroid administration.

A short, limited course of steroids or physiologic doses of corticosteroids may be used to treat medical conditions during the study after Sponsor notification and consultation.

The metabolism of paclitaxel is catalyzed by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. In the absence of formal clinical drug interaction studies, caution should be exercised when administering paclitaxel concomitantly with known substrates or inhibitors of the cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Caution should be exercised when paclitaxel is concomitantly administered with known substrates (eg, midazolam, buspirone, felodipine, lovastatin, eletriptan, sildenafil, simvastatin, and triazolam), inhibitors (eg, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin), and inducers (eg, rifampin and carbamazepine) of CYP3A4.
Note: A current list of strong/moderate inhibitors of CYP3A4 can be found at the following website. This list is not all-inclusive. Any substrates or inhibitors not approved in the US will not appear in the list. The investigator should also refer to local approved product labels and use their best medical judgment.
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

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

6.5.1 Rescue Medications and Supportive Care

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

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

6.6 Dose Modification (Escalation/Titration/Other)

Adverse events will be graded using NCI CTCAE v5.0. If appropriate, the investigator may attribute each toxicity event to pembrolizumab, paclitaxel, or carboplatin alone, or to the combination of all 3 drugs, and determine whether dose modification of paclitaxel or carboplatin is required.

Pembrolizumab dose reductions are not permitted. Pembrolizumab treatment may be interrupted or discontinued due to toxicity. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 5 below. See Section 6.5.1 for supportive care guidelines, including use of corticosteroids.

Participants may receive a total of 35 pembrolizumab treatments, 6 carboplatin treatments and paclitaxel treatments, that may be given either as a total of 6 treatments (175 mg/m^2 on Day 1) or 12 treatments (100 mg/m^2 on Day 1 and Day 8).

When pembrolizumab is withheld or discontinued, study treatment with chemotherapy (carboplatin and paclitaxel) may continue for a total of 6 study treatments or until a discontinuation criteria is met, whichever occurs first. If pembrolizumab and carboplatin are withheld or discontinued, treatment with paclitaxel alone may continue, if appropriate. If pembrolizumab and paclitaxel are withheld or discontinued, treatment with carboplatin alone may continue, if appropriate.

When chemotherapy (carboplatin and paclitaxel) is withheld or discontinued, treatment with pembrolizumab alone may continue, if appropriate. If carboplatin is withheld or discontinued, treatment with pembrolizumab and paclitaxel may continue, if appropriate. If paclitaxel is withheld or discontinued, treatment with pembrolizumab and carboplatin may continue, if appropriate.

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

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

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

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

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

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

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea/Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
AST or ALT Elevation or Increased Bilirubin	Grade 2 [a]	Withhold	• Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 [b] or 4 [c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [d]	• Initiate insulin replacement therapy for participants with T1DM • Administer antihyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hyperthyroidism	Grade 2	Continue	• Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d]		

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

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

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

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

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

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

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

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

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

Dose Modification and Toxicity Management of Infusion Reactions Related to Pembrolizumab

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 hrs	Stop Infusion Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (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 intervention.	Participant may be premedicated 1.5 h (±30 minutes) prior to infusion of study intervention 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 intervention.	No subsequent dosing
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 v5.0 (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 or surgical events and/or unforeseen circumstances not related to study intervention. However, study intervention is to be restarted within 3 weeks, 21 days of the originally scheduled dose and within 42 days of the previously administered dose, unless otherwise discussed with the Sponsor. The reason for study intervention interruption is to be documented in the participant's study record.

6.6.2 Dose Modifications for Standard Treatment Chemotherapy

For dose modifications of carboplatin or paclitaxel, refer to the approved product label.

In general, treatment with carboplatin or paclitaxel will be withheld for drug-related Grade 4 hematologic toxicities and for nonhematologic toxicity ≥Grade 3 and dose modifications will be applied for all subsequent doses. Dose modifications for intolerable Grade 2 drug-related AEs may be considered after consultation with the Sponsor.

Dose modifications for hematologic AEs must be based on hematology laboratory tests performed on or up to 3 days prior to Day 1 (and on or up to 3 days prior to Day 8 for

participants assigned to paclitaxel 100 mg/m^2) of the treatment cycle. Treatment-related toxicity must resolve to Grade ≤1 or baseline prior to resuming the subsequent cycle, with the exception of alopecia, Grade 2 fatigue, endocrine-related AEs requiring treatment or hormone replacement, which may be Grade ≤2.

If a dose reduction for toxicity occurs with any agent, the dose may not be re-escalated. Participants can have a maximum of 2 dose modifications (if applicable) to each of the components of study therapy throughout the course of the study for toxicities. If a participant experiences several toxicities and there are conflicting recommendations, the most conservative dose adjustment recommended should be followed (dose reduction appropriate to the most severe toxicity). Participants who require a third dose modification to any particular component will have that agent discontinued.

Reduction of one chemotherapy agent and not the other agent is appropriate if, in the opinion of the investigator, the toxicity is clearly related to one of the treatments. If, in the opinion of the investigator, the toxicity is related to the combination of both chemotherapy agents, both drugs should be reduced according to recommended dose modifications. If the toxicity is related to the combination of 3 agents, all 3 agents should be reduced (if applicable), interrupted or discontinued according to the recommended dose modifications.

Participants may have chemotherapy discontinued and continue on pembrolizumab. Similarly participants may discontinue pembrolizumab and continue on chemotherapy alone during the first 6 cycles, if appropriate.

Chemotherapy may be interrupted for a maximum of 6 weeks (calculated from the omitted Day 1 dose to the next planned dose and must be within 9 weeks of the previously administered Day 1 dose). Sponsor consultation is required to administer paclitaxel and/or carboplatin study intervention after a >6-week dose interruption of chemotherapy.

The CTCAE v5.0 must be used to grade the severity of adverse events. All dose modifications should be based on the AE requiring the greatest dose modification.

Dose modifications for participants receiving carboplatin are provided in Table 7 and Table 8. Please refer to the product insert for further details.

Carboplatin

Carboplatin is contraindicated in the following, and warrants discontinuation of carboplatin for:

- Participants with severe myelosuppression
- Participants with severe renal impairment (with CrCl of <30 mL per minute)
- Participants with bleeding tumors
- Concomitant use with yellow fever vaccine

- Participants with a history of severe allergic reaction to carboplatin or other platinum-containing compounds

Renal function impairment is defined as a decrease in the CrCl below 60 mL/min. In participants with impaired renal function, the dosage of carboplatin should be reduced, and hematological nadirs and renal function monitored. Please refer to Table 8 for additional dose modification guidelines.

