Title Page

THIS PROTOCOL AMENDMENT AND ALL OF THE INFORMATION RELATING TO IT ARE CONFIDENTIAL AND PROPRIETARY PROPERTY OF MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC., WHITEHOUSE STATION, NJ, U.S.A.

Protocol Title: A Phase 3 Randomized, Open-Label Clinical Study to Evaluate the Efficacy and Safety of Pembrolizumab plus Epacadostat, Pembrolizumab Monotherapy, and the EXTREME Regimen as First line Treatment for Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma (KEYNOTE-669/ECHO-304)

Protocol Number: 669-04/ECHO-304-04 / NCT03358472

Compound Number: MK-3475/INCB024360

This study is co-funded by Incyte and MSD.

Execution of Study:

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
(Referenced herein as MSD)

One Merck Drive
P.O. Box 100
Whitehouse Station, New Jersey, 08889-0100, U.S.A.

Global Sponsor of the Study:

Incyte Corporation (Referenced herein as Sponsor)
1801 Augustine Cut-Off
Wilmington, Delaware, 19803, U.S.A.

Regulatory Agency Identifying Number(s):

IND NUMBER: 134,159

EudraCT NUMBER: 2017-001338-24

Approval Date: 12-Jun-2018

MSD Signatory

Typed Name: Date
Title:

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

Investigator Signatory

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

Typed Name: Date
Title:

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment 04

Overall Rationale for the Amendment:

The external data monitoring committee (eDMC) analysis of the KEYNOTE-252/ECHO-301 blinded clinical study, a Phase 3 study evaluating epacadostat in combination with pembrolizumab in participants with unresectable or metastatic melanoma, determined that the study did not meet the pre-specified endpoint of improvement in progression-free survival for the combination of pembrolizumab and epacadostat compared to pembrolizumab and placebo. The eDMC further determined that the overall survival endpoint is not expected to reach statistical significance. These results are specific to melanoma, and cannot be extrapolated to other tumor types. Of note there were no new safety concerns with the pembrolizumab + epacadostat combination compared to pembrolizumab monotherapy. Given that there is no confirmed lack of efficacy of pembrolizumab + epacadostat in other tumor types, the Sponsor and MSD consider interruption of study treatment unnecessary in KEYNOTE-669/ECHO-304. Enrollment in this study was permanently stopped on 02-MAY-2018 as a strategic decision. For participants who are considered to be obtaining ongoing clinical benefit, continued study treatment will be at the discretion of the investigator, after a discussion with the participant of the observed results from KEYNOTE-252/ECHO-301.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
1 Synopsis 2. Schedule of Activities (SoA)	Addition of notes to clarify that after the first imaging assessment for efficacy analysis, participants may choose to discontinue from the study or continue study treatment as per protocol after participant discussion with the investigator.	Given the latest results for pembrolizumab plus epacadostat treatment from melanoma study ECHO-301/KEYNOTE-252, as of 02-MAY-2018 enrollment was permanently stopped in KEYNOTE-669/ECHO-304. 89 participants were randomized into the study. Participants will be given the option to discontinue from the study or continue study treatment. The study will remain open to allow participants access to study treatment and to allow collection of preliminary efficacy data in this HNSCC indication. Efficacy procedures after Week 9 are no longer being mandated.

Section # and Name	Description of Change	Brief Rationale
		Where deletion of text could cause confusion, due to the design of the study to date, the text has been left unchanged and a note has been added.
3.2.3 Ongoing Clinical Studies 5.1 Overall Design	KEYNOTE 252/ECHO-301 related text inserted. Inserted note that enrollment was stopped; after the first imaging assessment at Week 9 (± 7 days), participants have the option to continue on the study after participant discussion with the investigator, all study efficacy procedures will stop after Week 9 and thereafter will be performed as per local standard of care (SoC). Clarified safety procedures for Groups 1, 2, and 3.	
1. Synopsis 5.2 Number of Participants	Addition of text stating that as of 02-MAY-2018 enrollment was stopped and 89 participants were enrolled in the study.	
7.2.6 Second Course Phase 7.4 Blinding	Addition of note, and related changes, that imaging assessments will no longer be made by blinded independent central review (BICR); all disease progression will be assessed by the investigator based on RECIST 1.1.	
1. Synopsis 2. Schedule of Activities (SoA) 4. Objectives/Hypotheses and Endpoints 5.1 Overall Design 5.4.1 Rationale for Endpoints	Removed references to BICR assessment of disease progression.	

Section # and Name	Description of Change	Brief Rationale
8.1 Discontinuation of Study Treatment 9.1.9.1.3 Group 3 EXTREME Regiment Dose Administrations 9.2.1.3 End of Treatment and Follow-up Tumor Imaging 9.2.1.4 Second Course Phase Tumor Imaging 9.2.1.5 RECIST 1.1 Assessment of Disease 9.9.2 Treatment Phase		
9.2.1 Tumor Imaging and Assessment of Disease 9.2.1.1 Initial Tumor Imaging	Addition of note that central review of imaging and iRECIST is no longer applicable. Section updated accordingly.	
2. Schedule of Activities (SoA) 9.2.1.2 Tumor Imaging During the Study 9.2.1.4 Second Course Phase Tumor Imaging	Addition of note that central review of imaging and iRECIST is no longer applicable. After the first on-study imaging assessment at Week 9, further imaging will be performed as per local SoC guidelines. Section updated accordingly. Inserted text that imaging for disease assessments will be performed as per local SoC guidelines; only the date of scans performed as per SoC needs to be documented in the eCRF.	
9.2.1.3 End of Treatment and Follow-up Tumor Imaging	Addition of note that there is no protocol specified imaging after the Week 9 assessment for efficacy analysis. Section updated accordingly.	

Section # and Name	Description of Change	Brief Rationale
	Removal of reference to iRECIST. Addition of clarification that end of treatment (EOT) scan will be performed for participants who discontinue study treatment before the first scheduled on-study imaging for efficacy analysis.	
1. Synopsis 4. Objectives/ Hypotheses and Endpoints	Addition of notes to clarify the secondary efficacy endpoint of ORR based on RECIST 1.1 by investigator determination will become the primary endpoint; safety endpoints will remain unchanged; all other efficacy endpoints will no longer be collected after Week 9. ORR and safety objectives and endpoints reworded. All efficacy objectives/endpoints deleted.	The study scope has been reduced to collect preliminary efficacy data for combination treatment in recurrent or metastatic head and neck squamous cell carcinoma. Where deletion of text could cause confusion, due to the design of the study to date, the text has been left unchanged and a note has been added.
1. Synopsis	The estimated duration of the trial was decreased from 50 to 41 months.	
2. Schedule of Activities (SoA)	Deleted note that all post-study anticancer therapy needs to be recorded. Clarified that monthly pregnancy test should occur before each cycle. Removed text about repeating labs after the end of treatment and in regard to unresolved abnormal labs during Safety Follow-Up; added labs should be followed up as per sites' practices.	
2.1.2 EXTREME Regimen Arm (Group 3)	Safety Procedures/Assessments after Week 9 changed to as per SoC.	

Section # and Name	Description of Change	Brief Rationale
5.1 Overall Design	Inserted note that the primary objective will evaluate the endpoint of ORR based on RECIST 1.1, as assessed by the investigator, after completion of the first imaging assessment; all other efficacy endpoints will no longer be collected.	
5.1.1 Data Monitoring Committee 12.3 Appendix 3: Study Governance Considerations, Data Monitoring Committee	Removed text referring to an interim analysis.	
5.4 Scientific Rationale for Study Design	Removed text referring to PFS and OS endpoints supporting regulatory approval of pembrolizumab plus epacadostat for patients with R/M HNSCC.	
5.4.1.1 Efficacy Endpoints 5.4.1.1.1 RECIST 1.1	Addition of note that the primary endpoint will be ORR based on RECIST 1.1 as assessed by the investigator; transmission of images for central review of imaging is no longer required. After the Week 9 imaging, all other efficacy endpoints will no longer be collected or performed. Deletion of all text relating to PFS, OS, DOR.	
5.4.1.1.1 RECIST 1.1	Addition of note that RECIST 1.1 will be assessed by the investigator and transmission of images to the central review of imaging is no longer required.	

Section # and Name	Description of Change	Brief Rationale
5.4.1.1.2 Modified RECIST for Immune-based Therapeutics (iRECIST) 9.2.1.6 iRECIST Assessment of Disease Appendix 8	Addition of note that this section is no longer applicable; iRECIST data will no longer be collected. Participants with radiographic disease progression as determined by RECIST 1.1 will discontinue from the study and be followed for safety monitoring, as detailed in Section 9.3; no confirmatory scans are required.	
2.1 Initial Treatment Phase 5.4.1.5 Rationale for Patient Reported Outcomes 9.2.2 Patient Reported Outcomes	PROs will no longer be collected after Cycle 4 and the SoAs were revised accordingly and notes were added where applicable.	
7.2.6 Second Course Phase	Removed text referring to additional primary endpoints.	
12.2 Appendix 2: Clinical Laboratory Tests	Revised text to indicate that all laboratory tests will be performed by the local laboratory.	
10. Statistical Analysis Plan	Entire section revised to reflect changes in objectives and endpoints, as well as removed all references to BICR assessment of disease progression.	
1. Synopsis	Text relating to follow-up of participants that discontinue treatment for reasons other than disease progression and replaced with text relating to discontinuation from the study after the Safety Follow-up Visit.	The final visit in the study will be the Safety Follow-up Visit. There will be no follow-up for survival status. Participants currently in follow-up or in survival follow-up are considered to have completed the study. However, standard safety reporting should continue, as applicable.

Section # and Name	Description of Change	Brief Rationale
2. Schedule of Activities (SoA)	Deletion of columns for Follow-up and Survival Follow-up. Deletion of row for survival status assessment.	
5.1 Overall Design	Addition of note that the last study visit is the Safety Follow-up Visit.	
8.2 Withdrawal from the Study	Deletion of text indicating that participants who discontinue/withdraw should be encouraged to continue to be followed for Survival status.	
8.3 Lost to Follow-up	Addition of a note that this is no longer applicable. There will be no additional efforts to contact participants who are lost to follow-up.	
9.2.1.3 End of Treatment and Follow-up Tumor Imaging	Deletion of text relating to imaging follow-up after treatment discontinuation for reasons other than disease progression.	
9.9.4.1 Safety Follow-up Visit	Addition of note that the last study visit is the Safety Follow-up Visit. Added text that participants currently in follow-up or in survival follow-up are considered to have completed the study; these participants are not required to attend any further visits. Assessment and recording of AEs will be performed as per Section 9.3.	

Section # and Name	Description of Change	Brief Rationale
9.9.4.2 Follow-Up Visits	Addition of a note that this section is no longer applicable. Participants currently in post-treatment follow-up are considered to have completed the study once they have attended the Safety Follow-up Visit. Assessment and recording of AEs will be performed as per Section 9.3.	
9.9.4.3 Survival Follow-up	Addition of a note that this section is no longer applicable. Participants currently in Survival Follow-up are considered to have completed the study; these participants will no longer be contacted for survival information. Assessment and recording of AEs will continue as per Section 9.3.	
9.9.7 Survival Status	Addition of a note that this section is no longer applicable; survival data is no longer being collected.	
5.1 Overall Design	Changed carboplatin infusion time from 30 to 60 minutes.	Correction
7.2.1 Dose Modification for Immune-related AEs	Table 4 – Added that, in case of recurrent Grade 3 colitis, participants will permanently discontinue treatment.	To align with KEYTRUDA® Summary of Product Characteristics (SmPC) and Company Core Data Sheet (CCDS).
	Table note #4 – inserted clarification on grade of AE to which the note applies.	Consistency and alignment with current clinical information for pembrolizumab and epacadostat.

Section # and Name	Description of Change	Brief Rationale
7.2.1.2 Procedures for Participants Exhibiting Serotonin Syndrome	Added guidance for participants experiencing moderate or severe unconfounded SS, without concomitant SSRI or SNRI usage, or serotonergic concomitant medications.	Alignment with current clinical information for epacadostat.
7.2.5 Dose Interruptions Unrelated to Adverse Events	Added that dose interruptions are permitted for situations other than treatment-related AEs.	Clarification
7.2.6 Second Course Phase	Removed a note about participants' initial treatment.	Clarification
7.5.1 Dose Preparation	Addition of reference to the Pharmacy Manual for preparation of epacadostat in cases where a participant is unable to swallow or has feeding tube.	Clarification
7.7.3 Prohibited Medications and Measures	Removed mefenamic acid from the list of prohibited UGT1A9 inhibitors. Deleted a note that radiation therapy may be considered to a solitary lesion or to the brain.	This change was made to align with the current epacadostat IB. Clarification
9.1.9.1 Timing of Dose Administration	Deleted text from the sentence about Cycle 1 Day 1 regarding signing the ICF.	Correction
9.1.12 Calibration of Equipment	Updated equipment calibration language.	Textual revisions were applied to clarify investigator responsibility for calibration and maintenance of study equipment.
9.9.4.1 Safety Follow-up Visit	Updated Safety Follow-up Visit language.	To remove conflict for reporting AEs/SAEs

Section # and Name	Description of Change	Brief Rationale
6.2 Exclusion Criteria 7.1 Treatments Administered 7.7.4.3 Supportive Care Guidelines for Cisplatin and Carboplatin 12.9 Appendix 9	Removed Appendix 9: Cisplatin Market Authorization (only for sites conducting the study in France) and all references to this Appendix.	The information in this appendix is unnecessary as no participants were enrolled in France and enrollment is stopped.
Throughout	Correction of typographical, editorial and formatting errors.	Revisions were applied for consistency and as corrections.

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1. Synopsis

Protocol Title:

A Phase 3 Randomized, Open-Label Clinical Study to Evaluate the Efficacy and Safety of Pembrolizumab plus Epacadostat, Pembrolizumab Monotherapy, and the EXTREME Regimen as First line Treatment for Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma (KEYNOTE-669/ECHO-304)

Short Title:

Pembrolizumab plus epacadostat, pembrolizumab monotherapy, and the EXTREME regimen as first line treatment for R/M HNSCC (KEYNOTE-669/ECHO-304)

Objectives/Hypotheses and Endpoints:

All objectives apply to all randomized participants with recurrent or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC).

NOTE: As of Amendment 04, the primary endpoint of the study will be objective response rate (ORR) based on Response Evaluation Criteria in Solid Tumors (RECIST 1.1) as assessed by the investigator. A secondary endpoint will only examine the safety and tolerability of participants treated with pembrolizumab plus epacadostat, pembrolizumab monotherapy, and the EXTREME regimen (cetuximab + platinum [cisplatin or carboplatin] + 5-fluorouracil). All other endpoints, including imaging, will no longer be collected or performed after the imaging assessment at Week 9. This section has been amended accordingly.

Objective/Hypothesis	Endpoint
Primary	
• **Objective:** To estimate the objective response rate (ORR) of pembrolizumab + epacadostat, pembrolizumab monotherapy, and the EXTREME regimen based on RECIST 1.1 by investigator determination.	• ORR is defined as the proportion of participants in the analysis population who have a best response of complete response (CR) or partial response (PR).
Secondary	
• **Objective:** To evaluate the safety and tolerability of the 3 treatment groups.	• Adverse events (AEs) • Study treatment discontinuations due to AEs.

Overall Design:

Study Phase	Phase 3
Clinical Indication	The treatment of participants with (R/M) HNSCC.
Population	Participants with R/M HNSCC in the first line setting.
Study Type	Interventional
Type of Design	Multi-site, randomized and open-label
Type of Control	Active control without placebo
Study Blinding	Unblinded Open-label
Estimated Duration of Trial	The trial is estimated to require approximately 41 months from the time the first participant signs the informed consent until the last participant's last study-related phone call or visit.

Number of Participants:

Originally, approximately 625 participants were to be randomized in this study, but as of Amendment 04, on 02-MAY-2018, enrollment in the study was stopped. By the time the strategic decision was made to stop enrollment, 89 participants were randomized in this study.

Treatment Groups and Duration:

Treatment Groups	Participants will be randomized in a 2:1:2 ratio in 3 treatment groups: <u>Group 1:</u> • Pembrolizumab 200 mg IV infusion every 3 weeks (Q3W) ≤35 cycles; **AND** • Epacadostat 100 mg PO twice daily (BID) ≤35 cycles. <u>Group 2:</u> • Pembrolizumab 200 mg IV infusion Q3W ≤35 cycles. <u>Group 3: (EXTREME regimen):</u> • Cetuximab 400 mg/m^2 IV infusion Cycle 1 Day 1; followed by cetuximab 250 mg/m^2 IV infusion every week (QW) until disease progression or unacceptable toxicity; **AND** • Cisplatin 100 mg/m^2 IV infusion **OR** Carboplatin area under the curve 5 (AUC 5) IV infusion Q3W ≤6 cycles;

	AND • 5-fluorouracil (5-FU) 1000 mg/m^2/day continuous IV infusion over Days 1 to 4 Q3W ≤6 cycles. As of Amendment 04, after the participant completes Week 9 imaging, participants can choose to discontinue from the study or continue study treatment as per protocol after participant discussion with the investigator and if they are receiving clinical benefits.
Duration of Participation	Each participant will participate in the study from the time the participant signs the informed consent form (ICF) through the final protocol-specified contact. After a Screening Phase of 28 days, each participant will be assigned to receive study treatment until disease progression, unacceptable AEs, intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the participant, noncompliance with study treatment or procedure requirements or administrative reasons requiring cessation of treatment, or until the participant has received 35 administrations of pembrolizumab plus epacadostat or pembrolizumab monotherapy (approximately 2 years). Participants who stop study treatment after receiving 35 administrations of pembrolizumab plus epacadostat or pembrolizumab monotherapy, for reasons other than disease progression or intolerability, or participants who attain a CR and stop study treatment may be eligible for up to 17 additional cycles (approximately 1 year) of pembrolizumab plus epacadostat or pembrolizumab monotherapy upon experiencing disease progression. After the end of treatment (EOT), each participant will proceed to safety follow-up and will be followed for the occurrence of AEs and spontaneously reported pregnancy as described under Section 9.3.3.

A list of abbreviations used in this document can be found in Appendix 1. Study governance considerations are outlined in Appendix 3.

2. Schedule of Activities (SoA)

2.1 Initial Treatment Phase

2.1.1 Pembrolizumab plus Epacadostat and Pembrolizumab Monotherapy Arms (Group 1 and 2)

As of Amendment 04, after the Week 9 imaging assessment, participants can choose to discontinue from the study or continue study treatment as per protocol after participant discussion with the investigator and if they are receiving clinical benefits. For those participants remaining in the study, procedures are simplified. The SoA has been amended to only show the required assessments.

Study Period	Screen	Treatment (3-week cycles)					EOT	Post-treatment	Notes
Treatment Cycle/Title	Screen (V 1)	1	2	3	4	Cycle 5 to Cycle 35	Discon	Safety FU	Assessments/procedures are to be performed on Day 1 and prior to the first dose of treatment for each cycle unless otherwise specified. **Participants who discontinue study treatment for whatever reason will proceed directly to EOT and Safety Follow-up.**
Scheduled Window (Days):	-28 to -1	+5	±3	±3	±3	±3	At treatment discon	30 days after last dose (+7 days)	
Administrative Procedures									
Informed Consent	X								Written consent must be obtained prior to performing any protocol-specific procedures.
Participant Identification Card	X								
Inclusion/Exclusion Criteria	X								ECG and laboratory tests to determine eligibility are to be performed within 10 days prior to the first dose of study treatment. Screening labs should be collected and assessed prior to randomizing the participant.
Demographics and Medical History	X								
Disease Details	X								HPV p16 status is required for participants with oropharynx as the primary tumor site.

Study Period	Screen	Treatment (3-week cycles)					EOT	Post-treatment	Notes
Treatment Cycle/Title	**Screen (V 1)**	**1**	**2**	**3**	**4**	**Cycle 5 to Cycle 35**	**Discon**	**Safety FU**	Assessments/procedures are to be performed on Day 1 and prior to the first dose of treatment for each cycle unless otherwise specified. **Participants who discontinue study treatment for whatever reason will proceed directly to EOT and Safety Follow-up.**
Scheduled Window (Days):	**-28 to -1**	**+5**	**±3**	**±3**	**±3**	**±3**	**At treatment discon**	**30 days after last dose (+7 days)**	
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X	
Serotonin Syndrome Information Card (Group 1 only)		X							
Prior Oncological Treatment for HNSCC	X								
Post-study Anticancer Therapy Status							X	X	.
Study Treatment Administration									
Pembrolizumab Administration at Site		X	X	X	X	X			Cycle 1 treatment should be given within 5 days of randomization.
Dispense Epacadostat (Group 1 only)		X	X	X	X	X			
Epacadostat Administration at Site (Group 1 only)		X	X						Only morning dose will be administered at site.
Collect and Count Remaining Epacadostat (Group 1 only)			X	X	X	X	X		
Efficacy Procedures/Assessments									
Tumor Imaging and RECIST Assessments	X				X	**Per Standard of Care**			Imaging should be performed at Week 9 (±7 days) after randomization. .Thereafter imaging is to be performed as per SoC for the disease and local guidelines; only the date of scans performed as per SoC needs to be documented in the eCRF. Schedule should be followed regardless of treatment delays.

Study Period	Screen	Treatment (3-week cycles)					EOT	Post-treatment	Notes
Treatment Cycle/Title	**Screen (V 1)**	**1**	**2**	**3**	**4**	**Cycle 5 to Cycle 35**	**Discon**	**Safety FU**	Assessments/procedures are to be performed on Day 1 and prior to the first dose of treatment for each cycle unless otherwise specified. **Participants who discontinue study treatment for whatever reason will proceed directly to EOT and Safety Follow-up.**
Scheduled Window (Days):	**-28 to -1**	**+5**	**±3**	**±3**	**±3**	**±3**	**At treatment discon**	**30 days after last dose (+7 days)**	
Safety Procedures/Assessments									
Full Physical Examination	X						X		
Directed Physical Examination		X	X	X	X	X		X	
Height	X								
Vital Signs and Weight	X	X	X	X	X	X	X	X	Vital signs to include temperature, pulse, respiratory rate and blood pressure.
ECOG PS	X	X	X	X	X	X	X	X	ECOG PS is to be performed within 7 days of randomization and must be 0 or 1 on the first day of dosing.
12-lead ECG (Local)	X						X		ECGs at screening and EOT are required for all participants. ECGs should also be done when clinically indicated.
12-lead ECG (Local; Group 1 at select sites only)		X	X						Predose and 2 hours (±15 minutes) after the morning dose of epacadostat.
Pregnancy Test Serum or Urine (WOCBP only)	X								WOCBP require negative test within 72 hours prior to Cycle 1 Day 1. Monthly (ie, before each cycle) pregnancy testing should be conducted as per local regulations where applicable.
Coagulation	X								Any participant receiving anticoagulant therapy should have coagulation factors monitored closely throughout the study.

Study Period	**Screen**	**Treatment (3-week cycles)**					**EOT**	**Post-treatment**	**Notes**
Treatment Cycle/Title	**Screen (V 1)**	**1**	**2**	**3**	**4**	**Cycle 5 to Cycle 35**	**Discon**	**Safety FU**	Assessments/procedures are to be performed on Day 1 and prior to the first dose of treatment for each cycle unless otherwise specified. **Participants who discontinue study treatment for whatever reason will proceed directly to EOT and Safety Follow-up.**
Scheduled Window (Days):	**-28 to -1**	**+5**	**±3**	**±3**	**±3**	**±3**	**At treatment discon**	**30 days after last dose (+7 days)**	
Hematology	X		X	X	X	X	X	X	Urinalysis and thyroid panel should be repeated every 2 cycles. Unresolved abnormal labs during the Safety Follow-up Visit that are TRAEs should be followed up as per sites' practices. .
Urinalysis	X		X		X	X	X	X	
Chemistry	X		X	X	X	X	X	X	
T3 (total or free), FT4 and TSH	X		X		X	X	X	X	
Hepatitis B and C Serology	X								Testing may be performed up to 40 days prior to randomization if performed as part of the standard documented clinical activities.
AE/SAE Review	X	X	X	X	X	X	X	X	Report non-serious AEs occurring within 30 days after the last dose of study treatment. Report SAEs occurring within 90 days after the last dose of study treatment, or 30 days after the last dose of study treatment if a new anticancer therapy is initiated, whichever is first.

[redacted]

Study Period	Screen	Treatment (3-week cycles)					EOT	Post-treatment	Notes
Treatment Cycle/Title	**Screen (V 1)**	**1**	**2**	**3**	**4**	**Cycle 5 to Cycle 35**	**Discon**	**Safety FU**	Assessments/procedures are to be performed on Day 1 and prior to the first dose of treatment for each cycle unless otherwise specified. **Participants who discontinue study treatment for whatever reason will proceed directly to EOT and Safety Follow-up.**
Scheduled Window (Days):	**-28 to -1**	**+5**	**±3**	**±3**	**±3**	**±3**	**At treatment discon**	**30 days after last dose (+7 days)**	
[redacted]									
Patient Reported Outcomes (ePROs)									
EQ-5D		X	X	X	X				Prior to drug administration, AE evaluation, and disease status notification. Perform at every cycle through Cycle 4. Perform ePROs in the order listed in the SoA (EQ-5D first).
EORTC QLQ-C30		X	X	X	X				
EORTC QLQ-H&N35		X	X	X	X				

Abbreviations: AE = adverse events; C = cycle; D = day; Discon = Discontinuation Visit; DNA = deoxyribonucleic acid; ECG = electrocardiograms; ECOG PS = Eastern Cooperative Oncology Group performance status; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life questionnaire Core 30 ; EORTC QLQ-H&N35 = EORTC Head and Neck Specific QoL questionnaire; EOT = end of treatment; ePRO = electronic patient reported outcomes; EQ-5D = EuroQol 5 dimensions questionnaire; FT4 = free thyroxine; FU = follow-up; HNSCC = head and neck squamous cell carcinoma; HPV = Human Papilloma Virus; IEC = Institutional Ethics Committee; IRB = Institutional Review Board; [redacted]; RECIST = Response Evaluation Criteria in Solid Tumors; [redacted]; SAE = serious adverse events; SoA = schedule of activities; T3 = triiodothyronine; TRAE = treatment-related AE; TSH = thyroid-stimulating hormone; V = visit; WOCBP = women of childbearing potential.

2.1.2 EXTREME Regimen Arm (Group 3)

As of Amendment 04, after the Week 9 imaging assessment, participants can choose to discontinue from the study or continue study treatment as per protocol after participant discussion with the investigator and if they are receiving clinical benefits. For those participants remaining in the study, safety assessments are as per SoC. The SoA has been amended to only show the required assessments.

