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TITLE:

A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study of Pembrolizumab (MK-3475) in Combination With Epacadostat or Placebo in Subjects with Unresectable or Metastatic Melanoma (KEYNOTE-252 / ECHO-301)

IND NUMBER: 121,704

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SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
1.0	Trial Summary	Addition of notes to clarify the removal of epacadostat and placebo from the trial and that all subjects remaining in the trial will receive open-label pembrolizumab only as of Amendment 10.	An interim review of the data indicated no benefit of epacadostat over placebo when combined with pembrolizumab. The external Data Monitoring Committee (DMC) recommended that all subjects be unblinded and all epacadostat and placebo administration stop. The study will remain open so that subjects still on study will have continued access to pembrolizumab. All references to epacadostat and placebo, as well as assessments/ procedures specific to these treatments, are removed from the protocol. 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	Trial Design	Addition of a note to describe the removal of epacadostat and placebo and that all subjects remaining in the trial will receive open-label pembrolizumab only as of Amendment 10. Addition of text summarizing the DMC recommendations.	
2.2	Trial Diagram Figure 2 Study Design as of Amendment 10	New Figure 2 showing the updated study design.	
4.1 4.2 4.3	Background Rationale Benefit/Risk	Addition of notes to clarify which sections and text are no longer applicable due to removal of epacadostat and placebo.	
5.2	Trial Treatment(s)	Addition of note that only pembrolizumab will be administered. Other treatments (prior to this amendment) are deleted.	
5.2	Trial Treatment(s) Table 1 Trial Treatment	Deletion of epacadostat and placebo.	

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
5.2.1.2	Dose Modification (Escalation/Titration/Other)	Deletion of text relating to dose modification of epacadostat.	
5.2.1.2	Dose Modification (Escalation/Titration/Other) Table 2 Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab	The dose modification table has been reverted to the standard table for pembrolizumab alone.	
5.2.1.2	Dose Modification (Escalation/Titration/Other) Table 3 Dose Level Adjustment of Epacadostat or Matching Placebo	Deletion of table.	
5.2.3.2	Timing of Dose Administration of Epacadostat	Deletion of section.	
5.6.2	Supportive Care Guidelines for Epacadostat or Matching Placebo	Deletion of section.	
6.1	Trial Flow Chart	Deletion of rows for epacadostat and placebo administration and dispensing. Deletion of row for subject reminder card.	
7.1.1.8	Trial Compliance (Medication)	Deletion of text and subsections relating to epacadostat/placebo compliance.	

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
7.2.1	Definition of an Overdose for This Protocol and Reporting of Overdose	Deletion of the definition of overdose for epacadostat.	
9.1	Investigational Product	Deletion of information relating to epacadostat/placebo.	
9.2	Packaging and Labeling Information	Deletion of information relating to epacadostat/placebo.	
1.0	Trial Summary	Deletion of text relating to Second Course.	Given the findings of the study, subjects will be provided pembrolizumab monotherapy up to a total of 35 cycles, the Second Course of treatment will not be offered, and data collection will be limited.
5.2.2	Second Course Phase (Retreatment Period)	Deletion of section.	
5.8	Subject Withdrawal/ Discontinuation criteria	Deletion of text relating to retreatment.	
5.8.1	Discontinuation of Treatment	Deletion of text relating to Second Course (retreatment).	
6.2	Trial Flow Chart – Second Course Phase (Retreatment)	Deletion of Flow Chart.	
7.1.1.5.2	Concomitant Medications	Deletion of text relating to Second Course.	
7.1.5.2.2	Second Course (Retreatment) Tumor Imaging	Deletion of section.	
7.1.6	Laboratory Procedures/Assessments	Deletion of text relating to laboratory procedures for Second Course.	

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
7.1.8.4.1.1 (now Section 7.1.8.4.1)	Safety Follow-up Visit	Deletion of text relating to eligibility for Second Course treatment.	
1.0	Trial Summary	Addition of note that the last trial visit is the Safety Follow-up Visit.	Given the findings of the study, the study will close once all subjects complete treatment of pembrolizumab (up to a total of 35 cycles). The final visit in the study will be the Safety Follow-up Visit. There will be no follow-up for survival status. Subjects currently in follow-up or in survival follow-up are considered to have completed the study. However, standard safety reporting should continue, as applicable.
2.1	Trial Design	Deletion of text relating to follow-up of subjects who discontinue for reasons other than disease progression.	
5.8	Subject Withdrawal/ Discontinuation criteria	Deletion of text relating to follow-up of subjects for survival data.	
5.8.1	Discontinuation of Treatment	Deletion of text relating to follow-up of subjects after treatment discontinuation.	
6.1	Trial Flow Chart	Deletion of columns for Follow-up and Survival Follow-up. Deletion of row for survival status assessment.	
7.1.1.9	Poststudy Anticancer Therapy Status	Assessment of poststudy anticancer therapy will end at the Safety Follow-up Visit.	
7.1.5.2.1	End of Treatment and Follow-up Tumor Imaging	Deletion of text relating to follow-up of subjects after treatment discontinuation.	

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
7.1.7.1	Withdrawal/ Discontinuation	Deletion of text indicating that subjects who discontinue/withdraw from treatment prior to completion of the treatment regimen should be encouraged to continue to be followed for all remaining study visits. Subjects are considered to have completed the study after attending the Safety Follow-up Visit.	
7.1.7.1.2	Lost to Follow-up	Addition of a note that this is no longer applicable. There will be no additional efforts to contact subjects who are lost to follow-up.	
7.1.8.4.1.1 (now Section 7.1.8.4.1)	Safety Follow-up Visit	Addition of note that the last trial visit is the Safety Follow-up Visit. Addition of clarification that subjects currently in follow-up or in survival follow-up are considered to have completed the study; these subjects are not required to attend any further visits. Assessment and recording of AEs will be performed as per Section 7.2. Deletion of text about follow-up of AEs that is covered in Section 7.2.	
7.1.8.4.1.2 (now Section 7.1.8.4.2)	Follow-up Visits	Addition of a note that this section is no longer applicable. A subject will be considered to have completed this study once they have attended the Safety Follow-up Visit. Subjects currently in follow-up are considered to have completed the study; these subjects are not required to attend any further visits. Assessment and recording of AEs will be performed as per Section 7.2.	

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
7.1.8.4.1.3 (now Section 7.1.8.4.3)	Survival Follow-up	Addition of a note that this section is no longer applicable. Subjects currently in survival follow-up are considered to have completed the study; these subjects will no longer be contacted for survival information. Assessment and recording of AEs will be performed as per Section 7.2.	
7.1.8.6	Survival Status	Addition of a note that this section is no longer applicable. Subjects currently in survival follow-up are considered to have completed the study; these subjects will no longer be contacted for survival information. Assessment and recording of AEs will be performed as per Section 7.2.	
3.2	Secondary Objectives	Addition of a note that pharmacokinetic (PK) and antidrug antibodies (ADA) samples will no longer be collected.	Further collection of samples in subjects receiving pembrolizumab alone is not required. Blood samples for PK and ADA may be stored. Analysis will be performed if required.
4.2.3.5	Pharmacokinetic Endpoints	Addition of a note that PK and ADA samples will no longer be collected.	
6.1	Trial Flow Chart	Deletion of rows for samples collection for PK and ADA, and associated footnote.	
7.1.6.5 and subsections	Pharmacokinetic/ Pharmacodynamic Evaluations	Addition of a note that this section (and subsections) is no longer applicable.	

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
5.2.1.4	Procedures for Subjects Exhibiting Serotonin Syndrome (SS)	Addition of a note that this section is no longer applicable.	Subjects will no longer be receiving epacadostat, so activities and procedures relating to serotonin syndrome (an expected adverse reaction for epacadostat, but not for pembrolizumab) management and reporting is no longer needed.
6.1	Trial Flow Chart	Deletion of row for serotonin syndrome information sheet.	
7.2.3.2	Events of Clinical Interest	Deletion of text for serotonin syndrome.	
12.8	Publication on Serotonin Syndrome	Addition of a note that this section is no longer applicable.	
5.2.4 (now Section 5.2.3)	Trial Blinding	Addition of a note that blinding is no longer applicable – all subjects will receive open-label pembrolizumab alone.	Based on DMC recommendation, all subjects stopped receiving blinded epacadostat/placebo. All subjects remaining in the trial will continue on open-label pembrolizumab alone.
7.1.7.2	Blinding/Unblinding	Addition of a note that blinding is no longer applicable – all subjects will receive open-label pembrolizumab alone.	
9.3	Clinical Supplies Disclosure	Deletion of text relating to treatment blinding.	

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
5.5.2	Restricted Medications and Measures	Deletion of section.	Subjects will no longer be receiving epacadostat, so restricted concomitant medications and prohibited medications related to epacadostat are no longer needed.
5.5.3 (now Section 5.5.2)	Prohibited Medications and Measures	Removal of bullets for monoamine oxidase inhibitors and UGT1A9 inhibitors (or analogs).	
12.5	Prohibited Monoamine Oxidase Inhibitors and Drugs Associated with Significant Monoamine Oxidase Inhibitory Activity	Addition of a note that this section is no longer applicable.	
5.7.2 5.7.3 5.7.4	Contraception Pregnancy Use in nursing women	Text relating to epacadostat in these sections is no longer applicable and has been deleted.	Text relating to contraception, pregnancy and nursing requirements in subjects receiving epacadostat is no longer applicable. Pregnancy testing will revert to standard of care for subjects receiving pembrolizumab.
6.1	Trial Flow Chart	Pregnancy testing is changed to monthly per local regulations, as applicable.	
7.1.6.3	Pregnancy Testing	Pregnancy testing is changed to monthly per local regulations, as applicable.	

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
7.2	Assessing and Recording Adverse Events	Adverse events (AEs) will be reported from the time of treatment allocation/randomization through 30 days following cessation of treatment or if the subject initiates new anticancer therapy, whichever is earlier.	By the time Amendment 10 is approved and implemented, subjects will have been off of epacadostat for >~90 days. Thus, AE reporting will change to the pembrolizumab monotherapy standard.
7.2.3.1	Serious Adverse Events	Serious adverse events (SAEs) will be reported from treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of trial treatment if the subject initiates new anticancer therapy, whichever is earlier.	
7.2.4	Evaluating Adverse Events	Deletion of text stating that, 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.	As pembrolizumab is now administered as single agent (ie, not in combination), this text is no longer applicable.
4.2.3.1.1	Primary Efficacy Endpoints	Addition of a note that central imaging vendor assessment will no longer be required.	As all subjects are now receiving pembrolizumab, study procedures are reduced to the minimum requirement for investigational pembrolizumab administration to minimize subject assessment burden.
4.2.3.3	Patient Reported Outcomes	Addition of a note that ePRO assessments are no longer being collected.	
6.1	Trial Flow Chart (including footnotes)	Change of full physical examination to directed physical examination, per standard of care or as clinically indicated, at End of Treatment (EOT) and Safety Follow-up Visit. Change of ECG at EOT visit to be per standard of care or as clinically indicated.	

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
		Deletion of patient reported outcome (PRO) assessments and associated footnote. Change of laboratory assessments (including thyroid function and coagulation factors) from Cycle 4 onwards to be per standard of care or as clinically indicated. [redacted] Deletion of the optional request for tumor biopsy at Weeks 12, 24, and disease progression. Change of tumor imaging timing to standard of care. Removal of the requirement to send tumor imaging to the central imaging vendor. A repeat scan is not required if the investigator opts to discontinue the subject at the initial PD. Deletion of digital photography assessment and associated footnote. Addition of poststudy anticancer therapy status assessment at EOT and at Safety Follow-up Visit.	

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
7.1.2.2 7.1.2.3	Full Physical Examination Directed Physical Examination	Update to reflect the change from full physical examination to directed physical examination, per standard of care or as clinically indicated, at EOT and Safety Follow-up Visit.	Study procedures are reduced to the minimum requirement for investigational pembrolizumab administration to minimize subject assessment burden.
7.1.2.6.2	Patient Reported Outcomes	Addition of a note that this section (and subsections) is no longer applicable.	
7.1.4	Tumor Biopsy	Deletion of optional tumor biopsy collection at Week 12, Week 24, and at disease progression.	
7.1.5	Tumor Imaging and Assessment of Disease	Addition of a note that central imaging vendor assessment is no longer required. Disease assessments will be performed by the site investigator/radiology assessment, per standard of care. Amendment of subsections to remove specific timing of assessments; timing should follow the site's standard of care for oncologic tumor assessment until initial PD per RECIST 1.1. A repeat scan is not required if the investigator opts to discontinue the subject at the initial PD. Removal of text regarding repeat imaging to confirm PR and CR.	
7.1.5.4	Photography for Cutaneous Lesions	Addition of a note that this section is no longer applicable.	

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
[redacted]			
8.1	Statistical Analysis Plan Summary	Addition of a note that, based on recommendation from DMC at IA2, all subjects stopped oral therapy (epacadostat/placebo) and only selected analyses will be performed after study completion.	After their review of the second interim analysis (IA) results, the DMC indicated that the comparison of PFS by randomized treatment assignment did not reach the protocol specified criterion for statistical significance and further the co-primary endpoint OS was unlikely to reach statistical significance for the study. Therefore, the DMC recommended that the study will stop further efficacy analyses. Due to the current status of the study, the statistical analysis may be modified and will be reported in the CSR.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
5.2.1.2	Dose Modification (Escalation/Titration/Other)	Minor language change in paragraph 2.	To clarify the language.
5.2.1.2	Dose Modification (Escalation/Titration/Other) Table 2 Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab	Added that, in case of recurrent Grade 3 colitis, subjects will permanently discontinue treatment.	To align with KEYTRUDA® Summary of Product Characteristics and the Company Core Data Sheet.
5.2.1.5	Dose Interruptions Unrelated to Adverse Events	New text added.	To clarify the language.
5.5.3 (now Section 5.5.2)	Prohibited Medications and Measures	Bullet 2 split out into 3 separate bullets.	To clarify the language.
5.8.1	Discontinuation of Treatment	Addition of a note to bullet "Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment" that, **for France only**, a subject experiencing this condition must be discontinued from the trial.	French Health Authority (ANSM) requested to clarify that in the case of occurrence of another malignancy during the trial, the subject must discontinue the trial.
5.8.1	Discontinuation of Treatment	Minor language change in bullet 7.	To clarify the language.

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
5.8.2	Withdrawal from the Trial	Added: **For France only:** A subject must be discontinued from the trial for the following reason: - Any progression or recurrence of another malignancy, or any occurrence of another malignancy that requires active treatment.	ANSM requested to clarify that in the case of occurrence of another malignancy during the trial, the subject must discontinue the trial.
7.1.6.2	Serum Chemistry and Liver Function Tests	Deletion of duplicated sentence about liver function tests being done by local laboratories.	Correction.
		Deletion of text relating to the frequency/ duration of liver function monitoring in case of persistent low-grade abnormalities.	Instructions for monitoring of liver function abnormalities are included in Table 2 in Section 5.2.1.2.
7.1.8.4.1.1 (now Section 7.1.8.4.1) 7.1.8.4.1.2 (now Section 7.1.8.4.2) 7.1.8.4.1.3 (now Section 7.1.8.4.3)	Safety Follow-up Visit Follow-up Visits Survival Follow-up	Heading level changed from Level 6 to Level 5	Correction.

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
8.6.2	Statistical Methods for Safety Analyses	Deletion of phrase for clarification, "Continuous measures such as changes …and ECG parameters ~~that are pre-specified as Tier-1 endpoints~~ will be …"	Clarification.
Throughout		Minor typographical and formatting errors were corrected.	

1.0 TRIAL SUMMARY

Abbreviated Title	Phase 3 Study of Epacadostat and Pembrolizumab in Melanoma
Product Identifiers	MK-3475, INCB024360 Pembrolizumab, epacadostat **NOTE: As of Amendment 10, epacadostat is removed**.
Trial Phase	Phase III
Clinical Indication	Unresectable or metastatic melanoma
Trial Type	Interventional
Type of control	Placebo **NOTE: As of Amendment 10, placebo is removed.**
Route of administration	Intravenous, Oral **NOTE: As of Amendment 10, epacadostat (oral administration) is removed.**
Trial Blinding	Unblinded Open-label
Treatment Groups	pembrolizumab + epacadostat, pembrolizumab + placebo **NOTE: As of Amendment 10, epacadostat and placebo are removed. All subjects remaining in the trial receive open-label pembrolizumab only.**
Number of trial subjects	Approximately 700 subjects will be enrolled.
Estimated duration of trial	The Trial is estimated to require approximately 48 months from the time the first subject signs the informed consent until the last subject's last study-related phone call or visit.
Duration of Participation	Each subject will participate in the trial from the time the subject signs the informed consent form (ICF) through the final protocol-specified contact. After a screening phase of 28 days, each subject will be assigned to receive trial treatment until radiographically confirmed disease progression is confirmed by the site per immune related Response Evaluation Criteria in Solid Tumors (irRECIST), unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, noncompliance with trial treatment or procedures requirements or administrative reasons requiring cessation of treatment, or until the subject has received 35 administrations of pembrolizumab (approximately 2 years). After the end of treatment, each subject will be followed for the occurrence of adverse events and spontaneously reported pregnancy as described under Section 7.2 of the protocol. As of Amendment 10, the last trial visit is the Safety Follow-up Visit.

Randomization Ratio	1:1

A list of abbreviations used in this document can be found in Section 12.9.

2.0 TRIAL DESIGN

2.1 Trial Design

NOTE: As of Amendment 10, the epacadostat/placebo combination therapy is removed from both treatment groups. All subjects remaining in the trial continue on pembrolizumab alone in an open-label fashion. The Second Course retreatment phase is removed. The last trial visit is the Safety Follow-up Visit.

This is a randomized, placebo-controlled, parallel-group, multi-site, double-blind trial of pembrolizumab and epacadostat in subjects with unresectable or metastatic melanoma to be conducted in conformance with Good Clinical Practices. This Phase 3 study will be conducted in subjects with unresectable or metastatic melanoma. Subjects will be stratified by programed cell death ligand 1 (PD-L1) expression (positive versus negative/indeterminate) and BRAF mutation status (BRAF mutant and received prior BRAF directed treatment, BRAF mutant with no prior BRAF directed treatment and BRAF wild type) and then be randomized 1:1 (active:placebo) to Treatment A (pembrolizumab + epacadostat) or Treatment B (pembrolizumab + placebo). No treatment crossover is planned.

The treatment period with the combination therapy will continue every 21 days for up to 35 cycles (approximately 2 years) as long as subjects are receiving benefit from treatment and have not had disease progression or met any criteria for study withdrawal.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart - Section 6.0. Details of each procedure are provided in Section 7.0 – Trial Procedures.

This trial will use an adaptive design based on pre-specified criteria, using an independent, external Data Monitoring Committee (DMC) to monitor safety and efficacy. There will be 2 interim analyses, as stated in Section 8.7.

Results of the interim analysis will be reviewed by the external DMC, which will make recommendations to continue, modify or end the trial according to the plan described in detail in Section 8.0 - Statistical Analysis Plan.

An interim review of the data indicated no benefit of epacadostat over placebo when combined with pembrolizumab. The external DMC recommended that all subjects be unblinded and all epacadostat and placebo administration stop. The study will remain open so that subjects still on study will have continued access to pembrolizumab.

2.2 Trial Diagram

The original trial design is depicted in Figure 1. The revised trial design as of Amendment 10 is depicted in Figure 2.

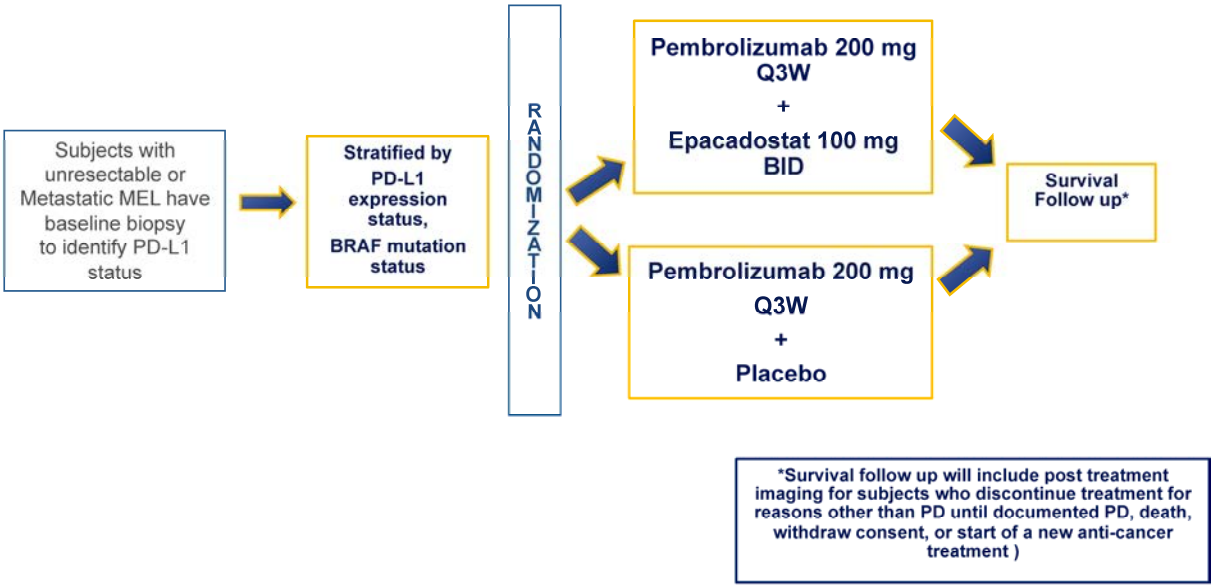


Figure 1 Original Study Design

Figure 2 Study Design as of Amendment 10

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

In all randomized male/female subjects with histologically confirmed diagnosis of melanoma with unresectable or metastatic melanoma of at least 18 years of age:

1) **Objective:** To compare the progression-free survival (PFS) of the combination of pembrolizumab and epacadostat versus pembrolizumab and placebo (i.e. 2 treatment groups) based on Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 by independent central review.

   Hypothesis (H1): The combination of pembrolizumab and epacadostat prolongs PFS based on RECIST 1.1 by independent central review compared to pembrolizumab and placebo.

2) **Objective:** To compare overall survival (OS) of the 2 treatment groups.

   Hypothesis (H2): The combination of pembrolizumab and epacadostat prolongs OS compared to pembrolizumab and placebo.

This study is considered to have met its study objective if pembrolizumab and epacadostat is superior to pembrolizumab and placebo in either PFS or OS.

3.2 Secondary Objective(s) & Hypothesis(es)

In all randomized male/female subjects with histologically confirmed diagnosis of melanoma with unresectable or metastatic melanoma of at least 18 years of age:

1) **Objective**: To compare the objective response rate (ORR) of the 2 treatment groups based on RECIST 1.1 by independent central review.

