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Protocol Title: A Phase 2, Randomized, Double-Blind Study of Pembrolizumab (MK-3475) plus Epacadostat (INCB024360) Versus Pembrolizumab plus Placebo as First-Line Treatment in Patients with Metastatic Non-Small Cell Lung Cancer Expressing High Levels of PD-L1

Protocol Number: 654-05/ECHO-305-05 / NCT03322540

Compound Number: MK-3475/INCB024360

This study is co-funded by Incyte and MSD.

Execution of Study:

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(Referenced herein as MSD)

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Approval Date: 04-March-2019

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:

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
3475-654-06	04-MAR-2019	Data from the final analysis of KEYNOTE-654/ECHO-305 (data cutoff: 10-JAN-2019) indicated that the study did not meet the pre-specified endpoint of improvement in objective response rate (ORR) for the combination of pembrolizumab plus epacadostat compared with pembrolizumab plus placebo. Based upon these data from the final analysis, the Sponsor and MSD implemented this Amendment 05 to direct that all epacadostat and placebo administration stop, and to reflect that the study is no longer blinded. The study will remain open so participants still on study will have continued access to pembrolizumab.
3475-654-04	31-MAY-2018	Updated Phase 3 design to Phase 2 design, title of protocol, primary and secondary endpoints.
3475-654-03	05-APR-2018	To align with regulatory requirements at French sites to exclude participants on coumarin-based anticoagulants and prohibit coumarin based anticoagulant treatment for participants receiving epacadostat. In addition, to provide specific dose modification and toxicity management guidelines for myocarditis.
3475-654-02	6-MAR-2018	To align HIV and pregnancy testing with regulatory requirements at German sites.
3475-654-01	3-NOV-2017	To provide specific dose modification and toxicity management guidelines for myocarditis.
3475-654-00	06-JUN-2017	Initial protocol

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment 05

Overall Rationale for the Amendment:

Data from the final analysis of KEYNOTE-654/ECHO-305 (data cutoff: 10-JAN-2019) indicated that the study did not meet the pre-specified endpoint of improvement in objective response rate (ORR) for the combination of pembrolizumab plus epacadostat compared with pembrolizumab plus placebo. Based upon these data from the final analysis, the Sponsor and MSD implemented this Amendment 05 to direct that all epacadostat and placebo administration stop, and to reflect that the study is no longer blinded. The study will remain open so participants still on study will have continued access to pembrolizumab.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
1. Synopsis	Revised text and added notes to clarify the removal of epacadostat and placebo treatments from the study; participants may choose to discontinue from the study or continue on study and receive open-label pembrolizumab monotherapy as per protocol. Updated the duration of participation to reflect the removal of the Second Course Phase, Survival Follow-up visits, and post-treatment follow-up imaging as endpoints will no longer be collected.	In accordance with the overall rationale for the amendment provided above, all references to epacadostat and placebo, as well as assessments/procedures specific to these treatments, are removed from the protocol. Participants remaining in the study will be treated according to the site's standard of care. The final visit of the study will be the Safety Follow-up Visit and 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. 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.
2.1 Initial Treatment Phase SoA	Epacadostat and matching placebo are removed from the study and procedures for participants remaining in study are simplified where possible. Second Course Phase, Follow-up visits, and Survival Follow-up are removed. There are no required tumor imaging assessments during the treatment phase or at EOT; rather, all imaging is to be performed per local standard of care (note, data will not be collected).	

Section # and Name	Description of Change	Brief Rationale
2.2 Second Course Phase	The Second Course Phase is removed from the protocol; thus, this schedule of activities has been deleted.	
3.3 Benefit/Risk Assessment	Addition of notes to clarify that the benefit/risk assessment of epacadostat and placebo in this section is no longer applicable and has been deleted.	Epacadostat has been removed from the study; thus, benefit:risk assessment for treatment arms containing epacadostat is no longer relevant.
4.0 Objectives/Hypotheses and Endpoints	Addition of a note to clarify that efficacy endpoints will no longer be collected and [redacted] may not be further pursued.	As the study did not meet the pre-specified endpoint for ORR, the scope of the study is reduced and further collection of efficacy data is not required.

Section # and Name	Description of Change	Brief Rationale
5.1 Overall Design 5.1.1 Data Monitoring Committee 5.1.2 Study Diagram	Addition of a note and revised text to address the following points: • Removal of epacadostat and placebo from study treatment groups and continuation of participants on pembrolizumab monotherapy only on study. • Removal of Second Course Phase, Follow-up, and Survival Status Follow-up. • Removal of central radiologist review of imaging and required schedule of imaging. Clarification that all imaging going forward is to be performed per local standard of care and assessed by the investigator for PD per RECIST 1.1. The use of iRECIST is discontinued. • Addition of text clarifying the results of the final analysis and rationale behind the changes in study design. • Clarification that no further DMC reviews will be conducted. An additional study diagram as of Amendment 05 is provided.	In accordance with the overall rationale for the amendment, removal of epacadostat and matching placebo, and reduced overall scope of the study. Participants may choose to discontinue from the study and be treated as per standard of care, or continue on study and receive pembrolizumab monotherapy as per protocol, if they will have access issues to standard of care outside the protocol.

Section # and Name	Description of Change	Brief Rationale
5.2 Number of Participants 9.9.1 Screening	Addition of a note that enrollment was completed as of 05-SEP-2018.	To clarify the current study status.
5.4.1 Rationale for Endpoints	Addition of notes to clarify which sections and text are no longer applicable since efficacy endpoints and [redacted] data will no longer be collected, and central review of imaging and the use of iRECIST for treatment decisions are discontinued.	In accordance with the overall rationale for the amendment, the removal of epacadostat and matching placebo from the study, and the reduced scope of the study, further collection of efficacy endpoints and [redacted] central review of imaging is no longer warranted. All imaging and treatment decisions are per local standard of care based on investigator assessment per RECIST 1.1.
5.4.2 Rationale for the Use of Comparator/Placebo 5.5.2 Rationale for Dose and Regimen of Epacadostat in Combination with Pembrolizumab	Addition of a note clarifying that this section is no longer applicable with the removal of epacadostat and matching placebo from the study.	Epacadostat and matching placebo have been removed from the study.

Section # and Name	Description of Change	Brief Rationale
7.1 Treatments Administered	Removal of epacadostat and matching placebo from the table of study treatments and clarification of the treatments to be administered to participants continuing in the study in each study arm.	Epacadostat and matching placebo have been removed from the study.
7.2.1 Dose Modification for Immune-related AEs	Removal of all text relating to dose modification of epacadostat/matching placebo and updates to text where appropriate to reflect the removal of epacadostat/matching placebo from the study. Table 3 (Dose Modification Guidelines) has been replaced with the current guidelines for pembrolizumab alone.	
7.2.3 Procedures for Participants Exhibiting Serotonin Syndrome	Text updated to reflect the removal of epacadostat/matching placebo from the study. Updated information regarding the risks of SS with the use of epacadostat is provided. Text is revised to clarify that the use of MAOIs is no longer prohibited in the study	To align with current practices across the epacadostat development program as supported in the current version of the epacadostat IB.
7.4 Blinding 9.1.11 Participant Blinding/Unblinding	Note that all text related to study treatment blinding is no longer applicable. Deletion of text related to blinding of epacadostat/matching placebo and emergency unblinding procedures.	As of Amendment 05, epacadostat and matching placebo are removed from the study and all study treatment is open-label.

Section # and Name	Description of Change	Brief Rationale
7.5.1 Dose Preparation	Text updated to reflect the removal of epacadostat/matching placebo from the study.	Epacadostat and matching placebo have been removed from the study.
7.6.2 Administration and Compliance of Oral Study Treatment (Epacadostat or Matching Placebo)	Addition of a note clarifying that this section is no longer applicable with the removal of epacadostat and matching placebo from the study. All text in this section is deleted.	
7.7.1 Acceptable Concomitant Therapies	Text updated to reflect the proper time frame for collection of concomitant medications following the removal of the Second Course Phase.	The Second Course Phase has been removed in accordance with the reduced scope of the study.
7.7.2 Prohibited Concomitant Therapies	Text updated to remove UGT1A9 inhibitors and MAOIs as prohibited concomitant therapy. Sentence about the Post-Treatment Follow-up Phase was deleted.	Per the latest IB for epacadostat, the use of MAOIs and UGT1A9 inhibitors are no longer prohibited with the 100 mg BID dose of epacadostat. The Follow-up Phase and Survival Follow-up are removed due to the reduced scope of the study.
7.7.3 Restricted Medications	Note added to clarify that as of Amendment 05, this section is no longer applicable to participants who were previously randomized to epacadostat/placebo and has been deleted.	There are no restricted medications for participants receiving pembrolizumab.

Section # and Name	Description of Change	Brief Rationale
7.9 Clinical Supplies Disclosure	Note added to clarify that emergency unblinding procedures are no longer applicable.	With the discontinuation of epacadostat and matching placebo, all study treatments in the study are open-label.
8.1 Discontinuation of Study Treatment	Note added to clarify the text is updated to reflect the following: • Discontinuation of BICR confirmation of imaging assessments. • Treatment unblinding is no longer a reason for treatment discontinuation.	With the unblinding of the study and discontinuation of BICR verification of imaging assessments, treatment discontinuation criteria are updated accordingly.
8.1.1 Second Course Phase	Note added to clarify that the Second Course Phase is removed; all text is no longer applicable and has been deleted.	The Second Course Phase, Follow-up Phase, and Survival Follow-up are removed due to the reduced scope of the study.
8.2 Withdrawal from the Study 9.1.10 Withdrawal/Discontinuation 9.9.3.1 Safety Follow-up Visit	Section updated to reflect the removal of the Follow-up Phase and/or Survival Follow-up as applicable.	
9.1.1.1 General Informed Consent	Text added to clarify that re-consent of participants who continue on study treatment after initial disease progression is required.	Program-wide change to comply with FDA request in alignment with PDUFA VI.

Section # and Name	Description of Change	Brief Rationale
9.1.6.2 Concomitant Medications	Section updated to reflect the removal of the Second Course Phase.	The Second Course Phase has been removed in accordance with the reduced scope of the study.
9.1.9 Treatment Administration 9.1.9.1.2 Timing of Dose Administration of Epacadostat or Matching Placebo	Section updated to reflect the removal of epacadostat/matching placebo from the study.	Epacadostat and matching placebo have been removed from the study.
9.2.1 Tumor Imaging and Assessment of Disease	Note added clarifying that as of Amendment 05, BICR and iRECIST are no longer applicable. All disease assessments will be performed by the site investigator per local standard of care. All text related to submission of images to BICR and use of iRECIST for treatment decisions has been deleted.	In accordance with the reduced scope of the study, further collection of efficacy endpoints is not required and central review of imaging and the use of iRECIST is no longer warranted. All imaging and treatment decisions are per local standard of care based on investigator assessment per RECIST 1.1.
9.2.1.2 Tumor Imaging During the Study	Note added clarifying that as of Amendment 05, BICR and iRECIST are no longer applicable. All disease assessments will be performed by the site investigator per local standard of care, but this data will not be collected and no on-study imaging schedule is mandated during the treatment phase or at EOT. All text related to submission of images to BICR, the use of iRECIST for treatment decisions, and required timing of imaging assessments has been deleted.	

Section # and Name	Description of Change	Brief Rationale
9.2.1.3 End of Treatment and Follow-Up Imaging	Note added clarifying that as of Amendment 05, there is no protocol-specified imaging at end of treatment and no follow-up imaging is required. All text in this section has been deleted.	
9.2.1.4 Second Course Phase Tumor Imaging	Note added clarifying that as of Amendment 05, the Second Course Phase is eliminated and this section is no longer applicable. All text in this section has been deleted.	The Second Course Phase has been removed in accordance with the reduced scope of the study.
9.2.1.5 RECIST 1.1 Assessment of Disease	Note added clarifying that BICR is no longer applicable and all imaging is to be performed as per local standard of care guidelines. Text relating to BICR verification of disease progression has been deleted.	In accordance with the reduced scope of the study, further collection of efficacy endpoints is not required and central review of imaging and the use of iRECIST is no longer warranted. All imaging and treatment decisions are per local standard of care based on investigator assessment per RECIST 1.1.
9.2.1.6 iRECIST Assessment of Disease	Note added clarifying that iRECIST is no longer applicable and all imaging should be performed per local standard of care guidelines and assessed per RECIST 1.1. All text is deleted from the section.	
9.2.2 Patient Reported Outcomes	Note added clarifying that as of Amendment 05, PROs will no longer be collected. All text in this section has been deleted.	In accordance with the reduced scope of the study, PROs are no longer required.
9.4 Treatment of Overdose	Note added that epacadostat is removed from the study.	Epacadostat has been removed from the study.

Section # and Name	Description of Change	Brief Rationale
9.5.1.1 Full Physical Exam	Requirement to perform a full physical exam at the discontinuation visit, Second Course Cycle 1, and Second Course discontinuation visit has been removed.	To reflect the removal of the Second Course Phase and to simplify study procedures in consideration of the reduced scope of the study.
9.5.3 Electrocardiograms	The requirement to obtain ECGs at EOT is removed. ECGs are to be obtained at screening; thereafter, ECGs may be performed according to local standard of care or as clinically indicated.	Simplification of study procedures due to reduced scope of the study.
9.9.2 Treatment Phase	This section has been updated to remove information regarding dosing of epacadostat and matching placebo.	Epacadostat and matching placebo have been removed from the study.
9.9.3.1 Safety Follow up Visit	Notes added clarifying that the Safety Follow-up Visit will be the last visit in the study and that recording of AEs will be performed as per Section 9.3. Removal of text detailed in Section 9.3.	The Second Course Phase, Follow-up Phase, and Survival Follow-up are removed due to the reduced scope of the study. Removes conflict in reporting of AE/SAEs for pembrolizumab.
9.9.3.2 Follow-up Visits 9.9.3.3 Survival Follow-up 9.9.3.4 Survival Status 9.9.4 Second Course Phase	Notes added clarifying that the Follow-up Visits, Survival Follow-up, and Second Course Phase have been removed from the study. Participants currently in Follow-up or Survival Follow-up as of Amendment 05 are considered to have completed the study once they have attended the Safety Follow-Up Visit. All other text in these sections has been deleted.	The Second Course Phase, Follow-up Phase, and Survival Follow-up are removed due to the reduced scope of the study.

Section # and Name	Description of Change	Brief Rationale
10.0 Statistical Analysis Plan	Note added to clarify that the final analysis has been performed, and, as the study did not meet the pre-specified primary endpoint, efficacy data will no longer be collected in the study, including central review of imaging. Thus, only selected analyses detailed in all subsections of Section 10 will be performed at study completion.	In accordance with the reduced scope of the study and discontinuation of efficacy data collection.
10.6.2 Statistical Methods for Safety Analyses	Methods for safety analyses were revised to reflect changes in objectives and endpoints.	As the study did not meet the pre-specified endpoint for ORR, the scope of the study is reduced.
12.2 Appendix 2: Clinical Laboratory Tests	Text regarding reporting of laboratory analyte results that could unblind the study has been deleted.	As of Amendment 05, the study is unblinded.
Nonsubstantive editorial and grammatical changes were made throughout the document.		

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LIST OF FIGURES

1. Synopsis

Protocol Title:

A Phase 2, Randomized, Double-Blind Study of Pembrolizumab (MK-3475) plus Epacadostat (INCB024360) Versus Pembrolizumab plus Placebo as First-Line Treatment in Patients with Metastatic Non-Small Cell Lung Cancer Expressing High Levels of PD-L1

Short Title:

Phase 2 Study of Pembrolizumab ± Epacadostat in PD-L1 High Metastatic NSCLC

Objectives/Hypotheses and Endpoints:

NOTE: As of Amendment 05, epacadostat and matching placebo are removed from the treatment groups. All participants remaining on study will continue on open-label pembrolizumab monotherapy. The study will therefore stop collecting efficacy endpoints and [redacted] may not be pursued.