Study Period	Screen	Treatment (3-week cycles)															EOT	Post-treatment	Notes
Treatment Cycle/Title	Screen (V1)	1			2			3			4			Cycle 5 Onwards			Discon	Safety FU	Assessments/procedures are to be performed on Day 1 and prior to the first dose of treatment for each cycle unless otherwise specified. **Participants who discontinue study treatment for whatever reason will proceed directly to EOT and Safety Follow-up.**
Treatment Day		1	8	15	1	8	15	1	8	15	1	8	15	1	8	15			
Scheduled Window (Days):	-28 to -1	+5	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	Per Standard of Care			At treatment discon	30 days after last dose +7	
Administrative Procedures																			
Informed Consent	X																		Written consent must be obtained prior to performing any protocol-specific procedures.
Participant Identification Card	X																		
Inclusion/Exclusion Criteria	X																		ECG and laboratory tests to determine eligibility are to be performed within 10 days prior to the first dose of study treatment. Screening labs should be collected and assessed prior to randomizing the participant.
Demographics and Medical History	X																		
Disease Details	X																		HPV p16 status is required for participants with oropharynx as the primary tumor site.
Prior/ Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Study Period	Screen	Treatment (3-week cycles)															EOT	Post-treatment	Notes
Treatment Cycle/Title	Screen (V1)	1			2			3			4			Cycle 5 Onwards			Discon	Safety FU	Assessments/procedures are to be performed on Day 1 and prior to the first dose of treatment for each cycle unless otherwise specified. **Participants who discontinue study treatment for whatever reason will proceed directly to EOT and Safety Follow-up.**
Treatment Day		1	8	15	1	8	15	1	8	15	1	8	15	1	8	15			
Scheduled Window (Days):	-28 to -1	+5	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	Per Standard of Care			At treatment discon	30 days after last dose +7	
Prior Oncological Treatment for HNSCC	X																		
Post-study Anticancer Therapy Status																	X	X	
Study Treatment Administration																			
Cetuximab		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			400 mg/m^2 on C1D1 then 250 mg/m^2 until PD or unacceptable toxicity.
Carboplatin or cisplatin		X			X			X			X			X					6 cycles maximum.
5-FU		X			X			X			X			X					Continuously on D1-4 of each cycle. 6 cycles maximum.
Efficacy Procedures/Assessments																			
Tumor Imaging and RECIST Assessments	X										X			Per Standard of Care					Imaging should be performed at Week 9 (±7 days) after randomization. Thereafter imaging is to be performed as per SoC for the disease and local guidelines; only the date of scans performed as per SoC needs to be documented in the eCRF. Schedule should be followed regardless of treatment delays.
Safety Procedures/Assessments																			
Full physical	X													Per Standard of Care					
Directed Physical Examination		X			X			X			X			Per Standard of Care					
Height	X																		

Study Period	Screen	Treatment (3-week cycles)															EOT	Post-treatment	Notes
Treatment Cycle/Title	Screen (V1)	1			2			3			4			Cycle 5 Onwards			Discon	Safety FU	Assessments/procedures are to be performed on Day 1 and prior to the first dose of treatment for each cycle unless otherwise specified. **Participants who discontinue study treatment for whatever reason will proceed directly to EOT and Safety Follow-up.**
Treatment Day		1	8	15	1	8	15	1	8	15	1	8	15	1	8	15			
Scheduled Window (Days):	-28 to -1	+5	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	Per Standard of Care			At treatment discon	30 days after last dose +7	
Vital Signs and Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	Per Standard of Care					Vital signs to include temperature, pulse, respiratory rate and blood pressure. Weight is only required on Day 1 of every cycle.
ECOG PS	X	X			X			X			X			Per Standard of Care					ECOG PS is to be performed within 7 days of randomization and must be 0 or 1 on the first day of dosing.
12-lead ECG (Local)	X													Per Standard of Care					ECGs should also be done when clinically indicated.
Hematology	X		X	X	X	X	X	X	X	X	X	X	X	Per Standard of Care					Unresolved abnormal labs during the Safety Follow-up Visit that are TRAEs should be followed up as per sites' practices.
Urinalysis	X				X						X			Per Standard of Care					
Chemistry	X		X	X	X	X	X	X	X	X	X	X	X	Per Standard of Care					
T3 (total or free), FT4 and TSH	X				X						X			Per Standard of Care					
Pregnancy Test Serum or Urine (WOCBP only)	X																		WOCBP require negative test within 72 hours prior to Cycle 1 Day 1. Monthly (ie, before each cycle) pregnancy testing should be conducted as per local regulations where applicable.
Coagulation	X																		Any participant receiving anticoagulant therapy should have coagulation factors monitored closely throughout the study.
Hepatitis B and C Serology	X																		Testing may be performed up to 40 days prior to randomization if performed as part of the standard documented clinical activities.
AE/SAE Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Report non-serious AEs occurring within 30 days after the last dose of study treatment. Report SAEs occurring within 90 days after the last dose of study treatment, or 30 days after the last dose of study treatment if a new anticancer therapy is initiated, whichever is first.

Study Period	Screen	Treatment (3-week cycles)															EOT	Post-treatment	Notes
Treatment Cycle/Title	Screen (V1)	1			2			3			4			Cycle 5 Onwards			Discon	Safety FU	Assessments/procedures are to be performed on Day 1 and prior to the first dose of treatment for each cycle unless otherwise specified. **Participants who discontinue study treatment for whatever reason will proceed directly to EOT and Safety Follow-up.**
Treatment Day		1	8	15	1	8	15	1	8	15	1	8	15	1	8	15			
Scheduled Window (Days):	-28 to -1	+5	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	Per Standard of Care			At treatment discon	30 days after last dose +7	
[redacted]																			
Patient Reported Outcomes (ePROs)																			
EQ-5D		X			X			X			X								Prior to drug administration, AE evaluation, and disease status notification. Perform at every cycle through Cycle 4. Perform ePROs in the order listed in the SoA (EQ-5D first).
EORTC QLQ-C30		X			X			X			X								
EORTC QLQ-H&N35		X			X			X			X								

Abbreviations: 5-FU = 5-fluorouracil AE =adverse events; C = cycle; D = day; Discon = Discontinuation Visit; DNA = deoxyribonucleic acid; ECG = electrocardiograms; ECOG PS = Eastern Cooperative Oncology Group performance status; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life questionnaire Core 30; EORTC QLQ-H&N35 = EORTC Head and Neck Specific QoL questionnaire; EOT = end of treatment; ePRO = electronic patient reported outcomes; EQ-5D = EuroQol 5 dimensions questionnaire; FT4 = free thyroxine; FU = follow-up; HNSCC = head and neck squamous cell carcinoma; HPV = Human Papilloma Virus; IEC = Institutional Ethics Committee; IRB = Institutional Review Board; PD = disease progression; RECIST = Response Evaluation Criteria in Solid Tumors; [redacted]; SAE = serious adverse events; SoA = schedule of activities; T3 = triiodothyronine; TRAE = treatment-related AE; TSH = thyroid-stimulating hormone; Visit = visit; WOCBP = women of childbearing potential.

2.2 Second Course Phase (Retreatment, Group 1 and 2 only)

As of Amendment 04, for participants remaining in the study who are eligible for the Second Course Phase, procedures are simplified. The SoA has been amended to only show required assessments. Disease assessments will be performed by the sites as per SoC for the disease and local guidelines.

Study Period	Treatment (3-week cycles)		EOT	Post-treatment	Notes
Treatment Cycle/Title	1	Cycle 2 to 17	Discon	Safety FU	Assessments/procedures are to be performed on Day 1 and prior to the first dose of treatment for each cycle unless otherwise specified.
Scheduled Window (Days):	+3	+3	At 2nd Course Treatment Discon	30 days after last dose (+7 days)	
Administrative Procedures					
Eligibility Criteria	X				ECG and laboratory tests to determine eligibility are to be performed within 10 days prior to the first dose of study treatment. Screening labs should be collected and assessed prior to randomizing the participant.
Concomitant Medication Review	X	X	X	X	
Post-study Anticancer Therapy Status			X	X	
Study Treatment Administration					
Pembrolizumab Administration at Site	X	X			Participants who restart treatment should resume at the same dose and cycle interval they were receiving prior to discontinuation.
Dispense Epacadostat (Group 1 only)	X	X			
Collect and Count Remaining Epacadostat (Group 1 only)		X	X		
Efficacy Procedures/Assessments					
Tumor Imaging and RECIST Assessments	**Per Standard of Care**				A scan must be performed within 28 days prior to restarting treatment. Imaging is to be performed as per SoC for the disease and local guidelines; only the date of scans performed as per SoC needs to be documented in the eCRF.
Safety Procedures/Assessments					
Full physical examination	X		X		
Directed Physical Examination		X		X	
Vital Signs and Weight	X	X	X	X	Vital signs to include temperature, pulse, respiratory rate and blood pressure.

Study Period	Treatment (3-week cycles)		EOT	Post-treatment	Notes
Treatment Cycle/Title	1	Cycle 2 to 17	Discon	Safety FU	Assessments/procedures are to be performed on Day 1 and prior to the first dose of treatment for each cycle unless otherwise specified.
Scheduled Window (Days):	+3	+3	At 2nd Course Treatment Discon	30 days after last dose (+7 days)	
ECOG PS	X	X	X	X	ECOG PS is to be performed within 7 days of randomization and must be 0 or 1 on the first day of dosing.
12-lead ECG (Local)	X		X		ECGs should also be done when clinically indicated.
Pregnancy Test Serum or Urine (WOCBP only)	X				WOCBP require negative test within 72 hours prior to Cycle 1 Day 1. Monthly (ie, before each cycle) pregnancy testing should be conducted as per local regulations where applicable.
Coagulation	X				Any participant receiving anticoagulant therapy should have coagulation factors monitored closely throughout the study.
Hematology	X	X	X	X	Urinalysis and thyroid panel should be repeated every 2 cycles. Unresolved abnormal labs during the Safety Follow-up Visit that are TRAEs should be followed until resolution as per sites' practices
Urinalysis	X	X	X	X	
Chemistry	X	X	X	X	
T3 (total or free), FT4 and TSH	X	X	X	X	
AE/SAE review	X	X	X	X	Report non-serious AEs occurring within 30 days after the last dose of study treatment. Report SAEs occurring within 90 days after the last dose of study treatment, or 30 days after the last dose of study treatment if a new anticancer therapy is initiated, whichever is first.

Abbreviations: AE = adverse events; C = cycle; D = day; Discon = Discontinuation Visit; ECG = electrocardiograms; ECOG PS = Eastern Cooperative Oncology Group performance status; EOT = end of treatment; FT4 = free thyroxine; FU = follow-up; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse events; T3 = triiodothyronine; TRAE = treatment-related AE; TSH = thyroid-stimulating hormone; WOCBP = women of childbearing potential.

3. Introduction

The efficacy and safety of combination therapy of pembrolizumab plus epacadostat, pembrolizumab monotherapy, and EXTREME regimen is being investigated as a first line treatment for participants with recurrent or metastatic (R/M) head and neck squamous cell cancers (HNSCC) in this randomized, open-label, Phase 3 study.

3.1 Study Rationale

Combining immunotherapies with differing mechanisms of action has the potential to further enhance their clinical benefits compared with using single agent immunotherapy. Preliminary data as of 27-Feb-2017 data cutoff from KEYNOTE-037/ECHO-202, suggested a 39% objective response rate (ORR) in 31 participants with HNSCC who received 1 to 2 prior lines of therapy when treated with pembrolizumab in combination with epacadostat [Hamid, O., et al 2017]. This ORR compares favorably to the ORR from pembrolizumab monotherapy (ORR of 16%) (see Section 5.4 for details). Given the comparability in ORR of the combination of pembrolizumab and epacadostat (in previously treated HNSCC participants) with the EXTREME regimen (in first line HNSCC participants), the promise of more durable responses with immunotherapy, and a favorable overall tolerability profile, further investigation of the combination in a larger study to compare efficacy, safety, and tolerability with standard of care (SoC) for participants with R/M HNSCC in the first line setting is warranted.

3.2 Background

Pembrolizumab (MK-3475; trade name KEYTRUDA®) is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. KEYTRUDA® is indicated for the treatment of patients across a number of indications. Accelerated approval was received for patients with R/M HNSCC with disease progression on or after platinum-containing chemotherapy. For more details on specific indications refer to the pembrolizumab Investigator Brochure (IB) [IB Edition 15 2017].

Epacadostat is a novel, potent, and selective inhibitor of the indoleamine 2,3 dioxygenase 1 (IDO1) enzyme in both human tumor cells and human dendritic cells (DCs). Because IDO1 catabolism of tryptophan inhibits T-cell–mediated immune responses and IDO1 expression has been shown to be elevated in many human cancers, IDO1 inhibition may restore an effective antitumor immune response and may provide a method to treat malignant diseases either alone or in combination with chemotherapeutics and/or immunotherapy-based strategies. Pembrolizumab in combination with epacadostat is in clinical development for several advanced malignancies. For more details on specific indications refer to the epacadostat IB [IB Edition 10, 2017].

3.2.1 Pharmaceutical and Therapeutic Background

3.2.1.1 Inhibition of PD-1 as a Target for Cancer

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [Disis, M. L. 2010]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T cells/FoxP3+ regulatory T cells (Tregs) correlates with improved prognosis and long-term survival in many solid tumors.

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

The structure of murine PD-1 has been resolved [Zhang, X., et al 2004]. PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type (IgV type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, Src homology region 2 domain-containing phosphatase (SHP)-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade [Okazaki, T., et al 2001] [Chemnitz, J. M., et al 2004] [Sheppard, K-A, et al 2004] [Riley, J. L. 2009]. The mechanism by which PD1 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 multiple tumor types including HNSCC.

3.2.1.2 Inhibition of Indoleamine 2,3–Dioxygenase as a Target for Cancer

Recent interest has focused on the role of IDO1 as a mechanism of induction of tolerance to malignancy [Godin-Ethier, J., et al 2011]. IDO1 is a heme containing, monomeric oxidoreductase that catalyzes the degradation of the essential amino acid tryptophan to N-formyl-kynurenine. Kynurenine can be subsequently metabolized through a series of enzymatic steps to nicotinamide adenine dinucleotide. IDO1 is the first rate limiting enzyme in one of the catabolic pathways of tryptophan. In another pathway, catalysis of tryptophan by the enzyme tryptophan hydroxylase leads to the formation of serotonin and melatonin.

The expression and activity profiles of IDO1 are distinct from those of tryptophan dioxygenase, an enzyme predominantly expressed in liver that catalyzes the same enzymatic reaction as IDO1 and maintains proper tryptophan balance in response to dietary uptake. In contrast to tryptophan dioxygenase, IDO1 is expressed in a variety of tissues, with particularly high levels found in areas of contact with potential sources of immune challenge (eg, gut, respiratory tract, placenta, spleen), consistent with a role for regulating tryptophan metabolism in a local microenvironment [Mellor, A. L. 2004]. Within the immune system, IDO1 activity is specifically induced in cells such as DCs and macrophages at localized sites of inflammation [Munn, D. H. 2007].

IDO1-driven oxidation of tryptophan results in a strong inhibitory effect on the development of T-cell–mediated responses by blocking T-cell activation and inducing T-cell apoptosis [Mellor, A. L., et al 2003]. Both the reduction in local tryptophan levels and the production of tryptophan catabolites that are inhibitory to cell proliferation contribute to the immunosuppressive effects [Frumento, G., et al 2002] such as DC maturation and T-cell growth arrest and cell death [Mellor, A. L. 1999]. IDO1 activity also promotes the differentiation of naive T cells to cells with a regulatory phenotype (Treg; [Fallarino, F., et al 2006]). Because increased Treg activity has been shown to promote tumor growth and Treg depletion has been shown to allow an otherwise ineffectual antitumor immune response to occur [Zou, W. 2006], IDO1 expansion of Treg may provide an additional mechanism whereby IDO1 could promote an immunosuppressive environment.

Within the context of cancer, there are several lines of evidence to suggest that IDO1 is a key regulator of the immunosuppressive mechanisms responsible for tumor escape from immune surveillance. Several groups have demonstrated that blockade of IDO1 activity can directly influence the ability of tumor-bearing animals to reject tumors [Uyttenhove, C., et al 2003] [Muller, A. J., et al 2005]. In addition, studies with 1-methyl-tryptophan demonstrate that IDO1 inhibition dramatically increases the efficacy of various chemotherapeutic agents (eg, platinum compounds, taxane derivatives, cyclophosphamide) without increased toxicity [Muller, A. J., et al 2005]. Although the specific mechanisms responsible for this potentiation remain to be fully elucidated, the effects were not observed in T-cell–deficient animals, suggesting that the results may be the consequence of the disablement of immunosuppressive mechanisms that exist within the tumor microenvironment.

Based on studies examining serum levels of tryptophan and kynurenine, IDO1 appears to be chronically activated in participants with cancer, and IDO1 activation correlates with more extensive disease [Huang, L., et al 2010] [Weinlich, G., et al 2007]. IDO1 has subsequently been found to be overexpressed by a wide variety of human tumor cell types, as well as by the DCs that localize to the tumor-draining lymph nodes [Uyttenhove, C., et al 2003] [Munn, D. H., et al 2004]. Increased expression of IDO1 in tumor cells has been shown to be an independent prognostic variable for reduced overall survival (OS) in participants with melanoma, ovarian, colorectal, and pancreatic cancers [Okamoto, A., et al 2005] [Brandacher, G., et al 2006] [Ino, K., et al 2006] [Nakamura, T., et al 2007] [Witkiewicz, A., et al 2008].

3.2.1.3 Combination Immunotherapy

Although pembrolizumab has demonstrated antitumor activity in patients with HNSCC when administered as monotherapy, multiple immune inhibitory mechanisms are present concurrently within the tumor microenvironment, suggesting that combination therapies may be required for optimal therapeutic effect [Quezada, S. A. 2013]. Given the evidence demonstrating the IDO1 pathway is a key regulatory element responsible for the induction and maintenance of tumor immune tolerance, small molecule inhibitors of IDO1 may provide an innovative and tractable method to treat malignancies in combination with other immunotherapy-based strategies such as inhibitors of the PD-1/PD-L1 axis.

3.2.2 Completed Clinical Studies

[redacted]

Further details of other completed clinical studies are provided in the pembrolizumab IB [IB Edition 15 2017] and epacadostat IB [IB Edition 10, 2017].

3.2.3 Ongoing Clinical Studies

Ongoing pembrolizumab clinical studies are being conducted in advanced melanoma, non-small cell lung cancer (NSCLC), a number of advanced solid tumor indications (including head and neck cancer) and hematologic malignancies. For study details please refer to the pembrolizumab IB [IB Edition 15 2017].

KEYNOTE-012 and KEYNOTE-055 are ongoing clinical studies evaluating pembrolizumab monotherapy in head and neck cancer that have demonstrated clinical activity in participants with R/M disease.

KEYNOTE-012 is a Phase 1b, multi-cohort study evaluating the activity of pembrolizumab in various solid tumors, including 2 cohorts of participants (Cohorts B and B2) with R/M HNSCC. Cohort B consisted of 60 participants with PD-L1 positive HNSCC who received pembrolizumab 10 mg/kg every 2 weeks (Q2W). Cohort B2 consisted of 132 participants regardless of PD-L1 status, who received pembrolizumab 200 mg every 3 weeks (Q3W). Responses were seen in both human papillomavirus (HPV)-positive and HPV-negative participants. This was the first immunotherapy demonstrating clinically meaningful anti-tumor activity in a heavily pretreated incurable HNSCC population with R/M disease [Mehra, R., et al 2016].

The efficacy and safety results after long term follow-up based on pooled data from Cohorts B and B2 were presented at ASCO 2016. The last participant was enrolled on 08-OCT-2014 and 32 (17%) participants were still on treatment as of the 01-SEP-2015 data

cutoff. Median age was 60 years; 83% of participants were male; 70% had Eastern Cooperative Oncology Group performance status (ECOG PS) 1; and 61% had received ≥2 therapies for recurrent disease. The ORR (confirmed) was 17.7% (95% CI, 12.6%-23.9%; 7 CRs, 27 PRs). Median follow-up duration in responders was 12.5 months (range, 8.4-24.4). As of the data cutoff, median duration of response (DOR) was not yet reached (range, 1.8+ to 21.8+ months) and responses were ongoing in 22 (76%) participants. Responses of ≥6 months and ≥12 months were noted in 25 participants and 4 participants, respectively. Thirty-three (17%) participants achieved SD. The ORR was 21.9% (95% confidence interval [CI], 12.5%-34.0%) in HPV-positive participants and 15.9% (95% CI, 10.0%-23.4%) in HPV-negative participants). The ORR seen with pembrolizumab treatment is greater than the existing standard single agent cytotoxic chemotherapies such as methotrexate, which in the setting of second line R/M disease has an ORR of approximately 4%. Median OS was 8.5 months (95% CI, 6.5 months-10.5 months), compared to the historical OS rate of 6 months for participants who progress following first line treatment. The 6-month progression-free survival (PFS) rate was 24.9%. The percentage of responders who were in response for at least 6 months was 85% and 71.0% of responders had ongoing responses at the data cutoff. These results demonstrate the consistent durability of responses seen with pembrolizumab treatment and compare favorably to SoC chemotherapy or epidermal growth factor receptor (EGFR) inhibitors, which have reported median DOR of 4 to 6 months.

Treatment-related AEs (TRAEs) occurred in 122 (64%) participants, and 23 (12%) participants had a Grade 3 to 4 TRAE. No participants died due to a TRAE. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) increases were the only Grade 3 to 4 TRAEs observed in >2 participants.

KEYNOTE-055 is a Phase 2, nonrandomized, single cohort study of pembrolizumab (200 mg Q3W) monotherapy in a heavily pretreated population of participants with R/M HNSCC who have progressed on prior platinum and cetuximab therapy. Participants received pembrolizumab 200 mg (Q3W). Among 171 participants treated, 75% received 2 or more prior lines of therapy for metastatic disease, 82% were PD-L1 positive, and 22% were HPV positive. At the time of analysis, 109 participants (64%) experienced a TRAE; 26 participants (15%) experienced a Grade ≥3 event [Bauml, J., et al 2017].

Seven participants (4%) discontinued treatment, and 1 died of TRAEs. Overall response rate was 16% (95% CI, 11% to 23%), with a median duration of response of 8 months (range, 2+ to 12+ months); 75% of responses were ongoing at the time of analysis. Response rates were similar in all HPV and PD-L1 subgroups. Median PFS was 2.1 months, and median OS was 8 months [Bauml, J., et al 2017]. These results presented confirm findings from KEYNOTE-012 in the R/M HNSCC population; pembrolizumab monotherapy demonstrates consistent and clinically meaningful activity of pembrolizumab 200 mg Q3W with an acceptable safety profile in heavily pretreated participants with HNSCC.

KEYNOTE-048 is an ongoing Phase 3, randomized, active-controlled, multi-site, open-label study of pembrolizumab, or pembrolizumab plus platinum plus 5-fluorouracil (5-FU) chemotherapies versus platinum plus 5-FU plus cetuximab (EXTREME regimen) in participants with advanced head and neck cancer. Approximately 825 participants with first line R/M HNSCC were planned to be randomized 1:1:1 between the 3 arms of the study to examine the efficacy and safety of pembrolizumab, pembrolizumab plus chemotherapy

versus SoC with cetuximab and chemotherapy. Prior to randomization, participants were stratified by PD-L1 tumor expression (strongly positive versus not strongly positive), HPV status (positive versus negative), and ECOG PS (0 vs. 1). The primary endpoints of the study are PFS, per RECIST 1.1 as assessed by BICR, and OS. Enrollment has been completed.

KEYNOTE-037/ECHO-202 is an ongoing Phase1/2 clinical study evaluating pembrolizumab in combination with epacadostat that has shown clinical activity in various tumor types including participants with R/M HNSCC. In Phase 1 (a dose-escalation phase), epacadostat doses of 25 mg, 50 mg, and 100 mg orally (PO) BID in combination with pembrolizumab 2 mg/kg IV Q3W and epacadostat 300 mg BID in combination with the fixed dose of pembrolizumab 200 mg IV Q3W were evaluated. Safety expansion cohorts also evaluated epacadostat doses of 50 mg, 100 mg, and 300 mg with the fixed dose of pembrolizumab 200 mg IV Q3W.

The combination of epacadostat 100 mg BID and pembrolizumab 200 mg IV Q3W was selected for further evaluation in Phase 2 (an open-label, single arm, cohort expansion phase). A total of 38 participants with metastatic HNSCC and ≥1 prior chemotherapy regimen with platinum were enrolled: 2 participants in Phase 1 and 36 participants in Phase 2.

Preliminary efficacy data as of 27-FEB-2017 data cutoff suggest enhanced response rates as compared to historical ORRs observed with pembrolizumab monotherapy. Among the 31 participants with HNSCC who received 1 to 2 prior lines of therapy, the ORR was 39% and disease control rate (DCR) was 65%, which includes 3 complete responses (CR). Responses were observed regardless of HPV association status or PD-L1 status. Among 7 participants with HNSCC who received ≥3 prior line of therapy, the ORR was 14% (1 PR) with DCR of 43% (2 SD). This compares favorably to historical ORRs for other antitumor agents in this heavily treated population [Hamid, O., et al 2017]. Similar durable responses were observed in other tumor types enrolled in this study (melanoma, renal cell carcinoma, urothelial cancer, and NSCLC).

Safety data as of 27-Feb-2017 data cutoff, is available for a total of 294-participants in various tumor types that have been treated in the Phase 2 part of KEYNOTE-037/ECHO-202 with epacadostat 100 mg PO BID and pembrolizumab 200 mg IV Q3W [Hamid, O., et al 2017]. Treatment-related AEs occurring in >10% of participants were fatigue (29%), rash (17%), nausea (11%), and pruritus (10%). A total of 52 participants (18%) had Grade ≥3 TRAEs and the most common Grade ≥3 TRAEs were asymptomatic increases in lipase (4%) and rash (3%). Treatment-related AEs led to treatment discontinuation in 5% of participants. There was 1 treatment-related death due to respiratory failure (secondary to aspiration pneumonia; pneumonitis could not be ruled out).

Epacadostat is currently being evaluated in combination with PD-1 inhibitors, PD-L1 inhibitors, and a Janus kinase (JAK) inhibitor with JAK1 selectivity. Further details of ongoing clinical studies of these combinations are provided in the epacadostat IB [IB Edition 10, 2017].

An uncommon concern of IDO1 inhibition is an increase in serotonin levels that could precipitate a cluster of AEs termed serotonin syndrome, when administered alone or in combination with other serotonergic agents. This rare syndrome has been associated with some monoamine oxidase inhibitors (MAOIs) and combinations of serotonergic drugs

[Boyer EW, Shannon M. 2005]. Nonclinical data suggest that serotonin syndrome is unlikely following treatment with either epacadostat alone or with combination with MAOIs such as linezolid [Zhang, Y., et al 2016].

As of 27-FEB-2017 data cutoff, 2 participants receiving epacadostat in combination with PD-1/PD-L1 inhibitors across the epacadostat program (958 participants treated) have reported serotonin syndrome or symptoms of serotonin syndrome and both were mild in their severity and resolved (Data on File). Although the incidence of serotonin syndrome is uncommon, use of MAOIs will be prohibited during the study, and all participants should be assessed for serotonin syndrome symptoms at an appropriate timeframe after dosing. Participants will be provided with a leaflet describing the signs and symptoms of the syndrome along with instructions to seek immediate medical care if any of these signs or symptoms is observed.

KEYNOTE-252/ECHO-301 is an ongoing Phase 3, randomized, double-blind, placebo-controlled study of pembrolizumab in combination with epacadostat or placebo in participants with unresectable or metastatic melanoma. The dual primary endpoints of the study are PFS per RECIST 1.1 as assessed by central imaging and OS. The eDMC concluded that the study did not meet the primary objective of improving PFS in the combination compared to pembrolizumab monotherapy during a second interim analysis. There were no new safety concerns. This study remains open so that participants still on study will have continued access to open-label pembrolizumab.

3.2.4 Information on Other Study-Related Therapy

A variety of chemotherapies are used for patients with R/M, first line HNSCC. Early studies demonstrated small survival benefits after treatment with cisplatin or methotrexate or chemotherapy combinations [Liverpool Head and Neck Oncology Group 1990]. In the 18 years following this early report from The Liverpool Head and Neck Oncology Group, cisplatin, carboplatin, methotrexate, paclitaxel, 5-FU, and their various combinations have been evaluated in several Phase 3 studies [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] [Schrijvers, D., et al 1998]. The combination of cisplatin and 5-FU showed generally better results than other regimens with overall response rates ranging from 11 to 37% and OS ranging from 23 to 36 weeks. Addition of cetuximab to platinum-5-FU demonstrated the first significant increase in OS in first line head and neck cancer in the EXTREME study [Vermorken, J. B., et al 2008]. Overall survival was increased from 7.4 months for platinum-5-FU to 10.1 months with the platinum/5-FU/cetuximab regimen. In the EXTREME group, the corresponding ORR increased from 20 to 36% and the PFS increased from 3.3 to 5.6 months. However, the EXTREME regimen is associated with an 82% frequency of Grade 3 or 4 toxicities.