HUS is a life-threatening side effect. Carboplatin should be discontinued at the first signs of any evidence of micro-angiopathic hemolytic anemia, such as rapidly falling hemoglobin with concomitant thrombocytopenia, elevation of serum bilirubin, serum creatinine, blood urea nitrogen, or LDH. Renal failure may not be reversible with discontinuation of therapy and dialysis may be required.

Participants should be monitored for signs and symptoms of abnormal liver function or portal hypertension, which do not obviously result from liver metastases.

Carboplatin dose interruption duration for AEs is as per local product label/local institutional guidelines. Dose interruption for chemotherapy is up to a maximum of 6 weeks.

Table 7 Dose Modification Guidelines for Febrile Neutropenia or Documented Infection

Adverse Event	**Number of Occurrences[b]**	**Treatment Modification[b]**
Febrile neutropenia[a] Documented infection	1	Reduce dose by 1 DL The use of growth factors and antibiotics should be considered per local standards.
	2	Reduce dose by 1 DL Consider prophylactic antibiotics for subsequent cycles. The use of growth factors should be strongly considered per local standards
	3	Discontinue carboplatin

ANC=absolute neutrophil count; DL=dose level.

[a] ANC <1000/mm^3 (1.0 x 10^9/L) and a single temperature >38.3°C or sustained temperature ≥38°C for >1 hour.

[b] The dose levels for carboplatin are as follows:

Dose Level 0 = AUC 5

Dose Level -1 = AUC 4 (20% decrease)

Dose Level -2 = AUC 3 (20% decrease)

Dose Level 3 = Discontinue

Table 8 Carboplatin Dose Modifications for Drug-related Adverse Events

Category	Toxicity	Hold Carboplatin Treatment for Grade	Timing for Restarting Carboplatin Treatment	Dose for Restarting Carboplatin Treatment[c]	Discontinue Carboplatin[c]
Hematologic	Neutropenia	Grade 3[a]	Neutrophil count resolves to ≥2,000/mm^3 (2.0 x 10^9/L)	No Reduction *consider G-CSF	Toxicity does not resolve within 6 weeks of expected infusion date or if >2 Dose Level reductions exceeded
		Grade 4[a]	Neutrophil count resolves to ≥2,000/mm^3 (2.0 x 10^9/L)	Reduce by 1 DL *consider G-CSF	Toxicity does not resolve within 6 weeks of expected infusion date or if >2 Dose Level reductions exceeded
	Thrombocytopenia	Grade 2	Platelet count resolves to ≥100,000/mm^3 (100 x 10^9/L) or baseline	No reduction	Toxicity does not resolve within 6 weeks of expected infusion date or if >2 Dose Level reductions exceeded
		Grade 3-4[a]	Platelet count resolves to ≥100,000/mm^3 (100 x 10^9/L) or baseline	Reduce by 1 DL	Toxicity does not resolve within 6 weeks of expected infusion date or if >2 Dose Level reductions exceeded

Category	Toxicity	Hold Carboplatin Treatment for Grade	Timing for Restarting Carboplatin Treatment	Dose for Restarting Carboplatin Treatment[c]	Discontinue Carboplatin[c]
Nonhematologic	Creatinine Increased	Grade 2-4[a]	Toxicity resolves to Grade 0-1	Reduce by 1 DL	Toxicity does not resolve within 6 weeks of expected infusion date or if >2 Dose Level reductions exceeded
	Ototoxicity or Sensory neuropathy	Grade 2	May continue treatment with carboplatin		
		Grade 3-4	Discontinue carboplatin		
	All other nonhematologic toxicities[b]	Grade 3-4[a]	Toxicity resolves to Grade 0-1	Reduce by 1 DL	Toxicity does not resolve within 6 weeks of expected infusion date or if >2 Dose Level reductions exceeded
	Laboratory adverse event[b]	Grade 4	Toxicity resolves to Grade 2 or less	Reduce by 1 DL	Toxicity does not resolve within 6 weeks of expected infusion date or if >2 Dose Level reductions exceeded

DL=dose level; G-CSF=Granulocyte Colony-Stimulating Factor.

[a] Permanent discontinuation should be considered for any severe or life-threatening event. Consult Sponsor before restarting treatment after Grade 4 drug-related AE.

[b] Participants with intolerable or persistent Grade 2 drug-related AE may hold at physician discretion. Permanently discontinue from agent for persistent Grade 2 adverse reactions for which treatment has been held, and did not recover to Grade 0-1 within 12 weeks of the last dose. With investigator and Sponsor agreement, participants with a laboratory adverse event still at Grade 2 after 12 weeks may continue in the study only if asymptomatic and controlled.

[c] The dose levels for carboplatin are as follows:

- Dose Level 0 = AUC 5
- Dose Level -1 = AUC 4 (20% decrease)
- Dose Level -2 = AUC 3 (20% decrease)
- Dose Level -3 = Discontinue

Paclitaxel

Duration of dose interruptions to paclitaxel for AEs is as per local product label/local institutional guidelines, and up to a maximum of 6 weeks.

Paclitaxel should not be administered to participants with neutrophil count <1500 cells/mm^3 (<1.5 × 10^9/L), as measured on or up to 3 days prior to Day 1 of the cycle (and on or up to 3 days prior to Day 8 for participants assigned to paclitaxel 100 mg/m^2).

Participants should not be retreated with subsequent cycles of paclitaxel until neutrophils recover to a level ≥1500 cells/mm^3 (≥1.5 × 10^9/L) and platelets recover to a level ≥100,000 cells/mm^3 (≥100 × 10^9/L).

For Grade 4 neutropenia (neutrophil count <500 cells/mm^3 or 1.5 × 10^9/L), delay paclitaxel until neutrophil count recovers to ≤Grade 1. Resume paclitaxel at a 20% dose reduction for all subsequent cycles, once neutrophil count recovers to ≥1500 cells/mm^3

Paclitaxel should not be given to participants with bilirubin >ULN, or to participants with AST and/or ALT >1.5 × ULN with concomitant alkaline phosphatase >2.5 × ULN as participants with laboratory values above these limits are at increased risk of SAEs (refer to local product label).

Hypersensitivity reactions: In order to avoid the occurrence of severe hypersensitivity reactions, participants should be premedicated with corticosteroids, antihistamines and H_2-receptor antagonists, as per local product label guidance. Minor symptoms such as flushing, skin reactions, dyspnea, hypotension, or tachycardia do not require interruption of paclitaxel therapy. However, severe hypersensitivity reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema, or generalized urticaria require immediate permanent discontinuation of paclitaxel, aggressive symptomatic therapy should be initiated, and the participant should not be challenged with paclitaxel.

If participants develop significant conduction abnormalities during paclitaxel administration, appropriate therapy should be administered and continuous cardiac monitoring (ie, ECG monitoring) should be performed during subsequent therapy with paclitaxel.