In all randomized participants with treatment-naïve, stage IV non-small cell lung cancer (NSCLC), highly expressing PD-L1 (TPS ≥50%):

Objective/Hypothesis	Endpoint
Primary	
• To compare objective response rate (ORR) of pembrolizumab plus epacadostat versus pembrolizumab plus placebo. • Hypothesis (H1): The combination of pembrolizumab plus epacadostat has superior ORR compared to pembrolizumab plus placebo.	• ORR is defined as the proportion of participants who have a confirmed complete response (CR) or partial response (PR) per RECIST 1.1 based on blinded independent central review (BICR).
This study will be considered to have met its success criteria if pembrolizumab plus epacadostat is superior to pembrolizumab plus placebo in ORR.	
Secondary	
• To compare progression-free survival (PFS) of the combination of pembrolizumab plus epacadostat versus pembrolizumab plus placebo. • Hypothesis (H2): The	• PFS is defined as the time from randomization to the first documented progressive disease (PD) per RECIST 1.1 based on blinded independent central review (BICR) or death due to any cause, whichever occurs first.

combination of pembrolizumab plus epacadostat has superior PFS compared to pembrolizumab plus placebo.	
• To compare overall survival (OS) of pembrolizumab plus epacadostat versus pembrolizumab plus placebo. • To evaluate duration of response (DOR) of the combinations of pembrolizumab plus epacadostat and pembrolizumab plus placebo. • To evaluate the safety and tolerability of the combinations of pembrolizumab plus epacadostat and pembrolizumab plus placebo.	• OS is defined as the time from randomization to death due to any cause. • DOR defined as the time from the earliest date of qualifying response until earliest date of disease progression or death from any cause, whichever comes first, per RECIST 1.1 based on BICR. • Number of participants experiencing AEs and number of participants discontinuing study drug due to AEs.

Overall Design:

Trial Phase	Phase II
Clinical Indication	First-line treatment of metastatic NSCLC with high PD-L1 expression (TPS ≥50%)
Population	Adult patients with treatment-naïve metastatic NSCLC (TPS ≥50%)
Trial Type	Interventional
Type of Design	Randomized, active comparator, parallel-group, multi-site, double-blind **NOTE: As of Amendment 05, the study is unblinded, open-label, single arm.**
Type of Control	Active Control **NOTE: As of Amendment 05, active control/placebo is removed.**
Trial Blinding	Double-blind **NOTE: As of Amendment 05, the study is unblinded.**
Estimated Duration of Trial	The study is estimated to require approximately 3 years 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:

Approximately 148 participants will be enrolled.

Treatment Groups and Duration:

Treatment Groups	• Pembrolizumab 200 mg IV every 3 weeks (Q3W), up to 35 cycles **NOTE: The original study design randomized participants into 2 treatment arms: pembrolizumab (open-label) plus epacadostat and pembrolizumab (open-label) plus matching placebo. As of Amendment 05, epacadostat and matching placebo are removed. All participants remaining in the study will receive pembrolizumab monotherapy as per protocol, unless they choose to discontinue from the study completely and be treated with standard of care.**
Duration of Participation	**NOTE: As of Amendment 05, this section has been updated.** Each participant will partake in the study from the time the participant signs the informed consent form through the final contact. After a screening phase of 30 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, withdrawal of consent, or until the participant has received 35 administrations of pembrolizumab (approximately 2 years). After the end of treatment, each participant will be followed for the occurrence of AEs and spontaneously reported pregnancy as described under Section 9.3.

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

2. Schedule of Activities (SoA)

2.1 Initial Treatment Phase

NOTE: As of Amendment 05, epacadostat and matching placebo administration are stopped and all participants remaining in the study will receive open-label pembrolizumab monotherapy. The final study visit will be the Safety Follow-up Visit and there will be no follow-up for survival status. For participants who were in Follow-up or Survival Follow-up, participation in the study is considered complete and no further visits are required. For those participants remaining in the study, procedures are simplified. The SoA has been amended and assessments no longer required have been deleted.

Study Period	Screen. Phase	Treatment Cycles (3-Week Cycles)						EOT	Post Treatment	Notes Participants who discontinue study treatment for whatever reason will proceed directly to EOT and Safety Follow-up.
Treatment Cycle	Screen. (V 1)	1	2	3	4	5	6 to 35	DC	Safety Follow-up[1]	
Scheduling Window (Days):	-30 to -1	+3	±3	±3	±3	±3	±3	At DC (+3)	30 Days Post-DC (+14)	
Administrative Procedures										
Informed Consent Form	X									Re-consent of participants is required at disease progression for participants continuing on treatment.
Inclusion/Exclusion Criteria	X									
Participant ID Card	X									
Demographics and Medical History	X									
Prior/Concomitant Meds	X	X	X	X	X	X	X	X	X	
NSCLC Disease Details and Prior Treatment	X									
Serotonin Syndrome Information Card		X								
Subsequent Anti-neoplastic Therapy Status								X	X	
Clinical Procedures / Assessments										
Review Adverse Events	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 anti-cancer therapy is initiated, whichever is earlier.

Study Period	Screen. Phase	Treatment Cycles (3-Week Cycles)						EOT	Post Treatment	Notes **Participants who discontinue study treatment for whatever reason will proceed directly to EOT and Safety Follow-up.**
Treatment Cycle	**Screen. (V 1)**	**1**	**2**	**3**	**4**	**5**	**6 to 35**	**DC**	**Safety Follow-up[1]**	
Scheduling Window (Days):	**-30 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At DC (+3)**	**30 Days Post-DC (+14)**	
Full Physical Exam	X									
Directed Physical Exam		X	X	X	X	X	X	X	X	
Vital Signs, Height, and Weight	X	X	X	X	X	X	X	X	X	Height at screening only
12-Lead ECG with QTc Measurement	X	X	X					*		At screening for all participants. At select centers, also perform on C1D1 and C2D1 at predose and 120 min (±15 min) after morning dose of epacadostat/placebo. * At EOT, perform ECG per SOC or as clinically indicated.
ECOG Performance Status	X	X	X	X	X	X	X	X	X	At screening, perform within 7 days prior to Cycle 1 but before randomization.
Laboratory Procedures / Assessments: Analysis Performed by Local Laboratory										
Pregnancy Test - Urine or Serum β-HCG	X									WOCBP require negative test within 72 hours prior to Cycle 1. Test monthly if required by local regulations.
Hepatitis B & C Serology	X									Hepatitis B surface antigen, HBV-DNA, HCV-RNA (or HCV antibody if HCV-RNA is not the local SOC). May use central lab only if local lab is not capable. If this testing was conducted per SOC within 42 days prior to randomization, testing does not need to be repeated.
HIV Testing	X									Not required unless mandated by local health authority.
PT/INR and aPTT/PTT	X									Perform eligibility labs within 10 days prior to Cycle 1. Participants receiving coumarin-based anticoagulants should have more frequent INR monitoring (weekly for first 4 weeks after initiation of therapy and upon DC of epacadostat/placebo). As of Amendment 05, testing after DC of epacadostat/placebo is no longer required.
CBC with Differential	X		X	X	X	X	X	X	X	Perform eligibility labs within 10 days prior to Cycle 1. After Cycle 1, may collect up to 3 days prior to dosing.
Chemistry Panel	X		X	X	X	X	X	X	X	
Urinalysis	X		X		X		X	X	X	Perform within 10 days prior to Cycle 1, then every 2nd cycle through Cycle 6, then every 6th cycle thereafter (Cycles 2, 4, 6, 12, 18, etc.).

Study Period	Screen. Phase	Treatment Cycles (3-Week Cycles)						EOT	Post Treatment	Notes **Participants who discontinue study treatment for whatever reason will proceed directly to EOT and Safety Follow-up.**
Treatment Cycle	**Screen. (V 1)**	**1**	**2**	**3**	**4**	**5**	**6 to 35**	**DC**	**Safety Follow-up[1]**	
Scheduling Window (Days):	**-30 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At DC (+3)**	**30 Days Post-DC (+14)**	
T3/FT3, FT4, and TSH	X		X		X		X	X	X	Perform within 10 days prior to Cycle 1, then every 2nd cycle (Cycles 2, 4, 6, 8, etc.). May use central lab only if local lab is not capable.
[redacted]										
[redacted]										
Efficacy Measurements										
Tumor Imaging	X	X								The timing of imaging during the treatment phase is according to the site's SOC for tumor assessment until PD or initiation of a new anticancer regimen.
Brain MRI	X									Perform only if required by local SOC. Perform at time of CR in participants with brain metastasis at Screening.

Study Period	**Screen. Phase**	**Treatment Cycles (3-Week Cycles)**						**EOT**	**Post Treatment**	**Notes** **Participants who discontinue study treatment for whatever reason will proceed directly to EOT and Safety Follow-up.**
Treatment Cycle	**Screen. (V 1)**	**1**	**2**	**3**	**4**	**5**	**6 to 35**	**DC**	**Safety Follow-up[1]**	
Scheduling Window (Days):	**-30 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At DC (+3)**	**30 Days Post-DC (+14)**	
Study Drug Administration – ***Per Randomized Assignment***										
Pembrolizumab		X	X	X	X	X	X			

Notes:
1. If Discontinuation Visit occurs ≥30 days from last dose of study treatment, a Safety Follow-up Visit is not required. Participants will be discontinued from the study after their 30-day Safety Follow-up Visit.

Abbreviations: AE= adverse event; aPTT= activated partial thromboplastin time; β-HCG= beta-human chorionic gonadotropin; BICR= blinded independent central (imaging) review; CBC= complete blood count; CR= complete response; CXDX= Cycle X Day X; d= days; DC= discontinuation; ECG= electrocardiogram; ECOG= Eastern Cooperative Oncology Group; EOT= end of treatment FT4= free thyroxine; H/hr= hours; HBV/HCV= hepatitis B/C virus; HIV= human immunodeficiency virus; ICF= informed consent form; ID= identification; INR= international normalized ratio; IRB/IEC= Institutional Review Board/Independent Ethics Committee; min= minutes; NSCLC= non-small cell lung cancer; PD= progressive disease; [redacted]; PT= prothrombin time; PTT=partial thromboplastin time; Q= every;; QTc= corrected QT interval; SAE= serious adverse event; SOC= standard of care; T3/FT3= free or total triiodothyronine; TSH= thyroid stimulating hormone; V=visit; W/wks= weeks; WOCBP= women of child-bearing potential.

3. Introduction

3.1 Study Rationale

The global incidence of lung cancer was 1.8 million in 2012, resulting in an estimated 1.6 million deaths [World Health Organization 2012]. In the United States, the 2016 estimated incidence of new diagnoses was 224,400 and estimated number of deaths was 158,100 [National Cancer Institute 2016]. Non-small cell lung cancer (NSCLC) represents approximately 80% to 85% of all lung cancers. Of the patients with NSCLC, tumor histology is approximately 40% to 60% adenocarcinoma, 10% to 15% squamous, 5% neuroendocrine, and the rest, "not otherwise specified" [Sulpher, J. A., et al 2013].

Approximately 70% of patients with NSCLC have advanced disease not amenable to surgical resection at the time of diagnosis. The 5-year relative survival for patients with any lung cancer overall and metastatic lung cancer specifically has been reported to be 17.7% and 4.3%, respectively [National Cancer Institute 2016].

Pembrolizumab monotherapy is the current standard of care (SOC) for the treatment of patients with good Eastern Cooperative Oncology Group (ECOG) performance status (ECOG 0 or 1) and previously untreated, advanced, or metastatic NSCLC with a programmed cell death ligand 1 (PD-L1) tumor proportion score (TPS) ≥50% with no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations. Approximately 30% of patients with newly diagnosed, advanced NSCLC highly express PD-L1 to a TPS ≥50% [Reck, M., et al 2016].

KEYNOTE-024, a Phase 3, randomized, controlled study, compared pembrolizumab monotherapy to standard first-line (1L) platinum-doublet therapy in 305 previously untreated participants with advanced NSCLC and a PD-L1 TPS ≥50%. Results from KEYNOTE-024 indicated a significant progression-free survival (PFS) benefit for pembrolizumab over platinum-doublet therapy with a hazard ratio (HR) of 0.50 (95% confidence interval [CI] 0.37-0.68, $p<0.001$; median PFS 10.3 months [95% CI 6.7 not reached] with pembrolizumab and 6.0 months [95% CI 4.2-6.2] with platinum-doublet), as well as an overall survival (OS) benefit with an HR of 0.60 (95% CI 0.41-0.89, $p=0.005$; median OS was not reached in either treatment arm). An estimated (Kaplan-Meier) 80.2% (95% CI 72.9-85.7) of participants treated with pembrolizumab and 72.4% (95% CI 64.5-78.9) of participants treated with platinum doublet therapy were alive at 6 months. Additionally, the objective response rate (ORR) was higher in the pembrolizumab arm than in the platinum-doublet arm (44.8% vs 27.8%, respectively) [Reck, M., et al 2016].

The results from KEYNOTE-024 established pembrolizumab as 1L therapy for patients whose tumors have a TPS ≥50% and with no EGFR or ALK genomic tumor aberrations. While the benefit observed in KEYNOTE-024 was substantial, with significant improvement in PFS and OS, the benefits may be improved further in this patient population, possibly through combination of pembrolizumab with other immunomodulators.

Epacadostat (formerly INCB024360) represents a novel, potent, and selective inhibitor of the enzyme indoleamine 2,3 dioxygenase-1 (IDO1) in both human tumor cells and human dendritic cells. The presence of the tryptophan-catabolizing enzyme IDO1 inhibits T-cell-mediated immune responses, and IDO1 expression has been shown to be elevated in many

human cancers; thus, IDO1 inhibition may restore an effective antitumor immune response.

KEYNOTE-037 (INCB 24360-202), a dose-escalation and expansion study of pembrolizumab in combination with epacadostat in participants with Stage IIIB, IV, or recurrent NSCLC, melanoma, transitional cell carcinoma, renal cell carcinoma, endometrial adenocarcinoma, or squamous head and neck carcinoma, is ongoing. ORR in 40 evaluable participants with previously-treated NSCLC was 35% (14/40) and disease control rate (DCR) was 60%, which includes 2 participants with a CR. Details of the results of this study thus far may be found in Section 3.2.3 and [Gangadhar, T. C. 2017].

Outcomes for patients evaluated in this study, with previously untreated metastatic NSCLC whose tumors express high levels of PD-L1 (TPS ≥50%), would be further improved if the safety profile of a pembrolizumab/epacadostat combination remains acceptable and is shown to improve outcomes compared to pembrolizumab monotherapy; thus, this study could support testing the hypothesis of having an improved outcome of the combination in this patient population.

3.2 Background

Pembrolizumab (MK-3475) is a potent and highly selective humanized monoclonal antibody (mAb) of the immunoglobulin (Ig)G4/kappa isotype directed against programmed cell death protein 1 (PD-1), thus inhibiting its interaction with PD-L1 and programmed cell death ligand 2 (PD-L2). Epacadostat (formerly INCB024360) represents a novel, potent, and selective inhibitor of the enzyme IDO1 in both human tumor cells and human dendritic cells. For a thorough discussion of the pharmacology of pembrolizumab and epacadostat, refer to the pembrolizumab Investigator's Brochure [IB Edition 15 2017] and the epacadostat Investigator's Brochure [Addendum 1 to IB Edition 9 2017].

3.2.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades [Disis, M. L. 2010]. The inability of the immune system to control tumor growth does not appear to result from an inability to recognize the tumor as foreign. Tumor cells have been shown to evade immune destruction despite displaying recognizable antigens on their surface and despite the presence of high avidity T-cells that are specific for these antigens [Boon, T. 1996], [Ercolini, A. M., et al 2005].

Histologic evaluation of many human cancers shows extensive infiltration by inflammatory and immune cells [Galon, J., et al 2006], suggesting that the immune system responds less effectively to malignancy. These observations have led to the hypothesis that dominant mechanisms of immune tolerance or immune suppression are responsible for the immune system's inability to effectively respond in a way that consistently results in rejection.

The PD-1 receptor is an immunoglobulin superfamily member 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 PD-1 pathway represents a major immune control switch, which can be exploited by tumor cells to overcome active T-cell immune surveillance. Expressed on the surface of activated T-cells under healthy conditions, the function of the PD-1 receptor is to down-modulate unwanted or excessive immune/autoimmune responses. A variety of cancers have been demonstrated to express abundant levels of PD-1 ligands, unlike healthy organs. The observed correlation of clinical prognosis with PD-L1 expression in multiple cancers suggests that the PD-1/PD-L1 pathway plays a critical role in tumor evasion and is thus an attractive target for therapeutic intervention.

Pembrolizumab is designed to directly block the interaction between PD-1 and its ligands PD-L1 and PD-L2. This blockade enhances functional activity of the target lymphocytes to facilitate tumor regression and ultimately immune rejection of the tumor.

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 metabolized subsequently through a series of enzymatic steps to nicotinamide adenine dinucleotide. IDO1 is the first rate-limiting enzyme in one of the breakdown pathways of tryptophan. In another pathway, tryptophan hydroxylase catalysis of tryptophan 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 dendritic cells 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]. IDO1 activity also promotes the differentiation of naive T-cells to cells with a regulatory phenotype (T-reg) [Fallarino, F., et al 2006]. Since increased T-reg activity has been shown to promote tumor growth and T-reg depletion has been shown to allow an otherwise ineffectual antitumor immune response to

occur [Zou, W. 2006], IDO1 expansion of T-regs may provide an additional mechanism whereby IDO1 could promote an immunosuppressive environment.