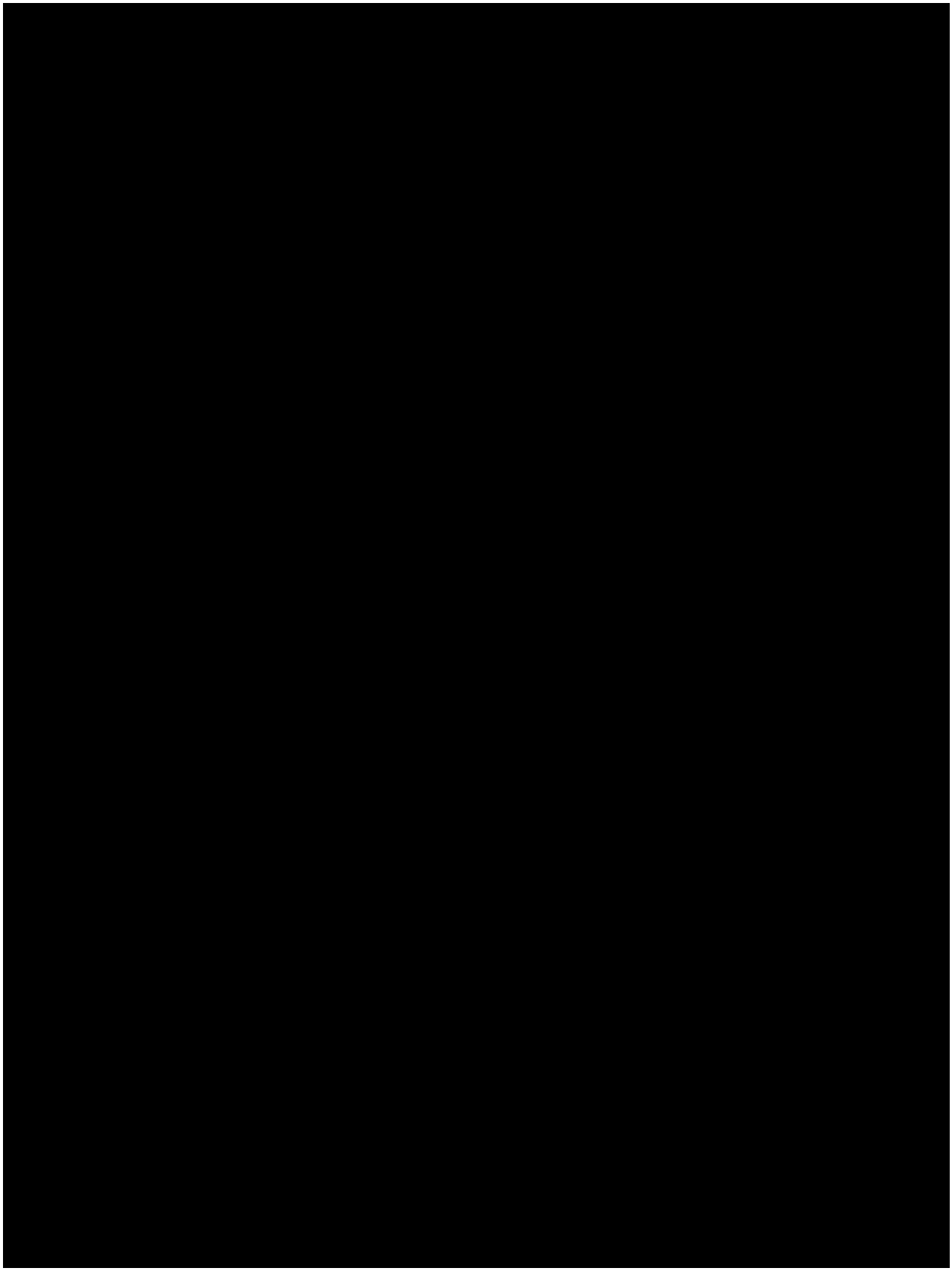
   Hypothesis (H1): The combination of pembrolizumab and epacadostat increases ORR based on RECIST 1.1 by independent central review compared to pembrolizumab and placebo.

2) **Objective**: To evaluate the safety and tolerability of the 2 treatment groups.

3) **Objective**: To evaluate the duration of response (DOR) of the 2 treatment groups based on RECIST 1.1 by independent central review.

4) **Objective**: To evaluate the pharmacokinetics (PK) and anti-pembrolizumab antibodies of pembrolizumab and epacadostat administered concomitantly.

   NOTE: As of Amendment 10, samples for PK and antidrug antibody (ADA) assessments are no longer being collected.



4.0 BACKGROUND & RATIONALE

4.1 Background

NOTE: As of Amendment 10, all text in this section relating to epacadostat is no longer applicable.

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

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 (DCs). Pembrolizumab is a potent and highly selective humanized monoclonal antibody of the immunoglobulin (Ig) G4/kappa isotype directed against programmed death receptor 1 (PD-1).

Refer to the respective Investigator's Brochure (IB) for detailed background information on pembrolizumab and epacadostat.

4.1.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades [1]. 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 [2], [3]. Histologic evaluation of many human cancers shows extensive infiltration by inflammatory and immune cells [4], 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.

There are a number of inhibitory mechanisms that have been identified to be involved in tumor-mediated immune suppression and include expression of the programmed death ligand 1 (PD-L1), which can engage the inhibitory receptor PD-1 on activated T cells; the presence of the tryptophan-catabolizing enzyme IDO1, which exposes the exquisite sensitivity of T cells to tryptophan depletion and tryptophan metabolites; and infiltration with $FoxP3^+$ regulatory T cells (Treg), which can mediate extrinsic suppression of effector T-cell function.

Therefore, 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.

4.1.1.1 Inhibition of PD-1 as a Target for Cancer

The PD-1 receptor-ligand interaction is a major pathway stimulated by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an immunoglobulin (Ig) superfamily member related to CD28 and cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4), which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [5], [6]. The mechanism by which PD-1 down modulates T-cell responses is similar to but distinct from that of CTLA-4, as both molecules regulate an overlapping set of signaling proteins [7], [8]. PD-1 has been shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, Tregs, and natural killer cells [9], [10]. Expression has also been shown during thymic development on CD4-CD8- (double negative) T cells as well as subsets of macrophages and dendritic cells [11]. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including nonhematopoietic tissues as well as in various tumors [12], [13], [14], [8]. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various nonhematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues [8]. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma [15]. This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

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

NOTE: As of Amendment 10, this section is no longer applicable.

Recent interest has focused on the role of indoleamine 2,3–dioxygenase (IDO1) as a mechanism of induction of tolerance to malignancy [16]. IDO1 is a heme-containing, monomeric oxidoreductase that catalyzes the degradation of the essential amino acid tryptophan to N-formyl-kynurenine. Kynurenine can be subsequently metabolized through a series of enzymatic steps to nicotinamide adenine dinucleotide. IDO1 is the first rate-limiting enzyme in one of the 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 (e.g., gut, respiratory tract, placenta, spleen), consistent with a role for regulating tryptophan metabolism in a local microenvironment [17]. Within the immune system, IDO1 activity is specifically induced in cells such as DCs and macrophages at localized sites of inflammation [18].

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 [19]. Both the reduction in local tryptophan levels and the production of tryptophan catabolites that are inhibitory to cell proliferation contribute to the immunosuppressive effects [20]. IDO1 activity also promotes the differentiation of naive T cells to cells with a regulatory phenotype (Treg) [21]. Since increased Treg activity has been shown to promote tumor growth and Treg depletion has been shown to allow an otherwise ineffectual antitumor immune response to occur [22], IDO1 expansion of Tregs 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 [23]. A critical role for IDO1 in immunomodulation has been confirmed in numerous animal models, including models of allograft tolerance, inflammation, and cancer [17]. While IDO1 inhibition can exacerbate disease in models of autoimmune disorders [17], IDO1 null mice show no evidence of susceptibility to developing spontaneous autoimmunity or alterations in immune system development [19], suggesting that IDO1 inhibition, in a therapeutic setting, may produce minimal side effects in subjects 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 [24], [25]. In addition, studies with 1-methyl-tryptophan, demonstrate that IDO1 inhibition dramatically increases the efficacy of various chemotherapeutic agents (e.g., platinum compounds, taxane derivatives, cyclophosphamide) without increased toxicity [25]. Although the specific mechanisms responsible for this potentiation remain to be fully elucidated, the effects were not observed in T-cell–deficient animals, suggesting that the results may be the consequence of the disablement of immunosuppressive mechanisms that exist within the tumor microenvironment.

Based on studies examining serum levels of tryptophan and kynurenine, IDO1 appears to be chronically activated in subjects with cancer, and IDO1 activation correlates with more extensive disease [26], [27]. IDO1 has subsequently been found to be overexpressed by a wide variety of human tumor cell types as well as by the DCs that localize to the tumor

draining lymph nodes [24]. Increased expression of IDO1 in tumor cells has been shown to be an independent prognostic variable for reduced overall survival (OS) in subjects with melanoma, ovarian, colorectal, and pancreatic cancers [28], [29], [30], [31], [32]. 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 either alone or in combination with chemotherapeutics and/or immunotherapy-based strategies.

4.1.1.3 Combined Immune Checkpoint Inhibition

NOTE: As of Amendment 10, this section is no longer applicable.

Blockade of immune inhibitory pathways is emerging as an important therapeutic modality for the treatment of cancer as evidenced by the clinical responses observed with antibodies to CTLA-4 and PD-1/PD-L1. Ipilimumab, a fully human, IgG1 monoclonal antibody blocking CTLA-4, improved OS in patients with advanced melanoma [9], [33]. Nivolumab, a fully human IgG4 antibody blocking PD-1, produced durable overall responses in patients with melanoma, renal cell cancer, and NSCLC [34], [35], [36]. Although these single agents have antitumor activity, multiple immune inhibitory mechanisms are present concurrently within the tumor microenvironment, suggesting that combination therapies may be required for optimal therapeutic effect [37].

For example, CTLA-4 and PD-1 appear to play complementary roles in regulating adaptive immunity. Whereas PD-1 contributes to T-cell exhaustion in peripheral tissues, CTLA-4 inhibits at earlier points in T-cell activation. In preclinical models, combined blockade of PD-1 and CTLA-4 achieved more pronounced antitumor activity than blockade of either pathway alone [38], [39].

On the basis of these observations, a Phase 3 study was conducted to investigate the safety and efficacy of combined CTLA-4 and PD-1 blockade (with the use of ipilimumab and nivolumab, respectively) in patients with advanced melanoma. The objective response rate (ORR; according to modified World Health Organization criteria) for all patients in the concurrent-regimen group was 61% among subjects with BRAF wild-type tumors versus 11% in the ipilimumab alone group. Median duration of response had not been reached in either group. Median PFS had not been reached with the combination therapy and was 4.4 months for ipilimumab monotherapy. Grade 3 or 4 AEs occurred in 54% of subjects in the concurrent-regimen group and were 24% in the ipilimumab monotherapy group [40]. Common Grade 3 or 4 selected AEs that were related to the combination therapy included colitis (17%), diarrhea (11%), and an elevated alanine aminotransferase level (11%). Diarrhea (11%) was the most frequently reported Grade 3 or 4 AE associated with ipilimumab monotherapy, followed by colitis (7%). In both regimen groups, treatment-related AEs were manageable and generally reversible with the use of immunosuppressants (or hormone-replacement therapy for endocrinopathies) according to previously established algorithms [40].

As described previously, IDO1 is another negative regulatory mechanism that contributes to tumor-derived immune suppression. In preclinical models, IDO1 inhibition has been shown to synergize with blockade of either anti–CTLA-4 or anti–PD-1/PD-L1 in delaying tumor growth and increasing OS [41], [42]. This effect was shown to be T-cell dependent, leading to enhanced T-cell proliferation and interleukin-2 production within the tumor and to a marked increase in the effector-to-regulatory T cell ratios in the tumors.

The IDO1 inhibitor epacadostat has completed a Phase 1 study and has several ongoing Phase 1 and Phase 2 studies in combination with immune-targeted agents, such as anti–PD-1, anti–PD-L1, and anti–CTLA-4 antibodies. In a study combining epacadostat and ipilimumab (INCB 24360-201) subjects received ipilimumab (3 mg/kg IV every 3 weeks for 4 cycles) with epacadostat at doses of 25 mg BID, 50 mg BID continuous, 50 mg BID intermittent (2 weeks on, 1 week off), and 75 mg (50 mg q AM/25 mg q PM). A total of 42 subjects were enrolled: 25 mg BID (n=8), 50 mg BID (continuous) (n=18), 50 mg BID (intermittent) (n=9), and 75 mg (n=7). DLTs were: 25 mg BID, Grade 3 increased AST (n=1); 50 mg BID (continuous), Grade 3 diarrhea, Grade 3 increased ALT/AST grade 3 colitis and grade 3 pneumonitis (n=1 each); 50 mg BID (intermittent), Grade 3 colitis (n=1); 75 mg, Grade 3 rash (n=1). The most common all Grade immune-related adverse events (irAEs) were rash (52%), pruritus (38%), diarrhea (33%), increased ALT (21%), increased AST (16%) hypothyroidism (12%) and colitis (10%). Grade ≥3 irAEs occurred in 23% of subjects. Grade ≥ 3 irAEs occurring in more than 1 subjects were increased AST and colitis (n=4 [9.5%] each). Among 32 immunotherapy-naïve subjects, ORR was 31% (10/32) per irRC and 28% (9/32) per RECIST and the CR rate per both criteria was 9.4%. At data cutoff, responses were ongoing in 6 subjects. The disease control rate (DCR; CR+PR+SD) was 62.5% per irRC and 53% per RECIST. Median PFS was 8.2 months by irRC and 5.3 months by RECIST. Among 10 subjects previously treated with immunotherapy, the DCR by both criteria was 30% (all SDs). In a study combining pembrolizumab and epacadostat (INCB 24360-202) similar efficacy and safety were also demonstrated.

In summary, both IDO1 and PD-1 have been shown to suppress T-cell–mediated antitumor immunity, and IDO1 and the PD-1 ligand PD-L1 have been shown to be coexpressed in multiple cancer types and to correlate with poor prognosis. Combined inhibition of both pathways may therefore lead to greater suppression of antitumor immunity and to increased efficacy. Preclinical and clinical data indicate that these pathways are important in melanoma as well as in other cancers, including NSCLC.

4.1.1.4 Overview of Metastatic Melanoma

Melanoma is the most serious form of skin cancer and strikes adults of all ages. The 5-year prevalence of melanoma in the European Union (EU) is approximately 159,000 patients with an incidence of approximately 41,000 per year and approximately 11,000 deaths annually as described in the World Health Organization (WHO) Europe region [43]. Melanoma accounts for approximately 5% of all new cases of cancer in the United States (US). The incidence of melanoma continues to rise by almost 3% per year in the US. This translates to 76,000 new cases a year with 9,000 associated deaths. The male-to-female incidence ratio of melanoma

is 1.4:1, respectively [44]. The 5-year survival rate is 15% once patients have progressed to late-stage disease [45].

4.1.1.5 Treatment for Advanced or Metastatic Melanoma

Surgical excision with wide margins is the standard of care for early-stage melanoma, and most patients with *in situ* or early-stage melanoma will be cured by primary excision alone. Metastatic melanoma, however, is very unlikely to be curable by surgery because of the likelihood of micrometastases too small to be found by CT, MRI, or PET scans [46]. National Comprehensive Cancer Network (NCCN) guidelines (Melanoma – Version 2.2016) endorse adjuvant treatment, including clinical study, observation, or high-dose interferon alfa for node-negative Stage IIB or IIC disease. For Stage III disease, ipilimumab may also be considered. Radiation therapy may have a role as adjuvant therapy after surgery for primary melanomas that are associated with a high rate of local recurrence despite apparently adequate excision, and in those with positive margins after surgical excision [48].

High-dose interleukin-2 (IL-2) was the first treatment to modify the natural history of patients with metastatic melanoma and may be curative for a small fraction of patients. However, its severe toxicity limits its application to carefully selected patients treated at centers with experience in managing the side effects of treatment. More recent research led to the development of immunotherapy using checkpoint inhibitors such as anti-PD1 antibodies, pembrolizumab and nivolumab, and the anti-CTLA4 antibody (ipilimumab) and to targeted therapy such as BRAF and/or MEK inhibition (dabrafenib and/or trametinib, respectively). Both of these approaches prolong progression free and overall survival compared with chemotherapy [48].

Ipilimumab, an anti-cytotoxic T lymphocyte associated antigen-4 (CTLA-4) blocking antibody, and vemurafenib, a BRAF inhibitor, were the only agents approved for advanced melanoma that have demonstrated overall survival (OS) benefit in randomized, comparative Phase 3 registration studies until just recently. In the Phase 3 study MDX010-20, ipilimumab monotherapy demonstrated a hazard ratio (HR) of 0.66 and a 4-month median OS benefit compared to gp100 in pretreated advanced melanoma subjects [58]. Grade 3 to 4 immune-related adverse events (AEs) included colitis (5.3%), diarrhea (4.6%), endocrinopathies (3.8%), and rash (0.8%). In the US, 3 mg/kg of ipilimumab was approved for advanced melanoma based on data from MDX010-20 and without restriction to line of therapy, in part because of the results of an additional Phase 3 randomized ipilimumab clinical study, CA184024. In the CA184024 study, treatment-naïve advanced melanoma subjects treated with 10 mg/kg ipilimumab in combination with dacarbazine (DTIC) demonstrated an HR of 0.72 and a 2-month median OS benefit compared with monotherapy dacarbazine [33]. In the EU, ipilimumab is currently approved for the treatment of advanced (unresectable and metastatic) melanoma in adults who have received prior therapy. Approximately 50% of cutaneous melanoma cases are BRAF V600E mutation positive. Vemurafenib is approved in the US and in the EU for the treatment of BRAF V600E mutation-positive advanced melanoma subjects regardless of line of therapy [49]. In the BRIM-3 Phase 3 study,

vemurafenib demonstrated a 48% response rate and an increased OS benefit compared to dacarbazine with a HR of 0.37, but with inadequate follow-up.

First line data in advanced or metastatic melanoma with pembrolizumab versus ipilimumab was recently presented at the AACR 2015 meeting with an estimated 46.4% 6-month PFS rate for pembrolizumab 10 mg/kg every 3 weeks versus 26.5% for ipilimumab. The ORR was 32.9% for pembrolizumab 2 mg/kg every 3 weeks (Q3W) versus 11.9% for ipilimumab. Responses were ongoing in 96.7% of subjects after a median follow-up of 7.9 months. Median PFS were 4.1 months for pembrolizumab versus 2.8 months for ipilimumab. The hazard ratio for the disease progression for pembrolizumab every 3 weeks versus ipilimumab was 0.58 (95% CI, 0.47 to 0.72; $p<0.001$). At the time of the data cut off for the second interim analysis in this study, which was driven by a minimum follow up of duration of 12 months for all subjects, 289 deaths occurred. One-year estimates of survival for subjects receiving pembrolizumab every 3 weeks were 68.4% as compared with ipilimumab 58.2% (HR for death as compared with ipilimumab group 0.69; 95% CI, 0.52 to 0.90; $p=0.0036$). Because the OS results were superior to those for the ipilimumab group the IDMC recommended stopping the study early to allow patients in the ipilimumab group the option of receiving pembrolizumab [50].

Similarly, nivolumab was studied in subjects with previously untreated advanced melanoma compared to dacarbazine and reported a 5.1 month median PFS compared to 2.2 months for the dacarbazine. The objective response rates were 40% in the nivolumab group and 13.9% in the dacarbazine group. At 1 year the overall rate of survival was 72.9% for the nivolumab group compared to 42.1% in the dacarbazine group. Nivolumab showed significant improvements in overall survival and PFS compared with dacarbazine among previously untreated patients who had metastatic melanoma without BRAF mutation [51].

In 2014, the FDA approved both nivolumab and pembrolizumab, human programmed death receptor-1 (PD-1) blocking antibodies, for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600E mutation positive, a BRAF inhibitor. This indication is approved under accelerated approval based on tumor response rate and durability of response. Both pembrolizumab and nivolumab received NCCN compendia listing recommendations for use in the first line metastatic melanoma setting based on these data. In November 2015, nivolumab received approval for first-line treatment of patients with BRAF V600 wild-type unresectable or metastatic melanoma. In December 2015, the pembrolizumab label was expanded to include first-line treatment of patients with unresectable or metastatic melanoma regardless of BRAF status. The European Commission has also approved pembrolizumab and nivolumab, for both first-line and previously-treated patients with advanced melanoma.

4.1.2 Pre-clinical and Clinical Trials

NOTE: As of Amendment 10, text in this section relating to epacadostat is no longer applicable.

Refer to the Investigator's Brochures (IBs) for pembrolizumab and epacadostat for preclinical and clinical study data.

4.1.3 Ongoing Clinical Trials

NOTE: As of Amendment 10, text in this section relating to epacadostat is no longer applicable.

Refer to the Investigator's Brochures (IBs) for pembrolizumab and epacadostat for preclinical and clinical study data.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

4.2.1.1 Rationale for Combining PD-1 Inhibitor and IDO1 Inhibitor in Melanoma

NOTE: As of Amendment 10, this section is no longer applicable.

If the safety profile is acceptable and this combination is shown to improve PFS and/or OS, this study could support the regulatory approval of this combination in subjects with unresectable or metastatic melanoma.

In an ongoing dose-escalation and expansion study of pembrolizumab in combination with epacadostat subjects with Stage IIIB, IV, or recurrent NSCLC, melanoma, transitional cell carcinoma (TCC), RCC, endometrial adenocarcinoma, or SCCHN are being enrolled. Subjects previously treated with PD-1 or CTLA-4 targeted therapies were excluded. Enrollment is complete in the epacadostat 25 mg BID, 50 mg BID, and 100 mg BID cohorts with pembrolizumab 2 mg/kg IV Q3W. Phase 1 expansion cohorts of epacadostat 50 mg BID, 100 mg BID, and 300 mg BID with pembrolizumab 200 mg IV Q3W are enrolling.

The Phase 2 portion of the study is ongoing in which the recommended Phase 2 dose of epacadostat 100 mg BID is being evaluated in combination with the fixed dose of pembrolizumab 200 mg IV Q3W. Tumor response is being assessed by the investigator using RECIST 1.1.

Among the 117 subjects that have received epacadostat 100 mg BID in combination with pembrolizumab, the most frequently reported (≥ 15%) adverse events (AEs) of any grade for the combined Phase 1 and Phase 2 treatment groups treated with epacadostat 100 mg BID were fatigue (35.0%), constipation (24.8%), diarrhea (20.5%), nausea (20.5%), vomiting (18.8%), pyrexia (16.2%) and dyspnea (15.4%). Fatigue (13.7%) and rash (11.1%)

(including the preferred terms rash, rash maculopapular, rash generalized, and rash macular) were the only treatment-related AE reported in > 10% of subjects. Treatment-related AEs of rash were only reported in the Phase 2 group.

Treatment-related AEs ≥ Grade 3 occurring in more than one subject in the combined Phase 1 and Phase 2 epacadostat 100 mg BID treatment group included rash (5 subjects, 4.3%) and dehydration, lipase increased, AST increased and nausea (2 subjects [1.7%] each).

Based on the Phase 1 safety data of epacadostat doses ranging from 25 mg BID up to 300 mg BID, a dose of 100 mg BID was selected for the Phase 2 portion of Study 202 and for this Phase 3 study of epacadostat to be combined with pembrolizumab 200 mg IV Q3W.

ORR in 19 evaluable subjects with treatment-naïve metastatic melanoma was 58% (11/19) with disease control rate of 74% (14/19). Median PFS has not been reached and all responses are ongoing with min follow up of 31.7 weeks.

4.2.2 Rationale for Dose Selection/Regimen/Modification

4.2.2.1 Justification for Treatment Regimen

NOTE: As of Amendment 10, this section is no longer applicable.

The dose selected for epacadostat for the current study was formed on the basis of having a well-tolerated safety profile as monotherapy and in combination with pembrolizumab, a robust objective response rate, durable disease control rates, as well as providing optimal target inhibition of IDO1 based on nonclinical models. Doses of epacadostat of up to 700 mg BID as monotherapy have been well tolerated and doses of 25 mg BID to 300 mg BID in combination with pembrolizumab, nivolumab, durvalumab and atezolizumab are currently being evaluated in several ongoing Phase 2 studies. Doses of pembrolizumab 2 mg/kg and 200 mg flat dose have been studied in the ongoing Phase 1/2 study of pembrolizumab in combination with epacadostat. Reductions in tumor burden were seen in 14 of 19 evaluable subjects across doses of 25 mg BID to 100 mg BID in combination with pembrolizumab 2 mg/kg and 200 mg flat dosing. Objective responses were observed in all tumor types and all are ongoing and this combination has been well tolerated.

Based on a pharmacokinetic-pharmacodynamic model for epacadostat, nearly all patients' C_{avg} exceeded the IC_{50}, the range of active drug exposure seen in non-clinical models; further dose of 100 mg BID and above exceeded the IC_{50} at trough in nearly all patients [52].

Based on observed systemic exposures and a pharmacokinetic-pharmacodynamic model for epacadostat, all patients who received 100 mg BID epacadostat in combination with pembrolizumab had time-averaged inhibition of IDO1 activity exceeding 50%, a level of PD activity associated with inhibition of tumor growth seen in non-clinical models. Dosing of 100 mg BID and above exceeded the IC_{50} at trough in nearly all patients [52]; further, the majority of patients had trough epacadostat exposures that were above the IC_{50} of IDO1 inhibition. Therefore, 100 mg BID was selected as the recommended Phase 2 dose for

epacadostat in study INCB 24360-202 because this regimen had better tolerability as demonstrated by the Phase 1 safety data including fewer dose modifications (suspension and reductions) and resulted in consistent inhibition of IDO1. The overall experience of the epacadostat 100 mg BID dose in combination with pembrolizumab in study INCB 24360-202 supports this dose selected for the Phase 3 study INCB 24360-301.

4.2.2.2 Rationale for a Fixed Dose of Pembrolizumab

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

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

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

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KEYNOTE-001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Secondly, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

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

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

4.2.3.1.1 Primary Efficacy Endpoints

The dual primary endpoints are PFS and OS.