Additional dose modifications for paclitaxel are provided in Table 9. Please refer to the local product label/institutional guidelines for further details.

If paclitaxel 100 mg/m^2 study intervention is administered on Day 1 and withheld on Day 8 (ie, for unacceptable toxicity) of a given treatment cycle, then paclitaxel should not be given at Day 15 of the respective treatment cycle. Instead, paclitaxel should be resumed at Day 1 of the subsequent treatment cycle.

Table 9 Paclitaxel Dose Modifications for Drug-related Adverse Events

Toxicity	Grade	Occurrence	Hold Treatment	Dose Modification	Treatment Discontinuation
Liver dysfunction	AST/ALT >2.5 to ≤5 × ULN and AP ≤2.5 × ULN, or AST/ALT >1.5 to ≤5 × ULN and AP >2.5 to ≤5 × ULN	First occurrence	Yes	Per product label	N/A
	AST/ALT >5 × ULN and/or AP >5 × ULN	Discontinue on onset	Yes	N/A	Discontinue on onset
Peripheral Neuropathy	Grade 3, 4	Discontinue on onset	Yes	N/A	Discontinue on onset
Ophthalmic adverse events[+]	≥Grade 2	First occurrence	Per product label	N/A	Consult the Sponsor
Oral Mucositis	Grade 3, 4	First occurrence	Hold until resolved	Per product label	Treatment discontinuation should be considered
	Grade 3, 4	Second occurrence	Hold until resolved	Per product label	Treatment discontinuation should be considered
		Third occurrence	Yes	N/A	Yes
ALT=alanine aminotransferase; AP=alkaline phosphatase; AST=aspartate aminotransferase; N/A=not applicable; ULN=upper limit of normal.					

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

Although this is an open-label study, the emergency unblinding call center will have the intervention schedule for the study available. The emergency unblinding call center should only be used in cases of emergency (see Section 8.1.10). The Sponsor will not provide random code/disclosure envelopes or lists with clinical supplies.

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 be monitored in this study and participate in the study visits and procedures as specified in Section 1.3 and Section 8.11.3 unless the participant has withdrawn from the study per Section 7.2.

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

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

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- Any prolonged interruption of study intervention beyond the permitted periods, for irAE management or other allowed dose interruptions, as noted in Section 6.6.1, require Sponsor consultation prior to restarting treatment. If treatment will not be restarted, the participant will continue to be monitored in the study and the reason for discontinuation of study intervention will be recorded in the medical record.
- Diagnosis of any condition or the need for therapy noted in the exclusion criteria.
- The participant has a confirmed positive serum pregnancy test.
- Radiographic disease progression outlined in Section 8.2.1.5.

  Note: The investigator may elect to continue treatment beyond disease progression after Sponsor communication and obtaining informed consent (addendum) from the participant.
- Any progression or recurrence of malignancy, or any occurrence of another malignancy that requires active treatment.

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

- Intercurrent illness that prevents further administration of treatment.

- Noncompliance with study intervention or procedure requirements.

- New anticancer therapy.

7.2 Participant Withdrawal From the Study

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

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

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from 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 (by education, training, and experience) staff. Delegation of study site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).

- All study-related medical (or dental) decisions must be made by an investigator who is a qualified physician (or dentist when appropriate).

- 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.

- The Day 8 and Day 15 visits are required for all participants for Cycles 1, 2, 3, and 4 to monitor the safety of the participant for the first 4 treatment cycles. However, paclitaxel study intervention administration on Day 8 is only applicable to participants assigned to receive paclitaxel 100 mg/m^2 Q1W. For Cycle 5 and Cycle 6, the Day 8 procedures are only applicable to participants assigned to receive paclitaxel 100 mg/m^2 Q1W. Per the SoA, Cycle 5 and Cycle 6 do not require a Day 15 Visit.

The maximum amount of blood collected from each participant over the duration of the study will be provided in the laboratory manual.

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

8.1 Administrative and General Procedures

8.1.1 Informed Consent

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

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, site personnel will add the treatment/allocation 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 important. Details regarding the disease for which the participant has enrolled in this study will be recorded separately and not listed as medical history.

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

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

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

Medications taken 28 days prior to the first dose of Second Course study intervention will be recorded.

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 (approximately 30 days after the last dose of study intervention). In addition, concomitant medications started during the Second Course Phase through the Second Course Safety Follow-up visit (approximately 30 days after the last dose) 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 intervention allocation. Each participant will be assigned only 1 screening number. Screening numbers must not be re-used for different participants.

8.1.7 Assignment of Treatment/Randomization Number

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

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

8.1.8 Study Intervention Administration

It is strongly preferred that participants receive the first dose of study intervention on the day of allocation. Study intervention should begin within 3 days of allocation. The order of administration of study intervention will be pembrolizumab, followed by paclitaxel, followed by carboplatin.

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

8.1.8.1 Timing of Dose Administration

Pembrolizumab: Pembrolizumab 200 mg will be administered prior to paclitaxel and carboplatin. Pembrolizumab will be administered on an outpatient basis as a 30-minute IV infusion on Day 1 of each 21-day cycle. Sites should make every effort to target infusion timing to be as closest to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of – 5 minutes to +10 minutes is permitted (ie, infusion time is 30 minutes: –5 min/+10 min). The Pharmacy Manual contains specific instructions for pembrolizumab reconstitution, preparation of the infusion fluid, and administration. After Cycle 1 Day 1, pembrolizumab may be administered up to 3 days before or after the scheduled Day 1 of each subsequent cycle due to administrative reasons.

Paclitaxel: Paclitaxel will be administered after pembrolizumab as an IV infusion over 3 hours for 6 cycles as per local practice and labels. All participants should be premedicated with oral or intravenous corticosteroid, antihistamines, and H_2-receptor antagonists prior to paclitaxel administration according to the approved product label and/or standard practice. Additional premedications should be administered as per standard practice. Paclitaxel should be completely administered before initiating carboplatin dose.

- **Paclitaxel (100 mg/m^2 Q1W):** Paclitaxel will be administered on an outpatient basis on Day 1 and Day 8 of each cycle.
- **Paclitaxel (175 mg/m^2 Q3W):** Paclitaxel will be administered on an outpatient basis on Day 1 of each cycle.

Carboplatin: Carboplatin AUC 5 mg/mL/min will be administered on an outpatient basis on Day 1 of each cycle.

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 as outlined in the SoA and Section 8.11.3.

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

8.1.9.1 Withdrawal From Future Biomedical Research

Participants may withdraw their consent for future biomedical research. Participants may withdraw consent at any time by contacting the 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 an open-label study; there is no blinding for this study.

Although there is no treatment blinding in this study, sites and participants are blinded/masked to central testing results for PD-L1 status and biomarker testing.