Since R/M first line HNSCC patients have somewhat heterogeneous characteristics, National Comprehensive Cancer Network (NCCN) guidelines generally highlight the importance of considering individualized systemic therapies based on patient characteristics, given the toxicity of the EXTREME regimen. NCCN guidelines offer consideration of the use of alternative combination regimens including platinum plus taxane, cisplatin plus cetuximab and cisplatin plus 5-FU, or the use of these agents as monotherapies. Paclitaxel or docetaxel-based regimens are used by many clinicians, but taxane-containing regimens have yet to be

directly compared with the EXTREME regimen in a randomized Phase 3 study. The EXTREME regimen is the only Category 1 evidence-supported combination regimen recommended by NCCN [National Comprehensive Cancer Network 2016].

3.3 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.

Additional details regarding specific benefits and risks for participants participating in this clinical study may be found in the accompanying IBs [IB Edition 15 2017] [IB Edition 10, 2017], Prescribing Information and Informed Consent documents.

3.3.1 Benefit/Risk of Pembrolizumab

Pembrolizumab monotherapy has a positive benefit-risk profile and is well tolerated in the approved indications. Publications of a significantly positive benefit/risk ratio have been reported for melanoma in a single arm study encompassing nearly 1000 participants (KEYNOTE-001), which led to US Food and Drug Administration (FDA) approval in September 2014. Pembrolizumab has subsequently received approval for several indications. The IB provides additional details about these approvals [IB Edition 15 2017]. The US FDA approval to treat patients with R/M HNSCC with disease progression on or after platinum-containing chemotherapy was based on the efficacy observed in KEYNOTE-012 and KEYNOTE-055. The potential benefits for patients with HNSCC are addressed in Section 3.2.3, which details responses of participants with HNSCC in KEYNOTE-012 and KEYNOTE-055.

Most common adverse reactions (reported in ≥20% of patients) were fatigue, pruritus, diarrhea, decreased appetite, rash, dyspnea, constipation, and nausea. In the pembrolizumab monotherapy studies, the incidence of Grade 3 to 5 drug-related AEs across studies is 13.8%. Pembrolizumab immune-mediated Adverse Events of Special Interest (AEOSIs) are relatively uncommon. The most frequently reported AEOSI is hypothyroidism, with an overall incidence of 8.5%. Furthermore, most AEOSIs are mild to moderate in severity, and are generally readily manageable with appropriate care in the clinical setting [IB Edition 15 2017].

[redacted]

3.3.3 Benefit/Risk of Pembrolizumab plus Epacadostat

Safety data as of 27-Feb-2017 data cutoff, for the 294 participants that have been treated in the Phase 2 part of KEYNOTE-037/ECHO-202 with epacadostat 100 mg PO BID and pembrolizumab 200 mg IV Q3W indicates a safety/tolerability profile of pembrolizumab plus epacadostat that is acceptable and manageable. Overall, 18% of participants had

Grade ≥3 TRAEs and TRAEs led to discontinuation in 5% of participants. See Section 3.2.3 for further details.

Preliminary data, as of 27-Feb-2017 data cutoff, suggest enhanced response rates as compared to historical ORRs observed with pembrolizumab monotherapy in HNSCC. For further details refer to Section 3.2.3.

The observed immunotherapeutic responses, together with the tolerability of pembrolizumab plus epacadostat argues strongly for a comparison with the EXTREME regimen in the first line in participants with HNSCC as proposed in this study.

3.3.4 Benefit/Risk of EXTREME

Benefits and risks of the EXTREME regimen are summarized in Section 3.2.4. The EXTREME regimen demonstrated the significant increase in PFS and OS in first line head and neck cancer compared with chemotherapy (platinum + 5-FU). A total of 82% of patients experienced a Grade 3 or 4 AE including neutropenia (22%), anemia (13%), and thrombocytopenia (11%). These AEs occurred in similar frequencies to platinum-5-FU-treated participants [Vermorken, J. B., et al 2008]. Additional details regarding specific benefits and risks for EXTREME-treated participants may be found in the prescribing information for these SoC treatments.

4. Objectives/Hypotheses and Endpoints

NOTE: As of Amendment 04, the primary endpoint of the study will be ORR based on RECIST 1.1 as assessed by the investigator. All other efficacy endpoints, including imaging, will no longer be collected or performed after the first imaging assessment at Week 9. This section has been updated accordingly.

As assessed in each of 3 treatment groups of participants with R/M HNSCC receiving pembrolizumab plus epacadostat, pembrolizumab and EXTREME regimen.

Objective	Endpoint
Primary	
• **Objective:** To estimate ORR of pembrolizumab + epacadostat, pembrolizumab monotherapy, and the EXTREME regimen based on RECIST 1.1 by investigator determination.	• ORR is defined as the proportion of participants in the analysis population who have a best response of CR or PR.
Secondary	
• **Objective:** To evaluate the safety and tolerability of the 3 treatment groups.	• AEs; • Study treatment discontinuations due to AEs.

Objective	Endpoint
[redacted]	

5. Study Design

5.1 Overall Design

Note: Enrollment was stopped strategically on 02-MAY-2018. 89 participants were randomized in the study. As of Amendment 04, all study efficacy procedures will discontinue after first on-study imaging at Week 9 (± 7 days); thereafter participants will be treated as per SoC for the disease and local guidelines. Safety procedures will continue as per protocol for all participants in Group 1 and 2 continuing study treatment. For Group 3 participants continuing study treatment after first on-study imaging at Week 9 (± 7 days), safety procedures will continue as per SoC. The last study visit is the Safety Follow-up Visit. This section has been updated accordingly.

This is a randomized, active-controlled, 3 parallel-groups, multi-site, open-label Phase 3 study evaluating pembrolizumab plus epacadostat, pembrolizumab monotherapy, and the EXTREME regimen in participants with R/M HNSCC who have not received prior systemic therapy for R/M disease. The EXTREME arm was selected as a comparator since it is the SoC per NCCN guideline, while the pembrolizumab monotherapy arm was included to identify the contribution of the individual components of the pembrolizumab plus epacadostat arm. The study has a primary endpoint of ORR. The study will be conducted in conformance with Good Clinical Practices (GCP).

The study includes a Screening period, a Treatment period, and a Post-treatment Safety Follow-up period. After signing the informed consent, candidate participants will be screened against all the eligibility criteria. Eligible participants will be centrally randomized in a 2:1:2 ratio and will be stratified based on:

- ECOG PS (0 vs. 1)
- HPV p16 expression status (either oropharynx-p16 positive vs. oropharynx-p16 negative or larynx/hypopharynx/oral cavity HNSCC); and
- Prior systemic oncological therapy (as part of the definitive treatment for locally advanced disease) (yes vs. no).

Originally, approximately 625 eligible participants with R/M HNSCC who meet the inclusion/exclusion criteria were to be enrolled in the study and centrally randomized in a 2:1:2 ratio in 3 treatment groups:

- Group 1: Pembrolizumab 200 mg 30-minute IV infusion Q3W ≤35 cycles plus epacadostat 100 mg PO BID ≤35 cycles
- Group 2: Pembrolizumab 200 mg 30-minute IV infusion Q3W ≤35 cycles
- Group 3: EXTREME regimen:
    - Cetuximab 400 mg/m^2 120-minute IV infusion Cycle 1 Day 1; followed by cetuximab 250 mg/m^2 60-minute IV infusion QW until radiographic PD or unacceptable toxicity; AND
    - Cisplatin 100 mg/m^2 60-minute IV infusion Q3W OR Carboplatin AUC 5 60-minute IV infusion Q3W ≤6 cycles; AND
    - 5-FU 1000 mg/m^2/day continuous IV infusion over Days 1 to 4 Q3W ≤6 cycles

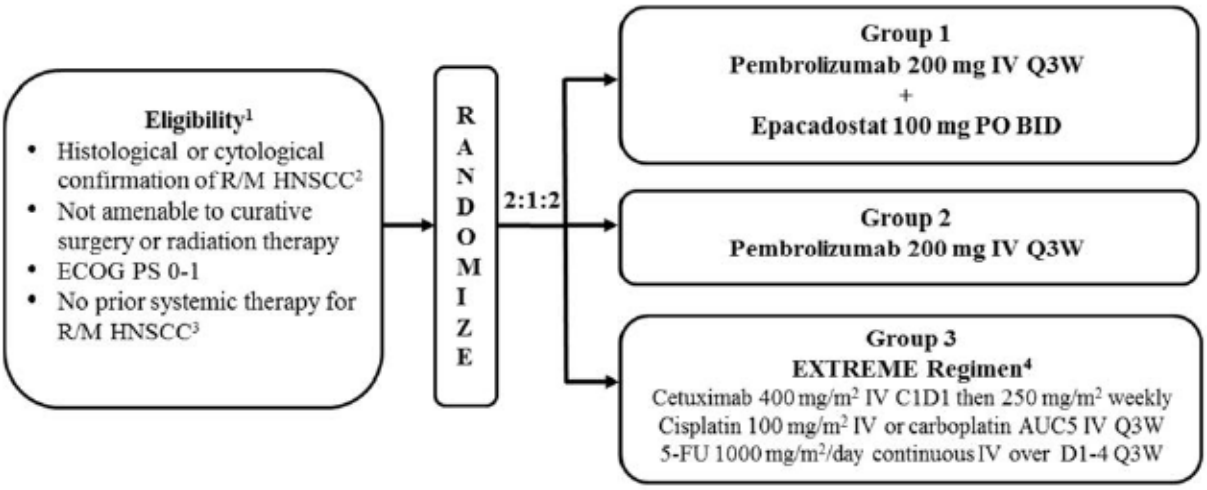
Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial SoA - Section 2. Details of each procedure are provided in Section 9 – Study Assessments and Procedures.

5.1.1 Data Monitoring Committee

This study will use an independent, external Data Monitoring Committee (eDMC) to monitor safety. Details are described in Section 10.7.

5.1.2 Study Diagram

The study design is depicted in Figure 1.



Abbreviations: 5-FU = 5-fluorouracil; AUC = area under the curve; C = Cycle; D = day; ECOG PS = Eastern Cooperative Oncology Group performance status; HNSCC = head and neck squamous cell carcinoma; IV = intravenously; Q3W = every 3 weeks; R/M = recurrent or metastatic.
1. Stratification by ECOG PS, HPV p16 status (oropharynx-p16 positive vs. oropharynx-p16 negative or larynx/hypopharynx/oral cavity HNSCC) and prior systemic oncological therapy (as part of the definitive treatment in the locally advanced disease) (yes vs. no).
2. Primary tumor location in the oral cavity, oropharynx, hypopharynx, and larynx.
3. Systemic therapy completed >6 months prior to signing consent if given as part of multimodal treatment for locally advanced disease is allowed.
4. 21-day cycle for a maximum of 6 cycles followed by maintenance therapy with cetuximab 250 mg/m^2 weekly until disease progression or unacceptable toxicity.

Figure 1 Study Design

5.2 Number of Participants

As of Amendment 04, on 02-MAY-2018 enrollment in the study was stopped and 89 participants were enrolled in the study.

5.3 Beginning and End of Study Definition

The overall study begins when the first participant signs the informed consent form (ICF). The overall study ends when the last participant completes the last study-related phone-call or visit, withdraws from the study or is lost to follow-up (i.e. the participant is unable to be contacted by the investigator).

5.3.1 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.

The investigator retains the right to terminate study participation at any time, according to the terms specified in the study contract. The investigator is to notify the IRB or Independent Ethics Committee (IEC) in writing of the study's completion or early termination, and send a copy of the notification to the MSD or MSD designee and retain 1 copy for the site study regulatory file.

The study may be terminated early if required by regulatory decision, or upon advice of the DMC. If the study is terminated prematurely, the investigators, the IRBs and IECs, and regulatory bodies will be notified of the decision and reason for termination of the study. The DMC will recommend termination of the study if warranted, as described in Section 10.2.

5.4 Scientific Rationale for Study Design

Head and neck squamous cell cancers arise from the epithelial cells that line the oral cavity, pharynx, and larynx and comprise the vast majority of head and neck cancers. Predominant risk factors for non-nasopharyngeal HNSCC (oral cavity, oropharynx, hypopharynx, and larynx) include prior alcohol consumption and tobacco use [National Comprehensive Cancer Network 2016]. In developed countries, infection with HPV, in particular HPV16, is an accepted risk factor for tumors specifically in the oropharynx [Gillison, M. L., et al 2015]. Analyses from clinical studies have shown improved prognosis and response to treatment in participants with HPV-positive tumors compared with those with HPV-negative tumors [Fakhry, C., et al 2008] [Ang, K. K., et al 2010]. Despite a shared cellular origin, HNSCC of the nasopharynx, however, is relatively uncommon and has differing risk factors (eg, Epstein-Barr virus infection, genetic susceptibility, and diet) compared with non-nasopharyngeal HNSCC; therefore, it is considered a separate clinical entity [Argiris, A., et al 2008] [Chua, M. L., et al 2016].

Recurrent/metastatic HNSCC has potentially devastating effects on basic functions such as eating, swallowing, speaking and breathing. In addition the pain associated with recurrence, and the social isolation as well as potential disfigurement from the disease in the head/neck region, all point to the value of preventing progression in this patient population. There is thus an unmet medical need to support the development of new treatment strategies to improve the outcome of patients.

A large number of patients with HNSCC initially present with locally advanced, Stage III/IV disease that is initially treated with combinations of chemotherapy, radiation and/or surgery. This initial treatment is generally designated as "definitive" therapy, which typically combines chemo-radiation and surgery and can result in DCRs ranging between 33 and 86% of patients. Patients who progress after initial definitive therapy require subsequent

treatment for recurrent (R) disease. Patients who initially present with metastatic (M) disease generally receive the same therapy as those with recurrent disease after definitive treatment.

Initial treatment options for patients with R/M disease include various chemotherapy agents (platinum [cisplatin or carboplatin], 5-FU, or taxanes), either alone or in combination, and the biologic agent cetuximab [National Comprehensive Cancer Network 2016] [Gregoire, V., et al 2010]. In participants with non-nasopharnygeal HNSCC, the addition of cetuximab to platinum [cisplatin or carboplatin] and 5-FU (EXTREME regimen) prolonged median OS from 7.4 months to 10.1 months (hazard ratio [HR] = 0.80; P = 0.04) and median PFS from 3.3 months to 5.6 months (HR = 0.54; P <0.001) compared with platinum−5-FU doublet. Additionally, ORR increased from 20% with platinum/5-FU to 36% with the EXTREME regimen (P <0.001; [Vermorken, J. B., et al 2008]). Based on these results, the EXTREME regimen is now the SoC for patients with non-nasopharyngeal R/M HNSCC [National Comprehensive Cancer Network 2016] [Gregoire, V., et al 2010].

While AEs of Grade ≥3 were comparable between the treatment groups (EXTREME: 82%; platinum/5-FU: 76%), the most common AEs observed with EXTREME (anemia, neutropenia, thrombocytopenia) and cetuximab-specific AEs (Grade 3 skin toxicities, Grade 3 or 4 infusion-related reactions) limit the use of this regimen to younger participants with good performance status. In those who are eligible to receive this regimen, many will stop therapy prematurely due to toxicity, as demonstrated by a 20% discontinuation rate for AEs in the pivotal Phase 3 study [Vermorken, J. B., et al 2008]. Common comorbidities in participants with HNSCC such as diminished hepatic, cardiac, and pulmonary function from previous alcohol and tobacco use and poor nutritional status from the clinical manifestations of the cancer and/or previous radiation can further limit the use of the EXTREME regimen. Second line treatment regimens are limited and primarily palliative resulting in very poor long-term survival rates for this patient population.

Given the limited tolerability profile of EXTREME and poor outcomes with second line therapies, there is a critical need for effective and well tolerated alternative regimen that offers sustained responses and prolonged survival compared with the EXTREME regimen in the first line setting for R/M HNSCC.

[redacted]

Pembrolizumab monotherapy in R/M HNSCC in participants who had disease progression on or after platinum-containing chemotherapy demonstrated confirmed ORR of 16% with a CR rate of 5% (refer to the KEYTRUDA® US prescribing information). A pembrolizumab monotherapy arm has been included in this current study to determine the contribution of epacadostat to the treatment effect of pembrolizumab plus epacadostat combination therapy. Pembrolizumab monotherapy in the first line setting is being studied in KEYNOTE-048 (see Section 3.2.3) Therefore the pembrolizumab monotherapy arm in this study will include a minimal number of participants as a concurrent control.

Based on the results detailed in Section 3.2.3 for KEYNOTE-037/ECHO-202, combination therapy with pembrolizumab and epacadostat demonstrated an acceptable safety profile with promising anti-tumor activity in patients with R/M HNSCC.

5.4.1 Rationale for Endpoints

5.4.1.1 Efficacy Endpoints

NOTE: As of Amendment 04, the primary endpoint will be ORR based on RECIST 1.1 as assessed by the investigator; transmission of images for central review of imaging is no longer required. After imaging at Week 9, all other efficacy endpoints, including imaging after the first on study scan at Week 9, will no longer be collected or performed. This section has been amended accordingly.

Objective response rate, based on RECIST 1.1 as assessed by the investigator, will serve as the primary measure of efficacy. ORR is an acceptable measure of clinical benefit for a late stage study that demonstrates safety and efficacy of a new antineoplastic therapy.

5.4.1.1.1 RECIST 1.1

Note: As of Amendment 04, RECIST 1.1 will be assessed by the investigator; transmission of images for central review of imaging is no longer required.

RECIST 1.1 will be used by the local site when determining eligibility and conducting site disease assessment. Although traditional RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, this protocol has implemented a modification to RECIST 1.1 to allow a maximum of 10 target lesions in total and 5 per organ. This will be termed as RECIST 1.1 throughout the protocol. Further details are found in Section 9.2.1.5.

5.4.1.1.2 Modified RECIST for Immune-based Therapeutics (iRECIST)

NOTE: As of Amendment 04, this section is no longer applicable; iRECIST data will no longer be collected. Participants with radiographic disease progression as determined by RECIST 1.1 will discontinue from the study and followed for safety monitoring, as detailed in Section 9.3; no confirmatory scans are required.

RECIST 1.1 will be adapted to account for the unique tumor response characteristics seen following treatment with immunotherapeutic agents. Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and participants treated with pembrolizumab may manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions.

Thus, standard RECIST 1.1 may not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab. Based on an analysis of participants with melanoma enrolled in KEYNOTE-001, 7% of evaluable participants experienced delayed or early tumor pseudo-progression. Of note, participants who had PD by RECIST 1.1 but not by the immune-related response criteria [Wolchok, J. D., et al 2009] had longer OS than participants with PD by both criteria [Hodi, F. S., et al 2014]. Additionally, the data suggest that RECIST 1.1 may underestimate the benefit of pembrolizumab in approximately 15% of participants [Hodi, F. S., et al 2016]. These findings support the need to apply a modification to RECIST 1.1 that takes into account the unique pattern of atypical responses in

immunotherapy and enables treatment beyond initial radiographic progression, if the participant is clinically stable.

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

The ORR, DOR, and PFS will also be evaluated per iRECIST by investigator assessment.

Refer to Section 9.2.1.5 and Section 9.2.1.6 for details on RECIST 1.1 and iRECIST, respectively.

5.4.1.2 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 va lues. Adverse events will be assessed as defined by NCI Common Toxicity Criteria for Adverse Events (CTCAE), version 4.0.

The objective is to characterize the safety and tolerability of the 3 treatment groups.

The primary safety analysis will be based on participants who experienced toxicities as defined by CTCAE. Safety will be assessed by quantifying the toxicities and grades experienced by participants who have received study treatment, including SAEs and events of clinical interest (ECIs). Safety will be assessed by reported adverse experiences using CTCAE, version 4.0. The attribution to drug, time-of-onset, duration of the event, its resolution, and any concomitant medications administered will be recorded. Adverse events will be analyzed including but not limited to all AEs, SAEs, fatal AEs, and laboratory changes. Furthermore, ECI will be collected and analyzed as described in Section 9.3.7.

[redacted]

[redacted]

5.4.1.5 Patient Reported Outcomes

NOTE: As of Amendment 04, PROs will no longer be collected and analyzed after the first on-study imaging assessment at Week 9.

As part of the analyses for this study, participants will provide information regarding their HRQoL using the EORTC QLQ-C30 and EORTC QLQ-H&N35 patient reported outcome (PRO) instruments. Health utilities will be evaluated using the EQ-5D PRO instrument. These PRO assessments are not pure efficacy or safety endpoints because they are affected by both disease progression and treatment tolerability.

5.4.1.5.1 EORTC QLQ-C30 and EORTC QLQ-H&N35

The EORTC QLQ-C30 is the most widely used cancer specific HRQoL instrument, which contains 30 items and measures 5 functional dimensions (physical, role, emotional, cognitive and social), 3 symptom items (fatigue, nausea/vomiting, and pain), 6 single items (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact), and a global health and QoL scale [Aaronson, N. K., et al 1993].

The EORTC QLQ-H&N35 is in use worldwide as one of the standard instruments for measuring QoL in head and neck cancer participants and consists of 7 multi-item scales measuring pain in the mouth, problems with swallowing, senses, speech, social eating and social contact, and 11 single-item scales assessing problems with teeth, mouth opening, dry mouth, sticky saliva, coughing, feeling ill, use of analgesics, use of nutritional supplements, use of feeding tube, weight gain, and weight loss [Bjordal, K., et al 1994].

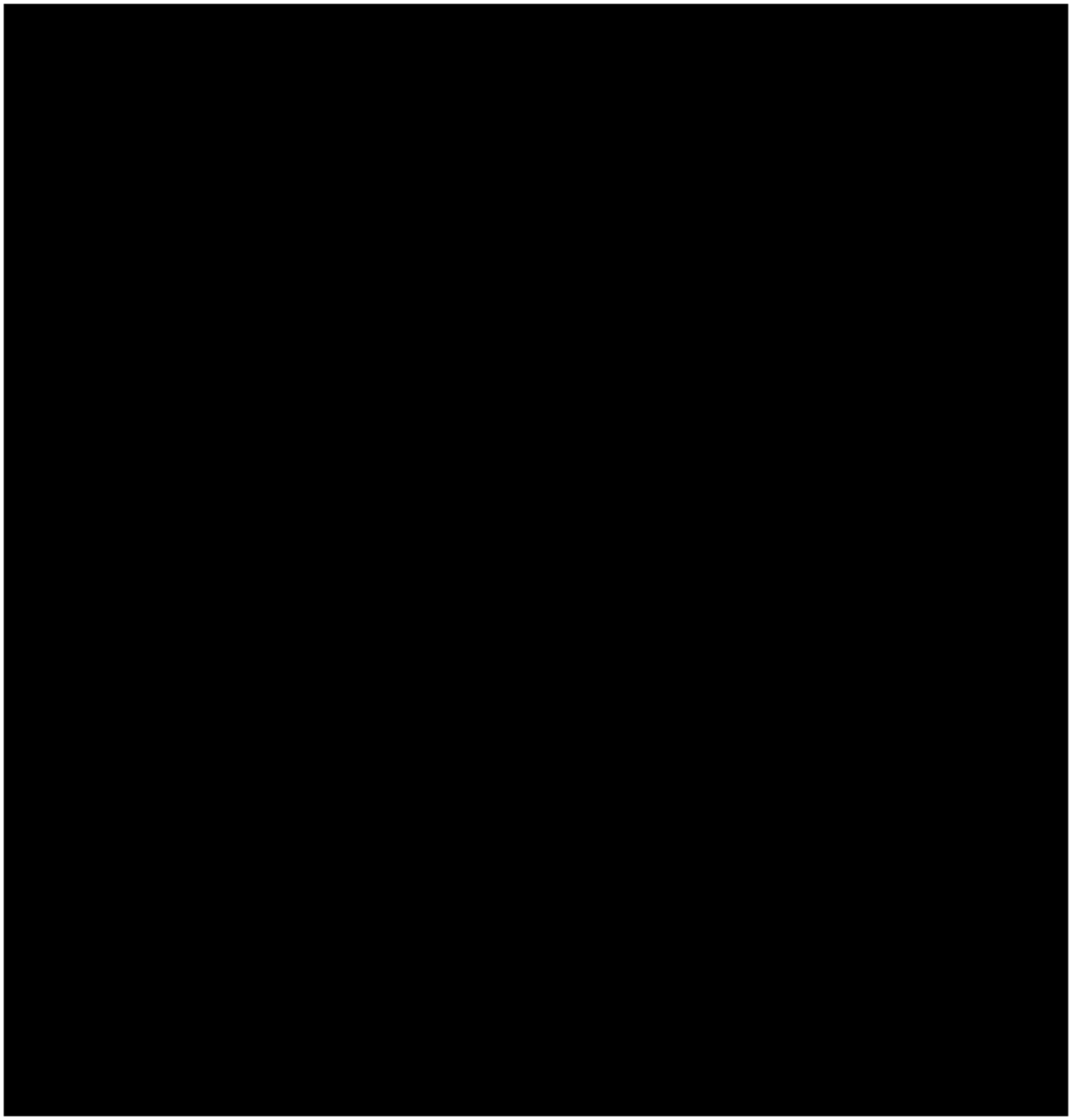
The EORTC QLQ-C30 and EORTC QLQ-H&N35 are psychometrically and clinically validated instruments appropriate for assessing QoL in participants with head and neck cancer [Bjordal, K., et al 1994] [Bjordal, K., et al 2000]. These instruments have been widely used in Phase 3 studies of participants with R/M HNSCC receiving chemotherapy [Mesia, R., et al 2010] [Machiels, J. P., et al 2015].