The biological relevance of IDO1 inhibition to immune tolerance was first demonstrated when it was shown that treating mice with a small molecule inhibitor of the IDO1 pathway, 1-methyl-tryptophan, could break the tolerogenic state that protects allogeneic concepti from the maternal immune system [Munn, D. H., et al 1998]. A critical role for IDO1 in immunomodulation has been confirmed in numerous animal models, including models of allograft tolerance, inflammation, and cancer [Mellor, A. L. 2004]. While IDO1 inhibition can exacerbate disease in models of autoimmune disorders [Mellor, A. L. 2004], IDO1 null mice show no evidence of susceptibility to developing spontaneous autoimmunity or alterations in immune system development [Mellor, A. L., et al 2003], suggesting that IDO1 inhibition, in a therapeutic setting, may produce minimal side effects in participants without pre-existing autoimmune conditions.

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 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 dendritic cells that localize to the TDLN [Uyttenhove, C., et al 2003]. Increased expression of IDO1 in tumor cells has been shown to be an independent prognostic variable for reduced OS in participants with melanoma, ovarian, colorectal, pancreatic, and non-small cell lung 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], [Hanagiri, T., et al 2014]. Together, these results suggest that 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 advanced malignancies in combination with chemotherapeutics and/or immunotherapy-based strategies.

As discussed above, there are a number of inhibitory mechanisms that have been identified to be involved in tumor-mediated immune suppression. Agents that target these negative regulatory pathways and thereby allow the expansion of effector T-cells present in the tumor may be beneficial in the clinic. Combined inhibition of both PD-L1 and IDO1 pathways may therefore lead to greater enhancement of antitumor immunity and to increased efficacy.

3.2.2 Completed Clinical Studies

Three completed clinical studies were conducted to evaluate the efficacy of pembrolizumab monotherapy in the treatment of NSCLC: KEYNOTE-001, KEYNOTE-010, and KEYNOTE-024.

KEYNOTE-001:

An open-label Phase 1 study (KEYNOTE-001) was conducted to evaluate the safety and clinical activity of single agent pembrolizumab. The dose escalation portion of this study evaluated three intravenous (IV) dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg administered every 2 weeks (Q2W), in participants with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. Based on pharmacokinetic (PK) data showing a half-life of 21 days, the protocol was amended to change the dosing frequency in the expansion cohort to every 3 weeks (Q3W). All cohorts have completed enrollment.

A total of 550 NSCLC participants were treated in several dose expansion cohorts with at least one dose of pembrolizumab. The initial data from 495 NSCLC participants were published and reported. The ORR was 19.4% (18.0% in the 394 previously treated participants and 24.8% in the 101 previously untreated participants). The response rate (RR) was similar regardless of dose, schedule, and histologic analysis. Current or former smokers had an RR of 22.5%, as compared with 10.3% among participants who had never smoked cigarettes.

Participants were required to submit a newly obtained tumor biopsy prior to initiating therapy with pembrolizumab for evaluation of PD-L1 expression. After evaluation of several methods for pathological assessment, in a training set, membranous PD-L1 expression in at least 50% of tumor cells (TPS ≥50%) was selected as the cutoff point defining PD-L1 high. In a validation set of 313 participants, the RR was 45.2% in the 73 participants with a TPS ≥50%, including 43.9% in previously treated participants and 50% in previously untreated participants, values that numerically exceeded the RR in the training group [Garon, E. B., et al 2015].

Pembrolizumab has been generally well tolerated. The most common treatment-related adverse events (AEs) were fatigue (19.4%), pruritus (10.7%), and decreased appetite (10.5%). Adverse events of Grade 3 or higher were reported in 47 of 495 patients (9.5%). The only treatment-related AEs of an inflammatory or immune-mediated nature that occurred in more than 2% of patients were infusion-related reactions (in 15 patients [3.0%]), hypothyroidism (in 34 patients [6.9%]), and pneumonitis (in 18 patients [3.6%]). One infusion reaction led to treatment discontinuation. All patients with hypothyroidism were successfully treated with medical therapy [Garon, E. B., et al 2015].

KEYNOTE-010:

KEYNOTE-010 was a randomized, adaptively designed Phase 2/3 study of pembrolizumab at two IV dose levels versus docetaxel in participants with NSCLC with PD-L1 positive tumors who had experienced disease progression after platinum-containing systemic therapy. Participants were randomized according to their TPS as follows: a TPS ≥50% was considered strongly positive and a TPS=1% to 49% was considered weakly positive. The study enrolled

1034 participants to examine the efficacy of pembrolizumab compared to docetaxel in an enriched population.

Pembrolizumab was superior to docetaxel in the strongly positive TPS ≥50% stratum (n=422) with regard to OS, with an HR of 0.54 (p = 0.00024) and 0.50 (p = 0.00002) for pembrolizumab 2 mg/kg Q3W and 10 mg/kg Q3W, respectively, compared to docetaxel. Pembrolizumab was superior to docetaxel in the overall positive TPS ≥1% population with regard to OS, with an HR of 0.71 (p=0.00076) and 0.61 (p<0.00001) for pembrolizumab 2 mg/kg Q3W and 10 mg/kg Q3W, respectively. Pembrolizumab was superior to docetaxel in the strongly positive TPS ≥50% stratum with regard to PFS, with an HR of 0.58 (p=0.00009) and 0.59 (p=0.00007) for pembrolizumab 2 mg/kg Q3W and 10 mg/kg Q3W, respectively, compared to docetaxel. Pembrolizumab also provided a numerically superior benefit in PFS in the overall positive TPS ≥1% population, with an HR of 0.88 and 0.79 for pembrolizumab 2 mg/kg Q3W and 10 mg/kg Q3W, respectively, compared to docetaxel; however, the differences were not statistically significant at the 0.001 level required per protocol.

The results of KEYNOTE-010 indicate that in previously treated participants with NSCLC with PD-L1 TPS ≥1%, and disease progression following platinum-containing chemotherapy, pembrolizumab provides a statistically significant and clinically meaningful OS benefit compared to standard docetaxel chemotherapy. Furthermore, the PD-L1 selection employed in KEYNOTE-010 identified patients more likely to benefit from pembrolizumab and resulted in favorable HR in OS compared to docetaxel.

Overall, the results from KEYNOTE-001 and KEYNOTE-010 demonstrated that pembrolizumab provided substantial, clinically meaningful benefits in OS, PFS, and ORR in participants with NSCLC who progressed after platinum-containing chemotherapy and whose tumor cells expressed PD-L1.

KEYNOTE-024:

KEYNOTE-024 was a multicenter, international, randomized, open-label, controlled study of IV pembrolizumab monotherapy versus the choice of multiple SOC platinum-based chemotherapies in participants previously untreated for their Stage IV NSCLC, whose tumors expressed PD-L1 at TPS ≥50%, and in whom EGFR or ALK-directed therapy is not indicated.

First-line treatment with pembrolizumab (n=154) significantly prolonged PFS (HR 0.50; 95% CI: 0.37, 0.68; p<0.001) and OS (HR 0.60; 95% CI: 0.41, 0.89; p = 0.005) compared with SOC chemotherapy (n=151), inclusive of pemetrexed maintenance for participants with non-squamous tumors. In addition, pembrolizumab was associated with a higher ORR, including a higher complete response (CR) rate, as well as a longer duration of response (DOR) as compared to SOC.

Pembrolizumab was better tolerated than chemotherapy and AEs were easily managed. The observed safety profile of the pembrolizumab arm was consistent with the safety profile for pembrolizumab established to date. Based on the mechanism of action of pembrolizumab, immune-related AEs (irAEs), including pneumonitis, occurred at a greater frequency with pembrolizumab compared to chemotherapy. Most irAEs were of Grade 1 or 2 severity and none led to death.

These data underscore the substantial benefit of pembrolizumab as initial therapy for participants with previously untreated, advanced NSCLC whose tumors express high levels of PD-L1 (TPS ≥50%), in whom EGFR or ALK-directed therapy is not indicated.

KEYNOTE-252/ECHO-301:

KEYNOTE-252/ECHO-301 is phase 3 study evaluating epacadostat in combination with pembrolizumab in subjects with unresectable or metastatic melanoma. The study did not meet the primary endpoint of improving progression-free survival in the overall population compared to pembrolizumab monotherapy. Of note, based on review of the safety analysis, the eDMC concluded that there were no safety concerns with the treatment (pembrolizumab + epacadostat) arm compared to control (pembrolizumab + placebo) arm.

3.2.3 Ongoing Clinical Studies

Pembrolizumab is under evaluation in patients with NSCLC as monotherapy and in combination with chemotherapy, immunotherapy, and targeted therapies. Epacadostat is undergoing studies in patients with NSCLC in combination with other immunotherapies including various PD-1/PD-L1 targeted therapies. A full list of ongoing studies can be found in the respective Investigator's Brochures of pembrolizumab [IB Edition 15 2017] and epacadostat [Addendum 1 to IB Edition 9 2017]. Details of the ongoing study KEYNOTE-037 is outlined below.

KEYNOTE-037 / ECHO-202

KEYNOTE-037 (ECHO-202) is a Phase 1/2 study, with Phase 1 being a dose-escalation of INCB024360 in combination with MK-3475 in participants with Stage IIIB, Stage IV, or recurrent NSCLC, melanoma, transitional cell carcinoma of the genitourinary tract, renal cell carcinoma, triple negative breast cancer, adenocarcinoma of the endometrium, or squamous cell carcinoma of the head and neck (SCCHN) who have disease progression on at least 1 line of therapy for advanced or metastatic cancer (except melanoma). Phase 2 is an open-label expansion evaluating the recommended dose (from Phase I) of epacadostat 100 mg twice daily (BID) in combination with the fixed dose of IV pembrolizumab 200 mg Q3W in participants with the following select tumors: NSCLC, melanoma, transitional cell carcinoma of the genitourinary tract, triple negative breast cancer, squamous cell carcinoma of the head and neck, ovarian cancer, clear cell renal cell carcinoma, microsatellite-instability high colorectal cancer, diffuse large B-cell lymphoma, gastric cancer, and hepatocellular carcinoma. There are two NSCLC cohorts in the Phase 2 expansion: one cohort with PD-L1 high expression (≥50%) and a second cohort with low/negative or indeterminate PD-L1 expression (<50%). Participants previously treated with PD-1 or CTLA-4 targeted therapies are excluded. Tumor response is being assessed by the Investigator using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.

As of 27-Feb-2017, a total of 294 participants were enrolled in Phase 2 and received at least 1 dose of epacadostat + pembrolizumab. The most frequently reported (≥ 10%) treatment-related AEs of any grade were fatigue (29%), rash (17%), nausea (11%), and pruritus (10%). Rash includes the preferred terms rash, rash generalized, rash macular, rash maculopapular, and rash pruritic. Treatment-related AEs Grade ≥3 were observed in 18% of participants. The most common treatment-related AEs Grade ≥3 were increased lipase (4%) and rash

(3%). There was one treatment-related death due to respiratory failure which was secondary to aspiration pneumonia [Hamid, O., et al 2017].

As of 27-Feb-2017, among the 40 evaluable previously-treated participants with NSCLC, the ORR was 35% and DCR was 63%, which includes 2 participants with a CR. For the 36 participants evaluable and with 0–2 prior lines of treatment, ORR was 39% (2 CR, 12 PR) and DCR was 64% (9 SD). Among these 36 participants treated with the recommended dose of epacadostat 100 mg BID, ORR and DCR for participants with TPS ≥50% and ≤2 prior treatments were 43% (3/7; all PR) and 57% (4/7; 1 SD), respectively; for participants with TPS <50% and ≤2 prior treatments, ORR and DCR were 33% (6/18; 1 CR) and 56% (10/18; 4 SD), respectively. The remaining 1 CR and 4 PRs were observed among 11/36 patients with unknown TPS [Gangadhar, T. C., et al 2017].

3.3 Benefit/Risk Assessment

NOTE: The results of the final efficacy analysis of this study indicated that the study did not meet the pre-specified endpoint of improvement in objective response rate (ORR) for the combination of pembrolizumab plus epacadostat compared with pembrolizumab plus placebo. As of Amendment 05, epacadostat and matching placebo have been removed from the study. Therefore, the benefit:risk assessment of epacadostat is no longer applicable and has been removed.

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.

Despite the substantial improvement in PFS and OS observed with pembrolizumab as compared to SOC platinum doublet chemotherapy in KEYNOTE-024, there remains a need to investigate new treatments which offer the prospect of added benefit for this patient population. Details regarding specific benefits and risks of pembrolizumab treatment for participants in this clinical study may be found in the Investigator's Brochure [IB Edition 15 2017] and Informed Consent Form (ICF).

4. Objectives/Hypotheses and Endpoints

NOTE: As of Amendment 05, epacadostat and matching placebo are removed from the treatment groups. All participants remaining on study will continue on open-label pembrolizumab monotherapy. The study will therefore stop collecting efficacy endpoints. [redacted]

In all randomized participants with treatment-naïve, stage IV NSCLC, highly expressing PD-L1 (TPS ≥50%):

Objective/Hypothesis	Endpoint
Primary	
• To compare ORR of the combination of pembrolizumab plus epacadostat versus pembrolizumab plus placebo. • Hypothesis (H1): The combination of pembrolizumab plus epacadostat has superior ORR compared to pembrolizumab plus placebo.	• ORR is defined as the proportion of participants who have a confirmed CR or PR per RECIST 1.1 based on BICR.
This study will be considered to have met its success criteria if pembrolizumab plus epacadostat is superior to pembrolizumab plus placebo in ORR.	
Secondary	
• To compare PFS of the combination of pembrolizumab plus epacadostat versus pembrolizumab plus placebo. • Hypothesis (H1): The combination of pembrolizumab plus epacadostat has superior PFS compared to pembrolizumab plus placebo.	• PFS is defined as the time from randomization to the first documented progressive disease (PD) per RECIST 1.1 based on blinded independent central review (BICR) or death due to any cause, whichever occurs first.
• To compare OS of the combination of pembrolizumab plus epacadostat versus pembrolizumab plus placebo.	• OS is defined as the time from randomization to death due to any cause.
• To evaluate DOR of the combinations of pembrolizumab plus epacadostat and pembrolizumab plus placebo.	• DOR defined as the time from the earliest date of qualifying response until earliest date of disease progression or death from any cause, whichever comes first, per RECIST 1.1 based on BICR.

Objective/Hypothesis	Endpoint
• To evaluate the safety and tolerability of the combinations of pembrolizumab plus epacadostat and pembrolizumab plus placebo.	• Number of participants experiencing AEs and number of participants discontinuing study drug due to AEs.
[redacted]	

[redacted]

5. Study Design

5.1 Overall Design

NOTE: As of Amendment 05, epacadostat and matching placebo are removed from the treatment groups. All participants remaining on study will continue open-label pembrolizumab monotherapy. Participants may choose to discontinue from the study and be treated as per standard of care, or continue on study and receive pembrolizumab monotherapy as per protocol, if they will have access issues to standard of care outside the protocol. The Second Course Phase is removed from the study. The last study visit is the Safety Follow-up Visit and there will be no follow-up for survival status. All imaging will be performed as per local standard of care, data will not be collected or sent for central radiologist review (BICR). This section has been updated accordingly.

This is a Phase 2 randomized, double-blind, active-controlled, parallel-group, multi-site study conducted in participants with metastatic NSCLC who have not previously received systemic therapy for metastatic disease, whose tumors express PD-L1 with a TPS ≥50%, and in whom EGFR, ALK, or ROS1-directed therapy is not indicated.

The original study design randomized participants into 2 treatment arms: pembrolizumab plus epacadostat and pembrolizumab (open-label) plus matching placebo (see Figure 1). As of Amendment 05, epacadostat and matching placebo are removed from the study. All participants remaining in the study receive open-label pembrolizumab monotherapy (see Figure 2).

Randomization into the original treatment arms in the study was stratified by predominant tumor histology (squamous vs. non-squamous).

Participants will be evaluated with radiographic imaging to assess response to treatment as per local standard of care until PD as assessed by the investigator/site radiologist using RECIST 1.1 or initiation of a new anti-cancer regimen.

Adverse event monitoring will be ongoing throughout the study and graded in severity according to the guidelines outlined in the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.0.

Treatment with pembrolizumab will continue until 35 treatment cycles (approximately 2 years), documented PD, unacceptable AEs, intercurrent illness that prevents further administration of treatment, Investigator's decision to withdraw the participant, participant withdrawal of consent, pregnancy of the participant, noncompliance with study treatment or procedure requirements, administrative reasons, or optionally for participants with a CR who have received at least 8 administrations of pembrolizumab (Section 8.1).