- Progression-free survival, defined as the time from date of randomization until the earliest date of disease progression, as determined by independent central review of objective radiographic disease assessments per RECIST 1.1, or death from any cause, whichever comes first.

- Overall survival, defined as the time from date of randomization to date of death due to any cause.

The study is considered to have met its study objective if the combination is superior to pembrolizumab and placebo in either PFS or OS.

RECIST 1.1 (Section 12.7) as assessed by independent central review will be used to determine the dates of progression as this methodology is accepted by regulatory authorities. Final determination of radiologic progressive disease (PD) will be based on the central imaging vendor assessment of progression, rather than local site investigator/radiology assessment.

NOTE: As of Amendment 10, central imaging vendor assessment will no longer be required.

4.2.3.1.2 Secondary Efficacy Endpoints

- Objective response rate, defined as the proportion of subjects who have best response as complete response (CR) or partial response (PR). Responses are based on independent central review using RECIST 1.1.

- Duration of response (DOR) determined by disease assessment 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. Response will be determined by independent central review using RECIST 1.1.

4.2.3.2 Immune-related RECIST (irRECIST)

RECIST 1.1 will be adapted to account for the unique tumor response characteristics seen with treatment of 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 can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard RECIST 1.1 may, thus, not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab. Based on an analysis of subjects with melanoma enrolled in KEYNOTE-001, 7% of evaluable patients experienced delayed or early tumor pseudoprogression. Of note, patients who had progressive disease by RECIST 1.1 but not by immune related Response Criteria had longer OS than patients with progressive disease by both criteria. Additionally, the data suggest that RECIST 1.1 may underestimate the benefit of pembrolizumab in approximately 15% of patients. These findings support the need to apply a modification to RECIST 1.1 that takes into account the unique patterns of atypical response in immunotherapy and enable treatment beyond initial radiographic progression.

Immune-related RECIST (irRECIST) is RECIST 1.1 adapted to account for the unique tumor response seen with immuno-therapeutics as described in Nishino et al., CCR 2013. The assessment of unidimensional target lesions and response categories per irRECIST are identical to RECIST 1.1. However, MSD has implemented an adaptation related to new lesions, non-target and tumor burden assessment in order to confirm radiographic progression. irRECIST will be used by local site investigators to assess tumor response and progression, and make treatment decisions as well as by independent central review in support of endpoints.

[redacted]

4.2.3.4 Safety Endpoints

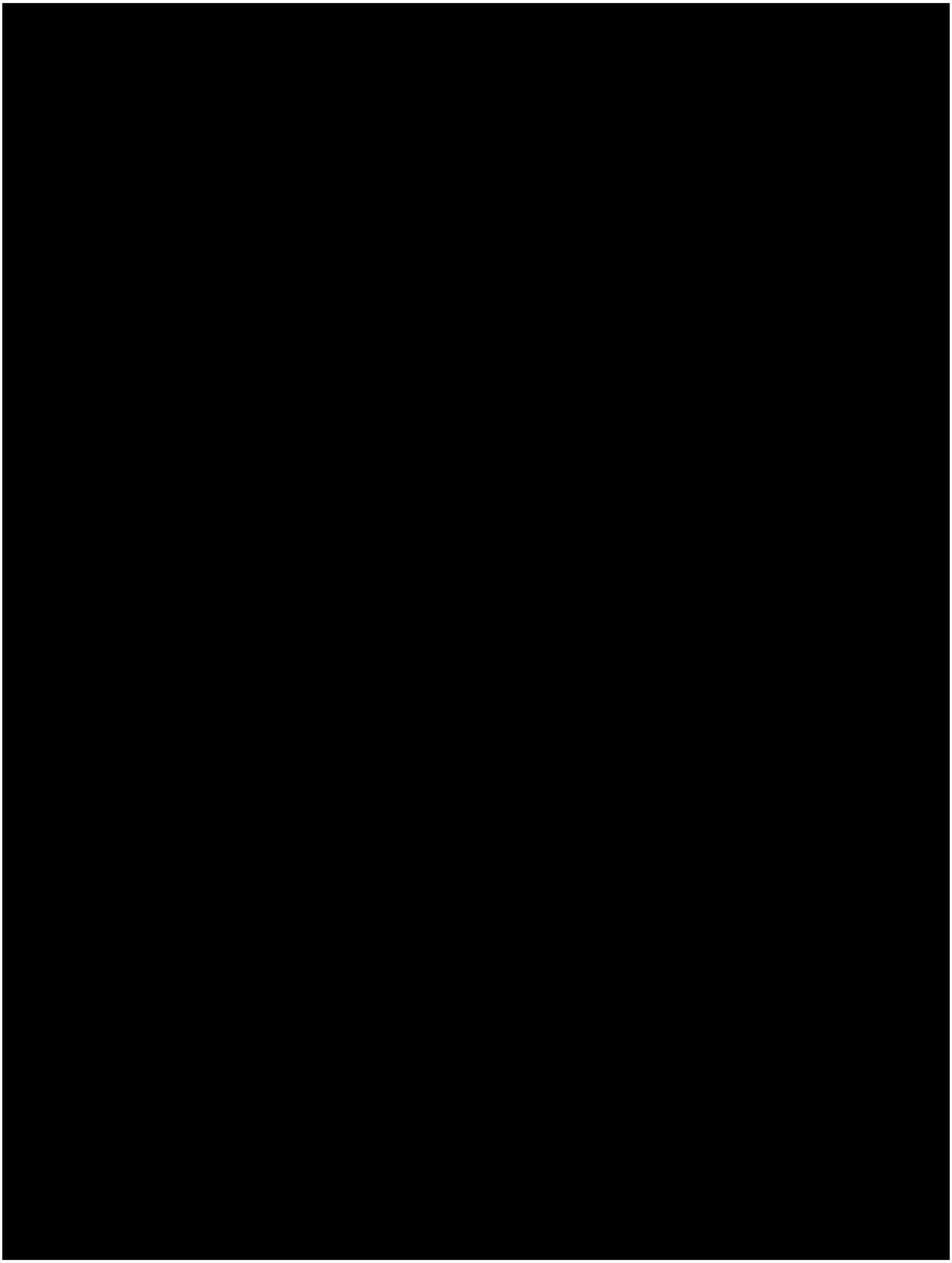
- Safety and tolerability of the treatment regimens through assessment of AEs and changes in safety assessments including laboratory parameters.

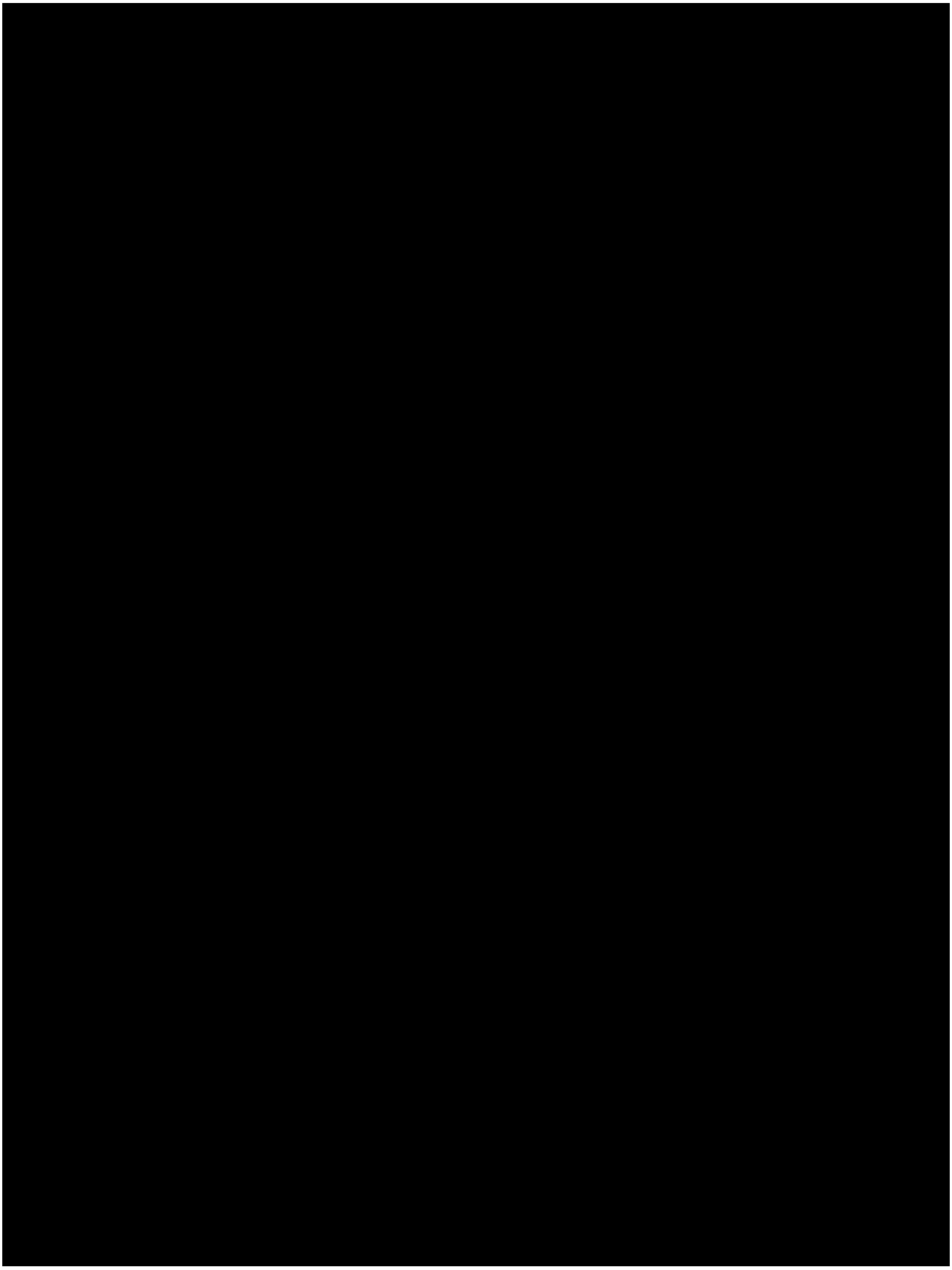
4.2.3.5 Pharmacokinetic Endpoints

- The PK parameters of epacadostat.
- The pharmacokinetics of pembrolizumab and formation of anti-pembrolizumab antibodies will be explored per existing modeling analysis plan (MAP).

NOTE: As of Amendment 10, samples for PK and ADA assessments are no longer being collected.

[redacted]





4.3 Benefit/Risk

It cannot be guaranteed that subjects in clinical trials will directly benefit from treatment during participation, as clinical trials are designed to provide information about the safety and effectiveness.

4.3.1 Risks from Epacadostat

NOTE: As of Amendment 10, this section is no longer applicable.

In 28-day toxicology studies, C_{max} values have exceeded the IC_{50} for the IDO1 enzyme in cells (7 nM) by up to 370-fold, and the IC_{50} for the vasopressin 1a receptor by up to 40-fold (130-fold in single dose studies) in the absence of any toxicity, so the risk of unintended pharmacological activity is expected to be low. In the Phase 1 clinical study in subjects with refractory solid tumors (INCB 24360-101) doses up to 700 mg BID were given without an MTD determined. Epacadostat was well tolerated with a single SAE of exacerbated radiation pneumonitis in a subject with metastases treated at 300 mg BID, 1 report of asymptomatic and reversible hypopituitarism despite continued administration of epacadostat, and 1 event of Grade 3 fatigue determined by the investigator to be related to study drug and considered a DLT in the 400 mg BID dose group.

An uncommon risk of IDO1 inhibition is an increase in serotonin levels that could precipitate a cluster of AEs termed serotonin syndrome (SS) when administered in combination with other serotonergic agents. This rare syndrome has been associated with some monoamine oxidase inhibitors (MAOIs) and combinations of serotonergic drugs [53]. The clinical manifestations of SS range from barely perceptible to lethal; onset is rapid (within 12 hours of drug(s) administration). Based on preliminary studies in the rat, concentrations of epacadostat in the cerebrospinal fluid were below the quantifiable limit of detection (2 nM) after IV dosing, and total brain homogenate concentrations were approximately 15% of corresponding plasma concentrations. In another preclinical study in rats, the effect of epacadostat on the brain extracellular fluid concentration of serotonin was evaluated either alone or when co-administrated with the MAO inhibitor linezolid with or without the Serotonin reuptake inhibitors (SSRI) fluoxetine. Both control conditions resulted in 2-6-fold increases in serotonin. In contrast, neither epacadostat alone or in combination with linezolid had an effect on the brain extracellular serotonin levels. These preclinical data suggest that SS is unlikely following treatment with either epacadostat alone or with combination with MAO inhibitors such as linezolid [61]. Therefore, taken together, epacadostat exhibits apparent limited penetration across the blood-brain barrier and is likely not associated with significant effects on tryptophan metabolism in the brain that might impact brain serotonin levels.

As of 27-FEB-2017, 2 subjects across the epacadostat program (958 subjects treated) have reported serotonin syndrome or symptoms of serotonin syndrome and both were mild in their severity and resolved. One subject reported shivers, increased blood pressure and temperature (Grade 1). The other subject reported Grade 1 tremors and Grade 2 agitation. One subject from Study INCB 24360-202 reported chills, increased blood pressure, and temperature (CTC Grade 1) on Cycle 1 Day 1 and resolved within one week while dosing was stopped. The subject was taking an SSRI and while [redacted] experienced mild symptoms the full constellation of SS was not observed nor could it be ruled out. The SSRI was discontinued and subject was able to restart epacadostat about one week later at the same dose level of 100 mg BID without further incidents. The other subject from Study INCB 24360-203 reported CTC Grade 1 tremors and CTC Grade 2 agitation on Cycle 4 Day 5 and assessed for SS on Cycle 5 Day 1. The subject was not on an SSRI but on a medication for anxiety (Alprazolam). The events resolved and the dosing with epacadostat was interrupted for one week. Retreatment started with a lower dose of epacadostat of 50 mg BID PO from 75 mg BID on Cycle 5 Day 3.

Although this incidence is uncommon, use of MAOIs will be prohibited during the study and all subjects will be provided with an informative subject leaflet describing the signs and symptoms of the syndrome along with instructions to seek immediate medical care if any of these signs or symptoms are observed.

4.3.2 Risks from Pembrolizumab

An open-label Phase I study (KEYNOTE--001) is being conducted to evaluate the safety and clinical activity of single agent pembrolizumab. The dose-escalation portion of this study evaluated 3 dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks in subjects with advanced solid tumors. All 3 dose levels were well tolerated and no DLTs were observed. Based on pharmacokinetic (PK) data showing a half-life of 21 days, the protocol was amended to include a dosing frequency of every 3 weeks in expansion cohorts. Of a total of 479 subjects who have received pembrolizumab in KEYNOTE-001, 466 (97.3%) experienced treatment-emergent AEs, of which 368 (76.8%) were considered drug-related. Serious AEs were reported in 30.1% of subjects, but SAEs that were attributed as potentially (possibly, probably, or definitely) drug-related by investigators were reported in 6.7% of subjects overall. Potential irAEs have been observed, including pneumonitis in both melanoma and NSCLC cohorts. The most commonly reported treatment-emergent AEs experienced have been fatigue, nausea, cough, pruritus, diarrhea, and rash. Most subjects continued treatment despite of AEs, and only 4.2% of subjects discontinued study treatment because of an AE that was considered related to study treatment by investigators. Thus, the overall AE summary suggests that pembrolizumab is generally tolerable, and AEs are generally manageable in subjects.

4.3.3 Risks for the Combination of Pembrolizumab and Epacadostat

NOTE: As of Amendment 10, this section is no longer applicable.

The combination of pembrolizumab and epacadostat has the potential to cause more frequent, more severe, and/or new immune-related toxicities as compared with each individually.

In the ongoing Phase 1/2 study combining pembrolizumab and epacadostat, preliminary data suggest that doses up to 300 mg BID of epacadostat are well tolerated with 200 mg IV of pembrolizumab. While 300 mg bid did not exceed the MTD, there were higher rates of dose holds and reductions compared to 100 mg bid supporting 100 mg bid as the Phase 2 dose (as is detailed later in this section). In the Phase 1 portion of the study, a DLT of Grade 3 rash and Grade 3 arthralgia were seen in 2/19 evaluable subjects with epacadostat 50 mg BID; 2 DLTs out of 15 evaluable subjects were seen with epacadostat 100 mg BID cohort (Grade 3 AST and Grade 2 nervous system disorder, other - ataxia), and 4 DLTs out of 19 evaluable subjects were seen at 300 mg BID (Grade 1 erythema, 2 Grade 3 rashes and 1 nervous system disorder – other – vomiting without nausea).

The most frequently reported (≥ 15%) adverse events (AEs) of any grade for the combined Phase 1 and Phase 2 treatment groups (n=117) treated with epacadostat 100 mg BID were fatigue (35.0%), constipation (24.8%), diarrhea (20.5%), nausea (20.5%), vomiting (18.8%), pyrexia (16.2%) and dyspnea (15.4%). Fatigue (13.7%) and rash (11.1%) (including the preferred terms rash, rash maculopapular, rash generalized, and rash macular) were the only treatment-related AE reported in > 10% of subjects. Treatment-related AEs of rash were only reported in the Phase 2 group.

Any Grade 3/4 AEs occurring in more than 1 subjects in the combined Phase 1 and Phase 2 epacadostat 100 mg BID group include: rash (n=5, 4.3%), dehydration (n=4 3.4%), nausea, vomiting and AST increased, (n= 3 each, 2.6%), diarrhea, small intestine obstruction, fatigue, lipase increased, hypercalcemia, hyponatremia, tumor pain, and pneumonia aspiration (n=2 each, 1.7%). Treatment-related AEs ≥ Grade 3 occurring in more than one subject included rash (5 subjects, 4.3%) and dehydration, lipase increased, AST increased and nausea (2 subjects [1.7%] each).

In subjects receiving epacadostat 300 mg BID, there was an observable trend in increased adverse events of rash (total events as well as severity) and the number of required dose holds and dose reductions for epacadostat, compared to subjects receiving 100 mg BID.

Although the rashes observed at the 300 mg BID dose level were reversible with dose interruptions and medical treatment, total dose interruptions were higher in the 300 mg BID group with 5/19 interrupting epacadostat and 3 requiring dose reductions due to adverse events compared to 1 subject in 100 mg BID requiring a dose interruption, 2 subjects in 50 mg BID and 1 subject in 25 mg BID. Based on the risk for early progression during dose interruptions and dose reductions associated with epacadostat 300 mg BID in combination with pembrolizumab 200 mg IV Q3W, 100 mg BID was selected as the dose for use in the proposed Phase 3 study.

Additional details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying pembrolizumab and epacadostat Investigators Brochures (IBs) and Informed Consent documents.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male/Female subjects with histologically confirmed diagnosis of melanoma with unresectable or metastatic melanoma of at least 18 years will be enrolled in this trial.

5.1.2 Subject Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

1. Have histologically or cytologically confirmed melanoma.

2. Have unresectable Stage III or Stage IV melanoma, as per American Joint Committee on Cancer (AJCC) staging system not amenable to local therapy.

3. Have been untreated for advanced or metastatic disease except as follows.

    a. BRAF V600 mutant melanoma may have received standard of care targeted therapy (e.g. BRAF/MEK inhibitor, alone or in combination) and be eligible for this study

    Note: Targeted therapy is not required for eligibility.

    b. Prior adjuvant or neoadjuvant melanoma therapy is permitted if it was completed at least 4 weeks before randomization and all related adverse events have either returned to baseline or stabilized (resolution of toxic effect(s) of the most recent prior therapy to Grade 1 or less (except alopecia).

    c. Prior adjuvant therapy containing immunotherapy such as interferon or anti-CTLA-4 therapy will only be permitted if relapse did not occur during treatment or within 6 months of treatment discontinuation.

    d. Prior anti-PD-1, anti-PD-L1, or IDO1 inhibitors are excluded.

4. Have documentation of V600-activating BRAF mutation status or consent to BRAF V600 mutation testing during the screening period.

5. Have laboratory parameters within Protocol-defined range. The screening laboratory tests below must be ≤ 7 days before treatment initiation.

    a. Absolute neutrophil count $\geq 1.5 \times 10^9$/L.

    b. Platelets $\geq 100 \times 10^9$/L.

    c. Hemoglobin ≥ 9 g/dL.

    d. Serum creatinine ≤ 1.5 × institutional upper limit of normal (ULN) OR measured or calculated creatinine clearance (glomerular filtration rate can also be used in place of creatinine or CrCl) ≥ 50 mL/min for subjects with creatinine levels > 1.5 × institutional ULN.

    e. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin, < 2.5 × ULN.

    f. Conjugated bilirubin < 2.0 × ULN (need only be tested if total bilirubin exceeds ULN).

    g. International normalized ratio (INR) or prothrombin time (PT) ≤1.5 × ULN unless subject is receiving anticoagulant therapy as long as PT or INR is within therapeutic range of intended use of anticoagulants.

h. Activated partial thromboplastin time (aPTT) ≤ 1.5 × ULN unless subject is receiving anticoagulant therapy, as long as PTT is within therapeutic range of intended use of anticoagulants.

6. Have the presence of at least one measurable lesion by CT or MRI per RECIST 1.1 criteria as determined by the local site investigator/radiology assessment. Cutaneous lesions and other superficial lesions are not considered measurable lesions for the purposes of this protocol, but may be considered as non-target lesions.

    a. If subjects have only 1 measurable lesion per RECIST 1.1, the biopsy specimen should be obtained from the non-target lesion or archival tissue.

    b. If subjects have only 1 measurable lesion per RECIST 1.1, this lesion should not have been in the field of prior irradiation unless there is documented progression of the lesion(s).

7. Provide a baseline tumor biopsy

    a. Subjects must submit the tumor sample during screening for PD-L1 expression testing at a central pathology laboratory. Subjects will be eligible to participate regardless of the level of PD-L1 expression, but will be stratified by PD-L1 expression level. Subjects who do not submit a sample adequate for PD-L1 determination will not be randomized. The biopsy may not be obtained from a lone target lesion.

    b. Newly-obtained tissue is preferred (no intervening treatment [local or systemic] involving the site of tissue biopsy once tissue biopsy is obtained at time of study enrollment). The only exception to this is a sample that was collected prior to BRAF +/- MEK targeted treatment, where the subject progressed on this targeted treatment, in cases where 1) fresh tissue or 2) archival tissue with no intervening local or systemic therapy is not possible to provide.

8. Have resolution of toxic effect(s) of the most recent prior therapy to Grade 1 or less (except alopecia). If a subject received major surgery or radiation therapy of > 30 Gy, they must have recovered from the toxicity and/or complications from the intervention.

9. Be male or female subjects, age 18 years or older on the day of signing consent.

10. [redacted]

11. Have an Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1.

12. If female of childbearing potential (Section 5.7.2), must have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

13. If female of childbearing potential (Section 5.7.2), must be willing to use an adequate method of contraception as outlined in Section 5.7.2 – Contraception, for the course of the study through 120 days after the last dose of study medication.

    Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

14. If male of childbearing potential (Section 5.7.2), must agree to use an adequate method of contraception as outlined in Section 5.7.2- Contraception, and not to donate sperm starting with the first dose of study therapy through 120 days after the last dose of study therapy.

    Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

5.1.3 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

1. Has received prior systemic treatment for unresectable or metastatic melanoma (except BRAF directed therapy as noted in the third inclusion criteria).

2. Has received prior therapy with an anti–PD-1, anti–PD-L1, anti–PD-L2, anti–CD137, or IDO1 inhibitor or any other antibody or drug specifically targeting checkpoint pathways other than anti-CTLA-4 which is permitted in the adjuvant setting.

3. Has received prior adjuvant therapy, monoclonal antibody, chemotherapy, or an investigational agent or device within 4 weeks or 5 half-lives (whichever is longer) before administration of study drug or not recovered (≤ Grade 1 or at baseline) from AEs due to previously administered agents. Exception to this rule would be use of denosumab, which is not excluded.

    Note: Subjects with ≤ Grade 2 neuropathy are an exception and may enroll.

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

5. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include early stage cancers (carcinoma in situ or stage 1) treated with curative intent, basal cell carcinoma of the skin, squamous cell carcinoma of the skin, in situ cervical cancer, or in situ breast cancer that has undergone potentially curative therapy.

6. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least 4 weeks before the first dose of study treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases confirmed by repeat imaging, and have not required steroids for at least 14 days before study treatment.

7. Has ocular melanoma.

8. Has a known hypersensitivity to active substances or any of their excipients including previous clinically significant hypersensitivity reaction to treatment with another monoclonal antibody. For a list of excipients, refer to the respective Investigator Brochure (Section 3.3).