8.1.11 Domiciling

At the discretion of the investigator, participants may report to the CRU the evening prior to the scheduled day of study intervention administration and remain in the unit until 24 hours postdose. At the discretion of the investigator, participants may be requested to remain in the CRU longer.

8.1.12 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical study that provides information

about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or maintained to ensure that the data obtained are reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

8.1.13 Tumor Tissue for Biomarker Status

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

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

  Or

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

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

Details pertaining to tumor tissue submission can be found in the laboratory manual.

The central laboratory will use the tissue sample to ascertain PD-L1 status. PD-L1 status will be determined by using the PD-L1 IHC 22C3 pharmDx (Investigational Use Only) diagnostic kit. The diagnostic test that will be used to confirm the PD-L1 [TPS or CPS] ≥1 status for eligibility is identical to the US FDA-approved Dako PD-L1 IHC 22C3 pharmDx diagnostic kit. The PD-L1 IHC 22C3 pharmDx assay kit is currently approved to assess PD-L1 status in participants with R/M HNSCC for treatment with pembrolizumab.

The PD-L1 result will be masked to the site.

8.2 Efficacy Assessments

8.2.1 Tumor Imaging and Assessment of Disease

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

In addition to survival, efficacy will be assessed based on evaluation of scan changes in tumor burden over time, until the participant is discontinued from the study or goes into survival follow-up. The process for scan collection and transmission to the iCRO can be found in the SIM. Tumor scans (head and neck, chest and abdomen) are strongly preferred to be acquired by CT. For the head and neck, abdomen and pelvis, contrast-enhanced MRI may be used when CT with iodinated contrast is contraindicated, or when mandated by local practice. The same scan technique should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the response assessment based on scans. Note: For the purposes of assessing

tumor scans, the term "investigator" refers to the local investigator at the site and/or the radiological reviewer at the site or at an offsite facility.

Scans should include the head and neck, chest and abdomen, at all timepoints specified in Section 1.3. Scans of the brain and pelvis are optional (if clinically indicated). For an individual participant, scans should be consistent at all timepoints, (ie, follow-up scans should image the same areas as the baseline area, using the same imaging modality).

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

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

Expedited confirmation of measurable disease based on RECIST 1.1 by BICR at Screening will be used to determine participant eligibility. Confirmation by the BICR that the participant's scans show at least 1 lesion that is appropriate for selection as a target lesion per RECIST 1.1 is required prior to participant allocation.

All scheduled scans for all study participants will be submitted to the iCRO. In addition, a scan that is obtained at an unscheduled time point, for any reason (including suspicion of progression or other clinical reason), should also be submitted to the iCRO if it shows progression, or if it is used to support a response assessment. All scans acquired within the protocol-specified window of time around a scheduled scan visit are to be classified as pertaining to that visit.

If a participant has local radiographic progression per RECIST 1.1, but the participant is achieving a clinically meaningful benefit, the investigator may decide to continue treatment beyond progression following Sponsor consultation. If approved by the Sponsor, study intervention may continue until the next protocol-specified scan or as specified by the Sponsor, until study intervention is discontinued. The Sponsor approval is required prior to obtaining informed consent addendum and the next dose of study intervention following disease progression. Any confirmatory unscheduled scan following initial documentation of disease progression is not required.

8.2.1.1 Initial Tumor Scans

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

The screening scans must be submitted to the iCRO to verify eligibility criteria have been met before allocation.

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

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

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

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

8.2.1.2 Tumor Scans During the Study

The first on-study scan should be performed at Week 6 (+7 days, no earlier than Day 42) from the date of allocation. Subsequent tumor scans should be performed every 6 weeks (42 days ±7 days) or more frequently if clinically indicated. After 1 year, participants who remain on treatment will have scans performed every 9 weeks (63 days ±7 days). Scan timing should follow calendar days and should not be adjusted for delays in cycle starts.

Scans are to be performed until disease progression per RECIST 1.1 is identified by the investigator, or until any of these conditions are met:

- the start of a new anticancer treatment
- pregnancy
- death
- withdrawal of consent
- the end of the study

All supplemental scans must be submitted to the iCRO if scans show PD or to support response assessments.

Objective response should be confirmed by a repeat scan. Tumor scans 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 the regular scan schedule, starting with the next scheduled time point. Participants who receive additional scans for confirmation do not need to undergo the next scheduled scan if it is less than 4 weeks later; scans may resume at the subsequent scheduled time point.

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

8.2.1.3 End of Treatment and Follow-up Tumor Scans

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

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

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

- disease progression as defined by RECIST 1.1 is identified by the investigator (refer to Section 8.2.1.5 for the alternative options available to the investigator)
- the start of a new anticancer treatment
- pregnancy
- death
- withdrawal of consent
- the end of the study

8.2.1.4 Second Course (Retreatment) Tumor Scans

Tumor scans must be performed within 28 days prior to restarting treatment with pembrolizumab. Local reading (investigator assessment with site radiology reading) will be used to determine eligibility. All second course scans should be submitted to the iCRO for quality control, storage, and possible retrospective review.

The first on-study scan should be performed at 6 weeks (+7 days, no earlier than Day 42) after the restart of treatment. Subsequent tumor scans should be performed every 6 weeks (42 days ±7 days) in Year 1 and every 9 weeks (63 days ±7 days) thereafter (a 12-weekly scan schedule may be implemented after Year 1 following consultation with the Sponsor) or more frequently, if clinically indicated.

Scans should continue to be performed until PD per RECIST 1.1 is identified by the investigator, the start of a new anticancer treatment, pregnancy, withdrawal of consent, death, or notification by the Sponsor, whichever occurs first.

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

For participants who discontinue Second Course study intervention without documented disease progression, every effort should be made to continue monitoring their disease status by tumor scans every 6 weeks (42 days ±7 days) in Year 1 and every 9 weeks (63 days ±7 days) thereafter (a 12-weekly scan schedule may be implemented after Year 1 following consultation with the Sponsor) until either the start of a new anticancer treatment, disease progression (per RECIST 1.1 as identified by the investigator), pregnancy, death, or the end of the study, whichever occurs first.

8.2.1.5 RECIST 1.1 Assessment of Disease

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

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

- investigator judgement will determine action
- if the participant is clinically stable and study intervention is to continue, communication with the sponsor is required and a reconsent addendum must be signed. In addition, the following [is/are] to occur:
  - continue scans per protocol schedule (the next scheduled scan should be ≥4 weeks from most recent scan acquired)
  - send scans to iCRO until any of these conditions are met:
    - the start of a new anticancer treatment
    - pregnancy
    - death
    - withdrawal of consent
    - the end of the study

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

- unacceptable toxicity
- clinical signs or symptoms indicating clinically significant disease progression
- decline in performance status

- rapid disease progression or threat to vital organs or critical anatomical sites (eg, CNS metastasis, respiratory failure due to tumor compression, spinal cord compression) requiring urgent alternative medical intervention.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided in Section 8. 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 physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) as per institutional standard.