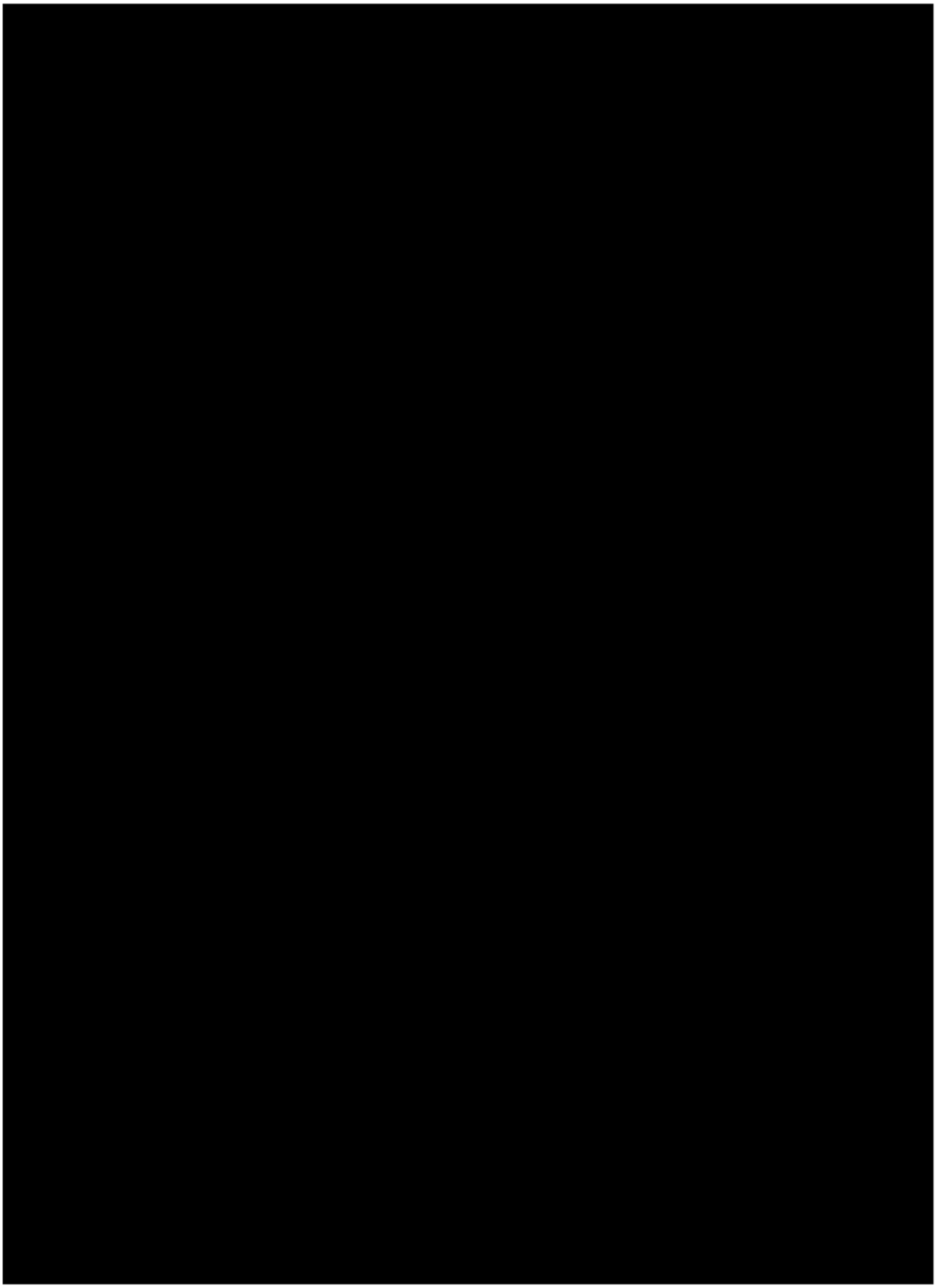
For the global health status/QoL and function scales, a higher value indicates a better level of function; for symptom scales and items, a higher value indicates increased severity of symptoms. Prior literature indicates that head and neck pain is a clinically relevant symptom measure in the R/M HNSCC population [Bjordal, K., et al 2000] [Chera, B. S., et al 2014] [Mesia, R., et al 2010] [Machiels, J. P., et al 2015]. Thus, TTD in the pain multi-item scale of the EORTC QLQ-H&N35, in addition to TTD and mean change from baseline in global health status/QoL scale of the EORTC QLQ-C30, will be evaluated as secondary objectives.

[redacted]

5.4.1.5.2 EuroQoL-5D

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





[redacted]

5.4.2 Rationale for the Use of Comparator

The EXTREME arm was included because this regimen is a Category 1 evidence-supported combination regimen recommended by NCCN (see Section 3.2.4).

A pembrolizumab monotherapy arm is added in this study in order to establish the magnitude of benefit from epacadostat in the pembrolizumab plus epacadostat combination regimen (see Section 5.4).

5.5 Justification for Dose

5.5.1 Rationale for Pembrolizumab Dosing Regimens

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

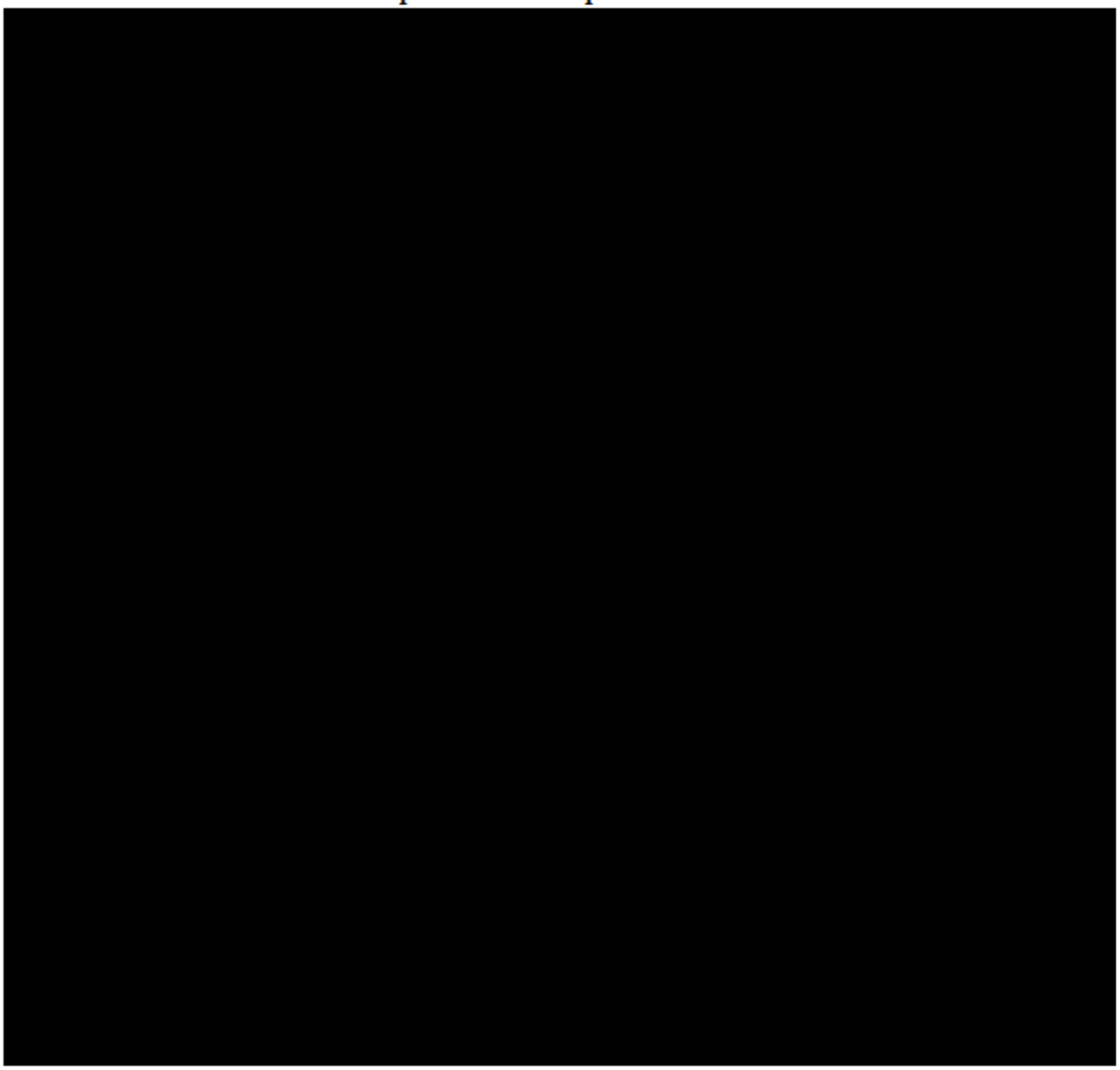
- Clinical data from 8 randomized studies demonstrating flat dose- and exposure- efficacy relationships from 2 mg/kg Q3W to 10 mg/kg Q2W,
- Clinical data showing meaningful improvement in benefit-risk including OS at 200 mg Q3W across multiple indications, and
- Pharmacology data showing full target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

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and NSCLC, covering different disease settings (treatment naïve, previously treated, PD-L1 enriched and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W (KEYNOTE-001 B2, KEYNOTE-001 D, KEYNOTE-002, KEYNOTE-010 and KEYNOTE-021), and 3 studies compared 10 mg/kg Q3W vs. 10 mg/kg Q2W (KEYNOTE-001 B3, KEYNOTE-001 F2 and KEYNOTE-006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5 to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-/exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KEYNOTE-001 evaluating target-mediated drug disposition conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Secondly, a PBPK analysis was conducted to predict tumor PD-1 saturation over a

wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

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



6. Study Population

Male and female participants with R/M HNSCC of at least 18 years of age without prior systemic treatment for R/M HNSCC will be enrolled in this trial.

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

6.1 Inclusion Criteria

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

Type of Participant and Disease Characteristics

1. Male/female participants who are at least 18 years of age on the day of signing informed consent with histologically or cytologically-confirmed R/M HNSCC that is considered incurable by local therapies will be enrolled in this study.

   Note: The eligible primary tumor locations are oropharynx, oral cavity, hypopharynx, and larynx.

Male participants:

2. A male participant must agree to use contraception as detailed in Appendix 5 of this protocol during the treatment period and for at least 120 days after the last dose of pembrolizumab and epacadostat, or pembrolizumab alone, and for at least 180 days after the last dose of the EXTREME regimen. He must also refrain from donating sperm during this period. Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the participant.

Female participants:

3. A female participant is eligible to participate if she is not pregnant (see Appendix 5), not breastfeeding, and at least one of the following conditions applies:
   a.) Not a woman of childbearing potential (WOCBP) as defined in Appendix 5 OR
   b.) A WOCBP who agrees to follow the contraceptive guidance in Appendix 5 during the treatment period and for at least 120 days after the last dose of pembrolizumab and epacadostat, or pembrolizumab alone, and for at least 180 days after last dose of the EXTREME regimen. Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the participant.

Informed Consent

4. The participant (or legally acceptable representative if applicable) provides written informed consent for the study.

Diagnostic Assessments

5. Have measurable disease by CT or MRI based on RECIST 1.1 as determined by site radiology. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions following radiation therapy.
6. Have an ECOG PS of 0 or 1 within 7 days prior to randomization.

7. Have adequate organ function as defined in the following table (Table 1). Specimens must be collected within ≤10 days prior to the start of study treatment. (Participants may be enrolled based on local laboratory results pending central laboratory results).

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/μL
Platelets	≥100 000/μL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[a]
Renal	
Creatinine OR Measured or calculated[b] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN OR ≥30 mL/min for participant with creatinine levels >1.5 × institutional ULN Note: Cisplatin should not be used if creatinine clearance is lower than 60 mL/min.
Hepatic	
Total bilirubin	≤1.5 × ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN[c]
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT) or partial thromboplastin time (PTT)[d]	≤1.5 × ULN unless participant is receiving anticoagulant therapy[e] as long as PT or PTT is within therapeutic range of intended use of anticoagulants

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

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

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

[c] If there is no institutional normal range available for the direct bilirubin, the direct bilirubin should be <40% of the total bilirubin. In no case should total bilirubin exceed 3.0 × ULN.

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

[e] Use of coumarin-based anticoagulants (eg, warfarin) with epacadostat is discouraged. Low-dose warfarin (1 mg) is acceptable; however, other higher doses are discouraged. If an alternative to coumarin-based anticoagulants cannot be used, the INR should be monitored closely per SoC when epacadostat is started.

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.

8. Have documentation of results from testing of HPV status for oropharyngeal cancer 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: Tumor p16 expression must be evaluated by assessment of IHC analysis with CINtec® p16 Histology assay (Ventana Medical Systems Inc., Tucson AZ) using 'Benchmark Ultra' autostainer (Ventana, Tucson, AZ) and standard protocol. Positive p16 expression is defined as strong and diffuse nuclear and cytoplasmic staining in 70% or more of the tumor cells.

   Note: HPV stratification in this study will be performed using local testing of HPV status in participants with oropharynx cancer using the specified method.

   Note: If local p16 testing results are not available, or cannot be assessed by the specified method, a tumor tissue sample may be submitted for p16 testing at the designated central laboratory.

   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. Have a baseline archival tumor specimen available or is willing to undergo a pre-study treatment tumor core or excisional biopsy of a tumor lesion not previously irradiated, to obtain the specimen. Fine needle aspirate (FNA) and bone metastases samples are not acceptable.

   Note: A newly obtained biopsy is strongly preferred, but an archival sample is acceptable. Tumor lesions used for newly obtained biopsies should not be the same lesions used as RECIST target lesions, unless there are no other lesions suitable for biopsy, in which case consultation with the MSD Clinical Director is required.

6.2 Exclusion Criteria

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

Medical Conditions

1. Has carcinoma of the nasopharynx, salivary gland, unknown primary origin, or nonsquamous histologies as primary tumors.
2. Has disease progression 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 history of bleeding requiring a medical intervention (eg, embolization procedure, RBC transfusion, or hospitalization) within 30 days of study enrollment.
5. Has a history of peripheral neuropathy ≥ Grade 2 for participants who may receive cisplatin.

6. Has a history of dihydropyrimidine dehydrogenase (DPD) deficiency (homozygous or heterozygous mutations).
7. Has a history of any contraindication or has a severe hypersensitivity to any components of epacadostat, pembrolizumab (≥Grade 3), cisplatin or carboplatin, cetuximab, and 5-FU.

   Note: Sites are instructed to refer to the approved product labeling for these therapies for information on contraindications or precautions for use.
8. Had an allogeneic tissue/solid organ transplant.
9. Has a history of gastrointestinal condition or procedure that may affect drug absorption.

   Note: Participants with feeding tubes are eligible.
10. Any history of Serotonin Syndrome after receiving serotonergic drugs.
11. A WOCBP who has a positive urine pregnancy test within 72 hours before the first dose of study treatment (see Appendix 5). If the urine test cannot be confirmed as negative, a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

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

Prior/Concomitant Therapy

12. Has received prior systemic therapy (as part of multimodal treatment) for HNSCC administered in the recurrent and/or metastatic setting for incurable disease.

    Note: Systemic therapy (as part of multimodal treatment) which was completed more than 6 months prior to signing consent if given as part of multimodal treatment for locally advanced disease is allowed.
13. Has not fully recovered (ie, ≤Grade 1 or at baseline) from AEs due to a previously administered treatment.

    Note: Participants with ≤Grade 2 alopecia are an exception to this criterion and may qualify for the study.

    Note: If participants have received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting study treatment.
14. Has received prior palliative radiotherapy within 2 weeks of start of study treatment. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis.
15. Has received prior therapy with epacadostat or any IDO1 inhibitor, an anti-PD-1, anti-PD-L1, or anti PD-L2 agent, or any agent directed to another stimulatory or co-inhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137).

16. Has received a live vaccine within 30 days prior to the first dose of study treatment. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines are live attenuated vaccines and are not allowed.
17. Has received therapy with an MAOI, or UGT1A9 inhibitor within 21 days prior to starting treatment, or anticipates requiring one of these prohibited medications during the treatment phase. Examples of medications in these classes are found in Section 7.7.3.
18. Current use of any prohibited medication as described in Section 7.7.3.

Prior/Concurrent Clinical Study Experience

19. 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 treatment.

    Note: Participants who have entered the Post-treatment 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

20. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone or equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment. Corticosteroid use as pre-medication for allergic reactions (eg IV contrast) is permitted.
21. Has a known additional malignancy that is progressing or has required active systemic treatment within the past 3 years.

    Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (eg, breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded. Participants with low-risk early stage prostate cancer defined as follows are not excluded; Stage T1c or T2a with a Gleason score ≤ 6 and prostatic-specific antigen (PSA) < 10 ng/mL either treated with definitive intent or untreated in active surveillance that has been stable for the past year prior to study enrollment. Other exceptions may be considered after consultation with the MSD Clinical Director.
22. Has known active central nervous system 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 14 days prior to first dose of study treatment.

23. 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, etc.) is not considered a form of systemic treatment and is allowed.
24. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.
25. Has an active infection requiring systemic therapy.
26. Has a known history of human immunodeficiency virus (HIV) infection. No HIV testing is required unless mandated by local health authority.
27. Has a known history of or is positive for active hepatitis B (defined as hepatitis B surface antigen [HBsAg] reactive) or hepatitis C (defined as HCV RNA [qualitative] is detected). **Note:** Testing must be performed to determine eligibility.
    a. HBV DNA must be undetectable and HBsAg negative at Screening Visit.
    b. Hepatitis C Ab testing is allowed for screening purposes in countries where HCV RNA is not part of SoC. In these cases, HCV antibody positive patients will be excluded.
    c. Participants who have had definitive treatment for HCV are permitted if HCV RNA is undetectable at Screening Visit.
28. Has known psychiatric or substance abuse disorders that would interfere with cooperating with the requirements of the study.
29. Has a history or current evidence of any condition, therapy or laboratory abnormality that might confound the results of the study, interfere with the participant's participation for the full duration of the study, or is not in the best interest of the participant to participate, in the opinion of the treating investigator.
30. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the study, starting with the Screening Visit through 120 days after the last dose of pembrolizumab and epacadostat or pembrolizumab monotherapy and up to 180 days after the last dose of EXTREME regimen.

Other Exclusions

31. Screening corrected QT (QTc) interval >480 milliseconds is excluded (Fridericia formula is the preferred method. Bazett formula is acceptable). In the event that a single QTc is >480 milliseconds, the participant may enroll if the average QTc for the 3 electrocardiograms (ECGs) is <480 milliseconds.

6.3 Lifestyle Restrictions

6.3.1 Meals and Dietary Restrictions

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

On Cycle 1 Day 1 and Cycle 2 Day 1 the participant should arrive to the clinic in a fasting state to coincide with the scheduled blood draw.

6.3.2 Contraception

Pembrolizumab, epacadostat, cetuximab, cisplatin, carboplatin and 5-FU may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab, epacadostat, cetuximab, cisplatin, carboplatin and 5-FU have transient adverse effects on the composition of sperm.

Developmental and reproductive toxicity studies have not been performed with epacadostat. Epacadostat should not be used by pregnant women.

Participants should be informed that taking the study treatment may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study, participants of childbearing potential must adhere to the contraception requirement from the day of study treatment initiation (or 14 days prior to the initiation of study treatment for oral contraception) throughout the study period and for at least 120 days after the last dose of pembrolizumab and epacadostat, or pembrolizumab monotherapy, and for at least 180 days after the last dose of the EXTREME regimen. If there is any question that a participant of childbearing potential will not reliably comply with the requirements for contraception, that participant should not be entered into the study.

Definitions of WOCBP and standards for adequate contraception are outlined in Appendix 5.

6.3.3 Pregnancy

If a participant becomes pregnant while on treatment on any arm of this study, the participant will be immediately discontinued from study treatment. The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to MSD without delay and within 24 hours if the outcome is a serious adverse experience (eg, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to MSD. If a male participant impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy must be reported to MSD and followed as described in Section 9.3.6.

6.3.4 Use in Nursing Women

Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, participants who are breastfeeding are not eligible for enrollment. Specific additional information follows for individual agents used in this study.

6.3.4.1 Pembrolizumab

It is unknown whether pembrolizumab is excreted in human milk.

6.3.4.2 Epacadostat

It is unknown whether epacadostat is excreted in human milk.

6.3.4.3 Cetuximab

It is not known whether cetuximab is secreted in human milk. IgG antibodies, such as cetuximab, can be excreted in human milk.

6.3.4.4 Cisplatin

Cisplatin has been reported to be found in human milk; participants receiving cisplatin injection should not breast-feed.

6.3.4.5 Carboplatin

It is not known whether carboplatin is excreted in human milk. Because there is a possibility of toxicity in nursing infants secondary to carboplatin treatment of the mother, it is recommended that breastfeeding be discontinued if the mother is treated with carboplatin injection.

6.3.4.6 5-fluorouracil

It is not known whether 5-FU is excreted in human milk. Because 5-FU inhibits DNA, RNA and protein synthesis, mothers should not nurse while receiving this drug.

6.4 Screen Failures

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

6.5 Participant Replacement Strategy

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

7. Treatments

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

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

7.1 Treatments Administered

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

Table 2 Study Treatments

Study Treatment Name	Dosage Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Sourcing
Pembrolizumab	Solution	25 mg/mL	200 mg Q3W	IV infusion	Central
Epacadostat	Tablet	100 mg	100 mg BID	Oral	Central
Epacadostat	Tablet	25 mg	25 mg[1] BID	Oral	Central
Cetuximab	Solution	5 mg/mL[3]	400 mg/m^2 on Cycle 1, Day 1 then 250 mg/m^2 QW	IV infusion	Central or Local[2]
Carboplatin	Solution	10 mg/mL[3]	AUC 5 Q3W	IV infusion	Central or Local[2]
Cisplatin	Solution	1 mg/mL[3]	100 mg/m^2 Q3W	IV infusion	Central or Local[2]
5-fluorouracil	Solution	50 mg/mL[3]	1000 mg/m^2/day over Days 1 to 4, Q3W	IV infusion	Central or Local[2]

Abbreviations: AUC = area under the curve; BID = twice daily; IV = intravenous; Q3W = every 3 weeks; QW = once weekly

[1] In case of planned dose reductions.

[2] Will be provided locally in some countries by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements.

[3] Or equivalent formulation

Study treatment should begin on the day of randomization or within 5 days of the date on which the participant is allocated/assigned.

All products indicated in Table 2 will be provided centrally by MSD or locally by the trial site, subsidiary, or designee, depending on local country operational or regulatory requirements. Every attempt should be made to source these supplies from a single lot/batch number.

Refer to Section 9.1.9 for details regarding administration of the study treatment.

7.2 Dose Modification

The CTCAE version 4.0 must be used to grade the severity of AEs. If appropriate, the investigator may attribute each toxicity event to pembrolizumab or epacadostat or the combination in Group 1 and use a stepwise dose reduction for epacadostat according to Table 3. For Group 3 (EXTREME regimen), the investigator may attribute each toxicity event to cisplatin or carboplatin, 5-FU, or cetuximab alone or in combination of 2 or 3, and

use a stepwise dose reduction according to Table 3. If a dose reduction for toxicity occurs with any agent, the dose may not be re-escalated. Dose modifications are always based on the previous cycle.

Participants can have 2 levels of dose reductions per agent to epacadostat, cisplatin, carboplatin, 5-FU, and cetuximab throughout the course of the study for toxicities as described in Table 3. Refer to the general instructions in Table 4 for guidance regarding the re-occurrence of an AE when a participant has had their epacadostat dose reduced to dose level -2. Dose reductions of pembrolizumab are not permitted. If further toxicity occurs or the criteria for resuming treatment are not met, the participant must be discontinued from that drug and may continue to participate in the study.

For platinum toxicities refer to Table 10 and Table 11, 5-FU toxicities refer to Table 12 and Table 13, and cetuximab toxicities refer to Table 7, Table 8, and Table 9. If a participant experiences several toxicities and there are conflicting recommendations, follow the most conservative dose adjustment recommended (dose reduction appropriate to the most severe toxicity).

For the EXTREME regimen, reduction or holding of one agent and not the other agents is appropriate if, in the opinion of the investigator, the toxicity is clearly related to one of the study treatments. If, in the opinion of the investigator, the toxicity is related to the combination of 2 agents, both drugs should be reduced or held according to recommended dose modifications. If the toxicity is related to the combination of 3 agents, all 3 agents should be reduced or held according to the recommended dose modifications. If one or more study agent(s) are held for toxicity, the schedule for restarting the agent(s) should correspond with the next treatment cycle once the toxicity has resolved according to the recommended guidelines.

Table 3 Dose Modifications for Study Treatments

	Dose level 0	**Dose level -1**	**Dose level -2**	**Dose level -3**
Epacadostat	100 mg BID	50 mg BID	25 mg BID	Discontinue
Cisplatin	100 mg/m^2	80 mg/m^2 (20% decrease)	64 mg/m^2 (20% decrease)	Discontinue
Carboplatin	AUC 5	AUC 4 (20% decrease)	AUC 3 (20% decrease)	Discontinue
5-fluorouracil	1000 mg/m^2/day	800 mg/m^2/day (20% decrease)	640 mg/m^2/day (20% decrease)	Discontinue
Cetuximab	400 mg/m^2 then 250 mg/m^2	200 mg/m^2 (20% decrease)	150 mg/m^2 (20% decrease)	Discontinue

Abbreviations: AUC = area under the curve; BID = twice daily.

Note: Pembrolizumab dose should not be modified for toxicity. See Table 4 for modification of pembrolizumab or epacadostat dosing schedule for drug-related AEs.

Investigators may follow the local prescribing information for dose modifications of EXTREME regimen. If a toxicity is not otherwise specified, investigators should refer to the label or local SoC for dose adjustments. Dose modification according to Table 3 is allowable for intolerable Grade 2 or 3 toxicities not specified in the tables below at the investigator's discretion. These dose modification decisions must be documented in the participant's study records and in the electronic case report form (eCRF).

Exceptional circumstances to following the dose modification tables below may be considered after consultation with MSD.

7.2.1 Dose Modification for Pembrolizumab and Epacadostat

Pembrolizumab plus epacadostat must be withheld for drug-related severe or life-threatening AEs. The treatment guidelines outlined in this section are intended to be applied when the investigator determines if the events are related to pembrolizumab, epacadostat, or the combination.

In all cases where pembrolizumab dosing is withheld, dosing for epacadostat should also be withheld until pembrolizumab is resumed. Participants are allowed, however, to receive pembrolizumab monotherapy if epacadostat is discontinued due to drug-related AEs.

Except in cases of emergency, it is recommended that the investigator consult with the MSD Clinical Director before temporarily interrupting therapy or permanently discontinuing any study treatment for reasons other than protocol-mandated medication hold or discontinuation.

Dose modification and toxicity management for immune-related AEs associated with pembrolizumab and/or epacadostat

Adverse events associated with pembrolizumab and/or epacadostat exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of 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 and/or epacadostat, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and/or epacadostat and administer corticosteroids. Participants who experience an unacceptable toxicity that is attributed to epacadostat and not pembrolizumab in the opinion of the investigator and MSD may permanently discontinue epacadostat but continue with pembrolizumab as monotherapy, upon improvement of toxicity as per the recommendations in Table 4.

Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab or epacadostat are provided in Table 4.

Table 4 Dose Modification and Toxicity Management Guidelines for Immune-Related AEs associated with Pembrolizumab or Epacadostat (Group 1 and 2 only)

Immune-related AEs	Toxicity Grade or Conditions (CTCAE v4.0)	Study Treatment	Action Taken with Study Treatment	irAE Management with Corticosteroid and/or Other Therapies	Monitor and Follow-up
Pneumonitis	Grade 2	Pembrolizumab	Withhold until Grade 0-1	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections.
		Epacadostat	Withhold until Grade 0-1 Once resolved to Grade 0-1, may restart: Related: Reduce by 1 dose level. Not Related: Same dose level.		
	Grade 3 or 4, or recurrent Grade 2	Pembrolizumab	Permanently discontinue		
		Epacadostat	Permanently discontinue		
Diarrhea / colitis	Grade 2 or 3	Pembrolizumab	Withhold until Grade 0-1	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
		Epacadostat	Withhold until Grade 0-1 Once resolved to Grade 0-1, may restart: Related: Reduce by 1 dose level. Not Related: Same dose level.		
	Grade 4 or recurrent Grade 3	Pembrolizumab	Permanently discontinue		
		Epacadostat	Permanently discontinue		

Immune-related AEs	Toxicity Grade or Conditions (CTCAE v4.0)	Study Treatment	Action Taken with Study Treatment	irAE Management with Corticosteroid and/or Other Therapies	Monitor and Follow-up
AST / ALT Elevation or Increased Bilirubin	Grade 2	Pembrolizumab	Withhold until Grade 0-1	• Administer corticosteroids (initial dose of 0.5-1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returns to baseline or is stable).
		Epacadostat	Withhold until Grade 0-1 Once resolved to Grade 0-1, may restart: Related: Reduce by 1 dose level. Not Related: Same dose level.		
	Grade 3 or 4	Pembrolizumab	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
		Epacadostat	Permanently discontinue		
Type 1 diabetes mellitus (T1DM) or Hyperglycemia[b]	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Pembrolizumab	Withhold until Grade 0-1	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
		Epacadostat	Withhold until Grade 0-1 Once resolved to Grade 0-1, may restart: Related: Reduce by 1 dose level. Not Related: Same dose level.		