9. Has an active autoimmune disease that has required systemic treatment in past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

10. Has an active infection requiring systemic therapy.

11. Has a known history of human immunodeficiency virus (HIV) (HIV 1/2 antibodies).

12. Has a known history of or is positive for Hepatitis B (HBsAg reactive) or Hepatitis C (HCV RNA [qualitative] is detected). Note: Without a known history, testing needs to be performed to determine eligibility. Hepatitis C Ab testing is allowed for screening purposes in countries where HCV RNA is not part of SOC.

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

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

15. 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.

16. Has received live vaccine within 30 days before the first dose of study treatment. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.

17. Has received monoamine oxidase inhibitors within 21 days prior to starting study treatment.

18. Has any history of Serotonin Syndrome after receiving serotonergic drugs.

19. Has presence of a gastrointestinal condition that may affect drug absorption.

20. 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 Fredericia or Bazett formula). In the event that a single QTc is > 480 milliseconds, the subject may enroll if the average QTc for the 3 ECGs is < 480 milliseconds.

21. Has clinically significant cardiac disease, including unstable angina, acute myocardial infarction within 6 months from Day 1 of study drug administration, New York Heart Association Class III or IV congestive heart failure, and arrhythmia requiring therapy. Medically controlled arrhythmia would be permitted.

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

23. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study.

24. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigation device within 4 weeks of the first dose of treatment.

5.2 Trial Treatment(s)

The treatments to be used in this trial are outlined below in Table 1.

NOTE: As of Amendment 10, only pembrolizumab will be administered. Other treatments (prior to this amendment) have been deleted.

Table 1 Trial Treatment

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
pembrolizumab	200 mg	Every 3 weeks	IV infusion	Day 1 of each cycle for up to 35 pembrolizumab infusions (approximately 2 years)	Experimental

Trial treatment for Cycle 1 should begin within 3 days of randomization. However, every effort should be made to begin trial treatment on day of randomization.

All supplies indicated in Table 16 will be provided centrally 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 trial treatments in accordance with the protocol and any applicable laws and regulations.

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection (Preparation)

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background & Rationale. There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each subject.

5.2.1.2 Dose Modification (Escalation/Titration/Other)

NOTE: As of Amendment 10, text in this section relating to dose modification of epacadostat is no longer applicable and has been deleted.

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, 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 2 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 2 Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab

NOTE: As of Amendment 10, this table was replaced with the guidelines for pembrolizumab alone.

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, or recurrent Grade 3	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	Newly 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		

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
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		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/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).

5.2.1.3 Dose Modification and Toxicity Management of Infusion-reactions Related to Pembrolizumab

Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

Table 3 shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 3 Infusion Reaction 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 subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion and monitor symptoms.** 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 subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., 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 subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing.
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov CTCAE=Common Terminology Criteria for Adverse Events, NCI=National Cancer Institute, NSAID=non-steroidal anti-inflammatory drug, po=oral		

5.2.1.4 Procedures for Subjects Exhibiting Serotonin Syndrome (SS)

NOTE: As of Amendment 10, this section is no longer applicable.

There is a rare chance that epacadostat could cause an increase in serotonin levels in the brain that might trigger serotonin syndrome [53], (Section 12.8) when administered in combination with other serotonergic agents. This syndrome has been most closely associated with use of MAOIs, meperidine, linezolid, or methylene blue; all of these agents are prohibited during the study (Section 5.5.3). Serotonin reuptake inhibitors (SSRIs) and serotonin/norepinephrine reuptake inhibitors (SNRIs) are permitted in the study. Serotonin syndrome usually manifests with autonomic changes, mental status changes, and neurological findings. These mild, moderate, and severe signs and symptoms of SS (summarized in Table 4) should be evaluated in the context of possible comorbid conditions as well.

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

- Immediately interrupt epacadostat or matching placebo and pembrolizumab administration.
- Immediately interrupt any SSRI or SNRI administration.
- Provide appropriate medical management of the subject until all signs/symptoms are resolved (e.g., 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 subject chooses to remain in the study, restart treatment with epacadostat or matching placebo after the SSRI or SNRI has been discontinued, no sooner than 5 half-lives have elapsed for the specific SSRI or SNRI in question, and after resolution of signs/symptoms of SS. The SSRI or SNRI dosing MAY NOT be restarted.
- If subject chooses to withdraw from the study, or must restart treatment with SSRI or SNRI, the subject should be scheduled for a follow-up visit.. Treatment with SSRI or SNRI may be initiated 2 weeks after resolution of signs and symptoms of SS.
- If a subject had experienced moderate or severe unconfounded SS in the opinion of the investigator, without concomitant SSRI or SNRI usage, or serotonergic concomitant medications, only pembrolizumab administration may be resumed; epacadostat/placebo treatment should be permanently discontinued.

Table 4 Sign 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: [62]

5.2.1.5 Dose Interruptions Unrelated to Adverse Events

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

5.2.2 Timing of Dose Administration

5.2.2.1 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 Trial Flow Chart (Section 6.0). 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 Cycle 1 Day 1, where 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 (i.e., infusion time is 30 minutes -5 min/+10 min).

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

5.2.3 Trial Blinding

NOTE: As of Amendment 10, blinding is no longer applicable – all subjects will receive open-label pembrolizumab alone.

A double-blinding technique with in-house blinding will be used. Epacadostat and matching placebo will be packaged identically so that blind is maintained. The subject, the investigator, and Sponsor and MSD study personnel or delegate(s) who are involved in the administration of epacadostat or matching placebo or clinical evaluation of the subjects are unaware of the group assignments.

5.3 Randomization or Treatment Allocation

Treatment allocation/randomization will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). There are 2 treatment arms. Subjects will be assigned randomly in a 1:1 ratio to pembrolizumab + epacadostat or pembrolizumab + matching placebo, respectively. No treatment crossover is planned.

5.4 Stratification

Subjects will be stratified by:

- PD-L1 expression
    - Positive (≥1% of tumor and associated immune cells displaying PD-L1 expression as determined by immunohistochemistry)
    - Negative (<1% expression/indeterminate)
- BRAF mutation status
    - BRAF mutant and received prior BRAF directed treatment
    - BRAF mutant and received no prior BRAF directed treatment
    - BRAF wild type

Recently acquired or archived tumor tissue (obtained since most recent therapy) from an unresectable or metastatic site must be analyzed and be evaluable for PD-L1 status during

screening in order to be randomized. BRAF mutation status will be determined by local standard of care.

5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy or vaccination 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 subject's primary physician. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the investigator, the MSD Clinical Director and the subject.

5.5.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the electronic Case Report Form (eCRF), 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 may also be included on the eCRF.

All concomitant medications received within 28 days before the first dose of study treatment and 30 days after the last dose of study treatment should be recorded. Concomitant medications administered after 30 days after the last dose of study treatment should be recorded for SAEs and AEs as defined in Section 7.2.

5.5.2 Prohibited Medications and Measures

NOTE: As of Amendment 10, prohibited concomitant medications that were specific to epacadostat administration were deleted.

Subjects are prohibited from receiving the following therapies during the screening and treatment phase of this study unless otherwise noted below:

- Any investigational medication other than the study drugs.
- Antineoplastic systemic chemotherapy or biologic therapy.
- Immunotherapy not specified in this protocol.
- Chemotherapy not specified in this protocol.

- Any chronic immunological-suppressive treatment for any reason other than the management of adverse events, as described in Section 5.6. (NOTE: Inhaled or topical steroids are allowed, and systemic steroids at doses ≤ 10 mg/day prednisone or equivalents are allowed, as described in Section 5.6, and immune suppressants are allowed as prophylaxis for contrast allergy for imaging procedures.)

- Radiation therapy or surgery

  Note: In the presence of a mixed response (some lesions improving or stable and other lesions progressing), radiation therapy or surgery to a symptomatic solitary lesion or to the brain is allowed, with MSD consultation. No pembrolizumab infusions are permitted during radiation therapy or procedure. Study medications may be resumed as early as 1 week after treatment if the subject's symptoms are improving and not requiring corticosteroids for management. If study medications are not resumed within 4 weeks of completing treatment, the subject should discontinue study treatment permanently.

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

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study treatment. Subjects may receive other medications that the investigator deems to be medically necessary.

The exclusion criteria (Section 5.1.3) describe other medications that are prohibited during this study. There are no prohibited therapies during the post-treatment follow-up phase.

5.6 Rescue Medications & Supportive Care

5.6.1 Supportive Care Guidelines for Pembrolizumab

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 5.2.1.2. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment

guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: if after the evaluation the event is determined not to be related to pembrolizumab, the investigator does not need to follow the treatment guidance. Refer to Table 2 and Table 3 in Section 5.2.1.2 for guidelines regarding dose modification and supportive care.

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

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

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

5.7.2 Contraception

Pembrolizumab may have adverse effects on a fetus (unborn baby) in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm.

For this trial, male subjects will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

Female subjects will be considered of non-reproductive potential if they are either:

1) postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);

OR

2) have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;

OR

3) has a congenital or acquired condition that prevents childbearing.

Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug and for 120 days after the last dose of study drug by complying with one of the following:

1) practice abstinence† from heterosexual activity;

OR

2) use (or have their partner use) acceptable contraception during heterosexual activity.

Acceptable methods of contraception are‡:

Single method (one of the following is acceptable):

- Intrauterine device (IUD)
- Vasectomy of a female subject's male partner
- Contraceptive rod implanted into the skin

Combination method (requires use of two of the following):

- Diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- Cervical cap with spermicide (nulliparous women only)
- Contraceptive sponge (nulliparous women only)
- Male condom or female condom (cannot be used together)
- Hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

†Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

‡If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

Subjects 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 subjects of childbearing potential must adhere to the contraception requirement (described above) 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 drugs. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

Below are the required contraceptions for countries where the health authority requests compliance with the Clinical Trial Facilitation Group (CTFG) Guidance:

Subjects should use birth control methods that can achieve a failure rate of less than 1% per year when used consistently and correctly and are considered as highly effective birth control methods. Such methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
    - Oral
    - Intravaginal
    - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
        - Oral
        - Injectable
        - Implantable
    - Intrauterine device (IUD)
    - Intrauterine hormone-releasing system (IUS)
    - Bilateral tubal occlusion
    - Vasectomised partner
    - Sexual abstinence

5.7.3 Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, the subject will be immediately discontinued from treatment. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to MSD without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to MSD. If a male subject 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 7.2.

5.7.4 Use in Nursing Women

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

5.8 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or MSD if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal procedures; [redacted] are provided in Section 7.1.7 – Other Procedures.

5.8.1 Discontinuation of Treatment

Discontinuation of treatment does not represent withdrawal from the trial.

As certain data on clinical events beyond treatment discontinuation may be important to the study, they must be collected through the subject's last scheduled follow-up, even if the subject has discontinued treatment. Therefore, all subjects who discontinue trial treatment prior to completion of the treatment period will still continue to participate in the trial as specified in Section 6.0 - Trial Flow Chart and Section 7.1.8.5 – Post-Trial.

Subjects may discontinue treatment at any time for any reason or be dropped from treatment at the discretion of the investigator should any untoward effect occur. In addition, a subject may be discontinued from treatment by the investigator or MSD if treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at treatment discontinuation are provided in Section 7.1.7 – Other Procedures.

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

- The subject or subject's legally acceptable representative requests to discontinue treatment.
- The subject has a medical condition or personal circumstance which, in the opinion of the investigator and/or MSD, placed the subject at unnecessary risk from continued administration of study drug/vaccine.
- The subject has a confirmed positive serum pregnancy test.
- Confirmed radiographic disease progression outlined in Section 7.1.5 (exception if MSD approves treatment continuation).
- Unacceptable adverse experiences as described in Section 7.2.

- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment. Note: **For France only**, a subject experiencing this condition must be discontinued from the trial.

- Intercurrent illness other than another malignancy as noted above that prevents further administration of treatment.

- Recurrent Grade 2 pneumonitis.

- Any toxicity listed in Section 5.2.1.2, Table 2, with a requirement to permanently discontinue.

- Non-compliance with trial treatment or procedure requirements.

- Investigator's decision to discontinue treatment.

- Administrative reasons.

- Completed 35 treatments with pembrolizumab.

  Note: 35 cycles (approximately. 2 years) are calculated from the first dose.

- Discontinuation of treatment may be considered for subjects who have attained a confirmed CR and have been treated for at least 8 cycles (at least 24 weeks) and had at least 2 cycles of the combination (at least 2 doses of pembrolizumab) beyond the date when the initial CR was declared.

The End of Treatment and Follow-up visit procedures are listed in Sections 7.1.8.4 and the Trial Flow Chart - Section 6.0.

For subjects who are discontinued from treatment but continue to be monitored in the trial, see Section 6.0 – Trial Flow Chart, and Section 7.1.8.4 – Post-Trial for those procedures to be completed at each specified visit.

5.8.2 Withdrawal from the Trial

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

For France only: A subject must be discontinued from the trial for the following reason:

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

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

Specific details regarding procedures to be performed at the time of withdrawal from the trial including the procedures to be performed should a subject repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the subject, [redacted] are outlined in Section 7.1.7 – Other Procedures.

5.9 Subject Replacement Strategy

A subject who discontinues from the trial will not be replaced.

5.10 Beginning and End of the Trial

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

5.11 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.

Early trial termination will be the result of the criteria specified below:

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

MSD in collaboration with the Sponsor may terminate the study electively, if required by regulatory decision, or upon advice of the DMC. If the study is terminated prematurely, the investigators, the IRBs and IECs, and regulatory bodies will be notified of the decision and reason for termination of the study. The DMC will recommend termination of the study if warranted, as described in Section 8.2.

In addition, early study termination may occur based on clinical criteria specified below:

1. Quality or quantity of data recording is inaccurate or incomplete;

2. Poor adherence to Protocol and regulatory requirements;

3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects;

4. Plans to modify or discontinue the development of the study drug.

In the event of a decision to no longer supply study drug, ample notification will be provided so that appropriate adjustments to subject treatment can be made.

6.0 TRIAL FLOW CHART

6.1 Trial Flow Chart

As of Amendment 10, epacadostat and placebo administration are stopped and all subjects remaining in the trial receive pembrolizumab alone. For those subjects remaining in the trial, procedures are simplified. The Flow Chart has been amended and assessments no longer required have been deleted.

	Screening Phase	Treatment Cycles				End of Treatment (EOT)	Post-treatment
Treatment Cycle	**Screening (Visit 1)**	**1**	**2**	**3**	**4 -35**	**Treatment Discontinuation**	**Safety Follow-Up**
						At time of Treatment Discontinuation	**30 Days Post-discontinuation**
Scheduling Window (Days)[a]	-28 to -1		± 3	± 3	± 3	± 5	+ 7
Administrative Procedures							
Informed Consent	X						
[redacted]							
Inclusion/Exclusion Criteria	X						
Subject Identification Card	X						
Demographics and Medical History	X						
Prior and Concomitant Medication Review	X	X	X	X	X	X	X
Post-study Anticancer Therapy Status						X	X
Clinical Procedures/Assessments							
Review Adverse Events	X	X	X	X	X	X	X
Full Physical Examination	X						
Directed Physical Examination		X	X	X	X	X[k]	X[k]

	Screening Phase	Treatment Cycles				End of Treatment (EOT)	Post-treatment
Treatment Cycle	**Screening (Visit 1)**	**1**	**2**	**3**	**4 -35**	**Treatment Discontinuation**	**Safety Follow-Up**
						At time of Treatment Discontinuation	**30 Days Post-discontinuation**
Scheduling Window (Days)[a]	-28 to -1		± 3	± 3	± 3	± 5	+ 7
Height, Weight, and Vital Signs (T,P,RR,BP)[b]	X	X	X	X	X	X	X
12-Lead Electrocardiogram (Local)[i]	X	X	X			X[k]	
BRAF Testing	X[j]						
ECOG Performance Status	X[j]	X	X	X	X	X	X
Trial Treatment Administration							
Pembrolizumab Administration		X[a]	X	X	X		
Laboratory Procedures/Assessments: Analysis performed by LOCAL laboratory							
Pregnancy Test[d]	X	X	X	X	X[k]		
PT/INR and aPTT	X[c]	X[k]			X[k]		
CBC with Differential	X[c]		X	X	X[k]		
Chemistry Panel	X[c]		X	X	X[k]		
Urinalysis	X[c]		X		X[k]		
T3, FT4, and TSH	X[c]		X		X[k]		
Hepatitis B and C Testing[l]	X						
Laboratory Procedures/Assessments: Analysis performed by CENTRAL/REFERAL laboratory							
[redacted]							

	Screening Phase	Treatment Cycles				End of Treatment (EOT)	Post-treatment
Treatment Cycle	**Screening (Visit 1)**	**1**	**2**	**3**	**4 -35**	**Treatment Discontinuation**	**Safety Follow-Up**
						At time of Treatment Discontinuation	**30 Days Post-discontinuation**
Scheduling Window (Days)[a]	-28 to -1		± 3	± 3	± 3	± 5	+ 7
Tumor Tissue Collection							
Newly-Obtained Tumor Tissue[e]	X						
Archival Tumor Tissue[f]	X						
Efficacy Measurements							
Tumor Imaging[n]	X[g]				X[h]	X	

a. Cycle 1 treatment must be given within 3 days of allocation. The window for each visit is ± 3 days unless otherwise noted.
b. Height will be measured at Visit 1 only.
c. ECOG Performance Status and Laboratory tests for screening are to be performed within 7 days prior to the first dose of trial treatment. If screening laboratory testing are performed within 7 days of Day 1 they are not required to be evaluated on Day 1 before treatment initiation.
d. For women of reproductive potential, monthly pregnancy testing should be conducted as per local regulations where applicable, and whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected. A serum test can be done if urine is not appropriate. Additionally, if urine test is positive or is not evaluable, a serum test is required. Subjects must be excluded/discontinued in the event of a positive test result.
e. Newly-obtained tissue is preferred (no intervening treatment [local or systemic] involving the site of tissue biopsy once tissue biopsy is obtained at time of study enrollment). Formalin-fixed, paraffin-embedded (FFPE) block specimens are preferred to slides.
f. Archived tissue samples obtained since last treatment may be acceptable. Refer to Section 7.1.4 for details.
g. Screening tumor imaging will be performed within 28 days prior to randomization. Scans performed as part of routine clinical management prior to consent are acceptable for use as the screening scan if they are of diagnostic quality and performed within 28 days before randomization. The same imaging technique should be used in a subject throughout the study. Local reading (investigator assessment with site radiology reading) will be used to determine eligibility and for subject management.
h. Imaging timing should be performed according to the site's standard of care for tumor assessment until initial PD per RECIST 1.1. A repeat scan at least 4 weeks later per irRECIST is not required if the investigator opts to discontinue the subject at the initial PD.
i. Baseline ECGs will be obtained at screening, with additional ECGs obtained at EOT, and as clinically indicated for all subjects. At select centers, additional ECGs will also be obtained at Cycle 1 Day 1 predose and approximately 60 to 90 minutes after the first dose of epacadostat, and Cycle 2 Day 1 predose and approximately 60 to 90 minutes after administration of epacadostat
j. BRAF V600 mutation analysis should be performed locally by the sites during screening in subjects without documented BRAF status. BRAF mutation status will be

	Screening Phase	Treatment Cycles				End of Treatment (EOT)	Post-treatment
Treatment Cycle	**Screening (Visit 1)**	**1**	**2**	**3**	**4 -35**	**Treatment Discontinuation**	**Safety Follow-Up**
						At time of Treatment Discontinuation	**30 Days Post-discontinuation**
Scheduling Window (Days)[a]	-28 to -1		± 3	± 3	± 3	± 5	+ 7

determined by local standard of care.

k. Per standard of care or as clinically indicated.

l. Hepatitis B and C serologies should be obtained for subjects without a known history of Hepatitis B or C. Those with a known history are ineligible. Include HCV RNA (qualitative), HBsAg. See Table 6 for list of laboratory tests. Hepatitis C Ab testing is allowed for screening purposes in countries where HCV RNA is not part of SOC. Hepatitis B and C testing should be performed within the 28 day screening period.

[redacted]

n. CT of C/A/P with contrast are mandatory at baseline, and at minimum, CT of known sites of disease be performed at all follow-up assessments.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

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

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

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

7.1.1.1.1 General Informed Consent

Consent must be documented by the subject's dated signature or by the subject'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 subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject'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 subject's dated signature or by the subject's legally acceptable representative's dated signature.

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

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

[redacted]

7.1.1.2 Inclusion/Exclusion Criteria

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

7.1.1.3 Subject Identification Card

All subjects will be given a Subject 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 subject with a Subject Identification Card immediately after the subject provides written informed consent. At the time of treatment allocation/randomization, site personnel will add the treatment/randomization number to the Subject Identification Card.

The subject identification card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about trial medication/vaccination in emergency situations where the investigator is not available.

7.1.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the investigator. Disease details regarding the subject's melanoma will be recorded separately and not listed as medical history.

7.1.1.5 Prior and Concomitant Medications Review

7.1.1.5.1 Prior Medications

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

7.1.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial through the Safety Follow-up visit.

All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2.

7.1.1.6 Assignment of Screening Number

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

Any subject 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 7.1.8.1.

7.1.1.7 Assignment of Treatment/Randomization Number

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

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

The IVRS/IWRS will be contacted to obtain a subject identification number when a subject enters the screening phase. Upon determining that the subject is eligible for study entry, the IVRS/IWRS will be contacted to obtain study drug assignment. Additionally, the IVRS/IWRS will be contacted at each regular study visit to update the study drug supply.

7.1.1.8 Trial Compliance (Medication)

Administration of trial medications and compliance are provided in Sections 7.1.1.8.

NOTE: As of Amendment 10, text in this section relating to epacadostat is no longer applicable and has been deleted.

Interruptions from the protocol specified treatment plan for > 12 weeks between pembrolizumab doses due to toxicity require consultation between the investigator and MSD and written documentation of the collaborative decision on subject management.

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

7.1.1.8.1 Administration of Pembrolizumab and Compliance

Administration of pembrolizumab (± 3 days) 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.

The instructions for preparing and administering pembrolizumab will be provided in the Pharmacy Manual.

7.1.1.8.2 Dispensing of Pembrolizumab

Site staff will contact IVRS to obtain the subject study drug assignment. The investigator or designee will select the assigned vials and dispense the medication. At subsequent medication dispensing visits, the investigator or designee will follow the same procedures as described above. Full details will be provided in the IVRS Manual.

7.1.1.8.3 Distribution of Subject Reminder Cards and Serotonin Syndrome (SS) Information Sheet

NOTE: As of Amendment 10, this section is no longer applicable.

Subjects will be provided with reminder cards to remind the subject when they should not take their morning dose of epacadostat or matching placebo. On Cycle 1 Day 1, subjects will also be given a serotonin syndrome (SS) information sheet for signs and symptoms of SS. This information sheet also instructs subjects to seek immediate medical care if any of these symptoms are observed.

7.1.1.9 Poststudy Anticancer Therapy Status

The investigator or qualified designee will review all new antineoplastic therapy initiated after the last dose of study treatment until the Safety Follow-up Visit.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Events

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart (Section 6.0) and more frequently if clinically indicated. Adverse events will be graded and recorded throughout the trial and during the follow-up period according to NCI CTCAE Version 4.0 (see Section 12.6). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

Please refer to Section 7.2 for detailed information regarding the assessment and recording of AEs.

7.1.2.2 Full Physical Examination

The investigator or clinical designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. After the first dose of trial treatment new clinically significant abnormal findings should be recorded as AEs.

7.1.2.3 Directed Physical Examination

For cycles that do not require a full physical exam per the Trial Flow Chart (Section 6.0), the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to dosing on Day 1 of each treatment cycle, then per standard of care or as clinically indicated at the EOT visit and 30-day Safety Follow-up Visit. New clinically significant abnormal findings should be recorded as AEs.

7.1.2.4 Vital Signs

Vital sign measurements include blood pressure, pulse, respiratory rate, body temperature, and weight. The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and during the follow-up period as specified in the Trial Flow Chart (Section 6.0). Height will be measured at screening only.