A brief directed physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard.

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

A full physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, skin, and a complete neurological examination. Height will be measured at Screening only.

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

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 study intervention administration. New clinically significant abnormal findings should be recorded as AEs.

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

8.3.2 Vital Signs

- Temperature, heart rate, respiratory rate, resting blood pressure and weight will be assessed.

- Blood pressure and heart rate measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

- Blood pressure and heart rate measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions.

- Vital signs will be measured in a semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, heart rate and respiratory rate.

8.3.3 Electrocardiograms

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

- Triplicate ECG may be performed, at the site investigator's discretion, if medically necessary or clinically indicated. At each time point when triplicate ECG are required, 3 individual ECG tracings should be obtained as close as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.

8.3.4 Clinical Safety Laboratory Assessments

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

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

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

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

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

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

8.3.4.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

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

8.3.4.2 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 24 hours of the first dose of study intervention. 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 requirements during study treatment and in post-treatment are described in Appendix 2.

8.3.5 Performance Assessments

8.3.5.1 Eastern Cooperative Oncology Group Performance Scale

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

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

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

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

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

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

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

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

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

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

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

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

- All pregnancies and exposure during breastfeeding, from the time of intervention allocation through 120 days following cessation of study intervention, or 30 days following cessation of study intervention if the participant initiates new anticancer therapy must be reported by the investigator.

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

Investigators are not obligated to actively seek AEs or SAEs or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the investigator

considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 10.

Table 10 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Time Period: Consent to Randomization/ Allocation**	**Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period**	**Reporting Time Period: After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Sponsor:**
NSAE	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
SAE including Cancer and Overdose	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/ Lactation Exposure	Report if: - participant has been exposed to any protocol-specified intervention (eg, procedure, washout or run-in treatment including placebo run-in) Exception: A positive pregnancy test at the time of initial screening is not a reportable event.	Report all	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event
ECI (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - potential DILI - require regulatory reporting	Not required	Within 24 hours of learning of event
ECI (do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event

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

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

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

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events, including pregnancy and exposure during breastfeeding, ECIs, cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in allocated participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

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

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

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

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

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), including the pregnancy of a male participant's female partner, that occurs during the study are reportable to the Sponsor.

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

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

The medical reason (example: maternal health or fetal disease) for an elective termination of a pregnancy will be reported as an AE or SAE. Prenatal testing showing fetus will be born

with severe abnormalities/congenital anomalies that leads to an elective termination of a pregnancy will be reported as an SAE for the fetus.

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

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

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

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

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

8.4.7 Events of Clinical Interest

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

Events of clinical interest for this study include:

- An overdose of Sponsor's product, as defined in Section 8.5.
- An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

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

8.5 Treatment of Overdose

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

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

For this study, an overdose of paclitaxel or carboplatin follow standard of care guideline per local package insert.

8.6 Pharmacokinetics

PK parameters will not be evaluated in this study.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Biomarkers

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

- Blood for Genetic Analysis
- Blood for RNA Analysis
- Blood for ctDNA Analysis
- Tumor Tissue

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

8.8.1 Planned Genetic Analysis Sample Collection

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

The planned genetic analysis sample should be obtained predose on Day 1, but may be collected at the next scheduled blood draw, if needed. Sample collection, storage, and shipment instruction for planned genetic analysis samples will be provided in the operations/laboratory manual.

8.9 Future Biomedical Research Sample Collection

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

- Leftover samples listed in Section 8.8

8.10 Medical Resource Utilization and Health Economics

All-cause hospitalizations and ED visits must be reported in the eCRF, from the time of treatment allocation/randomization through 90 days following cessation of study intervention, or 30 days following cessation of study intervention, if the participant initiates new anticancer therapy, whichever is earlier.

8.11 Visit Requirements

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

8.11.1 Screening

Documented informed consent must be obtained 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:

- Laboratory tests are to be performed within 7 days prior to the first dose of study intervention. An exception is hepatitis testing which may be performed up to 28 days prior to the first dose of study intervention. After Cycle 1, laboratory samples can be collected up to 3 days prior to Day 1 of subsequent cycles.

- Evaluation of ECOG is to be performed within 7 days (flexible with a maximum of 7 days) prior to the first dose of study intervention.

- For women of reproductive potential, a urine or serum pregnancy test will be performed within 24 hours prior to the first dose of study intervention. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory).

- Archival tumor sample collection is not required to be obtained within 28 days prior to the first dose of study intervention. Newly obtained tumor tissue may be obtained within 90 days of treatment initiation.

Participants may be rescreened after initially failing to meet the inclusion/exclusion criteria. Before a participant is rescreened, the participant must be screen failed in IRT and the Sponsor must be consulted. Results from assessments during the initial screening period are

acceptable in lieu of a repeat screening test if performed within the specified time frame and the corresponding inclusion/exclusion criteria is met. Participants who are rescreened will retain their original screening number.

8.11.2 Treatment Period

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

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

The Discontinuation Visit should take place at the time study intervention is discontinued for any reason. If the Discontinuation Visit takes place 30 days from the last dose of study intervention, at the time of the mandatory Safety Follow-up Visit, the safety visit is not required. All procedures required at the Discontinuation Visit and at the 30-day Safety Follow-up Visit should be performed. The Discontinuation Visit may either occur within 21 days after the last dose of study intervention, or approximately 30 days after the last dose of study intervention if combined with the 30-Day Safety Follow Visit. The study procedures for both visits (notably laboratory tests) should be performed before initiation of new anticancer therapy.

8.11.4 Post-treatment Visit

8.11.4.1 Safety Follow-up Visit

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

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

8.11.4.2 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 or the start of new anticancer therapy will begin Efficacy Follow-up and should be assessed as outlined in the SoA to monitor disease status. Every effort should be made to collect information regarding disease status and record it in the eCRF until the start of new anticancer therapy, disease progression, pregnancy, death, end of study (or if the participant begins retreatment with pembrolizumab as detailed in Section 6.1.2). Information regarding poststudy anticancer treatment will be collected if new treatment is initiated. Participants who completed all efficacy assessments and/or will not have further efficacy assessments (tumor scans) must enter Survival Follow-Up.

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

8.11.4.3 Survival Follow-up Contacts

Participants 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. Information regarding poststudy anticancer treatment will be collected and recorded in the eCRF if a new anticancer treatment is initiated.

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

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

- For participants who completed assessments in Efficacy Follow-up, the first survival follow-up contact will be scheduled 12 weeks after the last efficacy assessment follow-up visit has been performed.