Immune-related AEs	Toxicity Grade or Conditions (CTCAE v4.0)	Study Treatment	Action Taken with Study Treatment	irAE Management with Corticosteroid and/or Other Therapies	Monitor and Follow-up
Hypophysitis	Grade 2	Pembrolizumab	Withhold until Grade 0-1	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
		Epacadostat	Withhold until Grade 0-1 Once resolved to Grade 0-1, may restart: Related: Reduce by 1 dose level. Not Related: Same dose level.		
	Grade 3 or 4	Pembrolizumab	Withhold until Grade 0-1 or permanently discontinue[a]		
		Epacadostat	Withhold until Grade 0-1 or permanently discontinue[a] Once resolved to Grade 0-1, may restart: Related: Reduce by 1 dose level. Not Related: Same dose level.		
Hyperthyroidism[b]	Grade 2	Pembrolizumab	Continue	• Treat with non-selective beta-blockers (eg propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
		Epacadostat	Continue		
	Grade 3 or 4	Pembrolizumab	Withhold until Grade 0-1 or permanently discontinue[a]		
		Epacadostat	Withhold until Grade 0-1 or permanently discontinue[a] Once resolved to Grade 0-1, may restart: Related: Reduce by 1 dose level. Not Related: Same dose level.		

Immune-related AEs	Toxicity Grade or Conditions (CTCAE v4.0)	Study Treatment	Action Taken with Study Treatment	irAE Management with Corticosteroid and/or Other Therapies	Monitor and Follow-up
Hypothyroidism[b]	Grade 2-4	Pembrolizumab	Continue	• Initiate thyroid replacement hormones (eg levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
		Epacadostat	Continue		
Nephritis and Renal Dysfunction	Grade 2	Pembrolizumab	Withhold until Grade 0-1	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
		Epacadostat	Withhold until Grade 0-1 Once resolved to Grade 0-1, may restart: Related: Reduce by 1 dose level. Not Related: Same dose level.		
	Grade 3 or 4	Pembrolizumab	Permanently discontinue		
		Epacadostat	Permanently discontinue		
Myocarditis	Grade 1 or 2	Pembrolizumab	Withhold until Grade 0	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
		Epacadostat	Withhold until Grade 0 Once resolved to Grade 0, may restart: Related: Reduce by 1 dose level. Not Related: Same dose level.		
	Grade 3 or 4	Pembrolizumab	Permanently discontinue		
		Epacadostat	Permanently discontinue		

Immune-related AEs	Toxicity Grade or Conditions (CTCAE v4.0)	Study Treatment	Action Taken with Study Treatment	irAE Management with Corticosteroid and/or Other Therapies	Monitor and Follow-up
Rash	Grade 1 or 2	Pembrolizumab	Continue	• Manage with topical steroids with or without drug interruption.	
		Epacadostat	Continue		
	Grade 3 [c]	Pembrolizumab	Withhold until Grade 0-1	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper.	• Restart epacadostat at same dose if rash is mild and assessed as Grade 3 based only on body surface area and resolves without oral steroids. If oral steroids are required, or rash is severe, decrease by 1 dose level once resolved to Grade 0-1.
		Epacadostat	Withhold until Grade 0-1 Once resolved to Grade 0-1, may restart: Related: Reduce by 1 dose level. Not Related: Same dose level.		
	Grade 4	Pembrolizumab	Permanently discontinue		
		Epacadostat	Permanently discontinue		

Immune-related AEs	Toxicity Grade or Conditions (CTCAE v4.0)	Study Treatment	Action Taken with Study Treatment	irAE Management with Corticosteroid and/or Other Therapies	Monitor and Follow-up
Asymptomatic Amylase or Lipase Increased	Grade 3	Pembrolizumab	May continue treatment with MSD Clinical Director approval		• Permanently discontinue if clinical signs and symptoms of pancreatitis develop (abdominal pain, nausea, vomiting). • If toxicity does not resolve within 12 weeks of last dose after an interruption, must permanently discontinue unless approved by the MSD Clinical Director to continue. • If Grade 4 lipase/amylase elevation is asymptomatic and abdominal imaging suggests no pathology, study drug administration dosing may continue with MSD Clinical Director approval.
		Epacadostat	May continue treatment with MSD Clinical Director approval		
	Grade 4	Pembrolizumab	Withhold until toxicity resolves to Grade 0-1		
		Epacadostat	Withhold until toxicity resolves to Grade 0-1 Once resolved to Grade 0-1, may restart: Related: Reduce by 1 dose level. Not Related: Same dose level.		

Immune-related AEs	Toxicity Grade or Conditions (CTCAE v4.0)	Study Treatment	Action Taken with Study Treatment	irAE Management with Corticosteroid and/or Other Therapies	Monitor and Follow-up
All Other Immune-related AEs	Intolerable/ persistent Grade 2	Pembrolizumab	Withhold until Grade 0-1	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
		Epacadostat	Withhold until Grade 0-1 Once resolved to Grade 0-1, may restart: Related: Reduce by 1 dose level. Not Related: Same dose level.		
	Grade 3	Pembrolizumab	Withhold until Grade 0-1, or discontinue based on the type of event. Events that require discontinuation include and not limited to: Guillain-Barre Syndrome, encephalitis		
		Epacadostat	Withhold until Grade 0-1 Once resolved to Grade 0-1, may restart: Related: Reduce by 1 dose level. Not Related: Same dose level. Events that require discontinuation include and not limited to: Guillain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Pembrolizumab	Permanently discontinue		
		Epacadostat	Permanently discontinue		

Immune-related AEs	Toxicity Grade or Conditions (CTCAE v4.0)	Study Treatment	Action Taken with Study Treatment	irAE Management with Corticosteroid and/or Other Therapies	Monitor and Follow-up

Abbreviations: AEs = adverse events; ALT (SGPT) = alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT) = aspartate aminotransferase (serum glutamic oxaloacetic transaminase); CTCAE = Common Terminology Criteria for Adverse Events; GI = gastrointestinal; irAE = immune-related adverse events; IV = intravenous; T1DM = Type 1 diabetes mellitus.

General Instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab and epacadostat have been withheld, pembrolizumab and epacadostat can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab and epacadostat should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.
4. If the same AE that required epacadostat dose reductions to dose level -2 re-occurs, regardless of the causality to epacadostat, epacadostat should be discontinued. If a participant who is being treated at dose level -2 has a different Grade ≥3 AE that is considered unrelated to epacadostat by the investigator, the participant may resume study treatment at dose level -2 after discussion with MSD Clinical Director.

NOTES:

[a] Withhold OR permanently discontinue pembrolizumab or epacadostat at the discretion of the investigator.

[b] For participants with Grade 3 or 4 immune-related endocrinopathy where withholding of pembrolizumab and epacadostat is required, pembrolizumab and epacadostat may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

[c] Participants with Grade 3 rash in the absence of desquamation, no mucosal involvement, does not require systemic steroids, and resolves to Grade 1 within 14 days does not have to hold study treatment.

7.2.1.1 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 5.

Table 5 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 treatment**	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab 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 treatment.**	No subsequent dosing

Abbreviations: IV = intravenous; CTCAE – Common Terminology Criteria for AEs; NSAIDs = nonsteroidal anti-inflammatory drugs; NCI = National Cancer Institute

Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration.

For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov

7.2.1.2 Procedures for Participants Exhibiting Serotonin Syndrome

- There is a rare chance that epacadostat could cause an increase in serotonin levels in the brain that might trigger serotonin syndrome [Boyer EW, Shannon M. 2005], when administered in combination with other serotonergic agents. This syndrome has been most closely associated with use of MAOIs, meperidine, linezolid, or methylene blue; all of these agents are prohibited during the study (see Appendix 7). Selective serotonin reuptake inhibitors (SSRIs) and selective serotonin/norepinephrine reuptake inhibitors (SNRIs) are permitted in the study. Serotonin syndrome usually manifests with autonomic changes, mental status changes, and neurological findings. These mild, moderate, and severe signs and symptoms of serotonin syndrome (summarized in Table 6) should be evaluated in the context of possible comorbid conditions as well.
- The following procedures will be implemented if participants in Group 1 exhibit the signs/symptoms of serotonin syndrome described in Table 6, including tremor; hyperreflexia; spontaneous, ocular, or inducible clonus; together with agitation, fever, diaphoresis, or muscle rigidity:
- Immediately interrupt epacadostat and pembrolizumab administration.
- Immediately interrupt any SSRI or SNRI administration.

- Provide appropriate medical management of the participant until all signs/symptoms are resolved (eg, IV fluids and/or sympathomimetic amines for hypotension, benzodiazepines for agitation, administration of 5-hydroxytryptamine antagonists such as cyproheptadine).
- If etiologies other than serotonin syndrome are excluded, pembrolizumab administration may be resumed unless other AE management guidelines apply for the specific event.
- If participant chooses to remain in the study, restart treatment with epacadostat after the SSRI or SNRI has been discontinued, no sooner than after 5 half-lives have elapsed for the specific SSRI or SNRI in question, and after resolution of signs/symptoms of serotonin syndrome. The SSRI or SNRI dosing MAY NOT be restarted.
- If participant chooses to withdraw from the study, or must restart treatment with SSRI or SNRI, the participant should be scheduled for a Follow-up Visit. Treatment with SSRI or SNRI may be initiated 2 weeks after resolution of signs and symptoms of serotonin syndrome.
- If a participant had experienced moderate or severe unconfounded SS in the opinion of the investigator, without concomitant SSRI or SNRI usage, or serotonergic concomitant medications, only pembrolizumab administration may be resumed; epacadostat treatment should be permanently discontinued.

Table 6 Signs and Symptoms of Serotonin Syndrome

Seriousness	Autonomic signs	Neurological signs	Mental status	Other
Mild	Afebrile or low-grade fever Tachycardia Mydriasis Diaphoresis or shivering	Intermittent tremor Akathisia Myoclonus Mild hyperreflexia	Restlessness Anxiety	
Moderate	Increased tachycardia Fever (up to 41°C) Diarrhea with hyperactive bowel sounds Diaphoresis with normal skin color	Hyperreflexia Inducible clonus Ocular clonus (slow continuous lateral eye movements) Myoclonus	Easily startled Increased confusion Agitation and hypervigilance	Rhabdomyolysis Metabolic acidosis Renal failure Disseminated intravascular coagulopathy (secondary to hyperthermia)
Severe	Temperature often more than 41°C (Secondary to increased tone)	Increased muscle tone (lower limb > upper) Spontaneous clonus Substantial myoclonus or hyperreflexia	Delirium Coma	As above
Source: [Boyer EW, Shannon M. 2005]				

7.2.2 Dose Modifications for Cetuximab

For any delayed cetuximab treatment, do not repeat the initial dose of 400 mg/m². At the restart of cetuximab treatment, all subsequent infusions will be at the appropriate dose level according to Table 7, Table 8, and Table 9. If a participant develops a toxicity that mandates interruption of therapy, the toxicity must resolve within 12 weeks from the last dose of cetuximab or the drug should be discontinued with the exception of a participant who is clinically stable and clinically benefiting from cetuximab treatment. In this case, the investigator may request that MSD allow the participant to continue to receive cetuximab.

Cetuximab therapy will not be delayed for chemotherapy-related toxicity. If chemotherapy administration is delayed, the participant may continue to receive weekly infusions of cetuximab. After resolution of toxicity, platinum and/or 5-FU may be restarted at any weekly visit when cetuximab is given (ie Day 8 or Day 15 of a cycle) as long as there are ≥3 weeks duration between consecutive chemotherapy cycles. The interval between platinum and/or 5-FU infusions will continue as Q3W from the time of the restart. If participant on the cetuximab + platinum + 5-FU arm are required to have the platinum and/or 5-FU discontinued for toxicity, the participant may continue to receive cetuximab alone. In the case of cetuximab toxicity, participant may continue on chemotherapy alone.

Table 7 Dose Modification Guidelines for Cetuximab Drug-Related Adverse Events

Category	Toxicity	Hold Cetuximab Treatment for Grade	Timing for Restarting Cetuximab Treatment	Dose for Restarting Cetuximab Treatment	Discontinue Cetuximab
Nonhematologic	Infusion reaction	2-4	See Section 7.2.2.1 and Table 8		
	Rash	3-4	See Section 7.2.2.2 and Table 9		
	All other nonhematologic toxicities[1]	3-4	Toxicity resolves to Grade 0-1	Reduce by 1 dose level	Toxicity does not resolve within 12 weeks of last infusion or if >2 dose level reductions exceeded
	Laboratory AE[2]	4	Toxicity resolves to Grade 2 or less		

Abbreviations: AE = adverse event

Note: Permanent discontinuation should be considered for any severe or life-threatening event. Consult MSD before restarting treatment after Grade 4 drug-related AE.

[1] 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.

[2] With investigator and MSD agreement, participants with a laboratory AE still at Grade 2 after 12 weeks may continue in the study only if asymptomatic and controlled.

7.2.2.1 Infusion Reactions

Participants who experience cetuximab-related infusion reactions should have cetuximab reduced according to Table 8 and continue to receive antihistamine premedication prior to administration. Once the cetuximab infusion rate has been decreased due to an allergic/hypersensitivity reaction, it should remain decreased for all subsequent infusions.

If the participant experiences a second infusion reaction at the decreased rate, cetuximab must be discontinued. If any Grade 3 or 4 infusion reaction occurs, cetuximab treatment must be discontinued immediately. Participants who experience serious infusion reactions will be discontinued from cetuximab. The participant may continue to receive chemotherapy as scheduled.

Table 8 Cetuximab Dose Modification for Infusion Reactions

NCI CTCAE Grade	Hold Treatment (Yes/No)	Dose for Restarting Treatment
1	No	Decrease the cetuximab infusion rate by 50% and monitor closely for any worsening. Note: The total infusion time for cetuximab should not exceed 4 hours.
2	Yes Stop cetuximab infusion and administer bronchodilators, oxygen, etc. as medically indicated.	Resume infusion at 50% of previous rate once allergic/hypersensitivity reaction has resolved or decreased to Grade 1 in severity, and monitor closely for any worsening.
3-4	Yes Stop the cetuximab infusion immediately and disconnect infusion tubing from the participant	Stop the cetuximab infusion immediately and disconnect infusion tubing from the participant. Administer epinephrine, bronchodilators, antihistamines, glucocorticoids, intravenous fluids, vasopressor agents, oxygen, etc., as medically indicated. **Participant must discontinue treatment with cetuximab permanently**.

Abbreviations: NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events

7.2.2.2 Dermatologic Toxicity

The dosing of cetuximab will be omitted 1 to 2 weeks in the case of severe (Grade 3 or 4) acneiform rash. If acneiform rash improves during this time, then the dose of cetuximab should be reduced as indicated in Table 9. The dose modification guidelines in Table 7 should be followed for dermatologic toxicities other than acneiform rash.

If acneiform rash does not improve during this time, cetuximab will be discontinued.

Participants who have held cetuximab therapy for more than 2 consecutive infusions due to acneiform rash, and upon resolution of the toxicity are still felt to be benefiting from cetuximab treatment may resume cetuximab with MSD approval.

Table 9 Cetuximab Dose Modification for Severe Acneiform Rash

Severe Acneiform Rash (≥ Grade 3)	Dose Interruption	Outcome	Dose Modification
1st occurrence	Omit 1-2 doses	Improved[a]	None, continue at same dose
2nd occurrence	Omit 1-2 weeks	Improved[a]	Permanently reduce by 1 dose level [b]
3rd occurrence	Omit 1-2 weeks	Improved[a]	Permanently reduce by another dose level [b]
4th occurrence	Discontinue	N/A	N/A

Abbreviations: N/A = not applicable

[a] If rash does not improve, then discontinue cetuximab.

[b] Discontinue cetuximab if dose is less than 150 mg/m^2

7.2.3 Dose Modifications for Cisplatin or Carboplatin

Investigators may switch participants from cisplatin to carboplatin during the course of the study if toxicities occur. If the cisplatin dose was modified prior to switching, the participant may start at a carboplatin dose of AUC 5 and will be eligible to receive an additional 2 dose modifications of carboplatin.

Table 10 Dose Modification Guidelines for Febrile Neutropenia or Documented Infection

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

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

Table 11 Dose Modification Guidelines for Platinum Drug-Related Adverse Events

Category	Toxicity	Hold Platinum Treatment for Grade	Timing for Restarting Platinum Treatment	Dose for Restarting Platinum Treatment	Discontinue Platinum
Hematologic	Neutropenia	3[1]	Neutrophil count resolves to >1,000/mm^3 (1.0×10^9/L)	No reduction *consider G-CSF	Toxicity does not resolve within 12 weeks of last infusion or if >2 dose level reductions exceeded
		4[1]		Reduce by 1 dose level *consider G-CSF	
	Thrombocytopenia	2	Platelet count resolves to ≥75,000/mm^3 (75×10^9/L) or baseline	No reduction	
		3-4[1]		Reduce by 1 dose level	
Nonhematologic	Creatinine increased	2-4[1]	Toxicity resolves to Grade 0-1	For participants taking Carboplatin, reduce by 1 dose level For participants taking Cisplatin, change Cisplatin to Carboplatin	Toxicity does not resolve within 12 weeks of last infusion or if >2 dose level reductions exceeded
	Ototoxicity or sensory neuropathy	2	Change Cisplatin to Carboplatin May continue treatment with Carboplatin		
		3-4	May switch Cisplatin to Carboplatin if resolved to Grade ≤ 2 within 12 weeks of last infusion If already using carboplatin, then discontinue		
	All other nonhematologic toxicities[2]	3-4[1]	Toxicity resolves to Grade 0-1	Reduce by 1 dose level	Toxicity does not resolve within 12 weeks of last infusion or if >2 dose level reductions exceeded
	Laboratory AE[2]	4	Toxicity resolves to Grade 2 or less		

Abbreviations: AE = adverse event; G-CSF = granulocyte-colony stimulating factor.

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

[2] 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 MSD agreement, participants with a laboratory AE still at Grade 2 after 12 weeks may continue in the study only if asymptomatic and controlled.

7.2.4 Dose Modifications for 5-fluorouracil

Table 12 Dose Modification Guidelines for Febrile Neutropenia or Documented Infection

Adverse Event	Number of Occurrences	Treatment Modification
Febrile neutropenia[a] Documented infection	1	Reduce by 1 dose level The use of growth factors and antibiotics should be considered per local standards
	2	Reduce by 1 dose level Consider prophylactic antibiotics for subsequent cycles. The use of growth factors should be strongly considered per local standards
	3	Discontinue 5-fluorouracil
[a] ANC <1000/mm^3 (1.0 × 10^9/L) and a single temperature >38.3°C or sustained temperature ≥38°C for >1 hour.		

Table 13 Dose Modification Guidelines for 5-fluorouracil Drug-Related Adverse Events

Category	Toxicity	Hold 5-fluorouracil Treatment for Grade	Timing for Restarting 5-fluorouracil Treatment	Dose for Restarting 5-fluorouracil Treatment	Discontinue 5-fluorouracil
Hematologic	Neutropenia	3[1]	Neutrophil count resolves to >1,000/mm^3 (1.0×10^9/L)	No reduction *consider G-CSF	Toxicity does not resolve within 12 weeks of last infusion or if >2 dose level reductions exceeded
		4[1]		Reduce by 1 dose level *consider G-CSF	
	Thrombocytopenia	2	Platelet count resolves to ≥75,000/mm^3 (75×10^9/L) or baseline	No reduction	
		3-4[1]		Reduce by 1 dose level	
Nonhematologic	Creatinine increased	2-4[1]	Toxicity resolves to Grade 0-1	No reduction	Toxicity does not resolve within 12 weeks of last infusion or if >2 dose level reductions exceeded
	Mucositis Diarrhea	2-4[1]		Reduce by 1 dose level	
	Hand-foot syndrome	2		No reduction	
		3-4[1]		Reduce by 1 dose level	
	All other nonhematologic toxicities[2]	3-4[1]			
	Laboratory AE[2]	4	Toxicity resolves to Grade 2 or less		

Abbreviations: AE = adverse event; G-CSF = granulocyte-colony stimulating factor.

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

[2] 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 MSD agreement, participants with a laboratory AE still at Grade 2 after 12 weeks may continue in the study only if asymptomatic and controlled.

7.2.5 Dose Interruptions Unrelated to Adverse Events

Dosing interruptions are permitted for situations other than treatment-related AEs, such as in the case of medical/surgical events or logistical reasons not related to study treatment (eg, elective surgery, unrelated medical events, participant vacation, or holidays). Participants should be placed back on study treatment within 3 weeks of the scheduled interruption, unless otherwise discussed with MSD. The reason for interruption should be documented in the participant's study record.

7.2.6 Second Course Phase

Note: As of Amendment 04, imaging assessments will be no longer be made by BICR; all disease progression will be assessed by the investigator based on RECIST 1.1. This section has been updated accordingly.

Group 1 and 2 participants who stop pembrolizumab plus epacadostat or pembrolizumab monotherapy, with SD or better may be eligible for up to an additional 17 cycles (approximately 1 year) of pembrolizumab plus epacadostat, or pembrolizumab monotherapy if they progress and have a radiographic disease progression after stopping pembrolizumab plus epacadostat, or pembrolizumab monotherapy from the initial Treatment Phase. This retreatment is termed the Second Course Phase of this study and is only available if the study remains open and the participant meets the following conditions:

Either

- Stopped initial treatment of pembrolizumab plus epacadostat or pembrolizumab monotherapy after attaining a CR evaluated by the local investigator based on RECIST 1.1, and
    - Was treated with at least 24 weeks (at least 8 infusions of pembrolizumab) before discontinuing treatment, and
    - Received at least 2 cycles of the pembrolizumab plus epacadostat or pembrolizumab monotherapy beyond the date when the initial CR was declared

OR

- Had SD, PR, or CR and stopped study treatment after completion of 35 cycles of pembrolizumab plus epacadostat or pembrolizumab monotherapy (approximately 2 years) for reasons other than radiographic disease progression or intolerability

AND

- Experienced an investigator-determined radiographic disease progression by RECIST 1.1 after stopping initial treatment with pembrolizumab plus epacadostat or pembrolizumab monotherapy, and
    - No new anticancer treatment was administered after the last dose of pembrolizumab plus epacadostat or pembrolizumab monotherapy, and
    - Continues to meet all of the safety parameters listed in the inclusion criteria and none of the safety parameters listed in the exclusion criteria, and
    - The study is ongoing

Participants who enter the Second Course Phase will be retreated at the same combination, dose level, and frequency as when they last received pembrolizumab plus epacadostat or pembrolizumab monotherapy. Treatment will be administered for up to an additional 17 cycles (approximately 1 year) using the Second Course Phase SoA in Section 2.2.

7.3 Method of Treatment Assignment

Treatment allocation/randomization will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). There are 3 study treatment arms. Participants will be assigned randomly in a 2:1:2 ratio to pembrolizumab plus epacadostat, pembrolizumab monotherapy, and EXTREME regimen, respectively.

Investigators must choose which platinum drug will be used (carboplatin or cisplatin) prior to randomization. The selection will be documented in the study database via IVRS/IWRS (See Data Entry Guidelines).

7.3.1 Stratification

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

1. ECOG PS (0 vs. 1).
2. HPV p16 status (oropharynx-p16 positive vs. oropharynx-p16 negative or larynx/hypopharynx/oral cavity HNSCC).
3. Prior systemic oncological therapy (as the part of the definitive treatment for the locally advanced disease) (yes vs. no).

7.4 Blinding

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

Note: As of Amendment 04, imaging assessments will be no longer be made by BICR; all disease progression will be assessed by the investigator based on RECIST 1.1.

[redacted]

7.5 Preparation/Handling/Storage/Accountability

7.5.1 Dose Preparation

The rationale for selection of doses to be used in this study is provided in Section 5.5. Details on preparation and administration of IV pembrolizumab are provided in the Pharmacy Manual. Epacadostat is an oral tablet and does not require preparation.

For epacadostat in such cases where a participant is unable to swallow tablets or has a feeding tube instruction for dose crushing, administration and dose preparation are detailed in the Pharmacy Manual. In addition written guidance for safe handling of the epacadostat tablets will be provided to the participant/caregivers.

Group 3 (EXTREME regimen) treatments will be prepared and administered as per the approved product label. The body surface area in m^2 should be calculated per local guidance.

Cetuximab will be administered at a dose of 400 mg/m^2 as an IV infusion on Day 1 of the study followed by subsequent weekly doses of 250 mg/m^2 as IV infusions.

Carboplatin will be administered at an AUC of 5 mg/mL per minute as an IV infusion on Day 1 of a 3-week cycle. Pursuant to the CTEP Information Letter Regarding the AUC Based Dosing of Carboplatin, the maximum carboplatin dose should not exceed the target AUC (mg*min/mL)*150 mL/min, but it may be less. As well, the glomerular filtration rate (GFR) used in the Calvert formula to AUC-based dosing should not exceed 125 mL/min. For this study, the maximum dose of carboplatin cannot exceed a total dose of 750 mg. Alterations in renal function may require a recalculation of the carboplatin dose.

Cisplatin will be administered at a dose of 100 mg/m^2 as an IV infusion on Day 1 of a 3-week cycle.

5-FU will be administered at a dose of 1000 mg/m^2/day as a continuous IV infusion for 4 days on Days 1 to 4 of a 3-week cycle.

Preparation of study treatments should follow the local product label.

7.5.2 Handling, Storage and Accountability

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

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

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

For all trial sites, the local country MSD 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 trial 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 MSD.

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

7.6 Treatment Compliance

Compliance with study treatments should be emphasized to the participants by the site personnel, and appropriate steps should be taken to optimize compliance during the study.

Interruptions from the protocol-specified treatment plan for more than 3 weeks for nondrug-related or administrative reasons require consultation between the investigator and MSD and written documentation of the collaborative decision on participant management.

7.6.1 Compliance of Pembrolizumab

Administration of pembrolizumab will be witnessed by the investigator and/or study staff. The total volume of pembrolizumab infused will be compared to the total volume prepared to determine compliance with each dose administered.

7.6.2 Compliance of Epacadostat

Participants will self-administer epacadostat except on Cycle 1 Day 1 and Cycle 2 Day 1, when the morning dose will be given at the study site clinic. Participants will be instructed to bring all remaining epacadostat tablets with them to the study visits in order for site personnel to conduct tablet counts to assess study treatment accountability.

7.6.3 Compliance of EXTREME Regimen

Administration of cisplatin/carboplatin, 5-FU, and cetuximab will be witnessed by the investigator and/or study staff. Compliance with these reference therapies will be documented in the medical record and monitored by MSD or its designee.

7.7 Concomitant Therapy

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

7.7.1 Permitted Medications

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

All concomitant medications received within 28 days prior to the first dose of study treatment and up to 30 days after the last dose of study treatment should be recorded. Concomitant medications administered 30 days after the last dose of study treatment should be recorded for SAEs and events of ECIs as defined in Section 9.3. If a participant enters into Second

Course Phase, all concomitant medications received within 30 days before the first dose of Second Course study treatment should be recorded. Following Second Course Phase Safety Follow-up Visit, record all medications taken for SAEs and ECIs as defined in Section 9.3.

7.7.2 Restricted Medications

Listed below are specific restrictions for concomitant therapy during the course of the study:

- Use of coumarin-based anticoagulants (eg, warfarin) with epacadostat is discouraged. Low-dose warfarin (1 mg) is acceptable; however, other higher doses are discouraged. If an alternative to coumarin-based anticoagulants cannot be used, the INR should be monitored closely per SoC when epacadostat is started.

  Note: For participants randomized to either the EXTREME arm or pembrolizumab monotherapy arm, the use of coumarin-based anticoagulants is not restricted.