7.1.2.5 Twelve-Lead Electrocardiograms

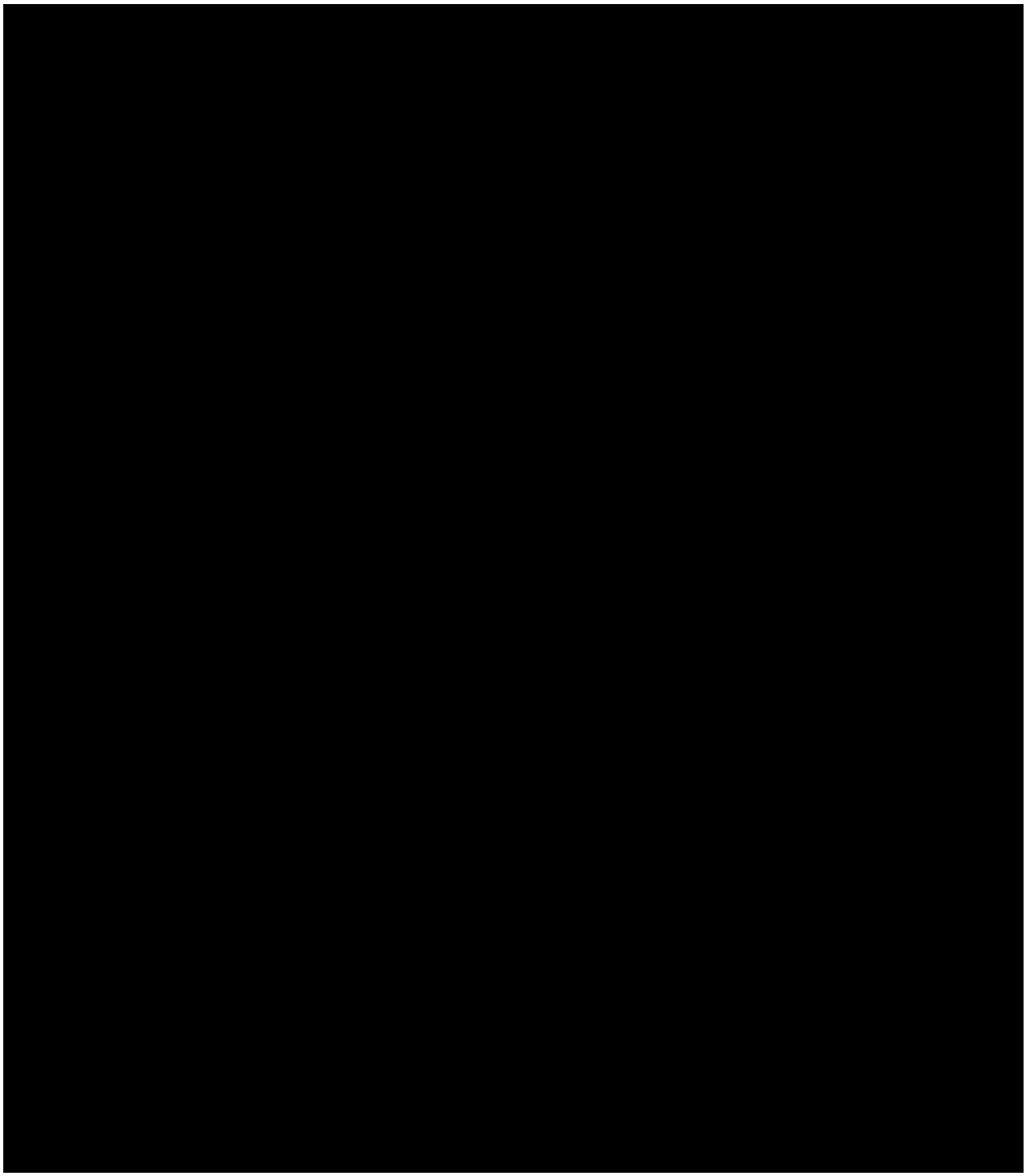
Baseline ECGs will be obtained at screening, with additional ECGs obtained at EOT, and as clinically indicated for all subjects. At select centers, additional ECGs will also be obtained at Cycle 1 Day 1 predose and approximately 60 to 90 minutes after the first dose of epacadostat, and Cycle 2 Day 1 predose and approximately 60 to 90 minutes after administration of epacadostat. Clinically significant abnormal findings prior to signing consent should be recorded as medical history. Clinically significant abnormal findings after signing consent should be recorded as an AE.

The 12-lead ECGs will be interpreted by the investigator at the site and will be used for immediate subject management. The decision to include or withdraw a subject 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 correction method (Fredericia or Bazett) used for calculating QTc will need to be provided in the eCRF.

7.1.2.6 Performance and Quality of Life Assessments

7.1.2.6.1 Eastern Cooperative Oncology Group Performance Status

The investigator or qualified designee will assess ECOG performance status (Section 12.4) at screening and before the administration of each cycle of study treatment and as specified in the Trial Flow Chart (Section 6.0).



[redacted]

7.1.3 Tumor Biopsy/Archival Tissue Collection

7.1.4 Tumor Biopsy

NOTE: As of Amendment 10, optional post-baseline tumor biopsy has been removed.

Fresh tumor biopsies or archived tumor sample will be required at baseline. Newly-obtained tissue is preferred (no intervening treatment [local or systemic] involving the site of tissue biopsy once tissue biopsy is obtained at time of study enrollment).

Note: Submission of formalin-fixed paraffin embedded tumor tissue sample blocks are preferred; if submitting unstained slides, the slides should be freshly cut and submitted to the testing laboratory per the specifications in the procedures manual.

Note: Subjects for whom newly obtained samples cannot be obtained (e.g. inaccessible or subject safety concern) may submit an archived specimen.

Detailed instructions for fresh tissue collection, as well as details for processing and shipping the archived tumor tissue samples will be provided in the Procedures Manual.

7.1.5 Tumor Imaging and Assessment of Disease

NOTE: As of Amendment 10, central imaging vendor assessment is no longer required. Disease assessments will be performed by the site investigator/radiology assessment, per standard of care.

The process for image collection and transmission to the central imaging vendor can be found in the Site Imaging Manual (SIM). Tumor imaging should be acquired by computed tomography (CT, strongly preferred). Magnetic resonance imaging (MRI) should be used when CT is contraindicated or for imaging in the brain. The same imaging technique regarding modality and use of contrast should be used in a subject throughout the trial to optimize the visualization of existing and new tumor burden.

7.1.5.1 Initial Tumor Imaging

Initial tumor imaging must be performed within 28 days before the first date of randomization. The site study team must review prestudy images to confirm the subject has measurable disease per RECIST 1.1. The baseline imaging scan should be submitted to the central imaging vendor for a retrospective analysis of this eligibility criterion.

Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 28 days before the first dose of study treatment. The same imaging technique should be used in a subject throughout the study. Baseline scan must be a CT or MRI, except in circumstances where there is a contrast allergy or with medical monitor approval. When the CT component of a positron emission tomography (PET)/CT uses higher energy and thinner slices, it may be acceptable (with medical monitor approval). A standard, full assessment for lesions should be conducted at baseline, including CT or MRI scans of chest, abdomen, and pelvis. The same modality (CT or MRI) should be used for follow-up assessments, and include radiological assessments of all sites of disease present at baseline. Timing should follow the site's standard of care for oncologic tumor assessment. In addition to radiological monitoring, all other lesions observed at the screening visit should be followed.

For selection of target lesions, RECIST 1.1 should be followed. For example, RECIST discourages selection of target lesions inside the field of prior irradiation. Lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless it is the solitary site of measurable disease AND there has been demonstrated progression in the lesion. Also, if a subject has only 1 measurable lesion, this lesion should not be biopsied.

Subjects with previously treated brain metastases may participate provided they have stable brain metastases, i.e. without evidence of progression by imaging (confirmed by magnetic MRI if MRI was used at prior imaging, or confirmed by CT imaging if CT used at prior imaging) for at least 4 weeks prior to the first dose of trial treatment. Any neurologic symptoms must have returned to baseline and subjects must have no evidence of new or enlarging brain metastases, and have not used steroids for brain metastases for at least 14 days prior to trial initiation as per local site assessment. This exception does not include carcinomatous meningitis, as subjects with carcinomatous meningitis are excluded regardless of clinical stability.

7.1.5.2 Tumor Imaging During the Study

NOTE: As of Amendment 10, central imaging vendor assessment is no longer required. Disease assessments will be performed by the site investigator/radiology assessment, per standard of care.

Tumor imaging may be performed by CT or MRI, but the same imaging technique should be used in a subject throughout the study. Scans must be a contrast CT or MRI, except in circumstances where there is a contrast allergy or with medical monitor approval. When the CT component of a PET/CT uses higher energy and thinner slices, it may be acceptable (with medical monitor approval) if it was the same technique used for baseline. Imaging should include radiological assessments of all sites of disease present at baseline. In addition to radiological monitoring, all other lesions observed at the screening visit should be followed.

Imaging should continue to be performed until documented disease progression, the start of new anticancer treatment, withdrawal of consent, death, or the end of the study, whichever

occurs first. Disease progression should be confirmed at least 4 weeks after the first scan indicating progressive disease in clinically stable subjects. Subjects who have unconfirmed disease progression may continue on treatment until progression is confirmed provided they have met the conditions detailed in Section 7.1.5.3. A repeat scan is not required if the investigator opts to discontinue the subject at the initial PD.

7.1.5.2.1 End of Treatment and Follow-up Tumor Imaging

In subjects who discontinue trial treatment, tumor imaging should be performed at the time of treatment discontinuation (± 4 week window). If a previous scan was obtained within 4 weeks prior to the date of discontinuation, then a scan at treatment discontinuation is not mandatory. In subjects who discontinue trial treatment due to documented disease progression, this is the final required tumor imaging.

7.1.5.3 Assessment of Disease According to irRECIST and RECIST 1.1

NOTE: As of Amendment 10, disease assessments will be performed by the site investigator/radiology using RECIST 1.1 and irRECIST; centralized review per RECIST 1.1 is no longer required.

Modifications to RECIST 1.1 Criteria (irRECIST) will be used for assessment of tumor response for the purposes of managing subjects on protocol treatment and decision making for discontinuation of study therapy due to disease progression. These disease assessments will be performed by the site investigator/radiology assessment. One exception is that for baseline tumor assessments, at least one measurable lesion according to RECIST 1.1 criteria must be present on a bi-dimensional imaging study (CT or MRI) at baseline.

For the purposes of the efficacy endpoints of the study, response assessment based on RECIST 1.1 by independent central review will be applied as the primary measure of progression.

RECIST 1.1 will be adapted for defining PD as follows to account for the unique tumor response seen in this class of therapeutics.

If imaging shows PD, it is at the discretion of the investigator to keep a subject on study treatment or to stop study treatment until imaging is repeated approximately 4 weeks later in order to confirm PD, as described in the irRECIST recommendations. A repeat scan is not required if the investigator opts to discontinue the subject at the initial PD. Subjects that are deemed clinically unstable or who have biopsy proven new metastatic lesions are not required to have repeat imaging for confirmation. This decision will be based on clinical judgment of a subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data. At a minimum, subjects must meet the following criteria for continued treatment on study after disease progression is identified at a tumor assessment:

Subjects may receive study treatment while waiting for confirmation of PD if they are clinically stable (see Table 5) as defined by the following criteria:

- No decline in ECOG performance status
- Absence of new or worsening symptoms
- Absence of rapid progression of disease
- Absence of progressive tumor at critical anatomical sites (e.g., spinal cord compression) requiring urgent alternative medical intervention.

Table 5 Imaging and Treatment after First Radiographic Evidence of Progressive Disease

	Clinically Stable		**Clinically Unstable**	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD	Option to repeat imaging at ≥ 4 weeks to confirm PD	May continue study treatment at the investigator's discretion while awaiting confirmatory imaging	Repeat imaging at ≥ 4 weeks to confirm PD if possible	Discontinue treatment
Repeat imaging confirms PD by irRECIST	No additional imaging required	Discontinue treatment	No additional imaging required	Not applicable
Repeat imaging shows SD, PR, or CR by irRECIST	Continue regularly scheduled imaging assessments per standard of care	Continue study treatment at the investigator's discretion	Continue regularly scheduled imaging assessments per standard of care	May restart study treatment if condition has improved and/or clinically stable per investigator's discretion
CR=complete response; irRECIST=immune-related response evaluation criteria in solid tumors; PD=progressive disease; PFS=progression-free survival; PR=partial response; SD=stable disease				

In determining whether the tumor burden has increased or decreased, investigators should consider all target lesions as well as non-target lesions (refer to the Site Imaging Manual). Subjects who are deemed clinically unstable are not required to have repeat imaging for confirmation. If radiologic progression is confirmed, then the subject will be discontinued from study treatment as specified in the protocol, and the first radiographic evidence of PD should be the date of progression. If radiologic progression is not confirmed, then the subject should resume/continue study treatment and have their next scan according to the Protocol-specified schedule. If progression is not confirmed and the subject continues on treatment,

the next imaging that documents disease progression (and is confirmed by a second tumor imaging at least 4 weeks later), will be considered the date of disease progression.

NOTE: If a subject with confirmed radiographic progression (i.e., 2 images at least 28 days apart demonstrating progressive disease) is clinically stable or clinically improved, and there is no further increase in the tumor dimensions at the confirmatory imaging, an exception may be considered to continue treatment upon consultation with MSD. Clinically stable subjects should also have at the confirmatory scan no further increase in the target lesions, no unequivocal increase in non-target lesions, and no additional new lesions develop (nonworsening PD) to continue study treatment.

7.1.5.4 Photography for Cutaneous Lesions

NOTE: As of Amendment 10, this section is no longer applicable.

Digital photographs documenting measureable cutaneous lesions should be obtained if the cutaneous lesion is included as part of the non-target lesions for disease assessment according to RECIST 1.1. Copies of the photograph should be forwarded to the central imaging vendor for potential retrospective analysis. The timing for capturing cutaneous lesion photographs should follow the same schedule as the imaging scans.

7.1.6 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial follow. The total amount of blood/tissue to be drawn/collected over the course of the trial (from pre-trial to post-trial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per subject can be found in the procedures manual.

After Cycle 1, predose laboratory procedures can be conducted up to 72 hours before study drug administration. Results must be reviewed by the investigator or qualified designee and found to be acceptable before each dose of study treatment.

7.1.6.1 Hematology, Hemostatic Panel, Serology, Urinalysis and Endocrine Function Testing

Hematology, hemostatic panel, urinalysis and endocrine function will all be analyzed by the site laboratory.

7.1.6.2 Serum Chemistry and Liver Function Tests

All serum chemistry testing and liver function testing as shown in the Trial Flow Chart (Section 6.0) will be performed by the site's local laboratory. Throughout the protocol, LFT refers specifically to liver chemistry testing, and required analytes for LFTs are listed in Table 6.

7.1.6.3 Pregnancy Testing

Monthly pregnancy testing should be conducted as per local regulations where applicable, and whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected. If a urine test is positive or not evaluable a serum test will be required. Subjects must be excluded/discontinued from study treatment in the event of a positive or borderline-positive test result.

7.1.6.4 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry and urinalysis are specified in Table 6.

Table 6 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Pregnancy test (serum or urine)[a]
Hemoglobin	Alkaline phosphatase	Glucose	Hepatitis • Hepatitis B surface antigen • Hepatitis B core antibody • HCV-RNA[f]
Platelet count	Alanine aminotransferase (ALT)	Protein	Hemostatic: • PT • aPTT • INR
WBC (total and differential)[e]	Aspartate aminotransferase (AST)	Specific gravity	Endocrine Monitoring: • Thyroid-stimulating hormone (TSH) • Free thyroxine (T4) • Total triiodothyronine (T3)[d]
Red blood cell count	Amylase	Microscopic exam, if abnormal results are noted	LFT Monitoring: • Alkaline phosphatase • ALT • AST • Total bilirubin
Differential count, including: • Basophils • Eosinophils • Lymphocytes • Monocytes • Neutrophils	Bicarbonate or Carbon Dioxide[c]		

Hematology	Chemistry	Urinalysis	Other
	Blood Urea Nitrogen/Urea[b]		IgG - Immunoglobulin G
	Calcium		C-reactive protein (CRP)
	Chloride		
	Creatinine		
	Glucose		
	Lactate dehydrogenase (LDH)		
	Phosphorus		
	Potassium		
	Serum lipase		
	Sodium		
	Total Bilirubin		
	Direct Bilirubin, if total bilirubin is elevated above the upper limit of normal		
	Total protein		

[a] Perform on women of childbearing potential only, 72 hours prior to Day 1 of each cycle and 30 days post treatment.
[b] Blood Urea Nitrogen is preferred; if not available urea may be tested.
[c] If these tests are not done as part of standard of care in your region then these tests do not need to be performed.
[d] T3 is preferred; if not available free T3 may be tested. If the local laboratory is unable to perform either of these tests the site should submit the sample to the central laboratory for testing. Details are provided in the procedures manual. Blood draws for thyroid function tests should be done prior to dosing at the scheduled time point; however results can be reviewed after dosing if they are not available at the time of the scheduled dosing.
[e] Report % or absolute results per standard of practice. Report the results in the same manner throughout the study.
[f] Hepatitis C Ab testing is allowed for screening purposes in countries where HCV RNA is not part of SOC.

Pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing.

7.1.6.5 Pharmacokinetic/Pharmacodynamic Evaluations

NOTE: As of Amendment 10, this section is no longer applicable.

The accumulation of robust PK and ADA data has allowed for the adequate characterization the clinical pharmacology of pembrolizumab across indications. Further collection of samples in subjects receiving pembrolizumab alone is not required. Blood samples for PK and ADA may be stored. Analysis will be performed only if required.

To evaluate the immunogenicity and exposure of pembrolizumab and epacadostat in this indication, sample collections for analysis of PK and anti-pembrolizumab antibodies (ADA)

are currently planned as shown in the Trial Flowchart (Section 6.0). Blood samples collected for PK and ADA may only be stored at this time. Further analysis may be performed if required. If ongoing PK and/or ADA sampling is deemed to be unnecessary by the Sponsor, it may be reduced or discontinued.

7.1.6.5.1 Blood Sample Collection for PK of Pembrolizumab

NOTE: As of Amendment 10, this section is no longer applicable.

Sample collection, storage and shipment instructions for serum samples will be provided in the Procedures Manual. PK samples should be drawn according to the PK collection schedule.

[redacted]

7.1.6.5.2 Blood Sample Collection for Anti-pembrolizumab Antibodies

NOTE: As of Amendment 10, this section is no longer applicable.

Sample collection, storage and shipment instructions for serum samples will be provided in the Procedures Manual. Anti- pembrolizumab antibody samples should be drawn according to the ADA collection schedule. Simultaneous PK sampling is required for interpretation of ADA analysis.

7.1.6.5.3 Blood Sample Collection for PK of Epacadostat

NOTE: As of Amendment 10, this section is no longer applicable.

Pharmacokinetics samples for epacadostat will be required for all subjects enrolled in this study as noted in Table 8 with sample collection times and windows shown. Subjects will arrive at clinic having withheld their morning dose of epacadostat or matching placebo. Pharmacokinetic samples will be obtained at the visits indicated in the Trial Flow Chart (Section 6.0.) Additional timed serial sample collection for epacadostat will be collected at SELECT centers for all subjects enrolled at those centers as indicated in Table 7. All sample times noted are required.

After the predose (predose is defined as within 24 hours before administration of pembrolizumab and before administration of epacadostat) PK sample is drawn, subjects will take epacadostat or matching placebo and then begin infusion of pembrolizumab. The exact date and time of the PK blood draws will be recorded along with the date and time of the last dose of study drug and last meal preceding the blood draw. Instructions for sample preparation and shipping will be provided in the Laboratory Manual.

Table 7 Sample Collection Time Windows for Pharmacokinetic Assessments for Epacadostat or Matching Placebo at SELECT Centers ONLY

Study Visit	Timing of Sample Relative to Epacadostat or Matching Placebo Administration			
C1D1	Predose	1 h ± 30 min	2 h ± 30 min	4-10 h
C2D1	Predose	1 h ± 30 min	2 h ± 30 min	4-10 h

Table 8 Sample Collection Time Windows for Pharmacokinetic Assessments for Epacadostat or Matching Placebo at ALL Centers

Study Visit	Timing of Sample Relative to Epacadostat or Matching Placebo Administration	
C1D1	Predose	1 h ± 30 min
C2D1	Predose	1 h ± 30 min

[redacted]

7.1.6.5.4 Pharmacodynamic Assessments

NOTE: As of Amendment 10, this section is no longer applicable.

Plasma PD samples will be analyzed for changes in the levels of tryptophan and kynurenine by liquid chromatography with tandem mass spectrometry to monitor systemic activity in modulating the IDO1 enzyme. Protein analytes such as relevant tumor markers and markers of immune function may be measured by enzyme-linked immunosorbent assay, or other relevant methods, using these samples.

Plasma samples will be obtained for pharmacodynamic assessments at the visits designated in the Trial Flow Chart (Section 6.0) and Table 9 and will be collected for subjects in the treatment phase only (not in Second Course Phase [Retreatment]). The plasma PD sample collection for epacadostat or matching placebo should occur in parallel with the predose PK sampling for epacadostat or matching placebo outlined in Table 8 for all centers.

Table 9 Plasma Samples for Pharmacodynamic Assessment

Study Visit	Timing of Sample Relative to Epacadostat or Matching Placebo Administration
C1D1	Predose
C2D1	Predose

[redacted]

[redacted]

[redacted]

7.1.7 Other Procedures

7.1.7.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. These subjects should return to the site for the Safety Follow-Up visit and will then be considered to have completed the study.

[redacted]

7.1.7.1.2 Lost to Follow-up

NOTE: As of Amendment 10, this section is no longer applicable. There will be no additional efforts to contact subjects who are lost to follow-up.

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

- The site must attempt to contact the subject and reschedule the missed visit. If the subject is contacted, the subject 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 subject at each missed visit (e.g. phone calls and/or a certified letter to the subject's last known mailing address or locally equivalent methods). These contact attempts should be documented in the subject's medical record.

- Note: A subject is not considered lost to follow up until the last scheduled visit for the individual subject. The amount of missing data for the subject will be managed via the pre-specified data handling and analysis guidelines

7.1.7.2 Blinding/Unblinding

NOTE: As of Amendment 10, blinding is no longer applicable – all subjects will receive open-label pembrolizumab alone.

When the investigator or sub-investigator needs to identify the drug used by a subject and the dosage administered in case of emergency e.g., the occurrence of serious adverse experiences, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or sub-investigator the emergency unblinding call center will provide the information to him/her promptly and report unblinding to MSD. The emergency unblinding call center will make a record promptly however, the investigator or sub-investigator must enter the toxicity grade of the adverse experiences observed, their relation to study drug, the reason thereof, etc., in the medical chart etc., before unblinding is performed.

Additionally, the investigator must go into the IVRS system and perform the unblind in the IVRS system to update drug disposition. In the event that the emergency unblinding call center is not available for a given site in this study, the IVRS/IWRS system should be used for emergency unblinding in the event that this is required for subject safety.

In the event that unblinding has occurred, the circumstances around the unblinding (e.g., date, reason and person performing the unblinding) must be documented promptly, and the MSD Clinical Director notified as soon as possible. Only the principal investigator or delegate and the respective subject's code should be unblinded. Trial site personnel and MSD personnel directly associated with the conduct of the trial should not be unblinded.

Section 5.8 outlines the criteria for allowing subjects who are discontinued from treatment to continue to be monitored in the trial.

At the end of the trial, random code/disclosure envelopes or lists and unblinding logs are to be returned to MSD or designee.

7.1.7.3 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical trial that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably

calibrated and/or maintained to ensure that the data obtained is reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the trial site**.**

Laboratory equipment – as required for inclusion labs and trial assessments

Imaging equipment – as required for study objectives

See protocol-specified guidance in the Administrative Binder, Procedures Manual and Site Imaging Manual.

7.1.8 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.8.1 Screening Visit

Approximately 28 days prior to treatment allocation/randomization, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1. Screening procedures may be repeated after consultation with MSD.

Screening is the interval between the signing of the inform consent form (ICF) and the day the subject received the first dose of treatment in the study (Cycle 1 Day 1). Informed consent must be obtained before performing any study-specific procedures. However, assessments done as part of standard of care prior to informed consent may be used if they are within the required screening period. Screening procedures may be repeated with MSD consultation. Results from the screening visit evaluations will be reviewed to confirm subject eligibility before randomization or the administration of study drug. Baseline radiographic imaging must be performed within 28 days of study start. Subjects may be rescreened after initially failing to meet the inclusion/exclusion criteria.

Subjects who are rescreened will retain their original screening number.

7.1.8.2 Treatment Period Visit

Visit requirements are outlined in the Trial Flow Chart (Section 6). Specific procedure-related details are provided in Section 7.1.

7.1.8.3 End of Treatment

If a decision is made that the subject will permanently discontinue study drug, the EOT visit should be conducted. If the EOT visit coincides with a regular study visit, the EOT evaluations will supersede those of that scheduled visit. The subject should be encouraged to return for the follow-up visit.