Participants are discontinued from the study after their 30-day Safety Follow-up Visit.

The study has no planned treatment crossover. The study will be conducted in conformance with Good Clinical Practices (GCP).

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 and Interim Analyses

This study will use an external Data Monitoring Committee (eDMC) to monitor safety. Details of the composition and procedures for the DMC may be found in the DMC Charter and Appendix 3. As of Amendment 05, no further DMC reviews will be conducted.

5.1.2 Study Diagram

The study design, as of Amendment 04, is depicted in Figure 1 and the study design as of Amendment 05 is depicted in Figure 2.

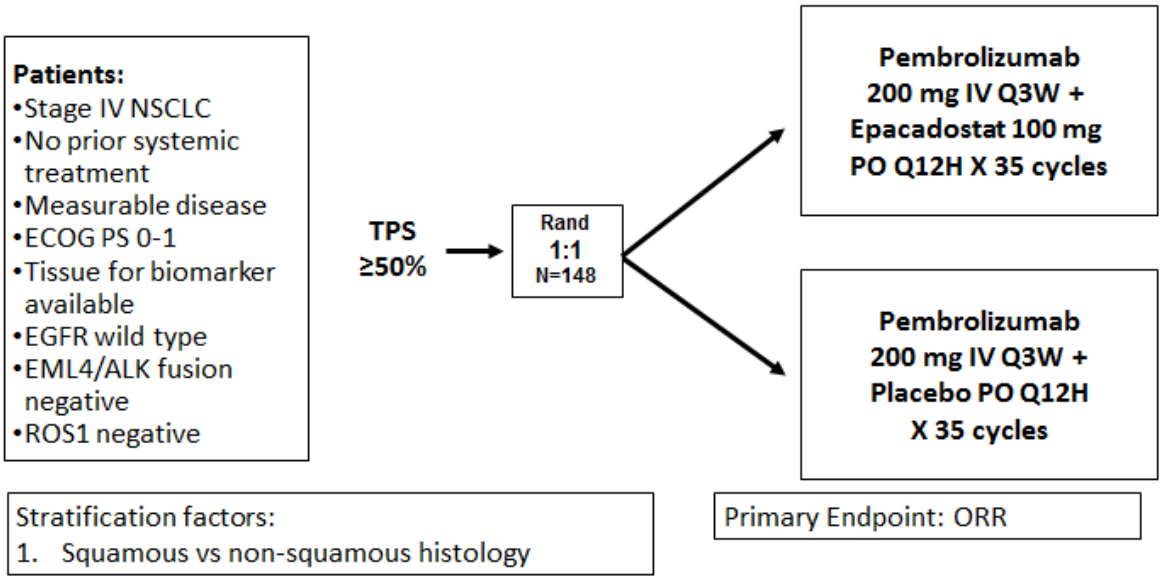


Figure 1 Original Study Diagram

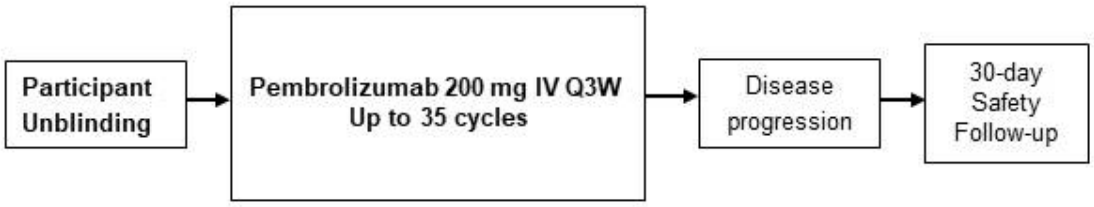


Figure 2 Study Diagram as of Amendment 05

5.2 Number of Participants

Approximately 148 participants will be randomized into the study. The study was initially designed to recruit 588 patients. With Amendment 04, the sample size was reduced to total 148 participants randomized, inclusive of participants who were enrolled prior to Amendment 04. It was estimated that approximately 90 additional participants would be required to be randomized into the 2 treatment arms based on enrollment at the time Amendment 04 was being released. Enrollment was completed on 05-SEP-2018.

5.3 Beginning and End of Study Definition

The overall trial begins when the first participant signs the informed consent form (ICF). The overall trial ends when the last participant completes the last study-related phone-call or visit, withdraws from the trial 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 Trial Termination

The clinical trial 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 trial population as a whole is unacceptable. In addition, further recruitment in the trial or at (a) particular trial site(s) may be stopped due to insufficient compliance with the protocol, GCP and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

5.4 Scientific Rationale for Study Design

5.4.1 Rationale for Endpoints

5.4.1.1 Efficacy Endpoints

NOTE: As of Amendment 05, data for efficacy endpoints, including disease assessments based on imaging, are no longer being collected. Imaging, performed per local standard of care, will be assessed by the investigator/site radiologist; data will not be collected and transmission of images for central review is no longer required.

This study will use a primary endpoint of ORR, as outlined in Section 4.

ORR by RECIST 1.1 criteria as assessed by BICR is considered preliminary evidence of efficacy and is a primary endpoint for this Phase 2 study.

OS, PFS and DOR are secondary endpoints for this study.

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

PFS is an acceptable measure of clinical benefit for a late stage study that demonstrates superiority of a new antineoplastic therapy, especially if the magnitude of the effect is large and the therapy has an acceptable risk/benefit profile. The use of BICR and RECIST 1.1 to assess PFS is typically considered acceptable by regulatory authorities. Images will be read by a central imaging vendor blinded to treatment assignment to minimize bias in the response assessments. In addition, the final determination of radiologic progression will be based on the central assessment of progression, rather than a local site assessment. Real time determination of radiologic progression as determined by central review will be communicated to the site

DOR by RECIST 1.1 criteria and assessed by BICR is a commonly accepted endpoint by both regulatory authorities and the oncology community.

The BICR consists of a group of highly qualified radiologists contracted by the central imaging vendor who are otherwise not involved in the study. The methodology of the BICR is described in the imaging review charter.

5.4.1.1.1 RECIST 1.1

RECIST 1.1 will be used by the BICR when assessing images for efficacy measures and by the local site when determining eligibility. 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 05, the use of iRECIST is discontinued. This section is no longer applicable. Participants with radiographic disease progression as determined by RECIST 1.1 by investigator assessment will discontinue from open-label pembrolizumab monotherapy; no confirmatory scans are required. However, if the participant is achieving a clinically meaningful benefit, an exception to continue with pembrolizumab monotherapy may be considered following consultation with MSD.

RECIST 1.1 will be adapted to account for the unique tumor response seen following treatment with pembrolizumab. 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. These findings support the need to apply a modification to RECIST 1.1 that takes into account the unique patterns of atypical responses in immunotherapy and enables treatment beyond initial radiographic progression, if the participant is clinically stable.

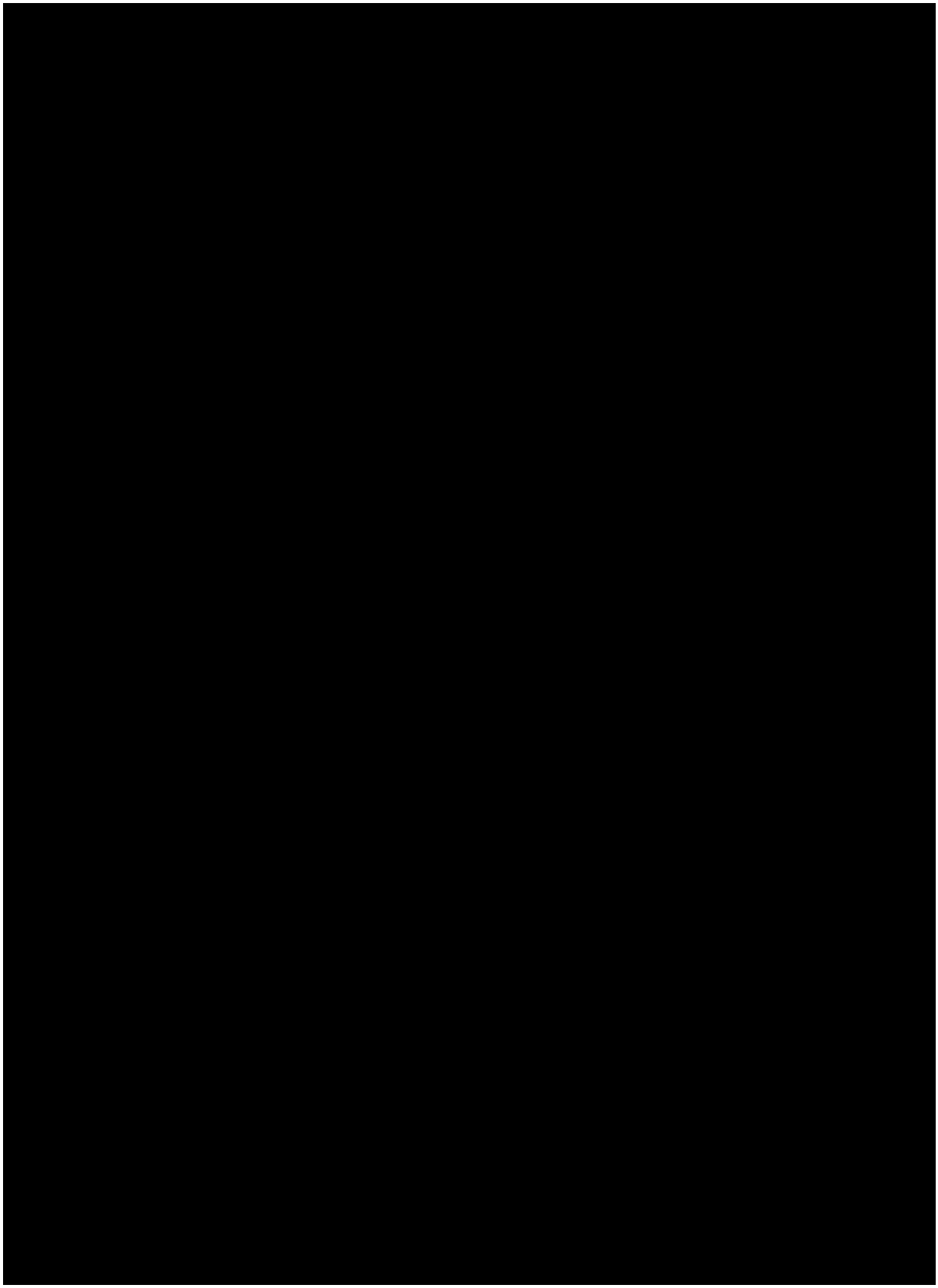
iRECIST assessment has been developed and published by the RECIST Working Group, with input from leading experts from industry and academia, along with participation from the US Food and Drug Administration and the European Medicines Agency [Seymour, L., et al 2017]. The unidimensional measurement of 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 site investigators to assess tumor response and progression, and make treatment decisions, [redacted].

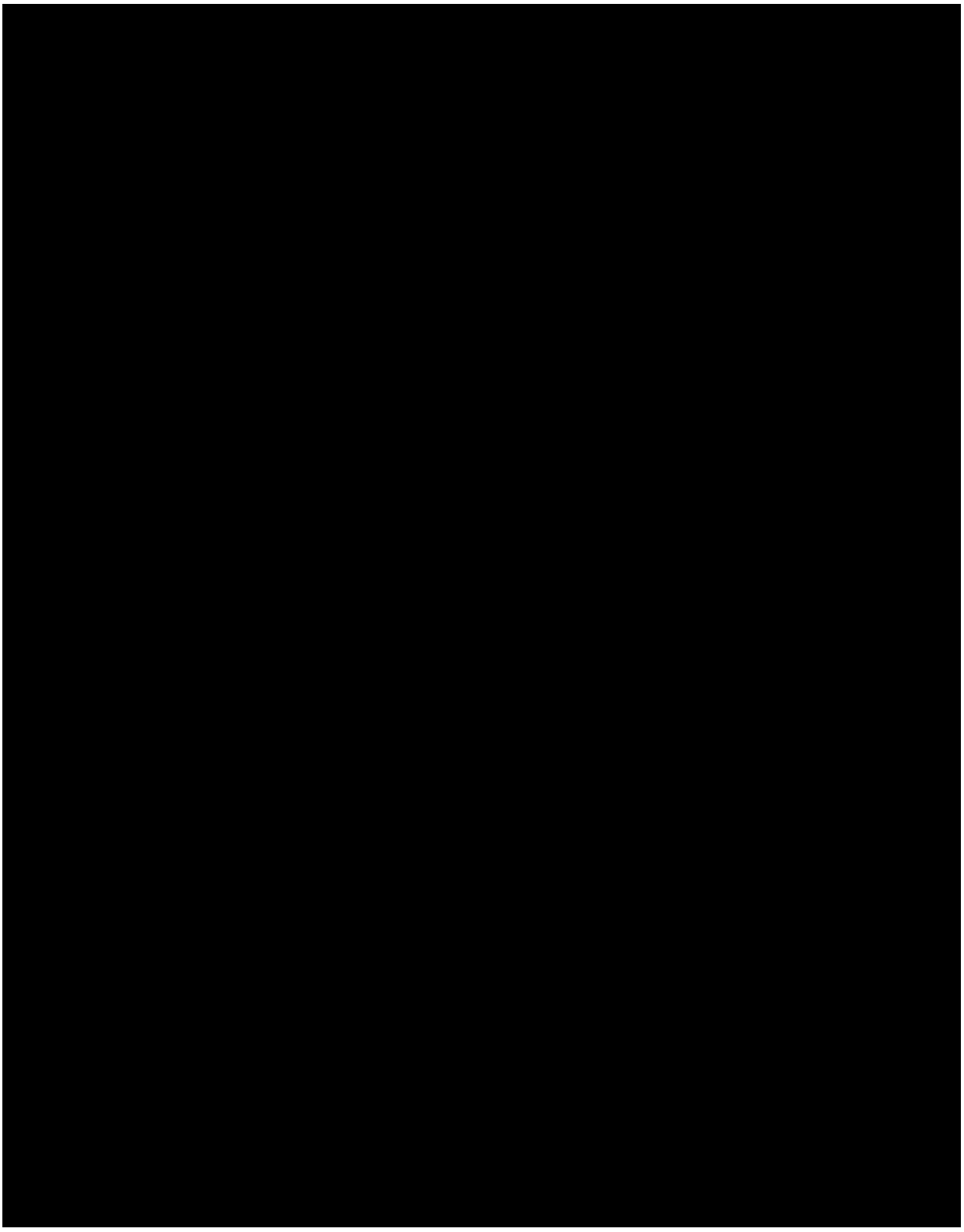
Refer to Section 9.2.1.6 for details on iRECIST.