- Use of any restricted medications as described in local package inserts or prescribing information for pembrolizumab, cetuximab, cisplatin, carboplatin, and/or 5-FU.

7.7.3 Prohibited Medications and Measures

Participants are prohibited from receiving the following therapies during the Screening and Treatment Phase of this study unless otherwise noted below:

- Any investigational medication other than the study treatments
- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an AE. The use of physiologic doses of corticosteroids may be approved after consultation with MSD. Additionally, a short, limited course of steroids may be used to treat medical conditions and/or AEs during the study after MSD notification and consultation.

  Note: For participants randomized to the EXTREME arm the use of systemic glucocorticoids on study treatment is acceptable and may be required for premedication.

  Note: Inhaled steroids are allowed for management of asthma/chronic obstructive pulmonary disease.

  Note: Use of prophylactic corticosteroids to avoid allergic reactions (eg, to IV contrast dye) is permitted.

- Oncologic surgery for tumor control.
- Radiation therapy

- Administration of a live attenuated vaccine within 30 days before the first dose of study treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines are live attenuated vaccines and are not allowed.

  Note: For participants randomized to the EXTREME arm the use of live vaccines is acceptable during the study.

- Any MAOI or drug associated with significant MAO inhibitory activity is prohibited from 21 days before starting study treatment through 2 weeks after the final dose of epacadostat has been taken. See Appendix 7 for prohibited agents.

  Note: For participants randomized to either the EXTREME arm or pembrolizumab monotherapy arm, the use of MOAI or drug associated with significant MAO inhibitory activity is acceptable during the study.

- Any UGT1A9 inhibitor, including: acitretin, amitriptyline, androsterone, cyclosporine, dasatinib, diclofenac, diflunisal, efavirenz, erlotinib, flutamide, gefitinib, gemfibrozil, glycyrrhetinic acid, glycyrrhizin, imatinib, imipramine, ketoconazole, linoleic acid supplements, mycophenolic acid, niflumic acid, nilotinib, phenobarbital, phenylbutazone, phenytoin, probenecid, quinidine, ritonavir, sorafenib, sulfinpyrazone, valproic acid, and verapamil.

  Note: For participants randomized to the EXTREME arm or pembrolizumab monotherapy arm, the use of UGT1A9 inhibitors is acceptable.

The exclusion criteria describe other medications that are prohibited in this study. There are no prohibited therapies during the Post-treatment Follow-up Phase.

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

7.7.4 Rescue Medications & Supportive Care

7.7.4.1 Supportive Care Guidelines for Pembrolizumab

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

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the investigator does not need to follow the treatment guidance. Refer to Table 4 and Table 5 in Section 7.2 for guidelines regarding dose modification and supportive care.

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

7.7.4.2 Supportive Care Guidelines for Epacadostat

Supportive care guidelines listed above in Section 7.7.4.1 are applicable to epacadostat as well. Additionally, the procedures in Section 7.2.1.2 will be implemented if participants exhibit the signs/symptoms of serotonin syndrome described in Table 6.

7.7.4.3 Supportive Care Guidelines for Cisplatin and Carboplatin

For participants randomized to Group 3 (EXTREME regimen) the use of systemic glucocorticoids during study treatment is acceptable and may be required for premedication.

Please refer to the product label or local standards of care for additional cisplatin and carboplatin supportive measures and AE management.

7.7.4.4 Supportive Care Guidelines for 5-fluorouracil

Please refer to the product label or local standards of care for 5-FU supportive measures and AE management.

7.7.4.5 Supportive Care Guidelines for Cetuximab

Participants receiving cetuximab should be pre-medicated with an H1 antagonist (eg, 50 mg of diphenhydramine) intravenously 30 to 60 minutes prior to the first dose. Premedication for subsequent doses of cetuximab should be given per medical judgment and history of prior infusion reactions.

Guidelines for medical therapy for infusion reactions detailed in Table 5 are also recommended for reactions due to cetuximab.

Refer to the approved product label for additional supportive care guidance and AE management.

7.8 Treatment After the End of the Study

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

7.9 Clinical Supplies Disclosure

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

8. Discontinuation/Withdrawal Criteria

8.1 Discontinuation of Study Treatment

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

As certain data on clinical events beyond study treatment discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study treatment. Therefore, all participants who discontinue study treatment prior to completion of the protocol-specified imaging requirements (ie, before Week 9 efficacy assessment, PD or initiation of a new anticancer treatment) will still continue to participate in the study as specified in Section 2 and Section 9.9.4.

Participants may discontinue study treatment at any time for any reason or be dropped from the study treatment at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study treatment by the investigator or MSD if study treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study treatment discontinuation are provided in Section 9.1.10.

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

- The participant or participant's legally acceptable representative requests to discontinue study treatment.
- Radiographic disease progression per RECIST 1.1.
- Unacceptable AEs as described in Section 7.2.1 with a requirement to permanently discontinue.
- The participant interrupts study treatment administration for any TRAE for more than 12 consecutive weeks or more than 3 weeks for interruptions unrelated to AEs, unless approved with written documentation from MSD.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or MSD, placed the participant at unnecessary risk from continued administration of study treatment.
- The participant has a confirmed positive serum pregnancy test.
- Administrative reasons.
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active systemic treatment.
- Noncompliance with study treatment or procedure requirements.
- Recurrent Grade 2 pneumonitis.
- Completion of 35 treatment cycles (approximately 2 years) with pembrolizumab plus epacadostat or pembrolizumab monotherapy.

- Discontinuation of treatment may be considered for participants who have attained a CR and have been treated for at least 8 cycles (at least 24 weeks), and received at least 2 cycles of pembrolizumab plus epacadostat or pembrolizumab monotherapy beyond the date when the initial CR was declared. These participants may be eligible for Second Course Treatment described in Section 7.2.6.

For participants who are discontinued from study treatment but continue to be monitored in the trial, see Section 2 and Section 9.9.4 for those procedures to be completed at each specified visit.

Participants may be allowed to begin study treatment again if deemed medically appropriate following consultation with MSD.

8.2 Withdrawal from the Study

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

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

Specific details regarding procedures to be performed at the time of withdrawal from the study are outlined in Section 9.1.10.

8.3 Lost to Follow-up

NOTE: As of Amendment 04, this section is no longer applicable. There will be no additional efforts to contact participants who are 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, phone 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 amount of missing data for the participant will be managed via the pre-specified data handling and analysis guidelines.

9. 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 assuring that procedures are conducted by appropriately qualified or trained staff. Delegation of trial site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- 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 MSD for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

9.1 Administrative and General Procedures

9.1.1 Informed Consent

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

9.1.1.1 General Informed Consent

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

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

The initial ICF, any subsequent revised written 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 trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's dated signature or by the participant's legally acceptable representative's dated signature.

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

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

9.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the participant qualifies for the study.

9.1.3 Participant Identification Card

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

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

9.1.4 Serotonin Syndrome Information Card

On Cycle 1 Day 1, Group 1 participants will also be given a serotonin syndrome information card listing signs and symptoms of serotonin syndrome. This information card also instructs participants to seek immediate medical care if any of these symptoms are observed.

9.1.5 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will collect all active conditions and any condition diagnosed within the prior 10 years that the investigator considers to be clinically significant. Details regarding the participant's HNSCC will be recorded separately and not listed as medical history.

9.1.5.1 Disease Details

The investigator or qualified designee will obtain prior and current details regarding the participant's head and neck cancer.

9.1.6 Prior and Concomitant Medications Review

9.1.6.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 28 days before the first dose of study treatment. Prior oncological treatment for head and neck cancer will be recorded separately and not listed as a prior medication.

9.1.6.1.1 Prior Oncological Treatment Details for Head and Neck Cancer

The investigator or qualified designee will review all prior cancer treatments including systemic treatments, radiation and surgeries.

9.1.6.2 Concomitant Medications

As specified in Section 7.7, the investigator or qualified designee will record medication, if any, taken by the participant during the study through the Safety Follow-up Visit. In addition, new medications started during the Second Course Phase through the Second Course Safety Follow-up Visit should be recorded.

9.1.7 Assignment of Screening Number

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

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

Specific details on the Screening Visit requirements (screening/rescreening) are provided in Section 9.9.1.

9.1.8 Assignment of Treatment/Randomization Number

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

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

9.1.9 Treatment Administration

Study Treatment should begin within 5 days of randomization.

9.1.9.1 Timing of Dose Administration

Study treatment with pembrolizumab, epacadostat, 5-FU, cisplatin, carboplatin, or cetuximab should be administered after all procedures/assessments have been completed as detailed in Section 2 – SoA and described henceforth. Cycle 1 Day 1 must be no more than 5 days after the date of randomization. Dates for subsequent study visits and study treatments will be determined based on this day and should occur within 3 days (±) of the scheduled date ie, Day 1 of each 21-day cycle unless delayed for safety reasons.

The ±3 day window for cetuximab generally applies to restarting cetuximab after a treatment delay; administering cetuximab with less than 7 days between doses is not recommended. Epacadostat is taken orally every morning and evening throughout the study.

Additional details for administration of study treatments are provided henceforth.

9.1.9.1.1 Group 1 Dose Administrations

1) Pembrolizumab Administration

Pembrolizumab will be administered as a dose of 200 mg using 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 close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (ie, infusion time is 30 minutes -5 min/+10 min).

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

2) Epacadostat Administration

Epacadostat 100 mg BID will be self-administered orally every day of each 21-day cycle. All BID doses will be taken morning and evening, approximately 12 hours apart without regard to food. If the participant vomits after taking study treatment, the participant should not take another dose. If a dose of epacadostat is missed by more than 4 hours, that dose should be skipped and the next scheduled dose should be administered at the usual time.

Participants will hold the morning dose of epacadostat for the Cycle 1 Day 1 and Cycle 2 Day 1 Visits where study treatment will be administered at the study site clinic. On days when epacadostat is administered in the clinic, participants will take epacadostat and then receive the infusion of pembrolizumab. [redacted]

For participants who cannot swallow tablets but can eat and/or drink, epacadostat tablets may be crushed and dissolved in water or dispersed in a medium such as applesauce, or a nutritional supplement such as Ensure® and administered orally. In the case of participants who are unable to eat or drink by mouth, the epacadostat tablet(s) may be crushed and dissolved in water and delivered to the participant through a feeding tube. Detailed information is provided in the Pharmacy Manual.

9.1.9.1.2 Group 2 Dose Administrations

Pembrolizumab will be administered as detailed for Group 1 above.

9.1.9.1.3 Group 3 EXTREME Regimen Dose Administrations

1) Cetuximab Administration

Cetuximab should be administered on Days 1, 8, and 15 of each 21 day cycle. Cetuximab will be administered as an initial loading dose of 400 mg/m^2 as a 120-minute IV infusion on Cycle 1, Day 1. For all subsequent infusions, the cetuximab dose is 250 mg/m^2 as a 60-minute IV infusion once weekly. The cetuximab infusion must be completed 1 hour before administration of the platinum and 5-FU. After platinum and 5-FU are completed, for participants with at least SD, cetuximab monotherapy may continue until radiographic disease progression or unacceptable toxicity occurs.

2) Cisplatin Administration

Cisplatin will be administered at 100 mg/m^2 as a 60-minute IV infusion (or infusion duration according to local practice) on Day 1 of each 21-day cycle.

3) Carboplatin Administration

Carboplatin will be administered at a dose of AUC 5 as a 60-minute IV infusion (or infusion duration according to local practice) on Day 1 of each 21-day cycle.

4) 5-fluorouracil Administration

5-fluorouracil will be administered at 1000 mg/m^2/day as a continuous IV infusion over Days 1 through 4 of each 21-day cycle.

Sites are instructed to consult local prescribing information for additional information and instructions for preparation and administration of the EXTREME regimen.

9.1.10 Withdrawal/Discontinuation

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

When a participant withdraws from participation in the study, all applicable activities scheduled for the final study visit should be performed at the time of withdrawal. Any AEs which are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 9.3.

9.1.11 Participant Blinding/Unblinding

This is an open-label study; there is no blinding for this study.

9.1.12 Calibration of Equipment

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

Documentation of equipment calibration must be retained as source documentation at the study site.

9.2 Efficacy Assessments

9.2.1 Tumor Imaging and Assessment of Disease

Note: As of Amendment 04, central review of imaging and iRECIST is no longer applicable. This section has been updated accordingly.

Tumor imaging is strongly preferred to be acquired by computed tomography (CT). For head and neck, abdomen and pelvis, magnetic resonance imaging (MRI) may be used when CT with iodinated contrast is contraindicated, or when mandated by local practice. Magnetic resonance imaging is the strongly preferred modality for imaging the brain (for brain metastases). The same imaging technique, including modality (ideally the same scanner) and the use of contrast, should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the assessment of response or progression based on imaging. Note: for the purposes of assessing tumor imaging, the term "investigator" refers to the local investigator at the site and/or the radiological reviewer located at the site or at an offsite facility.

Imaging should include the head and neck, chest, and abdomen at all timepoints specified in Section 2 - SoA. Imaging of the brain and pelvis are optional (if clinically indicated). For an individual participant, imaging should be consistent at all timepoints, (ie, follow-up scans should image the same areas as the baseline area, using the same imaging modality).

Participant eligibility will be determined using local assessment (investigator assessment) based on RECIST 1.1.

Treatment should continue until PD has been determined per investigator assessment.

9.2.1.1 Initial Tumor Imaging

Note: As of Amendment 04, central review of imaging is no longer applicable. This section has been updated accordingly.

Initial tumor imaging at screening must be performed within -28 to -1 days prior to the date of randomization. The site study team must review screening images to confirm the participant has measurable disease per RECIST 1.1.

Tumor imaging performed as part of routine clinical management is acceptable for use as screening tumor imaging if it is of diagnostic quality and performed within -28 to -1 days prior to the date of randomization and can be assessed by the central imaging vendor.

If brain imaging is performed to document the stability of existing metastases, MRI should be used if possible. If MRI is medically contraindicated, CT with contrast is an acceptable alternative.

9.2.1.2 Tumor Imaging During the Study

Note: As of Amendment 04, central review of images and iRECIST is no longer applicable. After the first on-study imaging assessment at Week 9, further imaging will be performed as per local SoC guidelines however these data will not be collected. This section has been updated accordingly.

The first on-study imaging assessment should be performed at Week 9 (63 days ± 7 days) from the date of randomization. No further imaging is mandated; any further imaging for disease assessments will be performed by site investigator/radiology assessment as per SoC for the disease and local guidelines; only the date of scans performed as per SoC needs to be documented in the eCRF.

9.2.1.3 End of Treatment and Follow-up Tumor Imaging

Note: As per Amendment 04, there is no protocol specified imaging after the Week 9 assessment. This section has been updated accordingly.

For participants who discontinue study treatment before the Week 9 imaging assessment for efficacy analysis, tumor imaging should be performed at the time of treatment discontinuation (±4 week window). If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory. For participants who discontinue study treatment due to radiographic disease progression, this is the final required tumor imaging.

9.2.1.4 Second Course Phase Tumor Imaging

Note: As of Amendment 04, Second Course imaging will be assessed by the investigator and iRECIST is no longer applicable; transmission of images to the central review of imaging is no longer required. Disease assessment will be performed by the investigator per SoC for the disease and local guidelines. This section has been updated accordingly.

Tumor imaging must be performed within 28 days prior to restarting treatment with pembrolizumab plus epacadostat, or pembrolizumab monotherapy. Before a participant may enter Second Course Phase, radiographic PD must have occurred. The PD imaging may also be used as the Second Course baseline imaging if it is within 28 days prior to restarting treatment.

Local reading (investigator assessment with site radiology reading) will be used to determine eligibility. Imaging for disease assessments will be performed by site investigator/radiology assessment as per SoC for the disease and local guidelines; only the date of scans performed as per SoC needs to be documented in the eCRF.

9.2.1.5 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 treatment). Although RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, this protocol allows a maximum of 10 target lesions in total and 5 per organ, if clinically relevant to enable a broader sampling of tumor burden.

9.2.1.6 iRECIST Assessment of Disease (Group 1 and 2)

NOTE: As of Amendment 04, this section is no longer applicable; iRECIST data will no longer be collected. Participants with radiographic disease progression as determined by RECIST 1.1 will discontinue from the study and be followed for safety monitoring, as detailed in Section 9.3; no confirmatory scans are required.

iRECIST is based on RECIST 1.1, but adapted to account for the unique tumor response seen with immunotherapeutic agents and therefore is only required for participants in Group 1 and Group 2. iRECIST will be used by the investigator to assess tumor response and progression, and make treatment decisions. When clinically stable, Group 1 and 2 participants should not be discontinued until progression is confirmed by the investigator, working with local radiology, according to the rules outlined in Appendix 8. This allowance to continue treatment despite initial radiologic PD takes into account the observation that some participants can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. These data will be captured in the clinical database.

Clinical stability is defined as the following:

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

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

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

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

If a participant has confirmed radiographic progression (iCPD) as defined in Appendix 8, study treatment should be discontinued; however, if the participant is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered following consultation with MSD. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 2 and be submitted to the central imaging vendor.

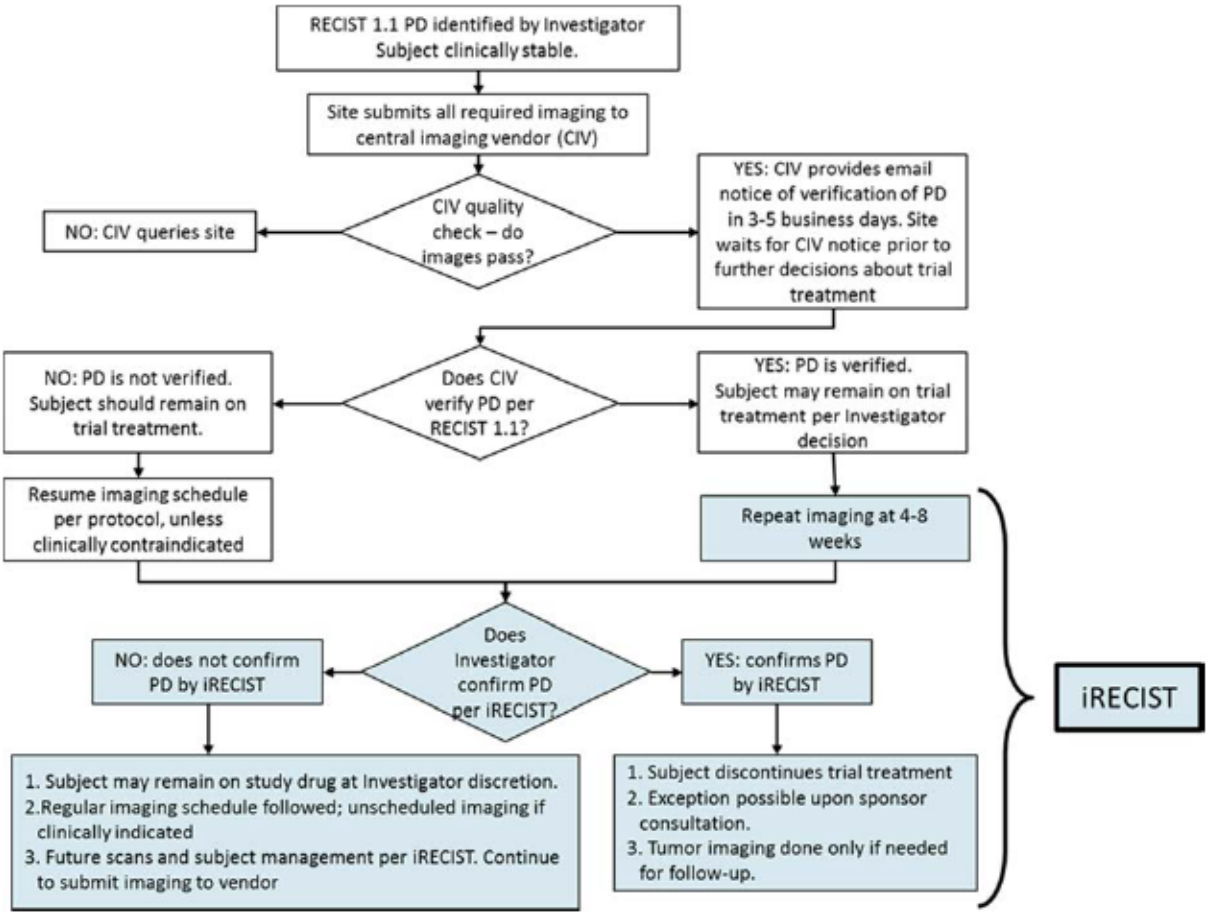
A description of the adaptations and iRECIST process is provided in Appendix 8, with additional details in the iRECIST publication [Seymour, L., et al 2017]. A summary of imaging and treatment requirements after first radiologic evidence of progression is provided in Table 14 and illustrated as a flowchart in Figure 2.

Table 14 Imaging and Treatment after First Radiologic Evidence of Progressive Disease

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

Abbreviations: BICR = blinded independent central review; iCPD = iRECIST confirmed progressive disease; iCR = iRECIST complete response; iRECIST = modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; iPR = immune partial response; iSD = iRECIST stable disease; iUPD = iRECIST unconfirmed progressive disease; PD = progressive disease; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors 1.1; VOP = verification of progression.

Note: If progression has been centrally verified, further management is by the site, based on iRECIST. Any further imaging should still be submitted to the central imaging vendor, but no rapid review will occur. If RECIST 1.1 disease progression has not been centrally verified, ideally the site should continue treatment. Whether or not treatment continues, imaging should be collected and submitted to the central imaging vendor with VOP request until RECIST 1.1 progression is verified by BICR.



Abbreviations: iRECIST = modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; PD = progressive disease; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors 1.1.

Figure 2 Imaging and Treatment for Clinically Stable Group 1 and 2 Participants after First Radiologic Evidence of Disease Progression Assessed by the Investigator

9.2.2 Patient Reported Outcomes

Note: As of Amendment 04, PROs will no longer be collected after the first on-study imaging assessment at Week 9.

The EQ-5D, EORTC QLQ-C30 and EORTC QLQ-H&N35 questionnaires will be administered by trained site personnel and completed electronically by participants in the following order: EQ-5D first, then EORTC QLQ-C30, followed by EORTC QLQ-H&N35. The questionnaires should be administered prior to dosing at Cycle 1, Cycle 2, Cycle 3, and Cycle 4.

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

9.2.3 Health Care Resource Utilization

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

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

The definitions of an adverse event (AE) or serious adverse event (SAE), as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE and other reportable safety event reports can be found in Appendix 4.

Progression of the cancer under study is not considered an adverse event as described in Section 9.3.5 – Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs, and Appendix 4.

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

The investigator, who is a qualified physician, and any designees are responsible for detecting, assessing, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AE, SAEs and other reportable safety events for outcome according to Section 9.3.3.

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

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

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

The investigator must report all pregnancies and exposure during breastfeeding from the time of treatment allocation/randomization through

- 120 days following last dose of pembrolizumab and/or epacadostat OR
- 180 days after last dose of chemotherapeutic agents OR
- 30 days following cessation of study treatment if the participant initiates new anticancer therapy.

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 MSD if the event is considered to be drug-related.

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

All initial and follow-up AEs, SAEs and other reportable safety events will be recorded and reported to MSD or designee within the timeframes as indicated in Table 15.

Table 15 Reporting Time Periods and Timeframes 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**	**Timeframe to Report Event and Follow-up Information to MSD:**
Non-Serious Adverse Event (NSAE)	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
Serious Adverse Event (SAE) including Cancer and Overdose	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/Lactation Exposure	Report if: - due to intervention - causes exclusion	Report all	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event

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	Timeframe to Report Event and Follow-up Information to MSD:
Event of Clinical Interest (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - Potential DILI - Require regulatory reporting	Not required	Within 24 hours of learning of event
Event of Clinical Interest (Do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event

9.3.2 Method of Detecting AE, SAE and Other Reportable Safety Events

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

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AE, SAE and other reportable safety events including pregnancy and exposure during breastfeeding, ECI, Cancer and Overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). In addition, the investigator will make every attempt to follow all non-serious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 4.

9.3.4 Regulatory Reporting Requirements for SAE

- Prompt notification (within 24 hours) by the investigator to MSD of SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The Sponsor and MSD have a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, ie, per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.

- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and MSD 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 MSD will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

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

Efficacy endpoints as outlined in this section will not be reported to MSD, as described in Section 9.3.1. Specifically, the suspected/actual events covered in this exception include any event that is disease progression of the cancer under study.

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

9.3.6 Pregnancy and Exposure During Breastfeeding

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

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

9.3.7 Events of Clinical Interest (ECI)

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to MSD.

Events of clinical interest for this trial include:

1. an overdose of study treatment, as defined in Section 9.4 – Treatment of Overdose, that is not associated with clinical symptoms or abnormal laboratory results.

2. 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 trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

It may also be appropriate to conduct additional evaluation for an underlying etiology in the setting of abnormalities of liver blood tests including AST, ALT, bilirubin, and alkaline phosphatase that do not meet the criteria noted above. In these cases, the decision to proceed with additional evaluation will be made through consultation between the study investigators and the MSD Clinical Director. However, abnormalities of liver blood tests that do not meet the criteria noted above are not ECIs for this study.

3. serotonin syndrome. The signs and symptoms of serotonin syndrome are described in Section 7.2.1.2.

9.4 Treatment of Overdose

Pembrolizumab or Epacadostat Overdose

For this study, an overdose will be defined as ≥1000 mg (≥5 times the dose) of pembrolizumab, ≥1000 mg of epacadostat daily, or as any dose ≥20% over the prescribed dose for the EXTREME regimen. No specific information is available on the treatment of an overdose of pembrolizumab or epacadostat. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

Cetuximab Overdose

There is no available information for the treatment of a cetuximab overdose. In cases of greater than recommended doses, the AEs were similar to the known safety profile. Appropriate supportive treatment should be provided if clinically indicated.

Otherwise, overdose should be managed according to local label and practice.

Carboplatin Overdose

There is no known antidote for carboplatin overdose. The anticipated complications of overdose may include myelosuppression and impairment of hepatic and renal function.

Otherwise, overdose should be managed according to local label and practice.

Cisplatin Overdose

There is no specific antidote for cisplatin overdose. Overdose may result in the side effects associated with the drug occurring in an excessive manner.

Otherwise, overdose should be managed according to local label and practice.

5-fluorouracil Overdose

Signs and symptoms of 5-FU overdose are similar to the adverse reactions associated with the drug and should be managed according to local label and practice. Participants who have a 5-FU overdose should be closely monitored for 4 weeks.

Otherwise, overdose should be managed according to local label and practice.

If an AE(s) is associated with ("results from") the overdose of study treatment, the AE(s) is reported as a SAE, even if no other seriousness criteria are met.

If a dose of study treatment meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious ECI, using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an AE must be reported within 24 hours to MSD either by electronic media or paper. MSD Contact information can be found in the Investigator Trial File Binder (or equivalent).

9.5 Safety

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

9.5.1 Physical Examinations

9.5.1.1 Full Physical Exam

The investigator or qualified designee will perform a full physical exam as per institutional standard during the screening period. Clinically significant abnormal findings should be recorded as medical history. The time points for full physical exams are described in Section 2 - SoA. After the first dose of study treatment, new clinically significant abnormal findings should be recorded as AEs.

9.5.1.2 Directed Physical Exam

For cycles that do not require a full physical exam, as specified in Section 2 - SoA, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to the administration of the study treatment. New clinically significant abnormal findings should be recorded as AEs.

9.5.2 Vital Signs

The investigator or qualified designee will take weight and vital signs at screening and as specified in Section 2 - SoA. Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions. Height will be measured at screening only.