7.1.8.4 Post-Treatment Visits

7.1.8.4.1 Safety Follow-Up Visit

NOTE: As of Amendment 10, the Safety Follow-up Visit will be the last visit in the study. This section has been amended as appropriate.

The Safety Follow-Up phase is the interval between the EOT visit and the scheduled Safety Follow-Up visit, which should occur 30 days after the EOT visit (or after the last dose of study drug if the EOT visit was not performed). A subject will be considered to have completed this study once they have attended this visit. Subjects currently in follow-up or in survival follow-up are considered to have completed the study; these subjects are not required to attend any further visits. Assessment and recording of AEs will be performed as per Section 7.2. If a subject initiates a new anticancer therapy within 30 days after the last dose of study treatment, the 30-day Safety Follow-Up visit should occur before the initiation of new anticancer therapy. Reasonable efforts should be made to have the subject return for the follow-up visit and report any AEs that may occur prior to initiating new anticancer therapy.

7.1.8.4.2 Follow-Up Visits

NOTE: As of Amendment 10, this section is no longer applicable. A subject will be considered to have completed this study once they have attended the Safety Follow-up Visit. Subjects currently in follow-up are considered to have completed the study; these subjects are not required to attend any further visits. Assessment and recording of AEs will be performed as per Section 7.2.

Subjects who discontinue study treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 9 weeks (63 ± 7 days) from Week 12 up to Week 102 by radiologic imaging to monitor disease status then every 12 weeks (84 days ± 7 days) thereafter. Every effort should be made to collect information regarding disease status until the start of new anti-cancer therapy, disease progression, death, and end of the study, or if the subject begins retreatment as detailed in Section 7.1.8.3. Information regarding poststudy antineoplastic treatment will be collected if new treatment is initiated.

Subjects who are eligible to receive retreatment according to the criteria in Section 5.2.2 will move from the Follow-Up Phase to the Second Course Phase (Retreatment) when they experience disease progression. Details are provided in Section 5.2.2. MSD consultation will be needed prior to starting Second Course Retreatment.

7.1.8.4.3 Survival Follow-Up

NOTE: As of Amendment 10, this section is no longer applicable. Subjects currently in survival follow-up are considered to have completed the study; these subjects will no longer be contacted for survival information. Assessment and recording of AEs will be performed as per Section 7.2.

Subjects who experience disease progression by site assessment or start a new anti-cancer therapy will move into the Survival Follow-Up Phase and should be contacted by telephone approximately every 9 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

7.1.8.5 Unscheduled Visits

Unscheduled study visits may occur at any time if medically warranted. Any assessments performed at those visits should be recorded in the eCRF.

7.1.8.6 Survival Status

NOTE: As of Amendment 10, this section is no longer applicable. Subjects currently in survival follow-up are considered to have completed the study; these subjects will no longer be contacted for survival information. Assessment and recording of AEs will be performed as per Section 7.2.

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

7.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of MSD's product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events.

Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

MSD's product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by MSD for human use.

Adverse events may occur during clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

A progression of the cancer under study is not considered an adverse event.

All adverse events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

From the time of treatment allocation/randomization through 30 days following cessation of treatment or if the subject initiates new anticancer therapy, whichever is earlier, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1. The investigator will make every attempt to follow all subjects with nonserious adverse events for outcome.

7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose

In this trial, an overdose is any dose higher than ≥1000 mg (5 times the dose) of pembrolizumab. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an adverse event(s) is associated with ("results from") the overdose of MSD's product or vaccine, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of MSD's product or vaccine 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 Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event 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 EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.2 Reporting of Pregnancy and Lactation

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial.

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. Pregnancies and lactations that occur from the time of treatment allocation/randomization through 120 days following cessation of MSD's product, or if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. 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.

Such events must be reported within 24 hours to MSD either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.3 Immediate Reporting of Adverse Events

7.2.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of MSD's product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is an other important medical event.

Note: 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.

Refer to Table 10 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, other than progression of the cancer under study (reference Section 7.2.3.3 for additional details) that occurs to any subject must be reported within 24 hours to MSD if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of trial treatment if the subject initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study (reference Section 7.2.3.3 for additional details) whether or not related to MSD's product, must be reported within 24 hours to MSD either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to MSD's product that is brought to the attention of the investigator at any time following consent through the end of the specified safety follow-up period specified in the paragraph above, or at any time outside of the time period specified in the previous paragraph also must be reported immediately to MSD.

All subjects with serious adverse events must be followed up for outcome.

7.2.3.2 Events of Clinical Interest

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

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to MSD if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 30 days following cessation of treatment, any ECI, or follow up to an ECI, whether or not related to MSD's product, must be reported within 24 hours to MSD, either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Events of clinical interest for this trial include:

1. an overdose of MSD's product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to MSD, 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).

7.2.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

Efficacy endpoints as outlined in this section will not be reported to MSD as described in Section 7.2.3. - Immediate Reporting of Adverse Events to MSD.

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

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

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version v4.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

Table 10 Evaluating Adverse Events

An investigator who is a qualified physician, will evaluate all adverse events as to:

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of MSD's product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new **cancer** (that is not a condition of the study) **(**although not serious per ICH definition, is reportable to MSD within 24 hours to meet certain local requirements); **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause MSD's product to be discontinued?	
Relationship to MSD's product	Did MSD's product cause the adverse event? The determination of the likelihood that MSD's product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between MSD's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely MSD's product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to MSD's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of MSD's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to MSD's product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was MSD's product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of MSD's product; or (3) the trial is a single-dose drug trial); or (4) MSD's product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to MSD's product in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) MSD's product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY MSD'S PRODUCT, OR IF REEXPOSURE TO MSD'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE MSD CLINICAL DIRECTOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding MSD's product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following	**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a MSD's product relationship).**	
Yes, there is a reasonable possibility of MSD's product relationship.	There is evidence of exposure to MSD's product. The temporal sequence of the AE onset relative to the administration of MSD's product is reasonable. The AE is more likely explained by MSD's product than by another cause.	
No, there is not a reasonable possibility of MSD's product relationship	Subject did not receive MSD's product OR temporal sequence of the AE onset relative to administration of MSD's product is not reasonable OR the AE is more likely explained by another cause than MSD's product. (Also entered for a subject with overdose without an associated AE.)	

7.2.5 Responsibility for Reporting Adverse Events

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.

7.3 TRIAL GOVERNANCE AND OVERSIGHT

7.3.1 Scientific Advisory Committee

The Scientific Advisory Committee (SAC) comprises both Sponsor and non-Sponsor scientific experts who provide input with respect to trial design, interpretation of trial results and subsequent peer-reviewed scientific publications.

7.3.2 Executive Oversight Committee

The 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.

7.3.3 Data Monitoring Committee

To supplement the routine trial monitoring outlined in this protocol, an external Data Monitoring Committee (DMC) will monitor the interim data from this trial. The voting members of the committee are external to the Sponsor. The members of the DMC must not be involved with the trial in any other way (e.g., 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 subject safety and the continued ethical integrity of the trial. Also, the DMC will review interim trial results, consider the overall risk and benefit to trial participants (see Section 8.7 - Interim Analyses) and recommend to the EOC if the trial should continue in accordance with the protocol.

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the protocol team; meeting facilitation; the trial governance structure; and requirements for and proper documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is reviewed and approved by the DMC. The DMC will monitor the trial at an appropriate frequency, as described in the detailed DMC charter.

A DMC recommendation will be communicated to as agreed to in the DMC charter.

8.0 STATISTICAL ANALYSIS PLAN

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

8.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 8.2-8.12.

Study Design Overview	A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study of Pembrolizumab in Combination With Epacadostat or Placebo in Subjects with Unresectable or Metastatic Melanoma
Treatment Assignment	Following stratification by PD-L1 expression (Positive; Negative/indeterminate) and BRAF mutation status (BRAF mutant and received prior BRAF directed treatment; BRAF mutant no prior BRAF directed treatment; BRAF wild type) patients will be randomized 1:1 to treatment with pembrolizumab in combination with either epacadostat or placebo
Analysis Populations	Efficacy: Intent to Treat (ITT) Safety: All Subjects as Treated (ASaT)
Primary Endpoint(s)	1. Progression-free survival (PFS) 2. Overall survival (OS)
Key Secondary Endpoints	1. Objective response rate (ORR)
Statistical Methods for Key Efficacy/Immunogenicity/ Pharmacokinetic Analyses	The primary hypotheses will be evaluated by comparing treatment with pembrolizumab and epacadostat to treatment with pembrolizumab and placebo on (1) PFS and (2) OS using a stratified log-rank test. Estimation of the hazard ratio will be done using a Cox regression model. Event rates over time will be estimated within each treatment group using the Kaplan-Meier method.
Statistical Methods for Key Safety Analyses	The analysis strategy for safety endpoints will depend upon the safety tier (see Section 8.6.2). There are no Tier 1 safety endpoints. Descriptive statistics will be provided for the rate of Tier 2 safety endpoints, as well as 95% confidence intervals for the treatment comparisons.

Interim Analyses	Two interim analyses will be performed in this study. Results will be reviewed by an external data monitoring committee. These interim analyses are summarized below. Details are provided in Section 8.7. An analysis of ORR may be conducted using data from interim analysis 2 (IA2). • IA 1: o Timing: To be performed when approximately 331 PFS events are observed. This analysis is expected to be performed about 12 months after enrollment starts. Approximately 100 OS events are expected at IA1. o Testing: Inferential analyses for PFS and OS will be performed. • IA 2: o Timing: to be performed when approximately 420 PFS events are observed. This is the final PFS analysis and is expected to be performed about 24 months after enrollment starts. Approximately 200 OS events are expected at IA2. o Testing: Inferential analyses for PFS and OS will be performed. • Final analysis o Timing: To be performed when approximately 293 OS events are observed. This is the final OS analysis and is expected to be performed about 45 months after enrollment starts. o Testing: Inferential analyses for OS will be performed.
Multiplicity	The Type-I error rate over the multiple endpoints tested, as well as for the multiple analyses planned, will be controlled by sequential interim monitoring and the methods of Maurer and Bretz [59]
Sample Size and Power	The planned sample size was initially approximately 600 subjects. Japan will begin enrolling late in the enrollment period, and must meet a minimum enrollment regulatory requirement. Therefore enrollment from Japan may continue after enrollment in other countries ends. Total enrollment is now expected to be approximately 700 subjects. For PFS, the trial has ~98% power to demonstrate that pembrolizumab and epacadostat is superior to pembrolizumab and placebo at an overall 1-sided 1.25% alpha-level. For OS, the trial has ~79% power to demonstrate that pembrolizumab and epacadostat is superior to pembrolizumab and placebo at an initial overall 1-sided 1.25% alpha-level. Should the PFS comparison be statistically significant, the 1.25% alpha will be re-assigned to OS. Should the OS comparison be statistically significant, the 2.5% alpha will be re-assigned to ORR. Should the total alpha assigned to OS be 2.5%, the power to demonstrate improved OS with the combination will be about 86%. The treatment effect (true hazard rate) is assumed to be 0.65 for PFS and 0.70 for OS.

Based on review of IA2 data, the DMC recommended that all subjects stop oral therapy (epacadostat/placebo). After study completion, only selected analyses will be performed.

8.2 Responsibility for Analyses/In-House Blinding

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

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

The Clinical Biostatistics department will generate the randomized allocation schedule(s) for study treatment assignment. Randomization will be implemented in an interactive voice response system (IVRS).

Planned interim analyses are described in Section 8.7. Study enrollment is expected to be completed at the time of any interim analyses. Blinding to treatment assignment will be maintained at all investigational sites. The results of interim analyses will not be shared with the investigators prior to the completion of the study. Subject-level unblinding will be restricted to an external unblinded statistician and scientific programmer performing the interim analysis for the DMC, who will have no other responsibilities associated with the study.

The external Data Monitoring Committee (DMC) will serve as the primary reviewer of the unblinded results of the interim analyses and will make recommendations for discontinuation of the study or modification to an Executive Oversight Committee (EOC). Depending on the recommendation of the DMC, a regulatory submission may be prepared. If the DMC recommends modifications to the design of the protocol or discontinuation of the study, this EOC and limited additional personnel may be unblinded to results at the treatment level in order to act on these recommendations. The extent to which individuals are unblinded with respect to results of interim analyses will be documented. Additional logistical details, revisions to the above plan, and data monitoring guidance will be provided in the DMC Charter.

Prior to final study unblinding, the external unblinded statistician will not be involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol deviations, or data validation efforts after the interim analyses.

8.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.0. The study is considered to have met its primary objective in the study population if the combination of pembrolizumab and epacadostat is superior to the pembrolizumab and placebo in PFS at an interim PFS analysis or at the final analysis (i.e., interim analysis 2) or in OS at an interim OS analysis or at the final OS analysis.

8.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated for between-treatment differences are listed below, followed by the descriptions of the derivations of selected endpoints.

8.4.1 Efficacy Endpoints

Dual-Primary

Progression-Free Survival – RECIST 1.1

Progression-free survival (PFS) is defined as the time from randomization to the first documented disease progression per RECIST 1.1 based on independent central review or death due to any cause, whichever occurs first. See Section 8.6.1.1 for definition of censoring.

Overall Survival

Overall Survival (OS) is defined as the time from randomization to death due to any cause. Patients without documented death at the time of the final analysis will be censored at the date of the last follow-up.

Secondary

Duration of response (DOR) determined by disease assessment is 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 based upon blinded independent radiologists' RECIST 1.1 assessment.

Objective response rate (ORR) is defined as the proportion of the subjects in the analysis population who have a confirmed complete response (CR) or partial response (PR) based on RECIST 1.1 by independent central review.

[redacted]

8.4.2 Safety Endpoints

Safety measurements are described in Section 8.6.2.

8.5 Analysis Population

8.5.1 Efficacy Analysis Population

The Intent to Treat (ITT) population will serve as the population for the analysis of efficacy data in this study. The ITT population consists of all randomized subjects.

Subjects will be included in the treatment group to which they are randomized for the analysis of efficacy data. Details on the approach to handling missing data are provided in Section 8.6 Statistical Methods.

8.5.2 Safety Analysis Populations

The All Subjects as Treated (ASaT) population will be used for the analysis of safety data in this study. The ASaT population consists of all randomized subjects who received at least one dose of study treatment. Subjects will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the ASaT population. For most subjects this will be the treatment group to which they are randomized. Subjects who take incorrect study treatment for the entire treatment period will be included in the treatment group corresponding to the study treatment actually received

At least one laboratory or vital sign measurement obtained subsequent to at least one 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.

8.6 Statistical Methods

Statistical testing and inference for efficacy analyses are described in 8.6.1. Efficacy results that will be deemed to be statistically significant after consideration of the Type I error control strategy are described in Section 8.8, Multiplicity. Nominal p-values may be computed for other efficacy analyses, but should be interpreted with caution due to potential issues of multiplicity, sample size, etc. Unless otherwise stated, all statistical tests will be conducted at α=0.05 (2-sided) level.

8.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary and secondary objectives. [redacted]

8.6.1.1 Progression-Free Survival (PFS)

To address the primary PFS hypothesis, the Kaplan-Meier method will be used to estimate the PFS curve in each treatment group. The treatment difference in PFS will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (i.e., hazard ratio) between the treatment groups. The hazard ratio and its 95% confidence interval from

the stratified Cox model with Efron's method of tie handling and with a single treatment covariate will be reported. The same stratification factors used for randomization (see Section 5.4) will be applied to both the stratified log-rank test and the stratified Cox model.

Since disease progression is assessed periodically, progressive disease (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. In the primary analysis, for the subjects who have PD, the true date of disease progression will be approximated by the date of the first assessment at which PD is documented based on RECIST 1.1 by independent central review, regardless of discontinuation of study drug. Death as a first event is always considered as a confirmed PD event.

In order to evaluate the robustness of the PFS endpoint, two sensitivity analyses will be performed, each with a different set of censoring rules. The first sensitivity analysis is the same as the primary analysis except that it censors at the last disease assessment without PD when PD or death is documented after more than one missed disease assessment. The second sensitivity analysis is the same as the primary analysis except that it considers discontinuation of treatment or initiation of new anticancer treatment, whichever occurs later, to be a PD event for subjects without documented PD or death. The censoring rules for primary and sensitivity analyses are summarized in Table 11.

Table 11 Censoring Rules for Primary and Sensitivity Analyses of PFS

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
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
PD or death documented 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

In case there is an imbalance between the treatment groups on disease assessment schedules or censoring patterns, the following two additional PFS sensitivity analyses may be performed: 1) a PFS analysis using time to scheduled tumor assessment visit from randomization as opposed to actual tumor assessment time; 2) Finkelstein's likelihood-based score test for interval-censored data [54] which modifies the Cox proportional hazard model for interval censored data, will be used as a supportive analysis for the PFS endpoint. The interval will be constructed so that the left endpoint is the date of the last disease assessment without documented PD and the right endpoint is the date of documented PD or death, whichever occurs earlier.

The proportional hazards assumption on PFS will be examined using both graphical and analytical methods if warranted. The log [-log] of the survival function versus time for PFS will be plotted for the comparison between pembrolizumab and the control group. If the curves are not parallel, indicating that hazards are not proportional, supportive analyses may be conducted to account for the possible non-proportional hazards effect associated with immunotherapies: for example, using Restricted Mean Survival Time (RMST) method [55], parametric method [56], comparison of PFS at fixed follow-up times (6 months; 1 year) etc. Further details of sensitivity analyses will be described in supplemental SAP.

8.6.1.2 Overall Survival (OS)

To address the primary OS hypothesis, the Kaplan-Meier method will be used to estimate the OS curves. The treatment difference in survival will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (i.e., the hazard ratio). The hazard ratio and its 95% confidence interval from the stratified Cox model with a single treatment covariate will be reported. The same stratification factors used for randomization (see Section 5.4) will be applied to both the stratified log-rank test and the stratified Cox model.

8.6.1.3 Objective Response Rate (ORR)

To address the secondary ORR hypothesis, stratified Miettinen and Nurminen's method [57] with weighting based on group size will be used for comparison of the objective response rates between the treatment groups. A 95% confidence interval for the difference in response rates between the pembrolizumab + epacadostat regimen and the pembrolizumab + placebo regimen will be provided. Sensitivity analyses will be performed for ORR using Cochran-Mantel-Haenszel test. Associated odds ratios and 95% CIs will be calculated. The same stratification factors used for randomization (see Section 5.4) will be applied to the analysis. Table 12 summarizes the key efficacy analyses.

Table 12 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
Dual Primary Hypotheses #1 and #2			
Progression free-survival (per independent central review as assessed by RECIST 1.1)	Testing: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Model based
Overall survival	Testing: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Model based
Secondary Objectives			
ORR (per independent central review as assessed by RECIST 1.1)	Testing and estimation: Stratified Miettinen and Nurminen's method	ITT	Model based
DOR (per independent central review as assessed by RECIST 1.1)	Testing: Stratified Log-rank test Estimation: Stratified Cox model with Model based Efron's tie handling method	ITT (responder subs Model based et)	Model based

The strategy to address multiplicity issues with regard to multiple efficacy endpoints and interim analyses is described in Section 8.7, Interim Analyses and in Section 8.8, Multiplicity.

8.6.2 Statistical Methods for Safety Analyses

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

The analysis of safety results will follow a tiered approach (Table 13). The tiers differ with respect to the analyses that will be performed. Safety parameters or adverse events of special interest that are identified *a priori* constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance with p-values and 95% confidence intervals provided for between-group comparisons. For this protocol, there are no Tier 1 events. Other safety parameters will be considered Tier 2 or Tier 3. Tier 2 parameters will be assessed via point estimates with 95% confidence intervals provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters.

Table 13 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint†	p-Value	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	Any AE		X	X
	Any Serious AE		X	X
	Any Drug-Related AE		X	X
	Any Serious and Drug-Related AE		X	X
	Discontinuation due to AE		X	X
	Specific AEs, SOCs, or PDLCs‡ (incidence ≥4/1% of subjects in one of the treatment groups)		X	X
Tier 3	Specific AEs, SOCs or PDLCs‡ (incidence <4/1% of subjects in all of the treatment groups)			X
	Change from Baseline Results (Labs, ECGs, Vital Signs)			X

† Adverse Event references refer to both Clinical and Laboratory AEs.

‡ Includes only those endpoints not pre-specified as Tier 1 or not already pre-specified as Tier-2 endpoints.

Note: SOC=System Organ Class; PDLC=Pre-Defined Limit of Change; X= results will be provided.

Adverse events (specific terms as well as system organ class terms) and predefined limits of change in laboratory, vital signs, and ECG parameters that are not pre-specified as Tier-1 endpoints will be classified as belonging to "Tier 2" or "Tier 3", based on the number of events observed. Membership in Tier 2 requires that at least 4 subjects in any treatment group exhibit the event; all other adverse events and predefined limits of change will belong to Tier 3.

The threshold of at least 4 events was chosen because the 95% confidence interval for the between-group difference in percent incidence will always include zero when treatment groups of equal size each have less than 4 events and thus would add little to the interpretation of potentially meaningful differences. Because many 95% confidence intervals may be provided without adjustment for multiplicity, the confidence intervals should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in adverse events and predefined limits of change.

Continuous measures such as changes from baseline in laboratory, vital signs, and ECG parameters will be considered Tier 3 safety parameters. Summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in table format. In addition, summary statistics for the difference between treatment groups will also be provided, along with nominal p-values for between-group differences. Mean change from baseline over time will be plotted with the corresponding standard errors.

The broad clinical and laboratory AE categories consisting of the percentage of subjects with any AE, a drug related AE, a serious AE, an AE which is both drug-related and serious, and who discontinued due to an AE will be considered Tier 2 endpoints. Ninety-five percent confidence intervals (Tier 2) will be provided for between-treatment differences in the

percentage of subjects with events; these analyses will be performed using the unstratified Miettinen and Nurminen method [57], an unconditional, asymptotic method.

8.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

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 subjects screened, randomized, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables, baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

8.7 Interim Analyses

If the statistical criterion for success for one or more of the primary hypotheses is met at an interim analysis, a regulatory submission may be prepared while the trial continues, and the Clinical Study Report (CSR) will comprise all available data used to draw the conclusion in the decisive interim analysis. The remaining data obtained afterwards (from additional visits and close-out visits) will be reported in a subsequent CSR.

8.7.1 Efficacy Interim Analyses

Three analyses (two interim and one final) are planned in this trial. Table 14 provides the summary of the strategy and timing of the interim and final analyses. Accrual is expected to be completed prior to the first interim analysis. The final analysis of PFS will be performed at interim analysis 2 (IA2) scheduled to be performed at about 420 PFS events (about 24 months following the start of enrollment). The final analysis of OS will be performed at about 293 OS events (about 45 months following the start of enrollment).

Table 14 Summary of Interim Analysis Strategy

Analysis	Key endpoints	Targeted number of events at the time of analysis	Expected approximate timing of analysis (from study start)	Primary purpose of analysis
IA 1	PFS OS	Approximately 331 total PFS events. About 100 OS events are expected at IA1.	About 12 months	First interim analysis of PFS: demonstrate superiority of combination in PFS. First interim analysis of OS; Demonstrate superiority of combination in OS.
IA 2	PFS OS	Approximately 420 total PFS events. This is the final PFS analysis. About 200 OS events are expected at IA2.	About 24 months	Final analysis of PFS: demonstrate superiority of combination in PFS. Second interim look at OS; Demonstrate superiority of combination in OS.
Final	OS	Approximately 293 total OS events. This is the final OS analysis.	About 45 months	Final OS analysis: Demonstrate superiority of combination in OS.

Table 15 provides the details of the interim efficacy monitoring boundaries for PFS and OS.

Table 15 Decision Guidance at IA1 and IA2 PFS Analyses and Each OS Analysis under a Hypothetical Timings of Interim Analyses and Initially Assigned Alpha

Analysis	Targeted number of PFS events	One-sided PFS Efficacy boundary p-value	PFS observed hazard ratio	OS events	One-sided OS efficacy boundary p-value	OS observed hazard ratio
IA 1	~331	< 0.0053	< ~0.75	~100	< 0.0001	< ~0.46
IA 2 (Final PFS analysis)	~420	< 0.0108	< ~0.80	~200	< 0.0029	< ~0.68
Final OS Analysis				Targeted for ~293	< 0.0115	< ~0.77

The final analysis will take place when about 293 deaths have occurred between the pembrolizumab + epacadostat regimen and the pembrolizumab + placebo regimen, which is expected to occur ~45 months after study start. According to Table 15 the nominal alpha for the final OS testing is 0.0115 (one-sided) if no alpha re-use occurs. A nominal alpha < 0.0115 corresponds to the approximate observed hazard ratio for OS superiority < 0.77. The nominal alpha level for PFS and OS interim hypothesis testing will be re-calculated if the actual number of events available at the times of the interim analyses is different from those specified above. The nominal alpha level for OS interim hypothesis testing will be re-

calculated if alpha is transferred to the OS hypothesis testing following a significant difference seen in PFS. A 95% confidence interval will be provided for the hazard ratios to characterize the PFS and OS effects in case the superiority of the combination is not demonstrated.