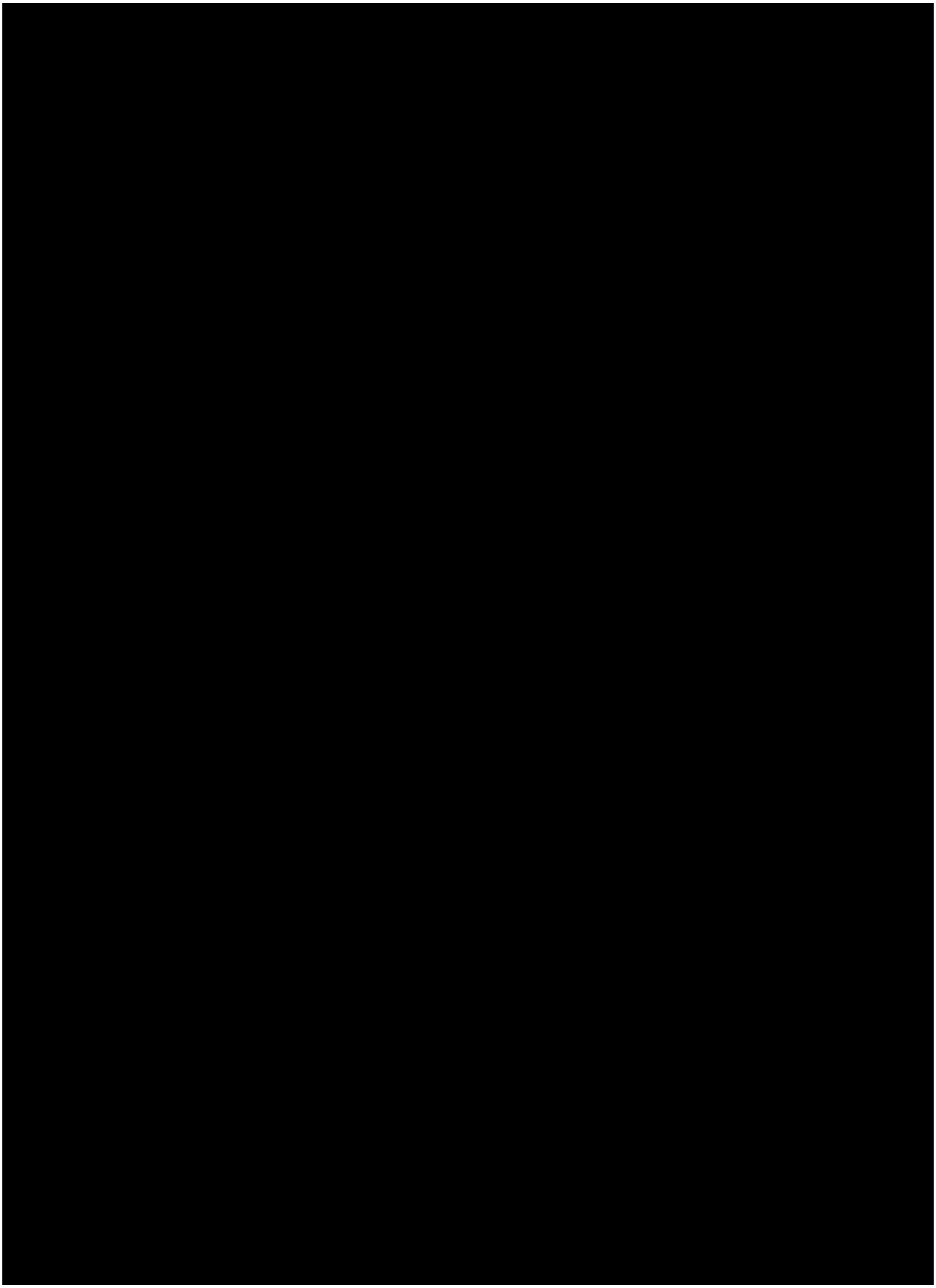
5.4.1.2 Safety Endpoints

Safety parameters commonly used for evaluating investigational systemic anticancer treatments are safety endpoints including, but not limited to, the incidence of, causality, severity, and outcome of AEs/ SAEs; and changes in vital signs and laboratory values. AEs will be assessed as defined by NCI CTCAE v4.0.

[redacted]







5.4.2 Rationale for the Use of Comparator/Placebo

NOTE: As of Amendment 05, epacadostat and matching placebo are removed from the study. This section is no longer applicable.

Based on the results of KEYNOTE-024, pembrolizumab monotherapy has become the SOC for treating stage IV NSCLC in patients with PD-L1 TPS ≥50% with no EGFR or ALK genomic tumor aberrations. The study resulted in a significant PFS benefit for pembrolizumab over the SOC at the time (platinum-doublet therapy), with an HR of 0.50 (95% CI 0.37-0.68, p <0.001; median PFS 10.3 months [95% CI 6.7 not reached] with pembrolizumab and 6.0 months [95% CI 4.2-6.2] with platinum-doublet), as well as an OS benefit with an HR of 0.60 (95% CI 0.41-0.89, p=0.005; median OS was not reached in either treatment arm)[Reck, M., et al 2016].

The results from KEYNOTE-024 established pembrolizumab as 1L therapy for patients whose tumors have a TPS ≥50% and in whom EGFR or ALK-directed therapies are not indicated, and the regimen has received regulatory approval for this use by the FDA and EMA.

The use of an epacadostat matching placebo in combination with pembrolizumab will ensure the objectivity of the local Investigators' treatment decision and AE causality assessments, while still providing participants the SOC treatment.

5.5 Justification for Dose

5.5.1 Rationale for Dose and Regimen of Pembrolizumab

The planned dose of pembrolizumab for this study is 200 mg Q3W. Based on the totality of data generated in the Keytruda® development program, 200 mg Q3W is 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 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 vs 10 mg/kg Q3W (KN001 B2, KN001 D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W vs 10 mg/kg Q2W (KN001 B3, KN001 F2, and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-/exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Secondly, a physiologically-based PK 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.

5.5.2 Rationale for Dose and Regimen of Epacadostat in Combination with Pembrolizumab

NOTE: As of Amendment 05, this section is no longer applicable.

The dose selected for epacadostat for the current study was formed on the basis of a well-tolerated safety profile as monotherapy and in combination with pembrolizumab, efficacy evidenced by robust, durable responses, and optimal target inhibition of IDO1 based on nonclinical models.

The first-in-human study INCB 24360-101 evaluated the pharmacodynamic effects of epacadostat dose/exposure on the tryptophan pathway using an ex vivo assay optimized for determining the inhibition of the metabolism of tryptophan to kynurenine by IDO1. Epacadostat treatment produced significant dose-dependent reductions in plasma kynurenine levels and plasma kynurenine/tryptophan ratios at all doses and in all participants. Near-

maximal changes were observed at doses of epacadostat ≥100 mg PO BID with >80% to 90% inhibition of IDO1 achieved throughout the dosing period [Beatty, G. L., et al 2017].

In the Phase 1 portion of ECHO-202/KEYNOTE-37, epacadostat doses of 25 mg, 50 mg, and 100 mg PO twice daily (BID) in combination with pembrolizumab 2 mg/kg IV every 3 weeks (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. Reductions in tumor burden were seen in 14 of 19 evaluable melanoma participants across doses of epacadostat 25 mg BID to 100 mg BID in combination with pembrolizumab 2 mg/kg and 200 mg fixed dose [Gangadhar, T. C., et al 2015]. Objective responses were observed in all tumor types and the majority are durable; this combination has been well tolerated with rates of irAEs that are similar to pembrolizumab monotherapy and low rates of treatment discontinuation due to irAEs [Gangadhar, T. C., et al 2017] [Hamid, O., et al 2017].

[redacted]

6. Study Population

Male/female participants with metastatic NSCLC, who express high levels of PD-L1 (TPS ≥50%), have received no systemic anti-cancer therapy for their metastatic NSCLC, and are at least 18 years of age 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. Have a histologically or cytologically confirmed diagnosis of stage IV (AJCC version 8 or current version as applicable) NSCLC.
2. Have confirmation that EGFR, ALK, or ROS1 directed therapy is not indicated as primary therapy (documentation of absence of tumor activating EGFR mutations

AND absence of ALK and ROS1 gene rearrangements OR presence of a KRAS mutation).

   a. If participant's tumor is known to have a predominantly squamous histology, molecular testing for EGFR mutation and ALK and ROS1 translocations will not be required, as this is not part of current diagnostic guidelines.

3. Have measurable disease based on RECIST 1.1 as determined by the local site.

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

4. Tumor tissue that demonstrates PD-L1 expression in ≥50% of tumor cells (TPS ≥50%) as assessed by IHC at a central laboratory.

   a. Assessment of PD-L1 expression must be made from provided archival tumor tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated. Formalin-fixed, paraffin-embedded tissue blocks are preferred to slides. Newly obtained biopsies are preferred to archived tissue.

Demographics

5. Be ≥18 years of age on the day of signing informed consent.
6. Have a life expectancy of at least 3 months.
7. Have an ECOG performance status of 0 or 1 within 7 days prior to the first dose of study treatment but before randomization.

Male participants:

8. 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 study treatment and 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:

9. 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 study treatment.
   Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the participant.

Informed Consent

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

Laboratory Values

11. Have adequate organ function as indicated by the laboratory values in Table 1. Specimens must be collected and reviewed within 10 days prior to the start of study treatment.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematologic	
Absolute neutrophil count	≥1500/µL
Platelets	≥100 000/µL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L[a] without a red blood cell transfusion within 2 weeks of the screening test
Renal	
Serum creatinine OR Measured or calculated CrCl [b] (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN **OR** ≥30 mL/min for participants with creatinine levels >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤1.5 × ULN **OR** direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN. If there is no institutional ULN, then direct bilirubin must be < 40% of total bilirubin to be eligible. Note: In no case can the total bilirubin exceed 3 x ULN.
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT) or partial thromboplastin time (PTT)[c]	≤1.5 × ULN unless the participant is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

Note: This table includes eligibility-defining laboratory value requirements for treatment.

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

b. CrCl should be calculated per institutional standard.

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

Abbreviations: ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); aPTT= activated partial thromboplastin time; AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); CrCl=creatinine clearance; GFR=glomerular filtration rate; INR=international normalized ratio; PT= prothrombin time; PTT=partial thromboplastin time; ULN=upper limit of normal.

6.2 Exclusion Criteria

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

Medical Conditions

1. Has known untreated central nervous system (CNS) metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable (without evidence of progression by imaging for at least 4 weeks prior to the first dose of study treatment), clinically stable, and have not required steroids for at least 14 days before first dose of study treatment.
2. Has a history of (non-infectious) pneumonitis that required systemic steroids or current pneumonitis/interstitial lung disease.
3. Has symptomatic ascites or pleural effusion. A participant who is clinically stable following treatment for these conditions (including therapeutic thoraco- or paracentesis) is eligible.
4. Has a known history of an additional malignancy, except if the participant has undergone potentially curative therapy with no evidence of that disease recurrence for 5 years since initiation of that therapy.
    a. Note: The time requirement for no evidence of disease for 5 years does not apply to the NSCLC for which a participant is enrolled in the study. The time requirement also does not apply to participants who underwent successful definitive resection of basal cell carcinoma of the skin, superficial bladder cancer, squamous cell carcinoma of the skin, in situ cervical cancer, or other in situ cancers.
5. Has an active autoimmune disease that has required systemic treatment in past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is allowed.
6. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (doses exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior the first dose of study treatment.
7. Has had an allogeneic tissue/solid organ transplant.
8. Has a known history of human immunodeficiency virus (HIV) infection. HIV testing is not required unless mandated by the local health authority.
9. Has known history of or is positive for active Hepatitis B (HBsAg reactive) or has active Hepatitis C (HCV RNA). Note: Testing must be performed to determine eligibility.
    a. HBV DNA must be undetectable and HBsAg negative at screening.
    b. Hepatitis C antibody testing is allowed for screening purposes in countries where HCV RNA is not part of SOC. In these cases, HCV antibody positive participants will be excluded.

c. Participants who have had definitive treatment for HCV are permitted if HCV RNA is undetectable at screening.

10. Has a history of a gastrointestinal condition or procedure that in the opinion of the Investigator may affect oral drug absorption.
11. Has a history or presence of an abnormal electrocardiogram (ECG) that, in the Investigator's opinion, is clinically meaningful. Screening QTc interval >480 msec is excluded (corrected by Fridericia or Bazett formula). In the event that a single QTc is >480 msec, the participant may enroll if the average QTc for 3 ECGs is <480 msec.
12. Has clinically significant cardiac disease, including unstable angina, acute myocardial infarction within 6 months from Day 1 of study drug administration, or New York Heart Association Class III or IV congestive heart failure. Medically controlled arrhythmia stable on medication is permitted.
13. Has a known history of active tuberculosis (TB; Bacillus tuberculosis).
14. Has an active infection requiring systemic therapy.
15. Has known psychiatric or substance abuse disorders that would interfere with the participant's cooperation for the requirements of the study.
16. Previously had a severe hypersensitivity reaction to treatment with a monoclonal antibody or has a known sensitivity to any component of epacadostat or pembrolizumab.
17. WOCBP who has a positive urine pregnancy test within 72 hours before the first dose of study treatment. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
    a. 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 participant to start receiving study treatment.
18. 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 study treatment.

Prior/Concomitant Therapy

19. Has received prior systemic chemotherapy or other targeted or biological anti-neoplastic therapy for their metastatic NSCLC.
    a. Note: Prior treatment with chemotherapy and/or radiation as part of neoadjuvant/adjuvant therapy is allowed as long as therapy was completed at least 6 months prior to the diagnosis of metastatic NSCLC.
20. Has received prior treatment with pembrolizumab or any other anti-PD-1, anti-PD-L1, anti-PD-L2 agent, with epacadostat or any anti-IDO1 agent, or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137, GITR).

21. Has received radiotherapy within 14 days before the first dose of study treatment or received lung radiation therapy of >30 Gy within 6 months before the first dose of study treatment.
    a. Note: Participants must have recovered from all radiation-related toxicities to grade 1 or less, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease.
22. Is receiving systemic steroid therapy ≤7 days prior to the first dose of study treatment or receiving any other form of immunosuppressive medication.
    a. Corticosteroid use after randomization is allowed for management of AEs, SAEs, and events of clinical interest (ECIs), as a pre-medication for IV contrast, or if considered necessary for a participant's medical condition.
    b. Participants who receive daily steroid replacement therapy ≤10 mg prednisone or equivalent are exempt.
23. Has received a live vaccine within 30 days prior to the first dose of study treatment.
    a. 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.
24. Has any history of Serotonin Syndrome after receiving serotonergic drugs.
25. 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 7.7.2.

Prior/Concurrent Clinical Study Experience

26. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of study treatment.
    a. Note: Participants who have entered the Follow-up phase of an investigational study may participate as long as it has been >4 weeks after the last dose of the previous investigational agent.

Other Exclusions

27. 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 ability to participate 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.

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.

[redacted]

6.3.2 Contraception

Pembrolizumab may have adverse effects on a fetus *in utero*.

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 medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study, participants of childbearing potential must adhere to the contraception requirements from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of study medication. 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 with pembrolizumab or epacadostat, 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 an SAE (eg, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The 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

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

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized. 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 treatments 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 treatments to be used in this trial are outlined below in Table 2.

NOTE: As of Amendment 05, epacadostat and matching placebo are removed from the study. This section has been updated accordingly.

Table 2 Study Treatments

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Treatment Period	Use	Sourcing
Pembrolizumab 25 mg/mL solution for infusion	200 mg	Q3W	IV infusion	Day 1 of each cycle for up to 35 administrations	Experimental / Standard of Care	Central
IV=intravenous; Q3W=every 3 weeks.						

All supplies indicated in Table 2 will be provided per the 'Sourcing' column depending upon local country operational 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 (Escalation/Titration/Other)

7.2.1 Dose Modification for Immune-related AEs

NOTE: As of Amendment 05, text in this section relating to dose modification of epacadostat/matching placebo is no longer applicable. This section has been updated accordingly.

Dose modification and toxicity management for immune-related AEs (irAEs) associated with pembrolizumab should be managed as follows.

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These 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, 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, or skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids.

Table 3 summarizes the irAE dose modification actions for pembrolizumab.

Except in cases of emergency, it is recommended that the Investigator consult with the medical monitor (or other representative of MSD) before temporarily interrupting therapy for reasons other than protocol-mandated medication hold.

Table 3 Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab

NOTE: As of Amendment 05, this table has been replaced with the current guidelines for pembrolizumab.

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 has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab must 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.

Immune-related AEs	**Toxicity grade or conditions (CTCAEv4.0)**	**Action taken to pembrolizumab**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
Pneumonitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	Monitor participants for signs and symptoms of pneumonitis Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue		

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
AST / ALT elevation or Increased Bilirubin	Grade 2	Withhold	Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 or 4	Permanently discontinue	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	Initiate insulin replacement therapy for participants with T1DM Administer anti-hyperglycemic in participants with hyperglycemia	Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	Administer corticosteroids and initiate hormonal replacements as clinically indicated	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or Permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	Monitor for signs and symptoms of thyroid disorders
Nephritis and renal dysfunction	Grade 2	Withhold	Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper	Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		

Immune-related AEs	**Toxicity grade or conditions (CTCAEv4.0)**	**Action taken to pembrolizumab**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
All Other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Guillain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		
1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. NOTE: For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).				

7.2.2 Infusion Reaction Dose Modifications

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 4.

Table 4 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 hours	**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 treatment with pembrolizumab.**	Participant may be premedicated 1.5 hr (± 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 treatment with pembrolizumab.**	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to CTCAE at http://ctep.cancer.gov CTCAE=Common Terminology Criteria for Adverse Events; IV=intravenous; NCI=National Cancer Institute; NSAIDs=nonsteroidal anti-inflammatory drugs; PO=oral.		

7.2.3 Procedures for Participants Exhibiting Serotonin Syndrome

NOTE: As of Amendment 05, this section has been updated to reflect the removal of epacadostat from the study and updated information regarding the risks of SS with the use of epacadostat.

There is a rare chance that epacadostat could cause an increase in serotonin levels in the brain that might trigger serotonin syndrome (SS) [Boyer, E. W. 2005], when administered in combination with other serotonergic agents. Selective serotonin reuptake inhibitors (SSRIs), selective serotonin/norepinephrine reuptake inhibitors (SNRIs), and MAOIs are permitted in the study. Due to the results of a preclinical study specifically evaluating the effect of epacadostat on the brain ECF concentrations of serotonin with linezolid [Zhang, Y., et al 2016], and the clinical experience with related medications (eg, SSRIs/SNRIs) that suggest that SS is low risk, the use of MAOIs is not prohibited in the current study.