9.5.3 Electrocardiograms

Baseline ECGs will be obtained at screening with additional ECGs obtained at EOT, and as clinically indicated for all participants. At select centers only, additional ECGs will also be obtained from Group 1 participants at Cycle 1 Day 1 predose and 2 hours (± 15 minutes) after the first dose of epacadostat and Cycle 2 Day 1 predose and 2 hours (± 15 minutes) after administration of epacadostat. The ECG measurement should always be performed prior to the PK sample blood draw if both are scheduled at the same nominal planned timepoint. Clinically significant abnormal findings prior to signing consent should be recorded as

medical history. Clinically significant abnormal findings after signing consent should be recorded as an AE.

The ECGs will be interpreted by the investigator at the site and will be used for immediate participant management. The decision to include or withdraw a participant from the study based on an ECG flagged as "Abnormal, Clinically Significant" is the responsibility of the investigator, in consultation with the MSD Clinical Director, as appropriate. The Fridericia (preferred) or Bazett correction method for calculating QTc will be used and recorded in the eCRF.

9.5.4 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 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 non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF.
- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days for all AEs and 90 days for all SAEs (or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever occurs first) after the last dose of study treatment, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

Laboratory tests for screening or entry into the Second Course Phase (Retreatment) should be performed within 10 days prior to the first dose of study treatment. Screening labs should be collected and assessed prior to randomizing the participant. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results for specific laboratory tests (ie, complete blood count with complete differential, serum creatinine, electrolytes, and urinalysis) must be available and reviewed by the investigator or qualified designee and found to be acceptable prior to administration of each dose of study treatment.

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 pre-study to post-study visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant can be found in the Laboratory Manual.

9.5.4.1 Laboratory Safety Evaluations (Hematology, Chemistry, Coagulation, and Urinalysis)

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

9.5.4.2 Pregnancy Test

All women who are being considered for participation in the study, and who are not surgically sterilized or postmenopausal (as defined in Appendix 5), must be tested for pregnancy within 72 hours of first dose of study treatment. If a urine test is positive or not evaluable, a serum test will be required. Participants must be excluded/discontinued from the study in the event of a positive test result. Repeated Pregnancy test (such as monthly test) may be conducted if required by local regulations.

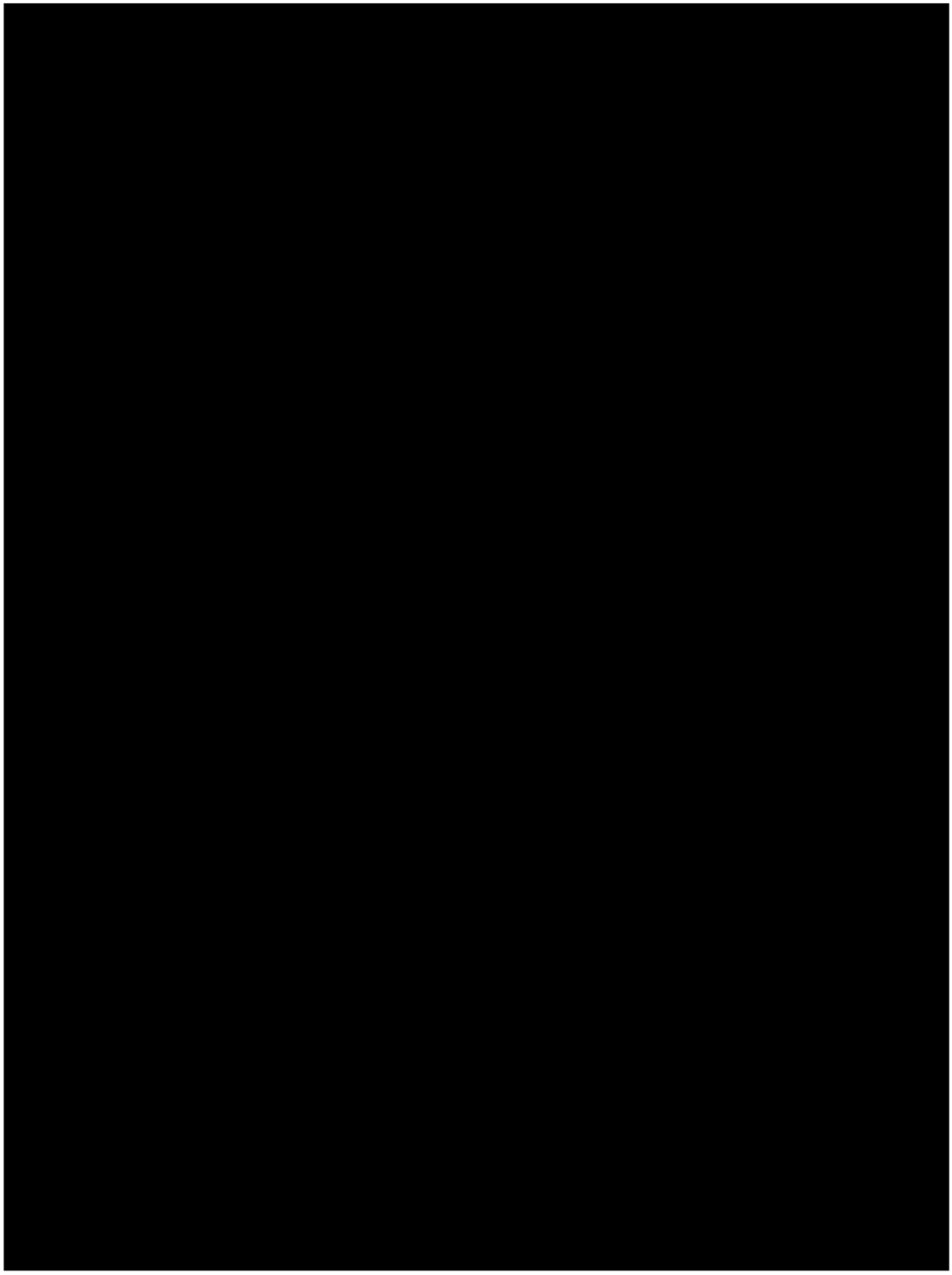
9.5.4.3 Hepatitis B and C Serology

Serology for Hepatitis B and Hepatitis C will be performed for all participants. Required tests are indicated in Table 21 in Appendix 2.

9.5.5 Performance Assessments

9.5.5.1 Eastern Cooperative Oncology Group Performance Scale

The investigator or qualified designee will assess ECOG PS (see Appendix 6) at screening (within 7 days of randomization), prior to the administration of each dose of study treatment, and during the Post-treatment Follow-up Phase as specified in Section 2 - SoA. ECOG PS must be 0 or 1 on the first day of dosing.



9.9 Visit Requirements

Visit requirements are outlined in Section 2 – Schedule of Activities (SoA). Specific procedure-related details are provided above in Section 9 – Study Assessments and Procedures.

9.9.1 Screening

Approximately 28 days prior to treatment randomization, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Sections 6.1 and 6.2. Screening procedures may be repeated after consultation with MSD.

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

- Laboratory tests are to be performed within 10 days prior to the first dose of study treatment. An exception is hepatitis testing which may be done up to 40 days prior to randomization if done as part of standard documented clinical activities. Screening labs should be collected and assessed prior to randomizing the participant.
- Evaluation of ECOG PS is to be performed within 7 days prior to date of randomization.
- For women of reproductive potential, a urine or serum pregnancy test will be performed within 72 hours prior to the first dose of study treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory).
- Tumor tissue sample collection is not required to be obtained within 28 days prior to the first dose of study treatment. Tumor specimen must be received by the central vendor before a participant is randomized.

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

9.9.2 Treatment Phase

Visit requirements are outlined in Section 2 - SoA. Specific procedure-related details are provided in Section 9.1. At Cycle 1 Day 1, results from Screening Visit evaluations should be reviewed to determine whether the participant continues to meet the eligibility requirements, as specified in Section 6.

Treatment with pembrolizumab will occur every 21 days (1 cycle) for up to 35 cycles (approximately 2 years). The maximum duration of the initial Treatment Phase is specified as 35 cycles of treatment (approximately 2 years) unless a discontinuation criterion is met (Section 8.1).

Epacadostat will be dosed BID during the Treatment Phase. Treatment may continue until Cycle 35 Day 21, unless a discontinuation criterion is met (Section 8.1).

The EXTREME regimen treatments will occur every 21 days (1 cycle) for up to 6 cycles for 5-FU and cisplatin/carboplatin. Cetuximab will be administered weekly until radiographic PD or unacceptable toxicity.

9.9.3 End of Treatment

When the participant permanently discontinues study treatments, the EOT Visit should be conducted. If the EOT Visit coincides with a regular study visit, the EOT evaluations will supersede those of that scheduled visit. The participant should be encouraged to return for the Post-treatment Safety Follow-up Visit.

9.9.4 Post-treatment Visits

9.9.4.1 Safety Follow-up Visit

NOTE: As of Amendment 04, the Safety Follow-up Visit will be the last visit in the study. This section has been amended accordingly.

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

A participant will be considered to have completed this study once they have attended this visit. Participants currently in Follow-up or in Survival Follow-up are considered to have completed the study; these participants are not required to attend any further visits. Assessment and recording of AEs will be performed as per Section 9.3.

Participants who are eligible to enter Second Course retreatment with pembrolizumab plus epacadostat or pembrolizumab monotherapy may have up to 2 Safety Follow-up Visits; 1 after the initial treatment period and 1 after the Second Course study treatment.

9.9.4.2 Follow-up Visits

NOTE: As of Amendment 04, this section is no longer applicable. Participants currently in post-treatment follow-up are considered to have completed the study once they have attended the Safety Follow-up Visit; assessment and recording of AEs will be performed as per Section 9.3.

Participants who discontinue study treatment for a reason other than BICR-verified radiographic disease progression will move into the Post-treatment Follow-up Phase and should be assessed by radiologic imaging every 6 weeks (42 days ± 7 days) for the first year and every 9 weeks (63 days ± 7 days) thereafter to monitor disease status. Every effort should be made to collect imaging until BICR-verified radiographic disease progression, the start of a new anticancer therapy, withdrawal of consent for imaging, pregnancy, death, or the end of the study. Information regarding post-study anticancer treatment will be collected if new treatment is initiated.

Participants who are eligible to receive retreatment with pembrolizumab plus epacadostat or pembrolizumab monotherapy according to the criteria in Section 7.2.6 will move from the Post-treatment Follow-up Phase to the Second Course Phase when they experience disease progression.

9.9.4.3 Survival Follow-up

NOTE: As of Amendment 04, this section is no longer applicable. Participants currently in survival follow-up are considered to have completed the study; these participants will no longer be contacted for survival information. Assessment and recording of AEs will continue as per Section 9.3.

Participants who experience BICR-verified PD or start a new anticancer therapy, whichever comes first, will move into the Survival Follow-up Phase and should be contacted by telephone approximately every 12 weeks starting from the last point of contact to assess for survival status along with new anticancer therapy until death, withdrawal of consent, lost to follow up or the end of the study, whichever occurs first.

9.9.5 Second Course Phase

Second Course Phase is described in Section 7.2.6. Visit requirements are outlined in Section 2.2 - SoA. Specific procedure-related details are provided in Section 9.1.

9.9.6 Unscheduled Visits

Unscheduled visits may occur at any time at the investigator's discretion or if medically warranted. Appropriate clinical and laboratory measurements may be performed based on AEs or other findings. The visit, and any assessments, must be recorded in eCRF.

9.9.7 Survival Status

NOTE: As of Amendment 04, this section is no longer applicable; survival data is no longer being collected.

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

10. Statistical Analysis Plan

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). [redacted]

10.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 10.2 through 10.12.

Study Design Overview	A Phase 3 Randomized, Open-Label Clinical Study to Evaluate the Efficacy and Safety of Pembrolizumab plus Epacadostat, Pembrolizumab monotherapy and the EXTREME Regimen as First line Treatment for Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma (KEYNOTE-669)
Treatment Assignment	Approximately 90 participants will be randomized 2:1:2 into 3 treatment arms, stratified by ECOG PS, HPV p16 status and prior systemic therapy (see Section 7.3.1 for details). The treatment arms are as follows: • pembrolizumab 200 mg Q3W + epacadostat; • pembrolizumab 200 mg Q3W • cetuximab + platinum + 5-FU (EXTREME) This study will be conducted as an open-label study.
Analysis Populations	Efficacy: Intention to Treat (ITT) Safety: All Participants as Treated (APaT)
Primary Endpoint(s)	Objective Response Rate (ORR) per RECIST 1.1 assessed by investigator determination
Statistical Methods for Key Efficacy Analyses	ORR will be estimated by treatment group with 95% CI calculated by Clopper and Pearson exact method [Clopper, C. J. and Pearson, E. S. 1934].
Statistical Methods for Key Safety Analyses	Point estimates (count and percentage) by treatment group will be provided for safety endpoints.
Interim Analyses	**Efficacy** • Final analysis Timing: When all randomized participants have one post-baseline imaging scan or discontinue the study. **Safety:** One safety review will be conducted at ~ 4 month after first participant is randomized.
Multiplicity	There will be no multiplicity adjustment.
Sample Size and Power	The sample size is approximately 90 participants with 36 participants in each of the pembrolizumab + epacadostat and EXTREME arms, and 18 participants in the pembrolizumab monotherapy arm. Section 10.9 provides the precision of the ORR estimates.

10.2 Responsibility for Analyses/In-House Blinding

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

MSD will generate the randomized allocation schedule(s) for study treatment assignment for this protocol, and the randomization will be implemented in IVRS.

Although the study is open-label, analyses or summaries generated by randomized treatment assignment and actual treatment received will be limited and documented.

The eDMC will serve as the primary reviewer of the unblinded safety data. Additional logistical details will be provided in the eDMC Charter.

10.3 Hypotheses/Estimation

Objectives of the study are stated in Section 4.0.

10.4 Analysis Endpoints

10.4.1 Efficacy Endpoint

Objective Response Rate (ORR) – RECIST 1.1 by investigator determination

Objective response rate (ORR) is defined as the proportion of the participants in the analysis population who have a best response of complete response (CR) or partial response (PR). Responses are based on RECIST 1.1 by investigator determination.

10.4.2 Safety Endpoints

Safety measurements are described in Section 5.4.1.2 and Section 9.

10.5 Analysis Populations

10.5.1 Efficacy Analysis Population

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

10.5.2 Safety Analysis Population

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

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

10.6 Statistical Methods

10.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary objective.

ORR will be estimated by treatment group. 95% CI for ORR will be provided using Clopper and Pearson exact method [Clopper, C. J. and Pearson, E. S. 1934].

10.6.2 Statistical Methods for Safety Analyses

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

Individual events and the broad AE categories consisting of the proportion of participants with any AE, a drug related AE, a serious AE, an AE which is both drug-related and serious, a Grade 3-5 AE, a drug related Grade 3-5 AE, a fatal AE, dose interruption due to an AE and discontinuation due to an AE, will be summarized by counts and percentages by treatment group (Table 18).

Table 18 Analysis Strategy for Safety Endpoints

Safety Endpoint	Descriptive Statistics
Any AE	X
Any Serious AE	X
Any Grade 3-5 AE	X
Any Drug-Related AE	X
Any Serious and Drug-Related AE	X
Any Grade 3-5 and Drug-Related AE	X
Dose Interruption due to AE	X
Discontinuation due to AE	X
Death	X
Specific AEs, SOCs	X
Change from Baseline Results (lab toxicity grade)	X

Abbreviations: AE = adverse event;

10.6.3 Summaries of Baseline Characteristics and Demographics

The comparability of the treatment groups for each relevant characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants screened, randomized, and the primary reason for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables (eg, age, race, etc.) and baseline characteristics will be summarized by treatment either by descriptive statistics or categorical tables.

10.7 Interim Analysis

No efficacy interim analysis will be conducted. One safety review by DMC is planned at ~4 months after the first participant is randomized.

10.8 Multiplicity

There is no hypothesis testing in this study, therefore no multiplicity adjustment is needed.

10.9 Sample Size and Power Calculations

The study will randomize approximately 90 participants in a 2:1:2 ratio into pembrolizumab plus epacadostat, pembrolizumab monotherapy and EXTREME arms, with 36 participants each in the pembrolizumab plus epacadostat and EXTREME arms respectively, and 18 participants in the pembrolizumab monotherapy arm. Two-sided 95% CI for ORR are shown in Table 19 and Table 20.

Table 19 Two-sided 95% CI for ORR with 36 participants

Number of Responders	ORR Estimate (%)	95% CI† of ORR (%)
11	~30	(16.4, 48.1)
13	~35	(20.8, 53.8)
14	~40	(23.1, 56.5)
16	~45	(27.9, 61.9)
18	50	(32.9, 67.1)

† Based on the two-tailed exact CI of a binomial proportion (Clopper and Pearson, 1934).

Table 20 Two-sided 95% CI for ORR with 18 participants

Number of Responders	ORR Estimate (%)	95% CI† of ORR (%)
5	~30	(9.7, 53.5)
6	~35	(13.3, 59.0)
7	~40	(17.3, 64.3)
8	~45	(21.5, 69.2)
9	50	(26.0, 74.0)

† Based on the two-tailed exact CI of a binomial proportion (Clopper and Pearson, 1934).

10.10 Subgroup Analyses

No subgroup analysis is needed.

10.11 Compliance (Medication Adherence)

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

10.12 Extent of Exposure

Extent of Exposure for a participant is defined as number of cycles in which the participant receives the study treatment infusion. Summary statistics will be provided on Extent of Exposure for APaT population.

11. References

[Aaronson, N. K., et al 1993]	Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85(5):365-76.	03Q3QL
[Ang, K. K., et al 2010]	Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tan PF, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med. 2010 Jul 1;363(1):24-35.	04FP0Y
[Argiris, A., et al 2008]	Argiris A, Karamouzis MV, Raben D, Ferris RL. Head and neck cancer. Lancet. 2008 May 17;371(9625):1695-709.	04N0CF
[Bauml, J., et al 2017]	Bauml J, Seiwert TY, Pfister DG, Worden F, Liu SV, Gilbert J, et al. Pembrolizumab for Platinum- and Cetuximab-Refractory Head and Neck Cancer: Results From a Single-Arm, Phase II Study. J Clin Oncol. 2017 May 10;35(14):1542-1549.	04QTG6
[redacted]		
[Bjordal, K., et al 1994]	Bjordal K, Ahlner-Elmqvist M, Tollesson E, Jensen AB, Razavi D, Maher EJ, et al. Development of a European Organization for Research and Treatment of Cancer (EORTC) questionnaire module to be used in quality of life assessments in head and neck cancer patients. Acta Oncol 1994;33(8):879-85.	03WNBB

[Bjordal, K., et al 2000]	Bjordal K, de Graeff A, Fayers PM, Hammerlid E, van Pottelsberghe C, Curran D, et al. A 12 country field study of the EORTC QLQ-C30 (version 3.0) and the head and neck cancer specific module (EORTC QLQ-H&N35) in head and neck patients. EORTC Quality of Life Group. Eur J Cancer. 2000 Sep;36(14):1796-807.	040VGM
[Boyer EW, Shannon M. 2005]	Boyer EW, Shannon M. The serotonin syndrome. N Engl J Med. 2005 Mar 17;352(11):1112-20.	04DJPV
[Brandacher, G., et al 2006]	Brandacher G, Perathoner A, Ladurner R, Schneeberger S, Obrist P, Winkler C, et al. Prognostic value of indoleamine 2,3-dioxygenase expression in colorectal cancer: effect on tumor-infiltrating T cells. Clin Cancer Res. 2006 Feb 15;12(4):1144-51.	049MFB
[Chemnitz, J. M., et al 2004]	Chemnitz JM, Parry RV, Nichols KE, June CH, Riley JL. SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T cell stimulation, but only receptor ligation prevents T cell activation. J Immunol 2004;173:945-54.	00VMPN
[Chera, B. S., et al 2014]	Chera BS, Eisbruch A, Murphy BA, Ridge JA, Gavin P, Reeve BB, et al. Recommended patient-reported core set of symptoms to measure in head and neck cancer treatment trials. J Natl Cancer Inst. 2014 Jul 8;106(7):[4 p.].	040WHF
[Chua, M. L., et al 2016]	Chua ML, Wee JT, Hui EP, Chan AT. Nasopharyngeal carcinoma. Lancet. 2016 Mar 5;387(10022):1012-24.	04N0CL
[Clopper, C. J. and Pearson, E. S. 1934]	Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 1934;XXVI:404-13.	03PHDN
[Disis, M. L. 2010]	Disis ML. Immune regulation of cancer. J Clin Oncol 2010;28(29):4531-8.	00VMNJ
[Fakhry, C., et al 2008]	Fakhry C, Westra WH, Li S, Cmelak A, Ridge JA, Pinto H, et al. Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. J Natl Cancer Inst 2008;100(4):261-9.	03WQ6Y
[Fallarino, F., et al 2006]	Fallarino F, Grohmann U, You S, McGrath BC, Cavener DR, Vacca C, et al. The combined effects of tryptophan starvation and tryptophan catabolites down-regulate T cell receptor zeta-chain and induce a regulatory phenotype in naive T cells. J Immunol. 2006 Jun 1;176(11):6752-61.	04N0CM

[Forastiere, A. A., et al 1992] Forastiere AA, Metch B, Schuller DE, Ensley JF, Hutchins LF, Triozzi P, et al. Randomized comparison of cisplatin plus fluorouracil and carboplatin plus fluorouracil versus methotrexate in advanced squamous-cell carcinoma of the head and neck: a Southwest Oncology Group study. J Clin Oncol 1992;10(8):1245-51. 03WN8M

[Forastiere, A. A., et al 2001] Forastiere AA, Leong T, Rowinsky E, Murphy BA, Vlock DR, DeConti RC, et al. Phase III comparison of high-dose paclitaxel + cisplatin + granulocyte colony-stimulating factor versus low-dose paclitaxel + cisplatin in advanced head and neck cancer: Eastern Cooperative Oncology Group Study E1393. J Clin Oncol. 2001 Feb 15;19(4):1088-95. 03YXNJ

[Francisco, L. M., et al 2010] Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. Immunol Rev 2010;236:219-42. 00VMNM

[Frumento, G., et al 2002] Frumento G, Rotondo R, Tonetti M, Damonte G, Benatti U, Ferrara GB. Tryptophan-derived catabolites are responsible for inhibition of T and natural killer cell proliferation induced by indoleamine 2,3-dioxygenase. J Exp Med. 2002 Aug 19;196(4):459-68. 049PSY

[redacted]

[Gibson, M. K., et al 2005] Gibson MK, Li Y, Murphy B, Hussain MH, DeConti RC, Ensley J, et al. Randomized phase III evaluation of cisplatin plus fluorouracil versus cisplatin plus paclitaxel in advanced head and neck cancer (E1395): an intergroup trial of the Eastern Cooperative Oncology Group. J Clin Oncol. 2005 May 20;23(15):3562-7. 048DV8

[Gillison, M. L., et al 2015] Gillison ML, Chaturvedi AK, Anderson WF, Fakhry C. Epidemiology of Human Papillomavirus-Positive Head and Neck Squamous Cell Carcinoma. J Clin Oncol. 2015 Oct 10;33(29):3235-42. 04DGDY

[Godin-Ethier, J., et al 2011]	Godin-Ethier J, Hanafi LA, Piccirillo CA, Lapointe R. Indoleamine 2,3-dioxygenase expression in human cancers: clinical and immunologic perspectives. Clin Cancer Res. 2011 Nov 15;17(22):6985-91.	049PSS
[Greenwald, R. J., et al 2005]	Greenwald RJ, Freeman GJ, Sharpe AH. The B7 family revisited. Annu Rev Immunol 2005;23:515-48.	00VMQL
[Gregoire, V., et al 2010]	Gregoire V, Lefebvre JL, Licitra L, Felip E; EHNS-ESMO-ESTRO Guidelines Working Group. Squamous cell carcinoma of the head and neck: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2010 May;21 Suppl 5:v184-6.	04D2F5
[Hamid, O., et al 2017]	Hamid O, Bauer TM, Spira AI, Olszanski AJ, Patel SP, Wasser JS, et al. Epacadostat Plus Pembrolizumab in patients with SCCHN: Preliminary Phase 1/2 Results from ECHO-202/KEYNOTE-037 [abstract]. Abstracts of the 2017 ASCO Annual Meeting; 2017 Jun 2-6; Chicago, IL: ASCO; 2017. p. 1- 19.	04PQC6
[Hamid, O., et al 2017]	Hamid O, Bauer TM, Spira AI, Smith DC, Olszanski AJ, Tarhini AA, et al. Safety of Epacadostat 100 mg BID Plus Pembrolizumab 200 mg Q3W in advanced solid tumors: Phase 2 data from ECHO-202/KEYNOTE-037. Poster session presented at: 53rd Annual Meeting of the American Society of Clinical Oncology; 2017 June 2–6; Chicago, IL.	04PQBR
[Hodi, F. S., et al 2014]	Hodi FS, Ribas A, Daud A, Hamid O, Robert C, Kefford R, et al. Patterns of response in patients with advanced melanoma treated with Pembrolizumab (MK-3475) and evaluation of immune-related response criteria (irRC). J Immunother Cancer. 2014;2(Suppl 3):P103.	0465RW
[Hodi, F. S., et al 2016]	Hodi FS, Hwu WJ, Kefford R, Weber JS, Daud A, Hamid O, et al. Evaluation of immune-related response criteria and RECIST v1.1 in patients with advanced melanoma treated with pembrolizumab. J Clin Oncol. 2016 May 1;34(13):1510-7.	04H0RY
[Huang, L., et al 2010]	Huang L, Baban B, Johnson BA 3rd, Mellor AL. Dendritic cells, indoleamine 2,3 dioxygenase and acquired immune privilege. Int Rev Immunol. 2010 Apr;29(2):133-55.	04B5FM
[IB Edition 10, 2017]	EPACADOSTAT (INCB024360) – Investigators Brochure v10, 11-Dec-2017.	04T9PC
[IB Edition 15 2017]	KEYTRUDA (pembrolizumab) Investigator's Brochure, Edition Number 15, 18-Sep-2017.	04R9W6

[Ino, K., et al 2006]	Ino K, Yoshida N, Kajiyama H, Shibata K, Yamamoto E, Kidokoro K, et al. Indoleamine 2,3-dioxygenase is a novel prognostic indicator for endometrial cancer. Br J Cancer. 2006 Dec 4;95(11):1555-61.	049NJ5
[Jacobs, C., et al 1992]	Jacobs C, Lyman G, Velez-Garcia E, Sridhar KS, Knight W, Hochster H, et al. A phase III randomized study comparing cisplatin and fluorouracil as single agents and in combination for advanced squamous cell carcinoma of the head and neck. J Clin Oncol. 1992 Feb;10(2):257-63.	03YXN5
[Liverpool Head and Neck Oncology Group 1990]	Liverpool Head and Neck Oncology Group. A phase III randomised trial of cistplatinum, methotrextate, cisplatinum + methotrexate and cisplatinum + 5-FU in end stage squamous carcinoma of the head and neck. Br J Cancer. Feb 1990; 61(2): 311–315.	03YXPF
[Machiels, J. P., et al 2015]	Machiels JP, Haddad RI, Fayette J, Licitra LF, Tahara M, Vermorken JB, et al. Afatinib versus methotrexate as second-line treatment in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck progressing on or after platinum-based therapy (LUX-Head & Neck 1): an open-label, randomised phase 3 trial. Lancet Oncol. 2015 May;16(5):583-94.	0488YQ
[Mehra, R., et al 2016]	Mehra R, Seiwert TY, Mahipal A, Weiss J, Berger R, Paul Eder J et al. Efficacy and safety of pembrolizumab in recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC): Pooled analyses after longterm followup in KEYNOTE012 [abstract]. J Clin Oncol. 2016;34(suppl). Abstract no. 6012.	04GZ3C
[Mellor, A. L. 1999]	Mellor AL, Munn DH. Tryptophan catabolism and T-cell tolerance: immunosuppression by starvation? Immunol Today. 1999 Oct;20(10):469-73.	04N0CP
[Mellor, A. L. 2004]	Mellor AL, Munn DH. IDO expression by dendritic cells: tolerance and tryptophan catabolism. Nat Rev Immunol. 2004 Oct;4(10):762-74.	049NJ7
[Mellor, A. L., et al 2003]	Mellor AL, Baban B, Chandler P, Marshall B, Jhaver K, Hansen A, et al. Cutting edge: induced indoleamine 2,3 dioxygenase expression in dendritic cell subsets suppresses T cell clonal expansion. J Immunol. 2003 Aug 15;171(4):1652-5.	049NJB
[Mesia, R., et al 2010]	Mesia R, Rivera F, Kawecki A, Rottey S, Hitt R, Kienzer H, et al. Quality of life of patients receiving platinum-based chemotherapy plus cetuximab first line for recurrent and/or metastatic squamous cell carcinoma of the head and neck. Ann Oncol. 2010 Oct;21(10):1967-73.	040WNJ