ORR analysis: Should the definitive OS analysis be statistically significant at any interim or final analysis, the definitive ORR analysis will be performed using the data available at IA2.

8.7.2 Safety Interim Analyses

The external Data Monitoring Committee (DMC) will perform ongoing review of the interim safety data from this trial, as described in Section 7.3.3.

8.8 Multiplicity

The multiplicity strategy specified in this section will be applied to the overall ITT population for the testing of primary hypotheses. The overall type I error is strongly controlled at 2.5% (one-sided) for the multiple endpoints tested, as well as for the multiple analyses of overall survival planned using the methods of Maurer and Bretz [59], with 1.25% allocated up front to the PFS hypothesis and 1.25% allocated up front to the OS hypotheses. The trial is considered statistically positive if either PFS or OS is positive.

The superiority of PFS will be tested at 1.25% in this study. If the pembrolizumab + epacadostat combination regimen demonstrates superior PFS, the 0.0125 alpha will be re-assigned to the comparison of OS. Should the OS comparison be statistically significant, the alpha assigned to OS will be reassigned to the comparison of ORR.

A graphical display of the plans for re-allocation of alpha is displayed in Figure 3.

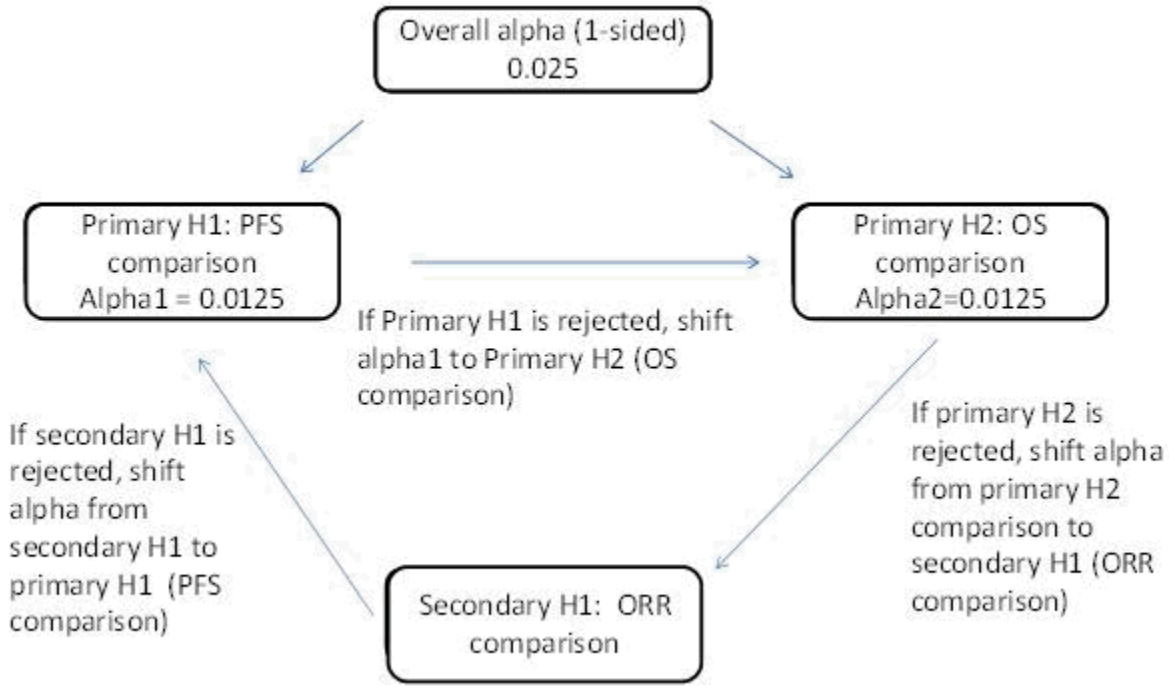


Figure 3 Graphical Display of Testing Strategy

For the PFS and OS hypothesis, an exponential alpha-spending function (see Anderson and Clark [60]) with nu=0.75 (approximating an O'Brien-Fleming boundary) will be used. For PFS the cumulative alpha will be 1.25% unless OS and ORR are statistically significant, in which case the 1.25% alpha associated with OS will be reallocated to PFS and testing will be done at 2.5% alpha. For OS, the cumulative alpha will be 1.25% (if PFS superiority is not demonstrated) or 2.5% (if PFS superiority is demonstrated).

8.9 Sample Size and Power Calculations

8.9.1 Sample Size and Power for Efficacy Analyses

The study will randomize subjects in a 1:1 ratio into the pembrolizumab + epacadostat regimen and the pembrolizumab + placebo regimen. The overall sample size for this study was projected to be ~600 subjects (maximum enrollment 660). Enrollment, excluding Japan, was 662 subjects, and is expected to be a total of 700 subjects after enrollment in Japan is completed.

The study is event driven (i.e., number of subjects and follow-up time are subject to change but number of events is not) and will complete after approximately 293 deaths have been observed between the two treatments.

***PFS analysis*:** The primary PFS analysis will be carried out at the second interim analysis, which occurs after about 420 PFS events have been observed, expected to occur about 24 months from the start of enrollment. An initial alpha of 1.25% will be allocated to the PFS analysis. If the number of PFS events is exactly as specified in Table 15, the study has about 98% power to detect a 0.65:1.00 hazard ratio favoring combination therapy. A p-value less than 0.0108 for PFS corresponds to an approximate observed hazard ratio < 0.80.

***OS analyses*:** OS efficacy analyses will be performed at the first and second interim analyses. The final analysis will be conducted when about 293 deaths have been observed. An initial alpha of 1.25% will be allocated to the OS analysis. If the comparison of PFS is not statistically significant, and the number of OS events is exactly as specified in Table 15, the study has about 79% power to detect a 0.70 hazard. Details on the nominal alpha and the approximate efficacy boundary at each interim analysis are summarized in Section 8.2.9. The nominal alpha levels will be re-calculated based upon the actual observed number of deaths at each interim analysis using the alpha-spending function. If the comparison of PFS is statistically significant, the 1.25% allocated to the PFS comparison will be re-allocated to the OS comparison. If superiority of the combination is demonstrated for PFS, the OS comparison will be performed at an alpha of 2.5% and, if the final analysis is done at 293 OS events, the power to detect a true hazard ratio of 0.70 will be approximately 86%. If the accumulation of the final number of OS events (293) is substantially delayed from the estimated 45 months, an additional interim analysis may be added.

ORR analysis: Should the definitive OS analysis be statistically significant, the definitive ORR analysis will be performed using the data available at IA2. Assuming the available alpha for the ORR comparison is 2.5% and an ORR of 35% for the pembrolizumab + placebo regimen, the study has ~97% power to detect an ORR rate for the combination regimen of 50%.

The above calculations are based on the following assumptions (in addition to the interim analysis plan in Section 8.7): 1) OS for the pembrolizumab + placebo regimen follows a distribution with a "cure" rate of 35%, with survival for the remaining 65% of patients following an exponential distribution with a median of 14 months; 2) PFS follows a distribution with a "cure" rate of 30%, with PFS for the remaining 70% of patients following an exponential distribution with a median of 4.75 months in the pembrolizumab + placebo regimen; 3) the hazard ratio for OS between the pembrolizumab + epacadostat combination and pembrolizumab + placebo is 0.7; 4) hazard ratio for PFS between the pembrolizumab + epacadostat combination and pembrolizumab + placebo is 0.65 and 5) an enrollment period of approximately 12 months. The sample size and power calculation were performed in the software R package gsDesign (see R code, Section 12.10).

8.10 Subgroup Analyses and Effect of Baseline Factors

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

- Age category (<65 vs. ≥65 years)
- Sex (female vs. male)
- Race (white vs. non-white)
- Disease stage (III vs. IVM1a vs. IVM1b vs. IVM1c)
- ECOG status (0 vs. 1)
- BRAF mutation status (wild type vs. mutant with prior BRAF directed therapy vs. mutant with no prior BRAF directed therapy)
- PD-L1 status (positive vs. negative [includes indeterminate])
- LDH (≤ ULN vs. > ULN but < 2X ULN vs. ≥ 2X ULN)

In addition, a Forest plot will be produced, which provides the estimated point estimates and confidence intervals for the treatment effect across the categories of subgroups listed above.

The consistency of the treatment effect will be assessed descriptively via summary statistics by category for the classification variables listed above.

8.11 Compliance (Medication Adherence)

Pembrolizumab: Drug accountability data for pembrolizumab will be collected during the study. Compliance with protocol-directed pembrolizumab will be measured by subjects: (1) receiving unscheduled study agent infusions/injections, (2) missing an infusion/injection, (3) receiving incorrect study agent dose, and (4) receiving an infusion at rate greater than 10 mL/min. Numbers and percentages of subjects and infusion/injection visits with any deviation in these measures will be reported for the ITT population.

Epacadostat: In this study, as part of the routine recording of the amount of study treatment taken by each subject will be counted, reviewed, and recorded at regular intervals. These results will be used to calculate subject compliance.

- For a subject who is followed for the entire study period, the "Number of Epacadostat Doses Should be on Therapy" is the total number of protocol specified doses from first treatment day to the last scheduled day for treatment administration for that subject. For a subject who discontinued from the study permanently, the "Number of Epacadostat Doses Should be on Therapy" is the total number of doses from first treatment day to the date the subject discontinued from the study.

Percent compliance is defined as "the number of doses the patient received on therapy" divided by "the number of doses the patient should have received on therapy" multiplied by 100.

Summary statistics will be provided on percent compliance by treatment group for the ITT population.

8.12 Extent of Exposure

The extent of exposure will be summarized by treatment as duration of treatment in cycles. Dose intensity will also be summarized as appropriate.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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 investigational product in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies will be provided by MSD as summarized in Table 16.

Table 16 Product Descriptions

Product Name & Potency	Dosage Form
pembrolizumab 100 mg/4 mL	Solution for Infusion

9.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

Pembrolizumab (MK-3475) will be provided as a kitted supply.

9.3 Clinical Supplies Disclosure

NOTE: As of Amendment 10, blinding is no longer applicable – all subjects will receive open-label pembrolizumab alone.

This is a blinded trial in which the epacadostat or epacadostat placebo treatment is blinded. However, the pembrolizumab (MK-3475) provided for the trial is open-label; therefore, the subject, the trial site personnel, the Sponsor, MSD and/or designee are not blinded to the

MK-3475 treatment. Treatment (name, strength or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

The emergency unblinding call center will use the treatment/randomization schedule for the study to unblind subjects and to unmask epacadostat or matching placebo treatment identity The emergency unblinding call center should only be used in cases of emergency (see Section 7.1.7.2). In the event that the emergency unblinding call center is not available for a given site in this study, the central electronic treatment allocation/randomization system (IVRS/IWRS) should be used in order to unblind subjects and to unmask study treatment identity. MSD will not provide random code/disclosure envelopes or lists with the clinical supplies.

Treatment identification information is to be unmasked ONLY if necessary for the welfare of the subject. Every effort should be made not to unblind the subject unless necessary.

In the event that unblinding has occurred, the circumstances around the unblinding (e.g., date, reason and person performing the unblinding) must be documented promptly, and MSD Clinical Director notified as soon as possible. Only the principal investigator or delegate and the respective subject's code should be unblinded. Trial site personnel, MSD, and Sponsor personnel directly associated with the conduct of the trial should not be unblinded to treatment assignment.

Section 5.8 outlines the criteria for allowing subjects who are discontinued from treatment to continue to be monitored in the trial.

9.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

9.5 Discard/Destruction/Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from MSD or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial. 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.

9.6 Standard Policies

Trial site personnel will have access to a central electronic treatment allocation/randomization system (IVRS/IWRS system) to allocate subjects, to assign treatment to subjects and to manage the distribution of clinical supplies. Each person accessing the IVRS system must be assigned an individual unique PIN. They must use only their assigned PIN to access the system, and they must not share their assigned PIN with anyone.

At the close of the trial after unblinding, a letter is to be sent by the investigator to those subjects who received placebos in the image of MSD'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."

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

By signing this protocol, the investigator affirms that information furnished to the investigator will be maintained in confidence, and such information will be divulged to the institutional review board, ethics review committee (IRB/ERC) 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.

10.1.2 Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor, MSD, or Sponsor or MSD representative, IRB/ERC, 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 subject agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission.

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

10.1.3 Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and trial site personnel, may be used and disclosed for trial management purposes, as part of a regulatory submissions, and as required by law. This information may include:

1. name, address, telephone number and e-mail address;

2. hospital or clinic address and telephone number;

3. curriculum vitae or other summary of qualifications and credentials; and

4. other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, MSD, and subsidiaries, affiliates and agents of the Sponsor or MSD, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory authorities or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

If this is a multicenter trial, in order to facilitate contact between investigators, an investigator's name and contact information may be shared with other participating investigators upon request.

10.1.4 Confidentiality of IRB/IEC Information

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

10.2 Compliance with Financial Disclosure Requirements

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

The investigator/subinvestigator(s) agree, if requested in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor and 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 provided Certification/Disclosure Form, commonly known as a financial disclosure form. The

investigator/subinvestigator(s) also consent to the transmission of this information to and within the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.3 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 (e.g., 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, is provided in Section 12.1 - Merck Code of Conduct for Clinical Trials.

The investigator also agrees to allow monitoring, audits, IRB/ERC review and regulatory authority inspection of trial-related documents and procedures and provide for direct access to all trial-related source data and documents.

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

The investigator shall prepare and maintain complete and accurate trial documentation in compliance with Good Clinical Practice standards and applicable federal, state and local laws, rules and regulations; and, for each subject participating in the trial, provide all data, and, upon completion or termination of the clinical trial, submit any other reports as required by this protocol or as otherwise required pursuant to any agreement.

Trial documentation will be promptly and fully disclosed 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 the Sponsor or MSD or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested as a result of an audit to cure deficiencies in the trial documentation and worksheets/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol,

the investigator agrees that documentation shall be retained until at least 2 years after the last approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. The MSD team will determine the minimum retention period and notify the investigator when documents may be destroyed. MSD will determine the minimum retention period and upon request, will provide guidance to the investigator when documents no longer need to be retained. MSD also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval by MSD prior to destroying trial and/or subject files.

ICH Good Clinical Practice guidelines recommend that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

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

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 trial. 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.

In the event a particular trial site is prematurely terminated, that trial site's IRB/IEC.

According to European legislation, a sponsor must designate an overall coordinating investigator for a multi-center trial (including multinational). When more than one trial site is open in an EU country, MSD will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different trial sites in that Member State, according to national regulations. For a single-center trial, the Protocol CI is the principal investigator. In addition, MSD must designate a principal or coordinating investigator to review the trial report that summarizes the trial results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the trial [Clinical Study Report (CSR) CI]. MSD may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the CI during the anticipated review process, thorough understanding of clinical trial methods, appropriate enrollment of subject cohort, timely achievement of trial milestones). The Protocol CI must be a participating trial investigator.

10.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. The Sponsor will review this protocol and submit the information necessary to fulfill these requirements. Entries are not limited to FDAMA/FDAAA mandated trials. Information posted will allow subjects 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 FDAMA/FDAAA are that of the Sponsor and agrees not to submit any information about this trial or its results to the Clinical Trials Data Bank.

10.5 Quality Management System

By signing this protocol and in contract with the Sponsor, MSD agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, 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.

10.6 Data Management

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.

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

10.7 Publications

Study results will be published in accordance with applicable local and national regulations. If necessary, the authorities will be notified of the investigator's name, address, qualifications, and extent of involvement. The terms regarding the publication of study results are contained in the agreement signed with the Sponsor and/or MSD. A signed agreement will be retained by the Sponsor and/or MSD.

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12.0 APPENDICES

12.1 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 subject 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 (e.g., 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 subject preferences, etc.

The design (i.e., subject population, duration, statistical power) must be adequate to address the specific purpose of the trial. Research subjects 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 subjects, 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. Subject Protection

A. IRB/ERC review

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

B. Safety

The guiding principle in decision-making in clinical trials is that subject welfare is of primary importance. Potential subjects 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. Subjects are never denied access to appropriate medical care based on participation in a Merck clinical trial.

All participation in Merck clinical trials is voluntary. Subjects are enrolled only after providing informed consent for participation. Subjects 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 subject 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 subject 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 subjects 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 subject referrals. However, Merck may compensate referring physicians for time spent on chart review to identify potentially eligible subjects.

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/ERC 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.

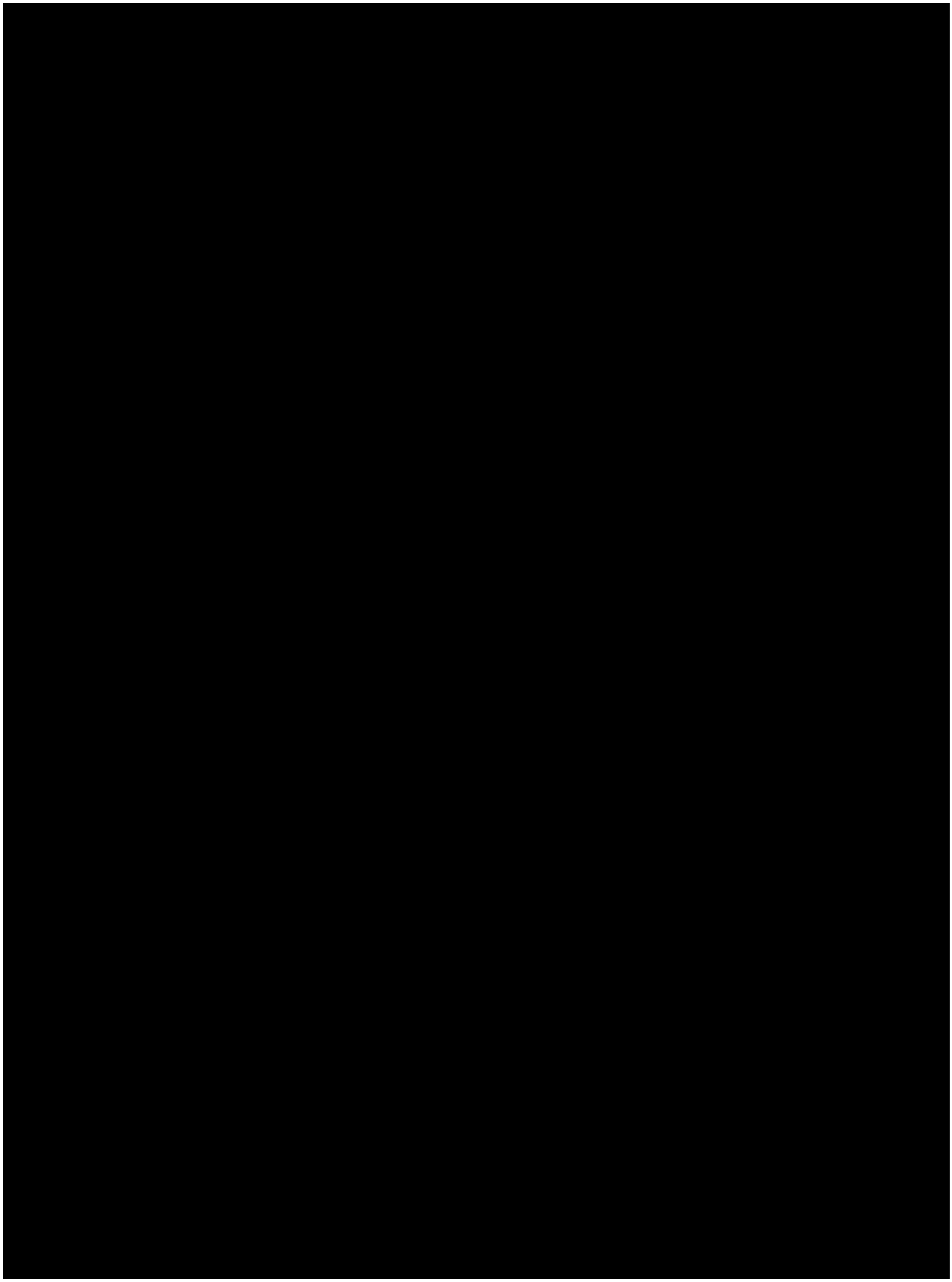
C. Funding for Travel and Other Requests

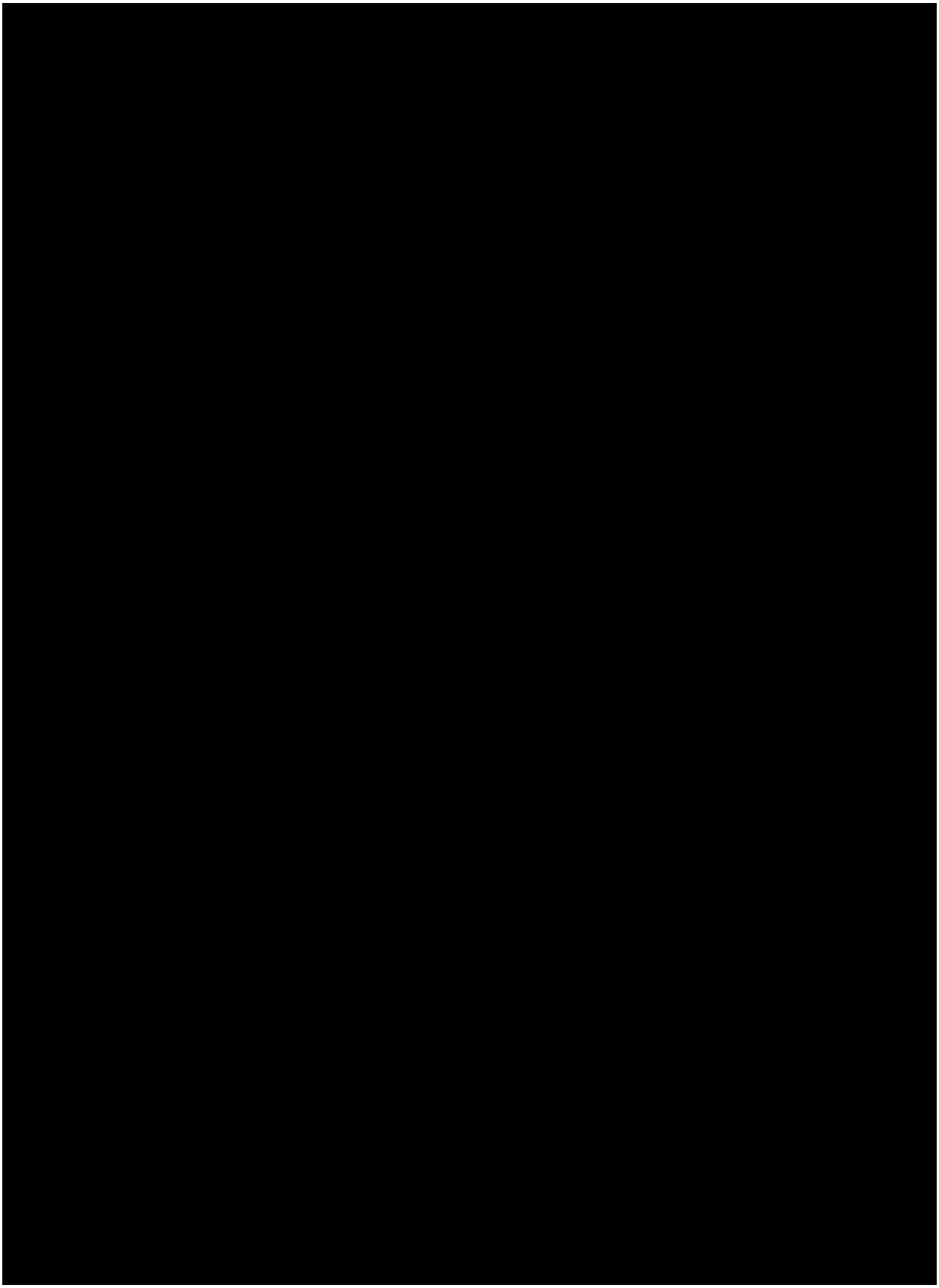
Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices including, in the U.S., those established by the American Medical Association (AMA).