Serotonin syndrome usually manifests with autonomic changes, mental status changes, and neurological findings. These mild, moderate, and severe signs and symptoms of SS (summarized in Table 5) should be evaluated in the context of possible comorbid conditions as well.

The following procedures will be implemented if participants exhibit the signs/symptoms of SS, including tremor; hyperreflexia; spontaneous, ocular, or inducible clonus; together with agitation, fever, diaphoresis, or muscle rigidity:

- Immediately interrupt all study treatment administration.

- Immediately interrupt any SSRI, SNRI, or MAOI 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 SS are excluded, pembrolizumab administration may be resumed unless other AE management guidelines apply for the specific event.
- If participant chooses to withdraw from the study, or must restart treatment with SSRI, SNRI, or MAOI, the participant should be scheduled for a Follow-up Visit. Treatment with SSRI, SNRI, or MAOI may be initiated 2 weeks after resolution of signs and symptoms of SS.
- If a participant had experienced moderate or severe unconfounded SS in the opinion of the investigator, without concomitant SSRI, SNRI, or MAOI usage, or serotonergic concomitant medications, pembrolizumab administration may be resumed.

Table 5 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, E. W. 2005]

7.2.4 Interruptions Unrelated to Adverse Events

Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons not related to study treatment (eg, elective surgery, unrelated medical events, participant vacation, and/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.

7.3 Method of Treatment Assignment

Treatment randomization will occur centrally using an interactive voice response system/integrated web response system (IVRS/IWRS). Participants will be assigned randomly in a 1:1 ratio to pembrolizumab + epacadostat or pembrolizumab + matching placebo.

Study treatment must begin as close to treatment randomization as possible but no more than 3 days later. If this cannot occur due to an AE or other reason, please contact MSD and document the reason in the participant's medical record.

7.3.1 Stratification

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

- Predominant tumor histology: squamous vs non-squamous

7.4 Blinding

NOTE: As of Amendment 05, blinding is no longer applicable as epacadostat and matching placebo have been removed from the study. All participants will receive open-label study treatment. This section is no longer applicable.

A double-blinding technique with in-house blinding will be used. Epacadostat and placebo will be packaged identically so that the blind is maintained. The participant, the investigator, the Sponsor, MSD study personnel, or delegates who are involved in the study treatment administration or clinical evaluation of the participants are unaware of the group assignments.
Pembrolizumab, which will be dosed to all participants in both treatment arms, will not be blinded.

See Section 9.1.11 for a description of the method of unblinding a participant during the study, should such action be warranted.

7.5 Preparation/Handling/Storage/Accountability

7.5.1 Dose Preparation

NOTE: As of Amendment 05, epacadostat and matching placebo are removed from the study. This section has been updated accordingly.

Details on preparation and administration of IV pembrolizumab are provided in the Pharmacy Manual.

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

Interruptions from the protocol-specified treatment plan for greater than 12 weeks from the last dose require consultation between the Investigator and MSD and written documentation of the collaborative decision on participant management.

7.6.1 Administration and Compliance of Pembrolizumab

Administration of IV pembrolizumab will be witnessed by the investigator and/or study staff. The total volume of study treatment infused will be compared to the total volume prepared to determine compliance with each dose administered. Pembrolizumab will be administered on an out-patient basis.

Instructions for preparing and administering pembrolizumab are provided in the Pharmacy Manual.

7.6.2 Administration and Compliance of Epacadostat or Matching Placebo

NOTE: As of Amendment 05, epacadostat and matching placebo are removed from the study. This section is no longer applicable and has been deleted.

7.7 Concomitant Therapy

7.7.1 Acceptable Concomitant Therapies

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 and prohibited medications in this study. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter, herbal supplements, and IV medications and fluids. If changes occur during the study period, documentation of drug dosage frequency, route, and date will also be included on the CRF.

Palliative and supportive care is permitted during the course of the study for underlying medical conditions and management of symptoms. Surgery for tumor control is not permitted during the study. Palliative radiotherapy is permitted to a limited number of lesions if considered medically necessary by the treating physician as long as the lesions are NOT a RECIST 1.1-defined target lesion. Study treatment should be held during the course of palliative radiotherapy and should be resumed no earlier than the next scheduled administration of study treatment. The specifics of the radiation treatment, including the location, will be recorded.

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

7.7.2 Prohibited Concomitant Therapies

NOTE: As of Amendment 05, this section is updated to reflect the removal of epacadostat from the study and current safety information for epacadostat.

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medication or vaccination specifically prohibited during the study, 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.

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

- Antineoplastic systemic chemotherapy or biological therapy not specified in this protocol.
    - Note: denosumab is permitted.
- Immunotherapy not specified in this protocol.
- Investigational agents other than pembrolizumab.
- Oncologic surgery for tumor control.

- Radiation therapy for disease control.
    - Note: Radiation therapy to symptomatic lesions or to the brain may be allowed at the Investigator's discretion, provided the lesions were not previously defined by the site as target lesions.
- Live vaccines within 30 days prior to 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, chickenpox, yellow fever, nasal seasonal flu, nasal H1N1 flu, rabies, BCG, and typhoid.
- Prolonged therapy with systemic glucocorticoids (>7 days) for any purpose other than to modulate symptoms from an AE, SAE, or ECI or for use as a pre-medication in participants with a known history of an IV contrast allergy administered as part of computed tomography (CT) radiography. Brief, limited use of systemic corticosteroids (≤7 days) are permitted where such use is considered SOC (eg, for chronic obstructive pulmonary disease [COPD] exacerbation).
    - Replacement doses of steroids (for example, prednisone 10 mg daily) are permitted while on study, as is the use of local steroid injections and topical steroids.

Participants who, in the assessment of the Investigator, require the use of any of the aforementioned treatments for clinical management should be removed from treatment but continue in study for assessment of disease status and survival.

The exclusion criteria describe other medications which are prohibited in this study.

7.7.3 Restricted Medications

NOTE: As of Amendment 05 and removal of epacadostat from the study, this section is no longer applicable and has been deleted.

7.7.4 Rescue Medications & Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating Investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined in Section 7.2.1.

7.7.4.1 Systemic Corticosteroid Use

Systemic corticosteroids are permitted in the following situations:

- To mediate potential immune-related AEs as guided in Table 3
- As pre/post-medication to prevent AEs associated with IV contrast.

- Brief, limited use of systemic corticosteroids (≤7 days) are permitted where such use is considered SOC (eg, for COPD exacerbation).
    - Replacement doses of steroids (for example, prednisone 10 mg daily) are permitted while on study, as is the use of local steroid injections and topical steroids.

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

NOTE: As of Amendment 05, epacadostat and matching placebo are removed from the study; thus, procedures related to emergency unblinding of these treatments are no longer applicable and have been deleted.

7.10 Standard Policies

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

"You have participated in a trial conducted by MSD under the sponsorship of Incyte. This is to advise you that you were among those who received a look-alike tablet created by the Sponsor to resemble the drug epacadostat as much as possible. You did not receive the active drug epacadostat as manufactured by Incyte Corporation."

NOTE: As of Amendment 05, epacadostat and matching placebo are removed from the study; thus, procedures related to emergency unblinding of these treatments are no longer applicable and have been deleted.

8. Discontinuation/Withdrawal Criteria

8.1 Discontinuation of Study Treatment

NOTE: As of Amendment 05, this section has been updated. Participants will be discontinued from the study after completing the Safety Follow-up Visit.

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 treatment period will still continue to participate in the study as specified in Section 2 and Section 9.9.3.

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 as assessed by the investigator per RECIST 1.1, as outlined in Section 9.2.1 (except if MSD approves treatment continuation).
- Unacceptable adverse experiences as described in Section 7.2.1.
- The participant interrupts study treatment administration for more than 12 consecutive weeks, 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.
- Noncompliance with study treatment or procedure requirements.
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active systemic treatment.
- Completion of 35 treatment administrations (approximately 2 years) with pembrolizumab.
- Discontinuation of treatment may be considered for participants who have attained a CR by local Investigator assessment and have been treated for at least 8 administrations of pembrolizumab and received at least 2 administrations beyond the date when the initial CR was declared.

For participants who are discontinued from study treatment but continue to be monitored in the trial, see Section 2 and Section 9.9.3 for those procedures to be completed at each specified visit.

8.1.1 Second Course Phase

NOTE: As of Amendment 05, the Second Course Phase is removed and this section is no longer applicable and has been deleted.

8.2 Withdrawal from the Study

NOTE: As of Amendment 05, the Follow-up Phase and Survival Follow-up have been removed. This section has been updated accordingly.

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 including the procedures to be performed should a participant repeatedly fail to return

for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 9.1.10.

8.3 Lost to Follow Up

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

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, 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.
- 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.

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. The participant or his/her legally acceptable representative will be asked to sign consent if treatment is warranted to continue as per investigator at the point of initial radiographic disease progression.

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 trial. 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, participants will be given a Serotonin Syndrome (SS) information card listing signs and symptoms of SS. This information card instructs participants to seek immediate medical care if any of the listed symptoms are observed.

9.1.5 Medical History

A medical history will be obtained by the investigator or qualified designee.

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 30 days before the first dose of study medication. A complete history of the participant's treatment of NSCLC (if any) will be recorded separately and not listed as a prior medication.

9.1.6.2 Concomitant Medications

The Investigator or qualified designee will record medication, if any, taken by the participant during the study through the Safety Follow-up Visit.

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

NOTE: As of Amendment 05, text in this section relating to epacadostat/matching placebo is no longer applicable and has been deleted.

Administration of pembrolizumab will be witnessed by the investigator and/or study staff.

Study treatment should begin on the day of treatment allocation/randomization or as close as possible to the date on which the participant is allocated/assigned.

9.1.9.1 Timing of Dose Administration

9.1.9.1.1 Timing of Dose Administration of Pembrolizumab

Study treatment with pembrolizumab should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed in the SoA (Section 2). All study treatments will be administered on an outpatient basis. Study treatment of pembrolizumab may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons except for C1D1, where the window is +3 days from randomization.

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

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

9.1.9.1.2 Timing of Dose Administration of Epacadostat or Matching Placebo

NOTE: As of Amendment 05, this section is no longer applicable and has been deleted.

9.1.10 Withdrawal/Discontinuation

NOTE: As of Amendment 05, Survival Follow-up has been discontinued. This section has been updated accordingly.

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 trial, all applicable activities scheduled for the Discontinuation Visit should be performed at the time of withdrawal. Any adverse events which are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 9.3 - Adverse Events.

9.1.11 Participant Blinding/Unblinding

NOTE: As of Amendment 05, the study will be unblinded and study treatment will continue as open-label. Text related to epacadostat/matching placebo and emergency unblinding in this section is no longer applicable and has been deleted.

Pembrolizumab is an open-label study treatment.

9.1.12 Calibration of Critical Equipment

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

Critical Equipment for this trial includes:

- Laboratory equipment – as required for inclusion labs and safety assessments
- Imaging equipment – as required for efficacy assessments

9.2 Efficacy Assessments

9.2.1 Tumor Imaging and Assessment of Disease

NOTE: As of Amendment 05, central review of imaging (BICR) and iRECIST are no longer applicable. Disease assessments will be performed by the site investigator/radiology assessment per local standard of care. This section has been updated accordingly.

Tumor imaging is strongly preferred to be acquired by CT. For the abdomen and pelvis, contrast-enhanced magnetic resonance imaging (MRI) may be used when CT with iodinated contrast is contraindicated or when local practice mandates it. MRI is the strongly preferred modality for imaging the brain. The same imaging technique regarding 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.

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

Treatment should continue until PD has been determined by investigator-assessed disease progression by RECIST 1.1; no confirmatory scans are required. However, if the participant is achieving a clinically meaningful benefit, an exception to continue with pembrolizumab monotherapy may be considered following consultation with the MSD.

9.2.1.1 Initial Tumor Imaging

Initial tumor imaging at screening must be performed within 30 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. The screening images must be submitted to the central imaging vendor for retrospective review.

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 30 days prior to the date of randomization and can be assessed by the central imaging vendor.

Baseline brain imaging, while not required, should be performed per the local standard of care, especially if the participant was previously treated for CNS metastases. 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 05, central review of imaging (BICR) and iRECIST are no longer applicable. All imaging will be performed as per local standard of care guidelines; however, the data will not be collected. This section has been updated accordingly.

No on-study imaging is mandated during the treatment phase. All imaging for disease assessment will be performed by the site investigator/radiology assessment as per standard of care for the disease and local guidelines; only the date of scans performed as per standard of care needs to be documented in the eCRF.

Imaging can be performed until PD is identified by the investigator, the start of new anti-cancer treatment, withdrawal of consent for imaging, or death, whichever occurs first.

Participants who have disease progression as assessed by the investigator per RECIST 1.1 will discontinue the treatment, unless treatment beyond progression is approved by MSD.

9.2.1.3 End of Treatment and Follow-Up Imaging

NOTE: As of Amendment 05, there is no protocol-specified imaging at end of treatment and no follow-up imaging is required. This section is no longer applicable and has been deleted.

9.2.1.4 Second Course Phase Tumor Imaging

NOTE: As of Amendment 05, the Second Course Phase is eliminated. This section is no longer applicable and has been deleted.

9.2.1.5 RECIST 1.1 Assessment of Disease

NOTE: As of Amendment 05, central review of imaging (BICR) is no longer applicable. All imaging will be performed as per local standard of care guidelines; however, the data will not be collected. This section has been updated accordingly.

RECIST 1.1 will be applied 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

NOTE: As of Amendment 05, iRECIST is no longer applicable and has been deleted from this section. All imaging will be performed as per local standard of care guidelines per RECIST 1.1. Participants with radiographic disease progression as determined by RECIST 1.1 by investigator assessment will discontinue from open-label pembrolizumab monotherapy; no confirmatory scans are required. However, if the participant is achieving a clinically meaningful benefit, an exception to continue with pembrolizumab monotherapy may be considered following consultation with the MSD.

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.

Adverse events will not be collected for participants during the pre-screening period (for determination of archival tissue status) as long as that participant has not undergone any protocol-specified procedure or intervention. If the participant requires a blood draw, fresh tumor biopsy etc., the participant is first required to provide consent to the main study and AEs will be captured according to guidelines for standard AE reporting.

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 study, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

- All AEs from the time of 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.
- All pregnancies and exposure during breastfeeding, from the time of treatment allocation/randomization through 120 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy must be reported by the investigator.
- Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately to the Sponsor if the event is considered 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 6.

Table 6 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 - subject 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 - subject 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, i.e., 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 a 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 that upon review is not progression of the cancer under study will be forwarded to MSD global safety as an 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).

3. Serotonin syndrome. The signs and symptoms of serotonin syndrome are described in Section 7.2.3.

9.4 Treatment of Overdose

NOTE: As of Amendment 05, epacadostat is removed from the study, and text relating to overdose of epacadostat is no longer applicable.

In this study, an overdose is defined as any dose ≥1000 mg (5 times the dose) of pembrolizumab or ≥1000 mg daily of epacadostat. No specific information is available on the treatment of 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.

If an AE is associated with ("results from") the overdose of study treatment, the AE is reported as an 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 by the investigator within 24 hours to MSD either by electronic media or paper. Electronic reporting procedures can be found in the electronic data collection data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

9.5 Safety

Details regarding specific safety procedures/assessments to be performed in this study are provided below. The total amount of blood/tissue to be drawn/collected over the course of the study (from 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 Trial Procedures Manual.

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. 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 the 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 vital signs at screening, prior to the administration of each dose of study treatment, and during the Follow-up Period as specified in the SoA. Vital signs include temperature, pulse, respiratory rate, weight, and blood pressure. Height will be measured at screening only.

9.5.3 Electrocardiograms

Baseline ECGs will be obtained at screening for all participants. Additional ECGs at EOT are only required if according to local standard of care or as clinically indicated. At SELECT centers only, additional ECGs will also be obtained at C1D1 predose and approximately 2 hours (±15 minutes) after the first dose of epacadostat, and C2D1 predose and approximately 2 hours (±15 minutes) after administration of epacadostat. The ECG measurement should always be performed prior to the [redacted] sample blood draw if both are scheduled at the same nominal planned timepoint. Clinically significant abnormal findings observed prior to signing the ICF should be recorded as medical history. Clinically significant abnormal findings observed after signing the ICF should be recorded as an AE.

The 12-lead 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 medical monitor, as appropriate. The Fridericia (preferred) or Bazett correction method for calculating QTc will be used and recorded in the electronic case report form (eCRF).