8.11.5 Survival Status

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

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. Changes to analyses made after the protocol has been finalized, but prior to final database lock, will be documented in an sSAP and referenced in the CSR for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

9.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 9.2-9.12.

Study Design Overview	A Phase 4 study to evaluate the efficacy and safety of MK-3475 plus carboplatin and paclitaxel as first-line treatment of R/M HNSCC
Treatment Assignment	Approximately 100 participants will be enrolled. This is a single-arm, open-label study.
Analysis Populations	Efficacy: All Participants as Treated (APaT) Safety: APaT
Primary Endpoint(s)	ORR per RECIST 1.1 as assessed by BICR
Secondary Endpoints	DOR per RECIST 1.1 as assessed by BICR PFS per RECIST 1.1 as assessed by BICR OS
Statistical Methods for Key Efficacy Analyses	The point estimate of ORR will be provided, together with 95% CI using exact binomial method proposed by Clopper and Pearson (1934) [Clopper, C. J. and Pearson, E. S. 1934].
Statistical Methods for Key Safety Analyses	Counts and percentages of participants with AEs will be provided.
Interim Analyses	No efficacy interim analysis is planned in this study. Periodic data monitoring per Sponsor medical monitoring process will be performed.
Multiplicity	No multiplicity adjustment is planned as there is no hypothesis testing.
Sample Size and Power	The planned sample size is approximately 100 participants. Section 9.9 provides the precision of the ORR estimates.

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 is being conducted as a nonrandomized, open-label study, ie, participants, investigators, and Sponsor personnel will be aware of participant treatment assignments after each participant is enrolled and treatment is assigned.

The clinical biostatistics department will generate the allocation schedule(s) for study intervention assignment.

9.3 Hypotheses/Estimation

Objectives of the study are stated in Section 3.

9.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated are listed below.

9.4.1 Efficacy Endpoints

The definitions of ORR, DOR and PFS below apply to the endpoints based on RECIST 1.1. Per RECIST 1.1, PR and CR should be confirmed by a repeat tumor scan obtained 4 weeks or longer from the date the response was first documented.

ORR: the percentage of participants who achieve a confirmed CR or PR per RECIST 1.1 as assessed by BICR.

DOR: for participants who demonstrate a confirmed CR or PR, DOR is defined as the time from first documented evidence of CR or PR until disease progression per RECIST 1.1 by BICR or death due to any cause, whichever occurs first.

PFS: time from the first dose to the first documented disease progression per RECIST 1.1 by BICR or death due to any cause.

OS: time from the first dose to death due to any cause.

9.4.2 Safety Endpoints

Safety measurements are described in Section 8.3 and Section 8.4.

9.5 Analysis Populations

9.5.1 Efficacy Analysis Population

The APaT population will be used for the analysis of ORR, PFS and OS. The APaT population consists of all allocated participants who received at least one dose of study intervention.

The analysis population for DOR consists of all responders.

9.5.2 Safety Analysis Population

Safety analyses will be conducted in the APaT population, which consists of all allocated participants who received at least one dose of study intervention.

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

9.6 Statistical Methods

9.6.1 Statistical Methods for Efficacy Analyses

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

The efficacy analyses for ORR, DOR and PFS will include responses and documented progression events that occur prior to Second Course treatment.

ORR

The point estimate of ORR will be provided, together with 95% CI using exact binomial method proposed by Clopper and Pearson (1934) [Clopper, C. J. and Pearson, E. S. 1934].

DOR

If sample size permits, DOR will be summarized descriptively using Kaplan-Meier median and quartiles. Only the subset of participants who show a confirmed CR or PR will be included in this analysis. Censoring rules for DOR are summarized in Table 11.

For the DOR analysis, a corresponding summary of the reasons responding participants are censored will also be provided. Responding participants who are alive, have not progressed, have not initiated new anticancer treatment, have not been determined to be lost to follow-up, and have had a disease assessment within approximately 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 anticancer therapy initiated	Last adequate disease assessment	Censor (non-event)
No progression nor death, new anticancer therapy initiated	Last adequate disease assessment before new anticancer therapy initiated	Censor (non-event)
Death or progression immediately after ≥2 consecutive missed disease assessments or after new anticancer therapy, if any	Earlier date of last adequate disease assessment prior to ≥2 missed adequate disease assessments and new anticancer therapy, if any	Censor (non-event)

Situation	Date of Progression or Censoring	Outcome
Death or progression after ≤1 missed disease assessments and before new anticancer therapy, if any	PD or death	End of response (Event)
DOR=duration of response; PD=progressive disease. A missed disease assessment includes any assessment that is not obtained or is considered inadequate for evaluation of response.		

PFS

The non-parametric Kaplan-Meier method will be used to estimate the PFS curve. Since disease progression is assessed periodically, PD can occur any time in the time interval between the last assessment where PD was not documented and the assessment when PD is documented. The true date of disease progression will be approximated by the earlier of the date of the first assessment at which PD is objectively documented per RECIST 1.1 by BICR and the date of death. Death is always considered a PD event. Censoring rules for PFS are summarized in Table 12.

Table 12 Censoring Rules for PFS

Situation	Date of Progression or Censoring
PD or death documented after ≤1 missed disease assessment	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 anticancer therapy	Censored at last disease assessment prior to the earlier date of ≥2 consecutive missed disease assessment and new anticancer therapy, if any
No PD and no death; new anticancer treatment is not initiated	Censored at last disease assessment
No PD and no death; new anticancer treatment is initiated	Censored at last disease assessment before new anticancer treatment
PD=progressive disease; PFS=progression-free survival.	

OS

The non-parametric Kaplan-Meier method will be used to estimate the OS curve.

A summary of the primary analysis strategy for the key efficacy endpoints is provided in Table 13.

Table 13 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable	Statistical Method	Analysis Population	Missing Data Approach
Primary Analyses			
ORR per RECIST 1.1 by BICR	Summary statistics with 95% CI using Exact method based on binomial distribution	APaT	Participants with missing data are considered non-responders
Secondary Analyses			
DOR per RECIST 1.1 by BICR	Summary statistics using Kaplan-Meier method	Responders in APaT population	Censored according to rules in Table 11
PFS per RECIST 1.1 by BICR	Summary statistics using Kaplan-Meier method	APaT	Censored according to rules in Table 12
OS	Summary statistics using Kaplan-Meier method	APaT	Censored at the date participant last known to be alive
APaT=all participants as treated; BICR=blinded independent central review; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; RECIST 1.1=Response Evaluation Criteria in Solid Tumors.			

9.6.2 Statistical Methods for Safety Analyses

The primary safety analyses will include only events that occur prior to Second Course Treatment.