[Muller, A. J., et al 2005]	Muller AJ, DuHadaway JB, Donover PS, Sutanto-Ward E, Prendergast GC. Inhibition of indoleamine 2,3-dioxygenase, an immunoregulatory target of the cancer suppression gene Bin1, potentiates cancer chemotherapy. Nat Med. 2005 Mar;11(3):312-9.	049PW6
[Munn, D. H. 2007]	Munn DH, Mellor AL. Indoleamine 2,3-dioxygenase and tumor-induced tolerance. J Clin Invest. 2007 May;117(5):1147-54.	049PWD
[Munn, D. H., et al 2004]	Munn DH, Sharma MD, Hou D, Baban B, Lee JR, Antonia SJ, et al. Expression of indoleamine 2,3-dioxygenase by plasmacytoid dendritic cells in tumor-draining lymph nodes. J Clin Invest. 2004 Jul;114(2):280-90. Erratum in: J Clin Invest. 2004 Aug;114(4):599.	049PWC
[Nakamura, T., et al 2007]	Nakamura T, Shima T, Saeki A, Hidaka T, Nakashima A, Takikawa O, et al. Expression of indoleamine 2, 3-dioxygenase and the recruitment of Foxp3-expressing regulatory T cells in the development and progression of uterine cervical cancer. Cancer Sci. 2007 Jun;98(6):874-81.	049PWN
[National Comprehensive Cancer Network 2016]	National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN Guidelines): head and neck cancers. Fort Washington, PA: National Comprehensive Cancer Network; 2016.	04FQDC
[Okamoto, A., et al 2005]	Okamoto A, Nikaido T, Ochiai K, Takakura S, Saito M, Aoki Y, et al. Indoleamine 2,3-dioxygenase serves as a marker of poor prognosis in gene expression profiles of serous ovarian cancer cells. Clin Cancer Res. 2005 Aug 15;11(16):6030-9.	049PTK
[Okazaki, T., et al 2001]	Okazaki T, Maeda A, Nishimura H, Kurosaki T, Honjo T. PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine. Proc Natl Acad Sci U S A 2001;98(24):13866-71.	00VMQ6
[Parry, R. V., et al 2005]	Parry RV, Chemnitz JM, Frauwirth KA, Lanfranco AR, Braunstein I, Kobayashi SV, et al. CTLA-4 and PD-1 receptors inhibit T-cell activation by distinct mechanisms. Mol Cell Biol 2005;25(21):9543-53.	00VMQ7
[Pickard, A. S., et al 2007]	Pickard AS, Wilke CT, Lin H-W, Lloyd A. Health utilities using the EQ-5D in studies of cancer. Pharmacoeconomics 2007;25(5):365-84.	03RLHG
[Quezada, S. A. 2013]	Quezada SA, Peggs KS. Exploiting CTLA-4, PD-1 and PD-L1 to reactivate the host immune response against cancer. Br J Cancer. 2013 Apr 30;108(8):1560-5.	049PTR

[Rabin, R. 2001]	Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Ann Med 2001;33:337-43.	03XLS2
[Riley, J. L. 2009]	Riley JL. PD-1 signaling in primary T cells. Immunol Rev 2009;229:114-25.	00VMQ9
[Schornagel, J. H., et al 1995]	Schornagel JH, Verweij J, de Mulder PHM, Cognetti F, Vermorken JB, Cappelaere P, et al. Randomized phase III trial of edatrexate versus methotrexate in patients with metastatic and/or recurrent squamous cell carcinoma of the head and neck: a European Organization for Research and Treatment of Cancer Head and Neck Cancer Cooperative Group study. J Clin Oncol 1995;13(7):1649-55.	03WN7G
[Schrijvers, D., et al 1998]	Schrijvers D, Johnson J, Jiminez U, Gore M, Kosmidis P, Szpirglas H, et al. Phase III trial of modulation of cisplatin/fluorouracil chemotherapy by interferon alfa-2b in patients with recurrent or metastatic head and neck cancer. J Clin Oncol. 1998 Mar;16(3):1054-9.	03YXNC
[Seymour, L., et al 2017]	Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekar S, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol. 2017 Mar;18(3):e143-e152.	04P9RV
[Sheppard, K-A, et al 2004]	Sheppard K-A, Fitz LJ, Lee JM, Benander C, George JA, Wooters J, et al. PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3zeta signalosome and downstream signaling to PKCtheta. FEBS Lett. 2004;574:37-41.	00VMQC
[Uyttenhove, C., et al 2003]	Uyttenhove C, Pilotte L, Theate I, Stroobant V, Colau D, Parmentier N, et al. Evidence for a tumoral immune resistance mechanism based on tryptophan degradation by indoleamine 2,3-dioxygenase. Nat Med. 2003 Oct;9(10):1269-74.	049PV2
[Vermorken, J. B., et al 2008]	Vermorken JB, Mesia R, Rivera F, Remenar E, Kawecki A, Rottey S, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med. 2008 Sep 11;359(11):1116-27.	03YXRJ
[Weinlich, G., et al 2007]	Weinlich G, Murr C, Richardsen L, Winkler C, Fuchs D. Decreased serum tryptophan concentration predicts poor prognosis in malignant melanoma patients. Dermatology. 2007;214(1):8-14.	049PV3

[Witkiewicz, A., et al 2008]	Witkiewicz A, Williams TK, Cozzitorto J, Durkan B, Showalter SL, Yeo CJ, et al. Expression of indoleamine 2,3-dioxygenase in metastatic pancreatic ductal adenocarcinoma recruits regulatory T cells to avoid immune detection. J Am Coll Surg. 2008 May;206(5):849-54; discussion 854-6.	049PV5
[Wolchok, J. D., et al 2009]	Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, LebbéC, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 2009;15(23):7412-20.	00VMNZ
[Zhang, X., et al 2004]	Zhang X, Schwartz J-CD, Guo X, Bhatia S, Cao E, Chen L, et al. Structural and functional analysis of the costimulatory receptor programmed death-1. Immunity 2004;20:337-47.	00VMQJ
[Zhang, Y., et al 2016]	Zhang Y, Bowman K, Diamond S, Yeleswaram S. Effects of Epacadostat with co-administration of Linezolid on brain extracellular fluid concentrations of Serotonin. Poster session presented at: 2016 AAPS Annual Meeting And Exposition; 2016 Nov 13-17; Denver, US.	04PCMR
[Zou, W. 2006]	Zou W. Regulatory T cells, tumour immunity and immunotherapy. Nat Rev Immunol. 2006 Apr;6(4):295-307.	049PV7

12. Appendices

12.1 Appendix 1: Abbreviations and Trademarks

Abbreviation/Term	Definition
5-FU	5-fluorouracil
AE	adverse event
AEOSI	adverse events of special interest
ALT (SGPT)	alanine aminotransferase (serum glutamic pyruvic transaminase)
ANC	absolute neutrophil count
APaT	All Participants as Treated
aPTT	activated partial thromboplastin time
AST (SGOT)	aspartate aminotransferase (serum glutamic oxaloacetic transaminase)
AUC	area under the curve
BCG	Bacillus Calmette–Guérin
BID	twice daily
BICR	blinded independent central review
CD28	cluster of differentiation 28
CD3ζ	CD3 zeta
CI	confidence intervals
cLDA	constrained longitudinal data analysis
C_{max}	maximum concentration
CONSORT	Consolidated Standards of Reporting Trials
CR	complete response
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CTLA-4	cytotoxic T lymphocyte associated protein 4
C_{trough}	minimum concentration
DCR	disease control rate
DCs	dendritic cells
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	duration of response
DPD	dihydropyrimidine dehydrogenase
ECGs	electrocardiograms
ECI	events of clinical interest

Abbreviation/Term	Definition
ECOG PS	Eastern Cooperative Oncology Group performance status
eCRF	electronic case report form
eDMC	External Data Monitoring Committee
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EOC	Joint Executive Oversight Committee
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ-C30	EORTC QoL questionnaire Core 30
EORTC QLQ-H&N35	EORTC Head and Neck Specific QoL questionnaire
EOT	end of treatment
ePROs	electronic patient reported outcomes
EQ-5D	EuroQol 5 dimensions questionnaire
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDAA	Food and Drug Administration Amendments Act
FNA	fine needle aspirate
FT4	free thyroxine
GCP	Good Clinical Practices
GFR	glomerular filtration rate
H1	hypothesis 1
H2	hypothesis 2
H3	hypothesis 3
HBsAg	Hepatitis B surface antigen
HIV	human immunodeficiency virus
HNSCC	head and neck squamous cell carcinoma
HPV	Human Papilloma Virus
HRQoL	Health-Related QoL
HSD	Hwang-Shih-Decani
IA	interim analysis
IAs	interim analyses
IB	Investigator Brochure
ICF	informed consent form
iCPD	confirmed progressive disease
iCR	immune confirmed response
IDO1	indoleamine 2,3 dioxygenase 1
IEC	Institutional Ethics Committee
Ig	immunoglobulin

Abbreviation/Term	Definition
IgG4	immunoglobulin G4
IgV type	Ig-variable–type
IHC	immunohistochemistry
INR	international normalized ratio
iPR	immune partial response
irAE	immune-related adverse event
IRB	Institutional Review Board
iSD	immune stable disease
iRECIST	modified Response Evaluation Criteria in Solid Tumors for immune-based therapeutics
ITT	Intention-to-Treat
iUPD	iRECIST unconfirmed progressive disease
IV	intravenous
IVD	in vitro diagnostic
IVRS	interactive voice response system
IWRS	integrated web response system
JAK	Janus kinase
mAb	monoclonal antibody
MAO	monoamine oxidase
MAOI	monoamine oxidase inhibitors
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
NCCN	National Comprehensive Cancer Network
NSAE	non-Serious Adverse Event
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
OTC	over-the-counter
PBPK	physiologically based PK
PD	progressive disease
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PFS	progression-free survival
PH	proportional hazard
PK	pharmacokinetics
PKCθ	protein kinase C-theta
PO	orally

Abbreviation/Term	Definition
PR	partial response
pRBC	packed red blood cell
PRO	patient-reported outcomes
PT	prothrombin time
PTT	partial thromboplastin time
Q2W	every 2 weeks
Q3W	every 3 weeks
QW	every week
QoL	Quality of Life
QLQ	QoL questionnaire
QTc	corrected QT interval
RECIST	Response Evaluation Criteria in Solid Tumors
R/M	recurrent or metastatic
RNA	ribonucleic acid
RPSFT	Rank Preserving Structural Failure Time
SAE	serious adverse events
SD	stable disease
SHP-1	Src homology region 2 domain-containing phosphatase-1
SHP-2	Src homology region 2 domain-containing phosphatase-2
SNRI	selective serotonin/norepinephrine reuptake inhibitors
SoA	Schedule of Activities
SoC	standard of care
sSAP	supplemental Statistical Analysis Plan
SSRI	selective serotonin reuptake inhibitors
SUSAR	suspected unexpected serious adverse reactions
T1DM	Type 1 diabetes mellitus
T3	triiodothyronine
TRAE	treatment-related adverse event
Tregs	regulatory T cells
TSH	thyroid-stimulating hormone
TTD	time to deterioration
ULN	upper limit of normal
[redacted]	[redacted]
WOCBP	women of childbearing potential
ZAP70	zeta-chain-associated protein kinase

12.2 Appendix 2: Clinical Laboratory Tests

- All the laboratory tests detailed in Table 21 will be performed by the local laboratory.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 21 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Chemistry	BUN	Potassium Magnesium Uric Acid Urea[a]	AST/ SGOT	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the upper limit of normal)
	Albumin	A measure of carbon dioxide (CO_2 or bicarbonate)[b]	Chloride	Phosphorous
	Creatinine	Sodium	ALT/ SGPT	Total Protein
	Glucose (nonfasting)	Calcium[c]	Alkaline phosphatase	Lipase
	Amylase			
Coagulation	• PT (INR) • aPTT or PTT[d]			
Routine Urinalysis	• Specific gravity • glucose, protein, blood, ketones by dipstick • Microscopic examination (if blood or protein is abnormal)			

Other Screening Tests	• T3 (total or free), FT4 and TSH
	• Follicle-stimulating hormone (as needed in women of non-childbearing potential only)
	• Serum or urine β human chorionic gonadotropin (β hCG) pregnancy test (as needed for women of childbearing potential)
	• Serology:
	  ○ HBsAg, HBV DNA
	  ○ HCV RNA or HCV antibody (if HCV RNA is not the local SoC)
	  ○ HIV RNA (if required by local regulations)			

Laboratory Assessments	Parameters
Abbreviations: ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; DNA = deoxyribonucleic acid; FT4 = free thyroxine; HCV = Hepatitis C Virus; INR = international normalized ratio; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; PT = prothrombin time; PTT = partial thromboplastin time; RNA = ribonucleic acid; RBC = red blood cells; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; SoC = Standard of Care; T3 = triiodothyronine; TSH = thyroid stimulating hormone (thyrotropin); WBC = white blood cells. NOTES: [a] Blood Urea Nitrogen is preferred; if not available urea may be tested. [b] If available as SoC in your region. The carbon dioxide may be either a measurement of CO_2 or bicarbonate as an electrolyte. [c] Corrected calcium should be checked for participants with hypoalbuminemia. [d] PTT may be performed if the local lab is unable to perform aPTT.	

Investigators must document their review of each laboratory safety report.

12.3 Appendix 3: Study Governance Considerations

Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

Merck, 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 participant safety is the overriding concern in the design of clinical trials. In all cases, Merck clinical trials will be conducted in compliance with local and/or national regulations and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

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

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 Merck or comparator products. Alternatively, Merck may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine participant preferences, etc.

The design (ie, participant population, duration, statistical power) must be adequate to address the specific purpose of the trial. Research participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

Trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice. Merck reviews clinical data for accuracy, completeness and consistency. Data are verified versus source documentation according to standard operating procedures. Per Merck policies and procedures, if fraud, misconduct or serious GCP-non-Compliance are suspected, the issues are promptly investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified and data disclosed accordingly.

B. Publication and Authorship

To the extent scientifically appropriate, Merck seeks to publish the results of trials it conducts. 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 of multiplicity.

Merck's policy on authorship is consistent with the requirements outlined in the ICH-Good Clinical Practice guidelines. 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. Merck funding of a trial will be acknowledged in publications.

III. Participant Protection

A. IRB/IEC review

All clinical trials will be reviewed and approved by an independent IRB/IEC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the IRB/IEC prior to implementation, except that changes required urgently to protect participant safety and well-being may be enacted in anticipation of IRB/IEC approval. For each site, the IRB/IEC and Merck will approve the participant informed consent form.

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care. Participants are never denied access to appropriate medical care based on participation in a Merck clinical trial.

All participation in Merck clinical trials is voluntary. Participants are enrolled only after providing informed consent for participation. Participants may withdraw from a Merck 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

Merck is committed to safeguarding participant confidentiality, to the greatest extent possible. Unless required by law, only the investigator, sponsor (or representative) and/or regulatory authorities will have access to confidential medical records that might identify the research participant by name.

D. Genomic Research

Genomic Research will only be conducted in accordance with informed consent and/or as specifically authorized by an Ethics Committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is Merck's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of Merck trials. Merck 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.

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (eg, to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices including, in the U.S., those established by the American Medical Association (AMA).

V. Investigator Commitment

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

* In this document, "Merck" refers to Merck Sharp & Dohme Corp. and Schering Corporation, each of which is a subsidiary of Merck & Co., Inc. Merck is known as MSD outside of the United States and Canada. As warranted by context, Merck also includes affiliates and subsidiaries of Merck & Co., Inc."

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 MSD'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 MSD in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor or MSD 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 MSD. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor and MSD in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

Data Protection

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

The participant must be informed that his/her personal study-related data will be used by the Sponsor and MSD 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 MSD, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Confidentiality of Data

By signing this protocol, the investigator affirms to MSD that information furnished to the investigator by MSD will be maintained in confidence, and such information will be divulged to the institutional review board, ethics review committee (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 trial 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.

Confidentiality of Participant Records

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

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

Confidentiality of IRB/IEC Information

MSD will record the name and address of each IRB/IEC that reviews and approves this trial. MSD will 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.

Committees Structure

Scientific Advisory Committee

This trial was developed in collaboration with a Scientific Advisory Committee (SAC). The SAC comprises Sponsor, MSD, and non-Sponsor scientific experts who provide input with respect to trial design, interpretation of trial results and subsequent peer-reviewed scientific publications.

Trial Steering Committee

This trial will be conducted in consultation with a Trial Steering Committee. The Trial Steering Committee comprises:

- Sponsor and MSD personnel
- Investigators participating in the trial
- Consulting therapeutic-area experts and clinical trialists

The Trial Steering Committee will provide guidance on the operational aspects of the trial.

Specific details regarding responsibilities and governance of the Trial Steering Committee will be described in a separate charter.

Joint Executive Oversight Committee

The Joint Executive Oversight Committee (EOC) comprises members of Sponsor and MSD Senior Management. The EOC will receive and decide upon any recommendations made by the Data Monitoring Committee (DMC) regarding the trial.

Data Monitoring Committee

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

The DMC will make recommendations to the EOC regarding steps to ensure both participant safety and the continued ethical integrity of the trial.

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

Publication Policy

The results of this study may be published or presented at scientific meetings. The Sponsor and MSD will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor and MSD 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 or MSD, the investigator agrees to submit all manuscripts or abstracts to the Sponsor and MSD before submission. This allows the Sponsor and MSD 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.

Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007 and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. The Sponsor will review this protocol and submit the information necessary to fulfill these requirements. Entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow participants to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial 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 trial or its results to those registries.

Compliance with Law, Audit and Debarment

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

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored or executed by MSD, is provided in this appendix under the Merck 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 trial reimbursed to the investigator by MSD.

The investigator will promptly inform MSD of any regulatory authority inspection conducted for this trial.

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

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

Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to MSD 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.

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

MSD 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 MSD. No records may be transferred to another location or party without written notification to MSD.

Source Documents

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

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

Study and Site Closure

MSD, in collaboration with the Sponsor 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 MSD prematurely terminates a particular trial site, MSD will promptly notify that trial site's IRB/IEC.

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

Definition of AE

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

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, or are considered clinically significant in the medical and scientific 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 treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. • For all reports of overdose (whether accidental or intentional) with an associated adverse event, 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). Note: Progression of the cancer under study is not a reportable event. Refer to Section 9.3.5 for additional details.

Events NOT Meeting the AE Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen. • Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened. • Refer to Section 9.3.5 for protocol specific exceptions

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

A 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 a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.
d. Results in persistent or significant disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

- in offspring of participant taking the product regardless of time to diagnosis

f. Other important medical events:

- Medical or scientific 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 one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Additional Events reported in the same manner as SAE

Additional Events which require reporting in the same manner as SAE

- In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to MSD in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by MSD for collection purposes.
  - Is a new cancer (that is not a condition of the study);
  - Is associated with an overdose.

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 Adverse Event case report forms/worksheets at each examination.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to MSD in lieu of completion of the AE CRF page.
- There may be instances when copies of medical records for certain cases are requested by MSD. 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 MSD.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.
- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.
  - Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
  - Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
  - Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
  - Grade 4: Life threatening consequences; urgent intervention indicated.
  - Grade 5: Death related to AE.

Assessment of Causality

- Did the study treatment cause the adverse event?
  - The determination of the likelihood that the study treatment caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the adverse event based upon the available information
  - **The following components are to be used to assess the relationship between the study treatment and the AE;** the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the study treatment caused the adverse event:
    - **Exposure:** Is there evidence that the participant was actually exposed to the study treatment such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
    - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the study treatment? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?

- **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors
- **Dechallenge:** Was the study treatment discontinued or dose/exposure/frequency reduced?
  - If yes, did the AE resolve or improve?
    - If yes, this is a positive dechallenge.
  - If no, this is a negative dechallenge.

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

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

NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE STUDY TREATMENT, OR IF RE-EXPOSURE TO THE STUDY TREATMENT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE MSD CLINICAL DIRECTOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL, AND IF REQUIRED, THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.

- **Consistency with Study treatment Profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the study treatment or drug class pharmacology or toxicology?

- The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.
- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a study treatment relationship).
  - Yes, there is a reasonable possibility of study treatment relationship:
    There is evidence of exposure to the study treatment. The temporal sequence of the AE onset relative to the administration of the study treatment is reasonable.

The AE is more likely explained by the study treatment than by another cause.

- No, there is not a reasonable possibility of study treatment relationship: Participant did not receive the study treatment OR temporal sequence of the AE onset relative to administration of the study treatment is not reasonable OR the AE is more likely explained by another cause than the study treatment. (Also entered for a participant with overdose without an associated AE.)

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

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to MSD. 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 MSD.

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

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

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

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by MSD 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 MSD within 24 hours of receipt of the information.

Reporting of AE, SAE, and Other Reportable Safety Events to MSD

AE, SAE, and Other Reportable Safety Event Reporting to MSD via Electronic Data Collection Tool

• The primary mechanism for reporting to MSD will be the electronic data collection (EDC) tool.
  • Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
  • If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
  • Reference section 9.3.1 – Time Period and Frequency for Collecting AE and SAE and Other Reportable Safety Event Information 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 electronic data collection 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 electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
• Contacts for SAE reporting can be found in the Investigator Trial File Binder (or equivalent).

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

12.5 Appendix 5: Contraceptive Guidance and Pregnancy Testing

Definitions

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP:

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

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Requirements

Male Participants

Male participants with female partners of childbearing potential are eligible to participate if they agree to one of the following during the protocol defined time frame in section 6.1:

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

- Use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.
  - The following are not acceptable methods of contraception:
    - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM).
    - Male condom with cap, diaphragm or sponge with spermicide.
    - Male and female condom cannot be used together.
  - 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 penetration.

Female Participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 22 during the protocol-defined time frame in Section 6.1 and Section 6.3.2.

Table 22 Highly Effective Contraception Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*

• Combined (estrogen- and progestogen- containing) hormonal contraception [b, c]
  ○ Oral
  ○ Intravaginal
  ○ Transdermal
  ○ Injectable

• Progestogen-only hormonal contraception [b, c]
  ○ Oral
  ○ Injectable

Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen- only contraceptive implant [b, c] • Intrauterine hormone-releasing system (IUS) [b] • Intrauterine device (IUD) • Bilateral tubal occlusion
• **Vasectomized partner** A vasectomized partner 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.
• **Sexual abstinence** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. a) Typical use failure rates are higher than perfect-use failure rates (i.e. when used consistently and correctly). b) If hormonal contraception efficacy is potentially decreased due to interaction with study treatment, condoms must be used in addition to the hormonal contraception during the treatment period and for at least 120 days after the last dose of pembrolizumab and epacadostat, or pembrolizumab monotherapy, and for at least 180 days after the last dose of the EXTREME regimen. c) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation.

Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test.

Following initiation of treatment, pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected; after the last dose of study treatment; and as required locally. Monthly pregnancy testing should be conducted as per local regulations where applicable.

12.6 Appendix 6: ECOG Performance Status Scale

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

*Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649-655

http://ecog-acrin.org/resources/ecog-performance-status

12.7 Appendix 7: Prohibited Monoamine Oxidase (MAO) Inhibitors and Drugs Associated with Significant Monoamine Oxidase Inhibitory Activity

Monoamine Oxidase Inhibitors	Drugs Associated With Significant Monoamine Oxidase Inhibitory Activity
Hydrazines (example phenelzine)	Meperidine
Caroxazone	Linezolid
Echinopsidine	Methylene blue
Furazolidone	
Tranylcypromine	
Brofaromine	
Metralindole	
Minaprine	
Moclobemide	
Pirlindole	
Toloxatone	
Lazbemide	
Pargyline	
Rasagiline	
Selegiline	

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

Note: As of Amendment 04, this section is no longer applicable; iRECIST data will no longer be collected. Participants with radiographic disease progression as determined by RECIST 1.1 will discontinue from the study and be followed for safety monitoring, as detailed in Section 9.3; no confirmatory scans are required.

Assessment at Screening and Prior to RECIST 1.1 Progression

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

Assessment and Decision at RECIST 1.1 Progression

For Group 1 and 2 participants who show evidence of radiological PD by RECIST 1.1 as determined by the investigator, the investigator will decide whether to continue a participant on study treatment until repeat imaging is obtained (using iRECIST for participant management (see Table 14 and Figure 2). This decision by the investigator should be based on the participant's overall clinical condition.

Clinical stability is defined as the following:

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

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

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

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

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

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

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

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

Assessment at the Confirmatory Imaging

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

Confirmation of Progression

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

- Any of the factors that were the basis for the iUPD at the previous visit show worsening
    - For target lesions, worsening is a further increase in the sum of diameters of ≥5 mm, compared to any prior iUPD time point
    - For non-target lesions, worsening is any significant growth in lesions overall, compared to a prior iUPD time point; this does not have to meet the "unequivocal" standard of RECIST 1.1
    - For new lesions, worsening is any of these:
        - An increase in the new lesion sum of diameters by ≥5 mm from a prior iUPD time point
        - Visible growth of new non-target lesions
        - The appearance of additional new lesions
- Any new factor appears that would have triggered PD by RECIST 1.1

Persistent iUPD

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

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

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

Resolution of iUPD

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

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

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

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

Management Following the Confirmatory Imaging

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

NOTE: If a participant has confirmed radiographic progression (iCPD) as defined above, but the participant is achieving a clinically meaningful benefit or if RECIST 1.1 PD has not been verified centrally, an exception to continue study treatment may be considered following consultation with MSD. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 2 and submitted to the central imaging vendor.

Detection of Progression at Visits after Pseudo-progression Resolves

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

- Target lesions
    - Sum of diameters reaches the PD threshold ($\geq$20% and $\geq$5 mm increase from nadir) either for the first time, or after resolution of previous pseudo-progression. The nadir is always the smallest sum of diameters seen during the entire study, either before or after an instance of pseudo-progression.
- Non-target lesions
    - If non-target lesions have never shown unequivocal progression, their doing so for the first time results in iUPD.

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

- New lesions
  - New lesions appear for the first time
  - Additional new lesions appear
  - Previously identified new target lesions show an increase of ≥ 5 mm in the new lesion sum of diameters, from the nadir value of that sum
  - Previously identified non-target lesions show any significant growth

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

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

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

Signature Manifest

Document Number: IC-DEV-PROT-AMEND-0352 **Revision:** 0

Title: INCB 24360-304 Protocol Amendment 4 (KEYNOTE-669/ECHO-304)

All dates and times are in Eastern Standard Time.

Quick Approval

Approve Now

Name/Signature	Title	Date	Meaning/Reason
[redacted]	[redacted]	13 Jun 2018, 11:04:24 AM	Approved