9.5.4 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The Investigator or qualified designee will assess ECOG status at screening (within 7 days prior to the first dose but before randomization), prior to the administration of each dose of study treatment, and during the Follow-up Period as specified in the SoA. The ECOG performance status scale is described in Appendix 6.

9.5.5 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.

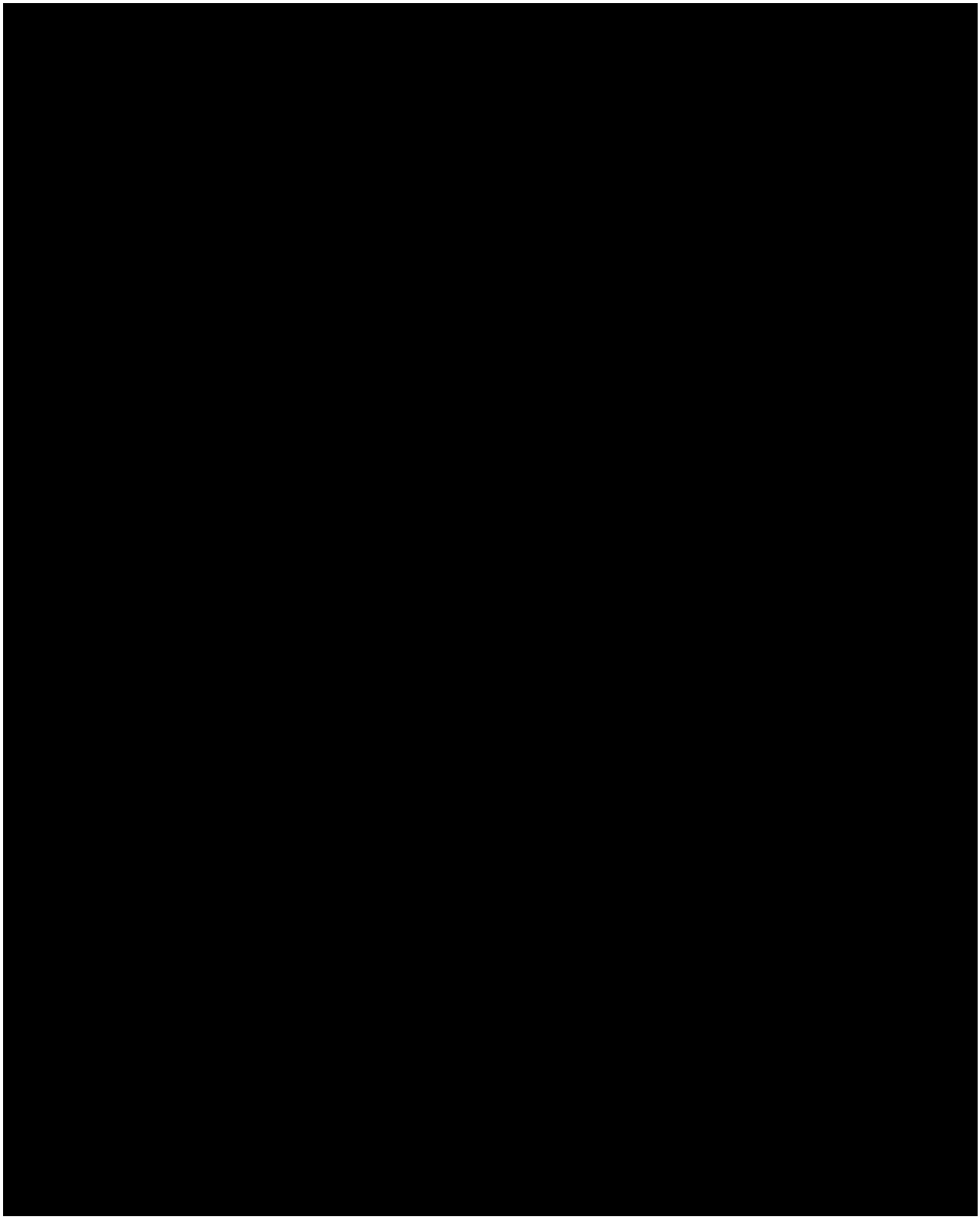
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in study participant 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 (eg, SLAB).
- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study 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.

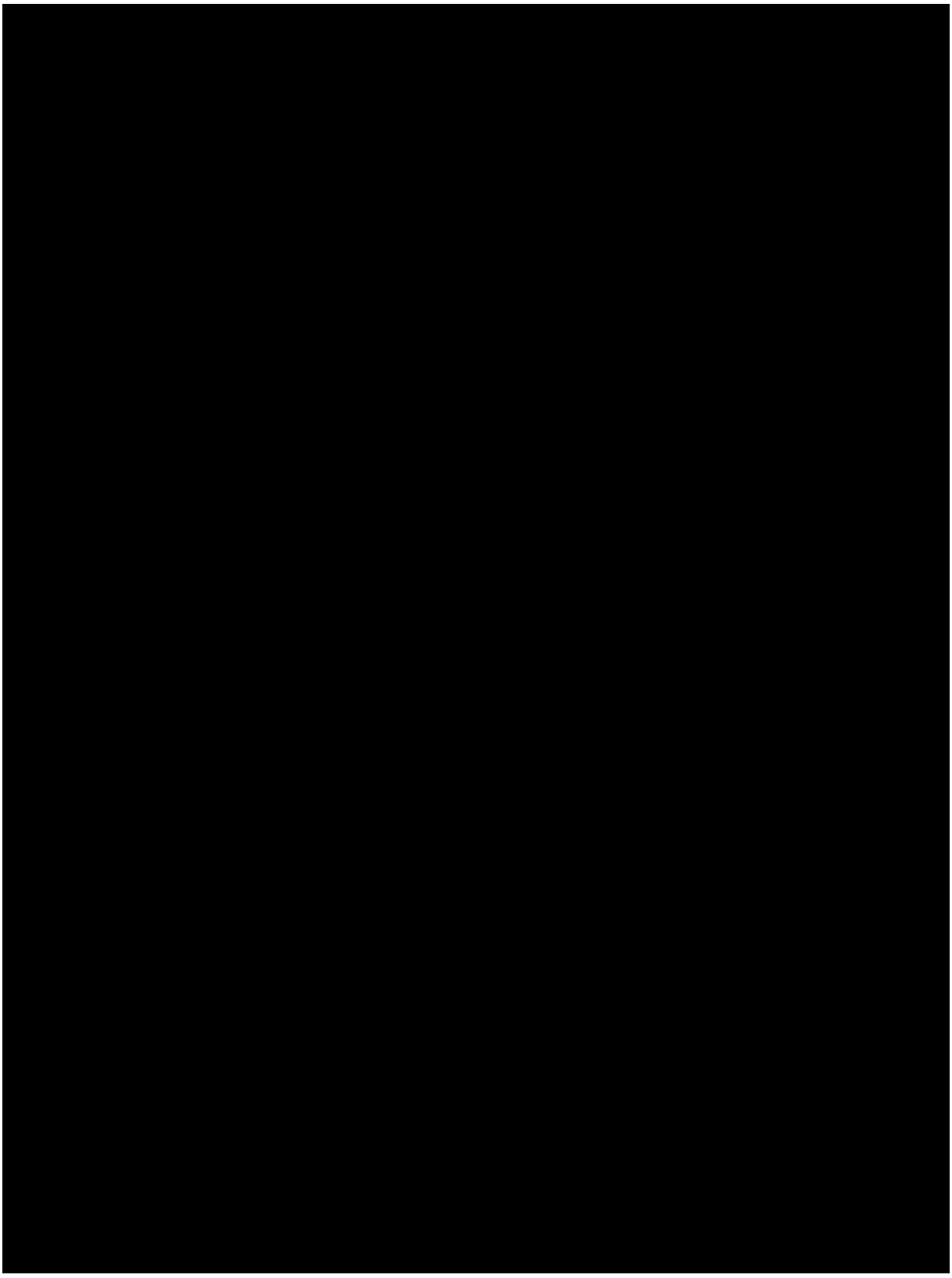
9.5.5.1 Laboratory Safety Evaluations (Hematology, Chemistry, Urinalysis)

Laboratory tests for hematology, chemistry, and urinalysis are specified in Appendix 2. Refer to the SoA for the timing of laboratory assessments.

9.5.5.2 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 the first dose of study treatment. Monthly pregnancy testing should be conducted as per local regulations where applicable. 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 or borderline-positive test result.





[redacted]

[redacted]

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 30 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 30 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 42 days prior to the first dose of study treatment.
- Evaluation of ECOG is to be performed within 7 days prior to the first dose of study treatment but before 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).

- Archival tumor sample collection is not required to be obtained within 30 days prior to the first dose of study treatment. Newly obtained tumor tissue may be obtained within 90 days of treatment initiation.

Participants may be rescreened after initially failing to meet the inclusion/exclusion criteria. 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.

NOTE: Enrollment was completed on 05-SEP-2018.

9.9.2 Treatment Phase

NOTE: As of Amendment 05, epacadostat and matching placebo are removed. This section has been updated accordingly.

Visit requirements are outlined in the SoA (Section 2). Specific procedure-related details are provided in Section 9.

Treatment with pembrolizumab will occur every 21 days (1 cycle) for up to 35 administrations (approximately 2 years). The maximum duration of the treatment phase is specified as 35 administration of pembrolizumab (approximately 2 years).

9.9.3 Discontinued Participants Continuing to be Monitored in the Study

9.9.3.1 Safety Follow-up Visit

NOTE: As of Amendment 05, 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. If the participant has a Discontinuation Visit ≥30 days after the last dose of study treatment, the Safety Follow-up Visit is not required.

A participant will be considered to have completed this study once they have attended this visit. Participants currently in Follow-up or 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.

9.9.3.2 Follow-up Visits

NOTE: As of Amendment 05, this section is no longer applicable and has been deleted. 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.

9.9.3.3 Survival Follow-up

NOTE: As of Amendment 05, this section is no longer applicable and has been deleted. 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 be performed as per Section 9.3.

9.9.3.4 Survival Status

NOTE: As of Amendment 05, this section is no longer applicable and has been deleted; survival data is no longer being collected.

9.9.4 Second Course Phase

NOTE: As of Amendment 05, this section is no longer applicable and has been deleted.

10. Statistical Analysis Plan

NOTE: The final analysis of the study was conducted as described below, with a data cutoff of 10-JAN-2019. Data from the final analysis showed the study did not meet the pre-specified primary endpoint of improvement in ORR for the combination of pembrolizumab plus epacadostat compared with pembrolizumab plus matching placebo. As of Amendment 05, the study will therefore stop collecting efficacy data, including central review of imaging. Thus, after study completion, only selected analyses as detailed in this section will be performed [redacted]

This section outlines the statistical analysis strategy and procedures for the study. If changes are made to primary and/or key secondary hypotheses or the statistical methods related to those hypotheses after the study has begun, but prior to any unblinding/final database lock, then the protocol will be amended (consistent with ICH Guideline E9). Changes to [redacted] other non-confirmatory analyses made after the protocol has been finalized, but prior to unblinding/final database lock, will be documented in a supplemental Statistical Analysis Plan (sSAP) and referenced in the Clinical Study Report (CSR) for the study. [redacted]

10.1 Statistical Analysis Plan Summary

Key elements of the Statistical Analysis Plan (SAP) are summarized in Table 9. The comprehensive plan is provided in Sections 10.2 through 10.12.

Table 9 Key Elements of the Statistical Analysis Plan

Study Design Overview	Phase 2 study of pembrolizumab + epacadostat vs pembrolizumab + placebo for first-line treatment of metastatic non-small cell lung cancer (NSCLC) in participants whose tumors express PD-L1 (TPS ≥50%)
Treatment Assignment	Approximately 148 participants will be randomized in a 1:1 ratio between two treatment arms: (1) pembrolizumab plus epacadostat and (2) pembrolizumab plus placebo. Stratification factor is predominant tumor histology (squamous vs non-squamous)
Analysis Populations	Efficacy: Intention to Treat (ITT) Safety: All Participants as Treated (APaT)
Primary Endpoints	• Objective response rate (ORR) per RECIST 1.1 based on BICR
Secondary Endpoints	• Progression-free survival (PFS) based on RECIST 1.1 as assessed by BICR. • Overall survival (OS). • Duration of response (DOR) based on RECIST 1.1 as assessed by BICR. • Safety and tolerability.
Statistical Methods for Key Efficacy Analyses	The primary hypothesis will be evaluated by comparing pembrolizumab plus epacadostat to pembrolizumab plus placebo in ORR using the stratified Miettinen and Nurminen method. The difference in PFS and OS will be evaluated using a stratified Log-rank test. The hazard ratio will be estimated using a stratified Cox regression model. Event rates over time will be estimated within each treatment group using the Kaplan-Meier method.
Statistical Methods for Key Safety Analyses	As of Amendment 05, 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.
Multiplicity	For this Phase 2 trial, the overall Type I error rate is strictly controlled at 5% (one-sided) for the primary analysis of ORR. If the primary hypothesis is rejected at the α=5% level (one-sided), then testing will continue to the key secondary hypothesis of PFS. Nominal p-value for other endpoints will be reported, where applicable.
Sample Size and Power	The planned sample size is approximately 148 participants with 74 participants in each arm. For the ORR test, based on all patients randomized with minimum 18 weeks of follow-up, the study has 81.7% power to detect a 20-percentage point difference in ORR for pembrolizumab+ epacadostat vs pembrolizumab+ placebo at α=5% (one-sided).

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 for study treatment assignment for this protocol and the randomization will be implemented in IVRS/IWRS.

An external DMC will be convened to review accumulating safety data to provide an opportunity to terminate the study early if there are concerns regarding safety. Treatment-level results of the safety analyses will be provided by the external unblinded statistician to the eDMC. The DMC responsibilities and review schedules will be outlined in the DMC charter. The recommendation of the DMC will be communicated to the Joint Executive Oversight Committee (EOC) and, in the event of a recommendation to halt the study early due to safety concerns, to the appropriate regulatory agencies. If the DMC recommends modifications to the design of the protocol or discontinuation of the study, the EOC and possibly other limited numbers of additional Sponsor/MSD personnel may be unblinded to results at the treatment level in order to act on these recommendations.

Participant-level unblinding to support regulatory filing, should one occur before the end of the study, will be restricted to a designated Sponsor/MSD team, who will have no other responsibilities associated with the study. The extent to which individuals are unblinded with respect to the results will be documented. Additional logistical details, revisions to the above plan, and data monitoring guidance will be provided in the DMC Charter.

10.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 4.0.

10.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated for within- and/or between-treatment differences are listed below. [redacted]

10.4.1 Efficacy Endpoints

Primary

Objective Response Rate: The proportion of participants who have a confirmed CR or PR per RECIST 1.1 based on BICR.

Secondary

Progression-free Survival: The time from randomization to the first documented PD per RECIST 1.1 based on BICR or death due to any cause, whichever occurs first. See Section 10.6.1 for the definition of censoring.

Overall Survival: The time from randomization to death due to any cause.

Duration of Response: The time from first documented evidence of CR or PR until PD per RECIST 1.1 as assessed by BICR or death due to any cause, whichever occurs first, in participants who demonstrate CR or PR.

10.4.2 Safety Endpoints

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, SAEs, fatal AEs, laboratory tests, and vital signs. Furthermore, specific events will be collected and designated as ECIs as described in Section 9.3.7.

10.5 Analysis Populations

10.5.1 Efficacy Analysis Populations

The analyses of primary efficacy endpoints are based on the intention-to-treat (ITT) population. All randomized participants will be included in this population. Participants will be analyzed in the treatment group to which they are randomized. Details on the approach to handling missing data are provided in Section 10.6.

10.5.2 Safety Analysis Populations

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

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

10.6 Statistical Methods

10.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary and secondary efficacy objectives. [redacted] Efficacy results that will be deemed to be statistically significant with Type I error strictly controlled at 5%. Nominal p-values will be computed for other efficacy analyses, but should be interpreted with caution due to potential issues of multiplicity.

10.6.1.1 Objective Response Rate

The stratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985] will be used for comparison of ORR between the treatment groups. The difference in ORR and its 95% CI from the stratified Miettinen and Nurminen method with strata weighting by sample size will be provided. The stratification factor (Section 7.3.1) based on tumor histology will be used in the analysis.

10.6.1.2 Progression-free Survival

The non-parametric Kaplan-Meier method will be used to estimate the PFS curve in each treatment group. The treatment difference in PFS will be assessed by the stratified log-rank test (based on the stratification factors defined in Section 7.3.1). A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, the HR) between the treatment arms. The HR and its 95% CI from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate will be reported. The stratification factor (Section 7.3.1) based on tumor histology will be applied to both the stratified log-rank test and the stratified Cox model.