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs and laboratory parameters. The percentage of participants with any AE, a Grade 3-5 AE, a drug-related AE, a serious AE, an AE which is both drug-related and serious, an AE which is both Grade 3-5 and drug-related, and who discontinued due to an AE will be summarized. The number and percentage of participants with increased laboratory toxicity grade shift from baseline will also be provided.

9.6.3 Summaries of Baseline Characteristics and Demographics

The comparability of the treatment group for each relevant demographic and baseline 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 screened, allocated, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables (such as age and gender) and baseline characteristics will be summarized either by descriptive statistics or categorical tables.

9.7 Interim Analyses

Periodic data monitoring per Sponsor medical monitoring process will be performed.

The final analysis is to be performed 9 months after the last participant is enrolled. Participants will continue to be followed after the final analysis until the overall study ends.

9.8 Multiplicity

No multiplicity adjustment will be applied.

9.9 Sample Size and Power Calculations

In this study, approximately 100 participants with R/M HNSCC will be allocated to receive pembrolizumab + carboplatin + paclitaxel. Table 14 shows the two-sided 95% CI for ORR with 100 participants for different observed ORR's based on the exact binomial method proposed by Clopper and Pearson (1934) [Clopper, C. J. and Pearson, E. S. 1934].

Table 14 Two-sided 95% CI for ORR with 100 Participants

Number of Observed Responders	ORR Estimate (%)	95% CI[a] of ORR (%)
30	30	(21.2, 40.0)
35	35	(25.7, 45.2)
40	40	(30.3, 50.3)
45	45	(35.0, 55.3)
50	50	(39.8, 60.2)

CI=Confidence interval; ORR=Objective response rate.
[a] Based on the two-tailed exact CI of a binomial proportion.

9.10 Subgroup Analyses

To determine whether the treatment effect is consistent across various subgroups, the estimate of ORR (with a nominal 95% CI) will be estimated and plotted within each category of the following classification variables:

- Age category (<65, ≥65 years)
- Sex (female, male)
- Race (white, all others)
- Region (North America, Rest of the World)
- ECOG performance status (0, 1)

- HPV status (positive, negative*)
- PD-L1 expression level defined by CPS 1, CPS 20, CPS 50 and TPS 50%, respectively
- Investigator's choice of paclitaxel dose (100 mg/m^2 Q1W, 175 mg/m^2 Q3W)

  * Note: that for primary tumor site outside oropharynx, the convention of negative HPV status will be used.

A Forest plot with point estimates and CIs will be produced to assess the consistency of the treatment effect across the categories of subgroup variables listed above. If the number of participants in a category of a subgroup variable is less than 10% of the APaT population, the subgroup analysis will not be performed for this category of the subgroup variable, and this subgroup variable will not be displayed in the forest plot.

9.11 Compliance (Medication Adherence)

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

9.12 Extent of Exposure

Extent of Exposure for a participant is defined as the number of cycles and number of days for which the participant receives the study intervention. Summary statistics will be provided on the extent of exposure for the overall study intervention, and for pembrolizumab, carboplatin and paclitaxel separately, for the APaT population.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Code of Conduct for Clinical Trials

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

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design 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. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel (or individuals acting on behalf of MSD) to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and 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

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

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

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

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

10.1.5 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical trial Directive 2001/20/EC, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical 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.

10.1.6 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP (eg, International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use GCP: Consolidated Guideline and other generally accepted standards of GCP); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical study.

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

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

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

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

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

10.1.7 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.

10.1.8 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's participants. Source documents and data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source documents are filed at the investigator's site.

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

10.1.9 Study and Site Closure

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

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

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 15 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.
- Pregnancy testing:
  - Pregnancy testing requirements for study inclusion are described in Section 5.1.
  - Pregnancy testing (urine or serum as required by local regulations) should be conducted at monthly intervals during intervention.
  - Pregnancy testing (urine or serum as required by local regulations) should be conducted for the time required to eliminate systemic exposure after the last dose of each study intervention(s) as noted in Section 5.1. The length of time required to continue pregnancy testing for each study intervention is as follows:
    - Pembrolizumab: 120 days
    - Paclitaxel: 30 days
    - Carboplatin: 6 months
  - Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.

Table 15 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count	White Blood Cell (WBC) count with Differential[a]: Neutrophils Lymphocytes Monocytes Eosinophils Basophils		
	Red Blood Cell (RBC) Count			
	Hemoglobin			
	Hematocrit			
Chemistry	Blood Urea Nitrogen (BUN)[b]	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	Bicarbonate or Carbon Dioxide (CO_2)	Chloride	Phosphorus
	Creatinine[c]	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic Pyruvic Transaminase (SGPT)	Total Protein
	Glucose	Calcium[d]	Alkaline phosphatase	
Thyroid Function Tests	Thyroid-stimulating hormone (TSH)	Triiodothyronine (T3) or FT3 (Free Triiodothyronine)	Thyroxine Total (T4) or Free Thyroxine (FT4)[e]	
Coagulation[f]	International normalized ration (INR) or Prothrombin Time (PT)	Activated Partial Thromboplastin Time (aPTT) or Partial Thromboplastin Time (PTT)[g]		
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, (bilirubin, urobilinogen, nitrite, leukocyte esterase) by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Tests	• Highly sensitive serum or urine human chorionic gonadotropin (hCG) pregnancy test (as needed for WOCBP). • Serology (HIV antibody, Hepatitis B surface antigen [HbsAg], and Hepatitis C virus antibody [HCV RNA]). (if mandated by local health authority).			

NOTES:
[a] Absolute Neutrophil Count (ANC) is required at Screening to confirm eligibility. After Screening, absolute or % is acceptable per institutional standard.
[b] Urea is acceptable if blood urea nitrogen (BUN) is not available as per institutional standard.
[c] Glomerular filtration rate (GFR; measured or calculated) or creatinine clearance can be used in place of creatinine.
[d] Corrected calcium should be checked for participants with hypoalbuminemia.
[e] FT4 is preferred, but T4 is acceptable if FT4 cannot be performed locally.
[f] Performed as part of the screening assessment and as clinically indicated for participants taking anticoagulants.
[g] PTT may be performed if the local laboratory is unable to perform aPTT.

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

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

10.3.1 Definition of AE

AE definition

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

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

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

Events meeting the AE definition

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

- Exacerbation of a chronic or intermittent 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."

- Any new cancer (that is not a condition of the study). Progression of the cancer under study is not a reportable event. Refer to Section 8.4.6 for additional details.

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of 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 8.4.6 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 time frame as SAEs to meet certain local requirements. Therefore, these events are considered serious by the Sponsor for collection purposes.

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

- Is associated with an overdose

10.3.4 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/toxicity

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

- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI CTCAE, version 5.0. Any AE that changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.

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

    - Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.

    - Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.

    - Grade 4: Life threatening consequences; urgent intervention indicated.

    - Grade 5: Death related to AE.

Assessment of causality

- Did the Sponsor's product cause the AE?

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

- **The following components are to be used to assess the relationship between the Sponsor's product and the AE; the greater the correlation with the components and**

their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the AE:

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

- **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with 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 study is a single-dose drug study; or (4) Sponsor's product(s) is/are only used 1 time.)

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

  - If yes, did the AE recur or worsen?

  - If yes, this is a positive rechallenge.

  - If no, this is a negative rechallenge.

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

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

MODIFICATION GUIDELINES IN THE PROTOCOL, AND IF REQUIRED, THE INIRB/IEC.

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

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

- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a 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.)

- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes.

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

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

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

- For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each AE causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (ie, to all agents in the regimen). However, causality attribution

may be assigned to a single agent if in the investigator's opinion, there is sufficient data to support full attribution of the AE to the single agent.

Follow-up of AE and SAE

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

- New or updated information will be recorded in the CRF.

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

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

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

- The primary mechanism for reporting to the Sponsor will be the EDC tool.
    - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
    - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
        - Reference Section 8.4.1 for reporting time requirements.

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

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

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

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

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure e-mail of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.

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

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

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

10.4 Appendix 4: Device Events, Adverse Device Events, and Medical Device Incidents: Definitions, Collection, and Documentation

Not applicable.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

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

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

Women in the following categories are not considered WOCBP:

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

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

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the 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.

Women of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

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

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

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

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt 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] • 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 can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
[a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. [b] If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. [c] IUS is a progestin releasing IUD. Note: The following are not acceptable methods of contraception: - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM. - Male condom with cap, diaphragm, or sponge with spermicide. - Male and female condom should not be used together (due to risk of failure with friction).

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

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

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

The specimens consented and/or collected in this study as outlined in Section 8.9 will be used in various experiments to understand:

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

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

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

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

a. Participants for Enrollment

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

b. Informed Consent

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

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

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen(s)

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

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

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

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

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

5. Biorepository Specimen Usage[3, 4]

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

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

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

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

7. Retention of Specimens[3, 4]

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

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

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

8. Data Security[3, 4]

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

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

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

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

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

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

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

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

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

12. Questions

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

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10.7 Appendix 7: Country-specific Requirements

Not applicable.

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

Not applicable.

10.9 Appendix 9: Abbreviations

Abbreviation	Expanded Term
5-FU	5-fluorouracil
1L	First Line
2L	Second Line
ADL	activities of daily living
AE	adverse event
AJCC	American Joint Committee on Cancer Staging Manual
ALT	alanine aminotransferase
APaT	All Participants as Treated
AP	alkaline phosphatase
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the curve
BCG	*Bacillus Calmette–Guérin*
BICR	blinded independent central review
BP	blood pressure
C1D1	Cycle 1, Day 1
CD3	cluster of differentiation 3
CD28	cluster of differentiation 28
CD3ζ	CD3 zeta
CI	confidence interval
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease caused by severe acute respiratory syndrome coronavirus 2
CPS	combined positive score
CrCl	creatinine clearance
CR	complete response
CRF	Case Report Form
CRU	clinical research unit
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTCAE 5.0	Common Terminology Criteria for Adverse Events, Version 5.0
ctDNA	circulating tumor deoxyribonucleic acid
CTFG	Clinical Trial Facilitation Group
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
d	Day(s)
D1	Day 1
DILI	drug-induced liver injury
DL	dose level
DNA	deoxyribonucleic acid
DOR	Duration of response
ECG	electrocardiogram
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
ED	emergency department
EDC	electronic data collection
eDMC	external Data Monitoring Committee

Abbreviation	Expanded Term
EEA	European Economic Area
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOT	End of Treatment
EU CTR	European Union Clinical Trials Regulation
FDAAA	Food and Drug Administration Amendments Act
FEV1	forced expiratory volume in 1 second
FFPE	formalin-fixed, paraffin embedded
FNA	fine needle aspirate
FSH	follicle stimulating hormone
FT3	free triiodothyronine
FT4	free thyroxine
FU	follow-up
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony-Stimulating Factor
GFR	glomerular filtration rate
GI	gastrointestinal
HBsAg	Hepatitis B surface antigen
hCG	human chorionic gonadotropin
HIV	human immunodeficiency virus
HNSCC	head and neck squamous cell carcinoma
HPV	human papillomavirus
HR	hazard ratio
HRT	hormone replacement therapy
HUS	hemolytic-uremic syndrome
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
iCRO	imaging clinical research organization
IEC	Independent Ethics Committee
Ig	immunoglobulin
IgG4	immunoglobulin G4
IgV	immunoglobulin-variable
IHC	immunohistochemistry
IMP	Investigational Medicinal Product
IND	Investigational New Drug
irAE(s)	immune-related AE(s)
IRB	Institutional Review Board
IRT	interactive response technology
ITT	intent-to-treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
IVD	in vitro diagnostic
LAM	lactational amenorrhea method
LDH	lactate dehydrogenase
mAb	monoclonal antibody
MRI	magnetic resonance imaging
mRNA	messenger RNA
MSI	microsatellite instability
NCCN	National Comprehensive Cancer Network

Abbreviation	Expanded Term
NCI	National Cancer Institute
NIMP	Non-Investigational Medicinal Product
NSCLC	non–small cell lung cancer
NSAIDS	nonsteroidal anti-inflammatory drugs
OP	oropharynx
OR	objective response
ORR	objective response rate
OS	overall survival
OTC	over-the-counter
PBPK	physiologically-based PK
PCL	Protocol Clarification Letter
PD	progressive disease
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PFS	progression-free survival
PK	pharmacokinetic
PKCθ	protein kinase C-theta
po	orally
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time
Q1W	weekly
Q2W	every 2 weeks
Q3W	every 3 weeks
Q6W	every 6 weeks
Q9W	every 9 weeks
Q12W	every 12 weeks
RECIST 1.1	Response Evaluation Criteria In Solid Tumors (update and clarification 1.1)
R/M	recurrent/metastatic
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
SHP-1/2	Src homology 2 domain-containing protein tyrosine phosphatase 1/2
SIM	site imaging manual
SNP	single nucleotide polymorphism
SoA	schedule of activities
SOC	Standard of Care
sSAP	supplemental Statistical Analysis Plan
SUSAR(s)	suspected unexpected serious adverse reaction(s)
TMDD	target-mediated drug disposition
TPS	tumor proportion scoring
ULN	upper limit of normal
US	United States
VOP	verification of progression
WBC	white blood cell
WOCBP	woman/women of childbearing potential
WONCBP	woman/women of nonchildbearing potential
ZAP70	zeta-chain-associated protein kinase

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