Since disease progression is assessed periodically, PD can occur any time in the time interval between the last assessment where PD was not documented and the assessment when PD is documented. For the primary analysis, for participants who have PD, the true date of disease progression will be approximated by the date of the first assessment at which PD is objectively documented per RECIST 1.1 (based on BICR), regardless of discontinuation of study drug. Death is always considered as a confirmed PD event.

In order to evaluate the robustness of the PFS endpoint per RECIST 1.1 based on BICR, two sensitivity analyses with a different set of censoring rules will be performed. For the first sensitivity analysis, participants who miss more than one disease assessment (with or without a subsequent death or progression) are censored at the last disease assessment prior to missing visits. The second sensitivity analysis handles participants who discontinue treatment or initiate an anticancer treatment subsequent to discontinuation of study-specified treatments differently from the primary analysis. The censoring rules for primary and sensitivity analyses are summarized in Table 10. If a participant meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied.

Table 10 Censoring Rules for Primary and Sensitivity Analyses of Progression-free Survival

Situation	Primary Analysis	Sensitivity Analysis 1	Sensitivity Analysis 2
No PD and no death; new anticancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment	Censored at last disease assessment if still on study therapy; progressed at treatment discontinuation otherwise
No PD and no death; new anticancer treatment is initiated	Censored at last disease assessment before new anticancer treatment	Censored at last disease assessment before new anticancer treatment	Progressed at date of new anticancer treatment
No PD and no death; ≥2 consecutive missed disease assessments	Censored at last disease assessment	Censored at last disease assessment prior to ≥2 consecutive missed visits	Censored at last disease assessment
PD or death documented after ≤1 missed disease assessment	Progressed at date of documented PD or death	Progressed at date of documented PD or death	Progressed at date of documented PD or death

Situation	Primary Analysis	Sensitivity Analysis 1	Sensitivity Analysis 2
PD or death documented at any time after ≥2 missed disease assessments	Progressed at date of documented PD or death	Censored at last disease assessment prior to the ≥2 missed disease assessment	Progressed at date of documented PD or death
PD=progressive disease			

10.6.1.3 Overall Survival

The non-parametric Kaplan-Meier method will be used to estimate the survival curves. The treatment difference in survival will be assessed by the stratified log-rank test (based on the stratification factor defined in Section 7.3.1). A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, the HR). The HR and its 95% CI from the stratified Cox model with a single treatment covariate will be reported. The stratification factor (Section 7.3.1) based on tumor histology will be applied to both the stratified log-rank test and the stratified Cox model. Participants without documented death at the time of analysis will be censored at the date of last known contact. Analysis using the Restricted Mean Survival Time method may be conducted for OS to account for the possible non-proportional hazards effect.

10.6.1.4 Duration of Response

For participants who demonstrate CR or PR, DOR is defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first. Censoring rules for DOR are summarized in Table 11. DOR will be assessed using RECIST 1.1 by BICR.

For each DOR analysis, a corresponding summary of the reasons responding participants are censored will also be provided. Responses in participants who are alive, have not progressed, have not initiated new anti-cancer treatment, and have not been determined to be lost to follow-up are considered ongoing at the time of analysis. If a participant meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied.

Table 11 Censoring Rules for Duration of Response

Situation	Date of Progression or Censoring	Outcome
No progression or death, new anti-cancer treatment not initiated	Last adequate disease assessment	Censor (non-event)
No progression or death, new anti-cancer treatment initiated	Last adequate disease assessment before new anti-cancer therapy initiated	Censor (non-event)
Death or progression after ≥2 consecutive missed disease assessments	Last adequate disease assessment prior to the after ≥2 missed adequate disease assessments	Censor (non-event)
Death or progression after ≤1 missed adequate disease assessments	Progressive disease or death	End of response (Event)
Note: A missed disease assessment includes any assessment that is not obtained or is considered inadequate for evaluation of response.		

10.6.1.5 Statistical Methods for Key Efficacy Endpoints

A summary of the primary analysis strategy for the key efficacy endpoints is provided in Table 12.

Table 12 Analysis Methods for Key Efficacy Endpoints

Endpoint/Variable	Statistical Method	Analysis Population	Missing Data Approach
Primary Analyses:			
ORR (RECIST 1.1) by BICR	Testing and Estimation: Stratified Miettinen and Nurminen method	ITT	Participants with missing data are considered non-responders
Secondary Analyses:			
PFS (RECIST 1.1) by BICR	Estimation: Stratified Cox model with Efron's tie handling method Stratified Log-rank test	ITT	Censored according to rules in Table 10
OS	Estimation: Stratified Cox model with Efron's tie handling method Stratified Log-rank test	ITT	Censored at last known alive date
DOR (RECIST 1.1) by BICR	Summary statistics using Kaplan-Meier method	All responders in ITT	Non-responders are excluded in analysis
Sensitivity analyses will be performed for PFS, ORR, and DOR based on investigator's assessment. BICR=blinded independent central review; DOR=duration of response; ITT=intent-to-treat; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; RECIST 1.1=Response Evaluation Criteria in Solid Tumors.			

10.6.2 Statistical Methods for Safety Analyses

As of Amendment 05, safety and tolerability will be assessed by clinical review of all relevant parameters including adverse experiences (AEs), laboratory tests, and vital signs.

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 13).

Table 13 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 (Laboratory toxicity grade)	X

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 randomized and the primary reason for discontinuation will be displayed. Demographic variables (such as age) and baseline characteristics will be summarized by treatment either by descriptive statistics or categorical tables. The reasons for exclusion from the ITT population (if any) will be summarized.

10.7 Interim Analyses

10.7.1 Safety Interim Analyses

The eDMC will conduct regular safety monitoring. The timing of the first safety monitoring will be specified in the DMC charter. As of Amendment 05, no additional eDMCs will take place.

10.7.2 Efficacy Interim Analyses

No efficacy interim analysis is planned for this study. The study will be unblinded at the database lock for the primary analysis for ORR.

10.8 Multiplicity

The overall Type I error rate is strictly controlled at 5% (one-sided) by fixed sequence, a closed-testing procedure. The closed testing procedure will be applied to the primary hypothesis of ORR first. If the primary hypothesis is rejected at the α=5% level (one-sided), then testing will continue to the key secondary hypothesis of PFS. Nominal p-value for each endpoint will be reported, where applicable, regardless of the outcome of the closed testing procedure dictated by the multiplicity strategy.

10.9 Sample Size and Power Calculations

10.9.1 Sample Size and Power for Efficacy Analyses

The study will randomize 148 participants in a 1:1 ratio into the pembrolizumab plus epacadostat and pembrolizumab plus placebo arms. ORR is a primary endpoint for the study and PFS and OS are secondary endpoints.

Figure 3 summarizes power calculations for the primary hypothesis under various ORR difference assumptions.

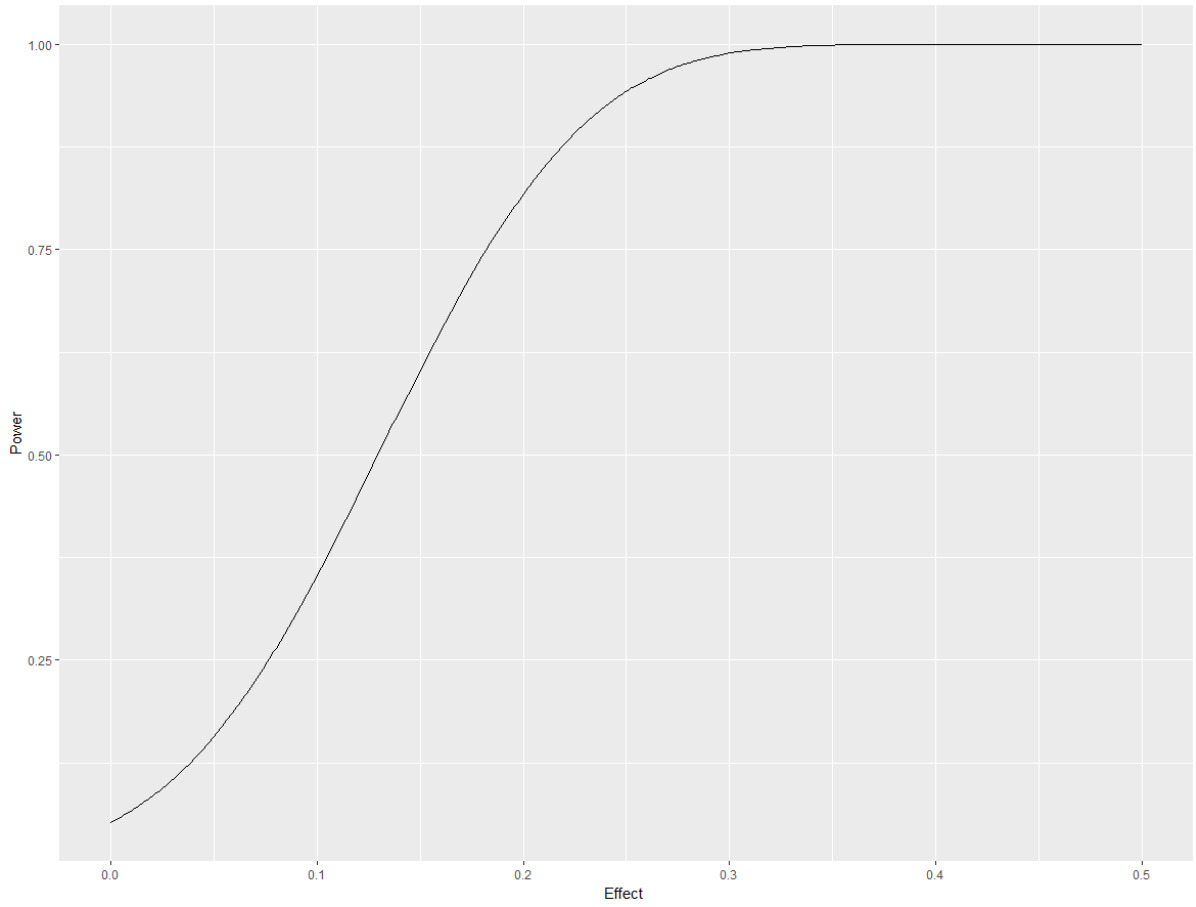


Figure 3 Power for Primary Hypothesis under Different Effect Size Assumptions

Based on the 148 participants in the control arm and the treatment arm under comparison, the power of the ORR testing at the α=0.05 (one-sided) is approximately 81.7% to detect a difference of 20 percentage points in ORR between an underlying 50% response rate in the control arm and a 70% response rate in the experimental arm.

With 95 PFS events, the study will have 80% power to detect a hazard ratio of 0.6 at an alpha level of 5% (1-sided).

The sample size and power calculations were performed in R (package "gsDesign").

10.10 Subgroup Analyses

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

- Stratification factor
    - Predominant tumor histology (squamous vs non-squamous)
- Geographic region (East Asia vs non-East Asia)
- ECOG performance status (0 vs 1)

- Age category (<65, ≥65 years)
- Sex (female, male)
- Race (white, non-white)
- Smoking status (never vs former/current smoker)
- Brain metastasis (presence vs absence)

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 medication. Summary statistics will be provided on extent of exposure for the APaT population.

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12. Appendices

12.1 Appendix 1: Abbreviations and Trademarks

Abbreviation	Definition
1L	first-line (therapy)
AE	adverse event
AEOSI	adverse events of special interest
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
APaT	all participants as treated (population)
AST	aspartate aminotransferase
BCG	Bacillus Calmette-Guérin
BICR	blinded independent central review
BID	twice daily
C1D1	Cycle 1 Day 1
C2D1	Cycle 2 Day 1
CI	confidence interval
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CR	complete response
CRF	case report form
CSR	Clinical Study Report
CT	computed tomography
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
DCR	disease control rate
DMC	Data Monitoring Committee
DOR	duration of response
ECG	electrocardiogram
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EGFR	epidermal growth factor receptor

Abbreviation	Definition
EMA	European Medicines Agency
EOC	Executive Oversight Committee
[redacted]	[redacted]
EOT	end of treatment
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
GCP	Good Clinical Practice
HBsAG	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	human immunodeficiency virus
HR	hazard ratio
[redacted]	[redacted]
HRT	hormonal replacement therapy
IA1	interim analysis 1
ICF	informed consent form
iCPD	iRECIST confirmed progressive disease
iCR	iRECIST complete response
IDO1	indoleamine 2,3 dioxygenase-1
IEC	Independent Ethics Committee
Ig	immunoglobulin
IHC	immunohistochemistry
INR	international normalized ratio
iPR	iRECIST partial response
irAE	immune-related adverse event
IRB	Institutional review board
iRECIST	modified RECIST for immune-based therapeutics

Abbreviation	Definition
iSD	iRECIST stable disease
ITT	intent to treat
iUPD	iRECIST unconfirmed progressive disease
IV	Intravenous
IVRS/IWRS	interactive voice response system/ integrated web response system
mAb	monoclonal antibody
MAOI	monoamine oxidase inhibitor
MRI	magnetic resonance imaging
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PFS	progression-free survival
[redacted]	[redacted]
PK	pharmacokinetic
PR	partial response
[redacted]	[redacted]
Q12H	every 12 hours
Q2W	every 2 weeks
Q3W	every 3 weeks
[redacted]	[redacted]
[redacted]	[redacted]
QoL	Quality of Life
QTc	corrected QT interval
RECIST	Response Evaluation Criteria in Solid Tumors 1.1
RR	response rate

Abbreviation	Definition
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
SNRI	serotonin-norepinephrine reuptake inhibitor
SoA	Schedule of Activities
SOC	standard of care
SS	serotonin syndrome
sSAP	supplemental Statistical Analysis Plan
SSRI	selective serotonin reuptake inhibitor
TB	tuberculosis
TDLN	tumor draining lymph nodes
TPS	tumor proportion score
T-reg	regulatory T-cell
[redacted]	[redacted]
[redacted]	[redacted]
WOCBP	woman of child bearing potential

12.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 14 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 14 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit PT or INR aPTT or PTT[a]		RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Chemistry	Blood Urea Nitrogen (BUN) or urea (one or the other should be collected per institutional standard; both tests are not required)	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the upper limit of normal)
	Albumin	A measure of carbon dioxide (CO_2 or bicarbonate)[b]	Chloride	Phosphorous
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose [Indicate if fasting, or nonfasting]	Calcium	Alkaline phosphatase	Amylase
	Lipase			
Routine Urinalysis	• Specific gravity • Glucose, protein, blood, ketones by dipstick • Microscopic examination (if blood or protein is abnormal) • Pregnancy test, as needed for woman of childbearing potential (WOCBP) within 72hrs before first dose			

Laboratory Assessments	Parameters
Other Tests (performed locally unless not feasible to perform at the site)	• Thyroid panel: TSH, FT4, FT3/T3 • Follicle-stimulating hormone (as needed in woman of non-childbearing potential only) • Serum β human chorionic gonadotropin (β-hCG) pregnancy test (as needed for WOCBP) • Serology: o Hepatitis B surface antigen, HBV-DNA o HCV-RNA, HCV antibody (if HCV-RNA is not the local standard of care) o HIV-RNA (if required by local regulations)

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. PTT may be performed if the local lab is unable to perform aPTT.
b. If available as SoC in your region. The carbon dioxide may be either a measurement of CO_2 or bicarbonate as an electrolyte.

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

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; 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 participant 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 <u>Meeting</u> 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 an MSD 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. 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 mid 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 or hospitalization indicated; disabling; limiting self-care ADL.
  - Grade 4: Life threatening consequences; urgent intervention indicated.
  - Grade 5: Death related to AE.

Assessment of Causality

- Did the 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 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 (i.e., 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

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 a contraceptive method with a failure rate of <1% per year as described in Table 15 when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.
  - Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile 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 15 during the protocol-defined time frame in Section 6.1.

Table 15 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 study treatment. 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 within 72 hours of the first dose. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required. Monthly pregnancy testing should be conducted as per local regulations where applicable.

Following initiation of treatment, pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected and as required locally.

12.6 Appendix 6: Eastern Cooperative Oncology Group (ECOG) Performance Status

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all 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

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

Signature Manifest

Document Number: IC-DEV-PROT-AMEND-0456 **Revision:** 0

Title: INCB 24360-305 Protocol Amendment 5 (3475-654-05, ECHO-305)

All dates and times are in Eastern Standard Time.

Quick Approval

Approve Now

Name/Signature	Title	Date	Meaning/Reason
[redacted]	[redacted]	04 Mar 2019, 11:31:44 AM	Approved