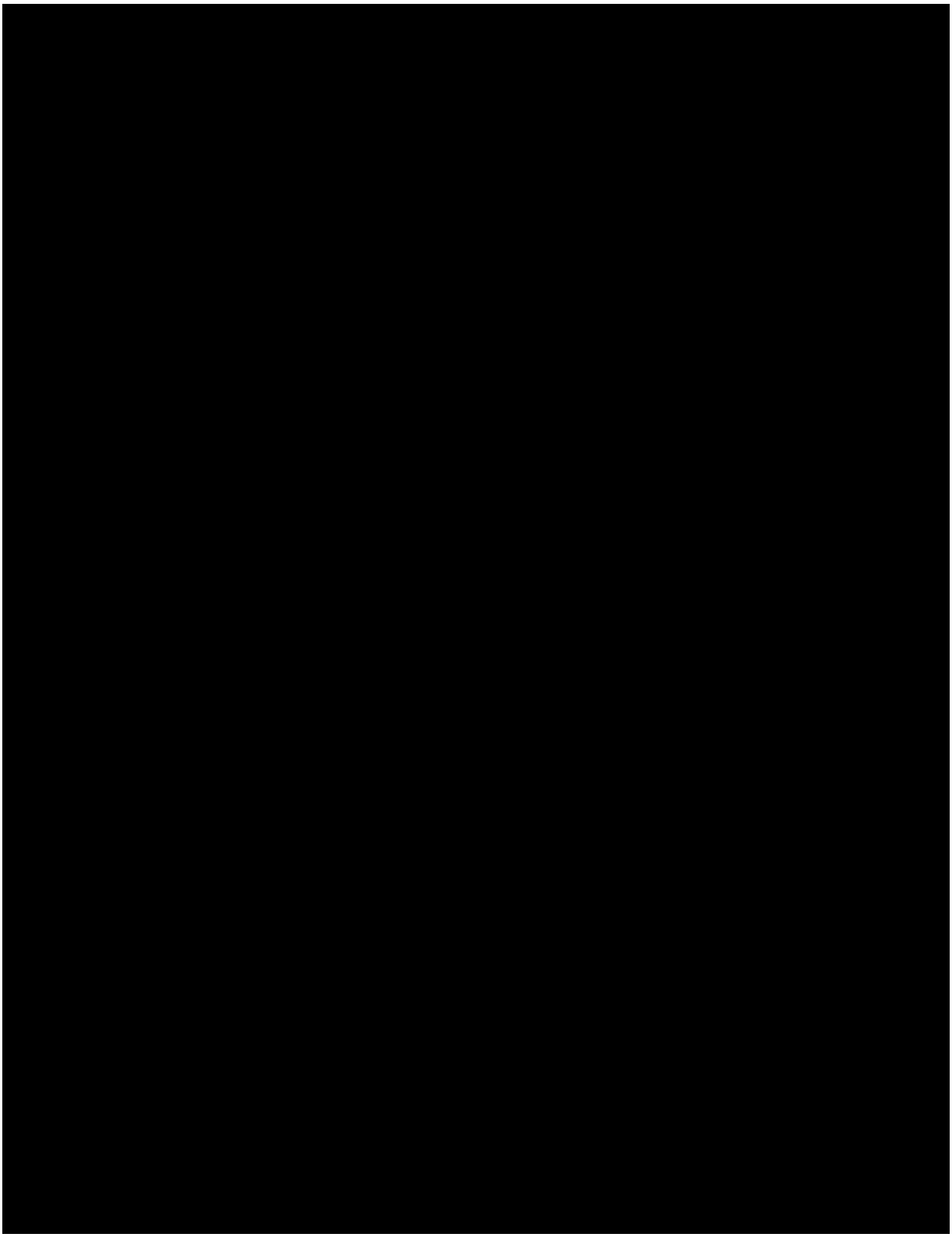
V. Investigator Commitment

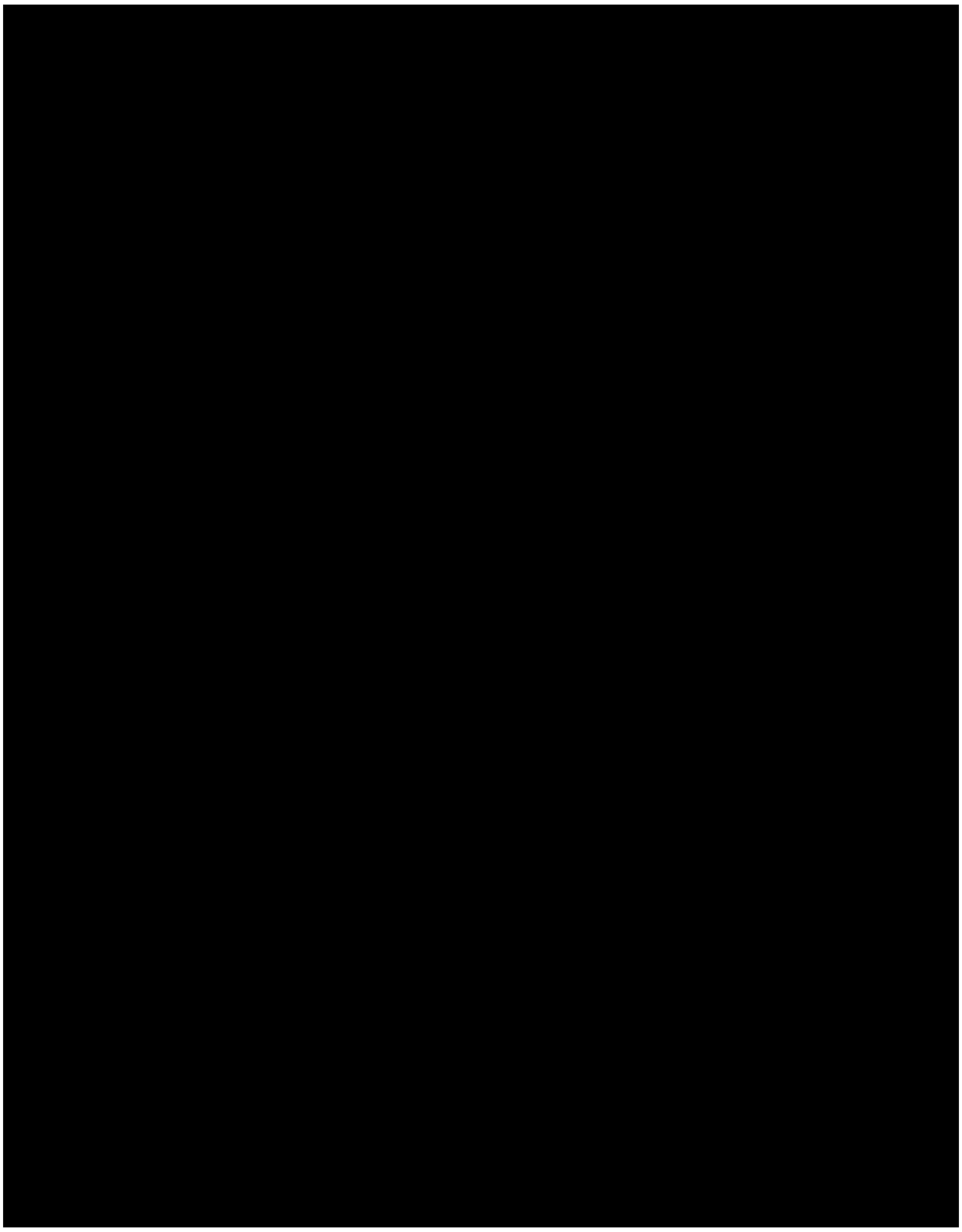
Investigators will be expected to review Merck's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

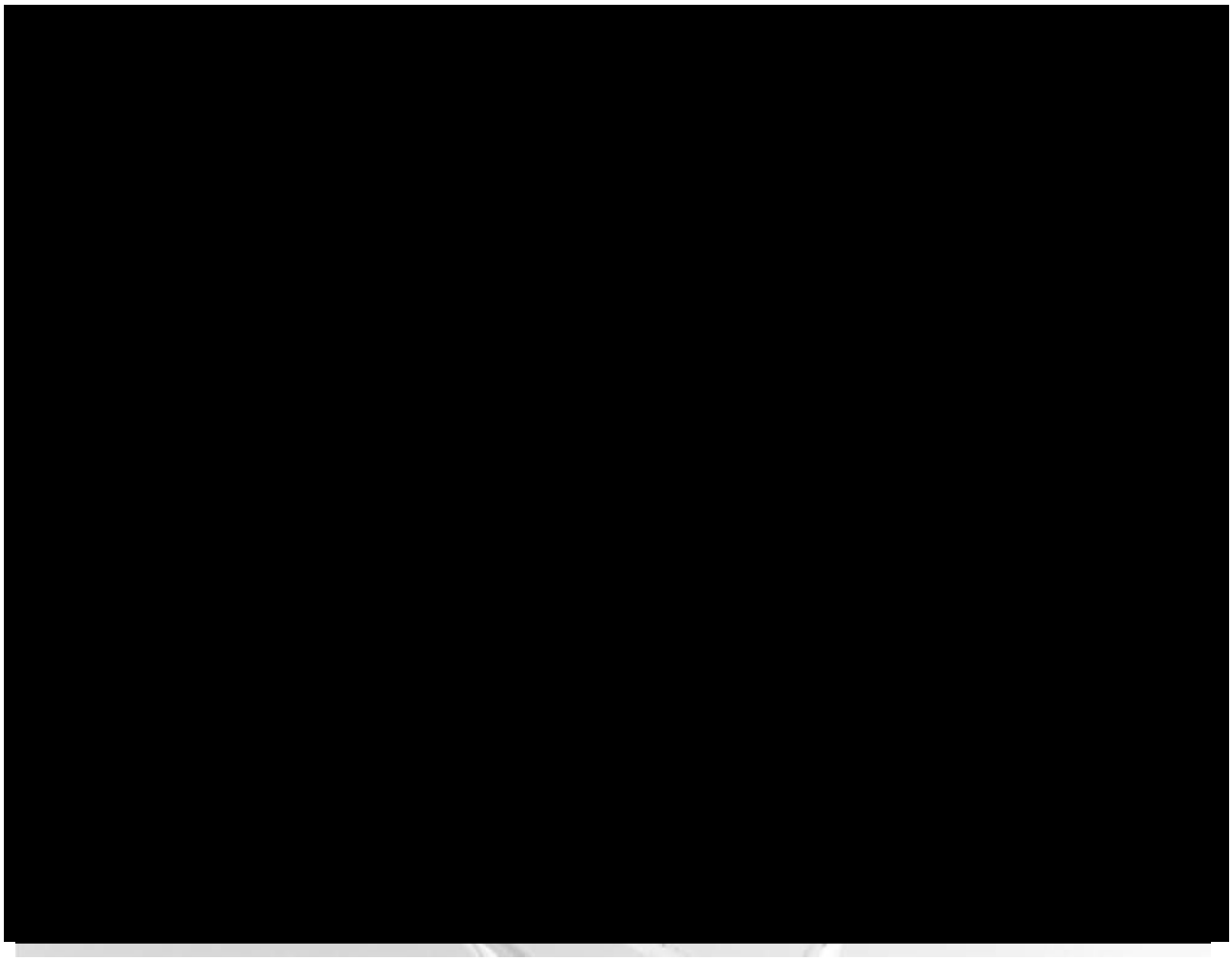
* In this document, "Merck" refers to Merck Sharp & Dohme Corp. and Schering Corporation, each of which is a subsidiary of Merck & Co., Inc. Merck is known as MSD outside of the United States and Canada. As warranted by context, Merck also includes affiliates and subsidiaries of Merck & Co., Inc."











12.4 Eastern Cooperative Oncology Group Performance Status

Grade	Performance Status
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

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

12.5 Prohibited Monoamine Oxidase Inhibitors and Drugs Associated with Significant Monoamine Oxidase Inhibitory Activity

NOTE: As of Amendment 10, this section is no longer applicable.

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

12.6 Common Terminology Criteria for Adverse Events v4.0

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be used for adverse event reporting (https://ctep.cancer.gov/).

12.7 Response Evaluation Criteria in Solid Tumors (RECIST) 1.1

RECIST 1.1* will be used in this study for assessment of tumor response. While either CT or MRI may be utilized, as per RECIST 1.1, CT is the preferred imaging technique in this study.

* As published in the European Journal of Cancer

12.8 Publication on Serotonin Syndrome

NOTE: As of Amendment 10, this section is no longer applicable.

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

CURRENT CONCEPTS

The Serotonin Syndrome

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N Engl J Med 2005;352:1112-20.

THE SEROTONIN SYNDROME IS A POTENTIALLY LIFE-THREATENING adverse drug reaction that results from therapeutic drug use, intentional self-poisoning, or inadvertent interactions between drugs. Three features of the serotonin syndrome are critical to an understanding of the disorder. First, the serotonin syndrome is not an idiopathic drug reaction; it is a predictable consequence of excess serotonergic agonism of central nervous system (CNS) receptors and peripheral serotonergic receptors.[1,2] Second, excess serotonin produces a spectrum of clinical findings.[3] Third, clinical manifestations of the serotonin syndrome range from barely perceptible to lethal. The death of an 18-year-old patient named Libby Zion in New York City more than 20 years ago, which resulted from coadministration of meperidine and phenelzine, remains the most widely recognized and dramatic example of this preventable condition.[4]

DEFINITION AND EPIDEMIOLOGY

The serotonin syndrome is often described as a clinical triad of mental-status changes, autonomic hyperactivity, and neuromuscular abnormalities, but not all of these findings are consistently present in all patients with the disorder (Fig. 1).[5,6] Signs of excess serotonin range from tremor and diarrhea in mild cases to delirium, neuromuscular rigidity, and hyperthermia in life-threatening cases. The difficulty for clinicians is that mild symptoms may be easily overlooked, and an inadvertent increase in the dose of the causative agent or the addition of a drug with proserotonergic effects may provoke a dramatic clinical deterioration.

The incidence of the serotonin syndrome is thought to mirror the increasing number of proserotonergic agents being used in clinical practice.[7] In 2002, the Toxic Exposure Surveillance System, which receives case descriptions from office-based practices, inpatient settings, and emergency departments, reported 26,733 incidences of exposure to selective serotonin-reuptake inhibitors (SSRIs) that caused significant toxic effects in 7349 persons and resulted in 93 deaths.[8,9] The assessment of the serotonin syndrome in therapeutic drug dosing has relied on post-marketing surveillance studies, one of which identified an incidence of 0.4 case per 1000 patient-months for patients who were taking nefazodone.[10] Performing a rigorous epidemiologic assessment of the serotonin syndrome, however, is difficult, since more than 85 percent of physicians are unaware of the serotonin syndrome as a clinical diagnosis.[10] The syndrome occurs in approximately 14 to 16 percent of persons who overdose on SSRIs.[8]

Although the serotonin syndrome has occurred in a broad range of clinical environments, several barriers limit the ability of clinicians to diagnose the condition. First, the syndrome may be missed because of its protean manifestations. Clinicians and patients may dismiss symptoms such as tremor with diarrhea or hypertension as inconsequential or unrelated to drug therapy; anxiety and akathisia may be misattributed to the patient's mental state.[5,10] Second, a strict application of the diagnostic criteria proposed

by Sternbach potentially rules out what are now recognized as mild, early, or subacute cases of the disorder.[1,11] Third, clinicians cannot diagnose a condition of which they are unaware, even though the serotonin syndrome is not rare and has been identified in patients of all ages, including the elderly, children, and newborn infants.[10,12-14]

A striking number of drugs and drug combinations have been associated with the serotonin syndrome (Table 1). These include monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants, SSRIs, opiate analgesics, over-the-counter cough medicines, antibiotics, weight-reduction agents, antiemetics, antimigraine agents, drugs of abuse, and herbal products; the withdrawal of medications has also been associated with the syndrome.[1,4,12,15-23] A single therapeutic dose of an SSRI has caused the serotonin syndrome.[12] Moreover, the addition of drugs that inhibit cytochrome isoforms CYP2D6 and CYP3A4 to therapeutic SSRI regimens has been associated with the condition.[16,24,25] Administration of serotonergic agents within five weeks after the discontinuation of fluoxetine therapy has produced a drug interaction culminating in the serotonin syndrome, presumably the result of the demethylation of fluoxetine to norfluoxetine, a serotonergic metabolite with a longer serum half-life than its parent compound.[13] Specific drugs, such as MAOIs that are irreversible or nonselective or that inhibit monoamine oxidase subtype A, are strongly associated with severe cases of the syndrome, especially when these agents are used in combination with meperidine, dextromethorphan, SSRIs, or methylenedioxymethamphetamine (MDMA, or "ecstasy").[4,8,15,26,27]

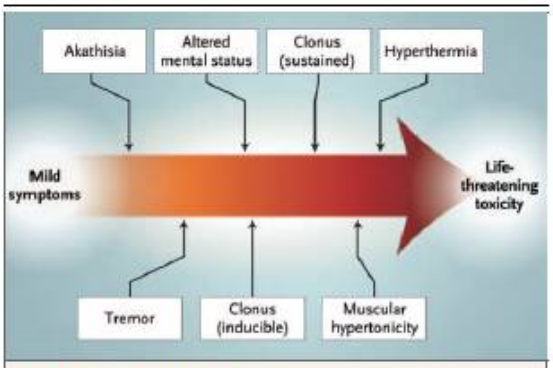

Figure 1. Spectrum of Clinical Findings.
Manifestations of the serotonin syndrome range from mild to life-threatening. The vertical arrows suggest the approximate point at which clinical findings initially appear in the spectrum of the disease, but all findings may not be consistently present in a single patient with the serotonin syndrome. Severe signs may mask other clinical findings. For example, muscular hypertonicity can overwhelm tremor and hyperreflexia.

MANIFESTATIONS

The serotonin syndrome encompasses a range of clinical findings. Patients with mild cases may be afebrile but have tachycardia, with a physical examination that is notable for autonomic findings such as shivering, diaphoresis, or mydriasis (Fig. 2). The neurologic examination may reveal intermittent tremor or myoclonus, as well as hyperreflexia.

A representative example of a moderate case of the serotonin syndrome involves such vital-sign abnormalities as tachycardia, hypertension, and hyperthermia. A core temperature as high as 40°C is common in moderate intoxication. Common features of the physical examination are mydriasis, hyperactive bowel sounds, diaphoresis, and normal skin color. Interestingly, the hyperreflexia and clonus seen in moderate cases may be considerably greater in the lower extremities than in the upper extremities; patellar deep-tendon reflexes often demonstrate clonus for several seconds after a single tap of the tendon, whereas the brachioradialis reflex is only slightly increased. Patients may exhibit horizontal ocular clonus. Changes in mental status include mild agitation or hypervigilance, as well as slightly pressured speech. Patients may easily startle or adopt a peculiar head-turning behavior characterized by repetitive rotation of the head with the neck held in moderate extension.

In contrast, a patient with a severe case of the serotonin syndrome may have severe hypertension and tachycardia that may abruptly deteriorate into frank shock. Such patients may have agitated delirium as well as muscular rigidity and hypertonicity. Again, the increase in muscle tone is considerably greater in the lower extremities. The muscle hyperactivity may produce a core temperature of more than 41.1°C in life-threatening cases. Laboratory abnormalities that occur in severe cases include metabolic acidosis, rhabdomyolysis, elevated levels of serum aminotransferase and creatinine, seizures, renal failure, and disseminated intravascular coagulopathy. Many of these abnormalities arise, however, as a consequence of poorly treated hyperthermia.

Table 1. Drugs and Drug Interactions Associated with the Serotonin Syndrome.

Drugs associated with the serotonin syndrome
Selective serotonin-reuptake inhibitors: sertraline, fluoxetine, fluvoxamine, paroxetine, and citalopram
Antidepressant drugs: trazodone, nefazodone, buspirone, clomipramine, and venlafaxine
Monoamine oxidase inhibitors: phenelzine, moclobemide, clorgiline, and isocarboxazid
Anticonvulsants: valproate
Analgesics: meperidine, fentanyl, tramadol, and pentazocine
Antiemetic agents: ondansetron, granisetron, and metoclopramide
Antimigraine drugs: sumatriptan
Bariatric medications: sibutramine
Antibiotics: linezolide (a monoamine oxidase inhibitor) and ritonavir (through inhibition of cytochrome P-450 enzyme isoform 3A4)
Over-the-counter cough and cold remedies: dextromethorphan
Drugs of abuse: methylenedioxymethamphetamine (MDMA, or "ecstasy"), lysergic acid diethylamide (LSD), 5-methoxydiisopropyltryptamine ("foxy methoxy"), Syrian rue (contains harmine and harmaline, both monoamine oxidase inhibitors)
Dietary supplements and herbal products: tryptophan, *Hypericum perforatum* (St. John's wort), Panax ginseng (ginseng)
Other: lithium
Drug interactions associated with severe serotonin syndrome
Zoloft, Prozac, Sarafem, Luvox, Paxil, Celexa, Desyrel, Serzone, Buspar, Anafranil, Effexor, Nardil, Manerix, Marplan, Depakote, Demerol, Duragesic, Sublimaze, Ultram, Talwin, Zofran, Kytril, Reglan, Imitrex, Meridia, Redux, Pondimin, Zyvox, Norvir, Parnate, Tofranil, Remeron
Phenelzine and meperidine
Tranylcypromine and imipramine
Phenelzine and selective serotonin-reuptake inhibitors
Paroxetine and buspirone
Linezolide and citalopram
Moclobemide and selective serotonin-reuptake inhibitors
Tramadol, venlafaxine, and mirtazapine

To better delineate the signs and symptoms that define the serotonin syndrome, the clinical findings in 2222 consecutive cases of self-poisoning with serotonergic drugs were rigorously assessed on the basis of information from a detailed toxicology registry.[2] These findings were then compared with the "gold standard," the assignment of a diagnosis of the serotonin syndrome by a medical toxicologist.[2] The clinical findings that had a statistically significant association with the diagnosis of the syndrome were primarily neuromuscular, including hyperreflexia, inducible clonus, myoclonus, ocular clonus, spontaneous clonus, peripheral hypertonicity, and shivering.[2] Autonomic derangements were tachycardia on admission, mydriasis, diaphoresis, and the presence of bowel sounds and diarrhea.[2] Abnormalities in mental status that were significantly associated with the serotonin syndrome were agitation and delirium.[2] Hyperthermia that was caused by muscular hypertonicity, defined in this study as a temperature of more than 38°C, was not as strongly associated with the diagnosis of the serotonin syndrome but occurred in severely intoxicated patients.[2]

The onset of symptoms is usually rapid, with clinical findings often occurring within minutes after a change in medication or self-poisoning.[28] Approximately 60 percent of patients with the serotonin syndrome present within six hours after initial use of medication, an overdose, or a change in dosing.[28] Patients with mild manifestations may present with subacute or chronic symptoms, whereas severe cases may progress rapidly to death. The serotonin syndrome is not believed to resolve spontaneously as long as precipitating agents continue to be administered.

PATHOPHYSIOLOGY AND MOLECULAR MECHANISMS

Serotonin is produced by the decarboxylation and hydroxylation of L-tryptophan. Its quantity and actions are tightly regulated by a combination of reuptake mechanisms, feedback loops, and metabolizing enzymes (Fig. 3). Serotonin receptors are divided into seven 5-hydroxytryptamine (5-HT) families (5-HT_1 to 5-HT_7), several of which have multiple members (e.g., 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1C}, 5-HT_{1D}, 5-HT_{1E}, and 5-HT_{1F}). Further structural and operational diversity is achieved by allelic polymorphisms, splice variants, receptor isoforms, and the formation of receptor heterodimers.[29]

Serotonergic neurons in the CNS are found primarily in the midline raphe nuclei, located in the brain stem from the midbrain to the medulla.[30] The rostral end of this system assists in the regulation of wakefulness, affective behavior, food intake, thermoregulation, migraine, emesis, and sexual behavior.[30] The neurons of the raphe in the lower pons and medulla participate in the regulation of nociception and motor tone.[30] In the periphery, the serotonin system assists in the regulation of vascular tone and gastrointestinal motility.[30]

No single receptor appears to be responsible for the development of the serotonin syndrome, although several lines of evidence converge to suggest that agonism of 5-HT_{2A} receptors contributes substantially to the condition.[31-35] Additional subtypes of serotonin receptors, such as 5-HT_{1A}, may contribute through a pharmacodynamic interaction in which increased synaptic concentrations of serotonin agonist saturate all receptor subtypes. Nora-

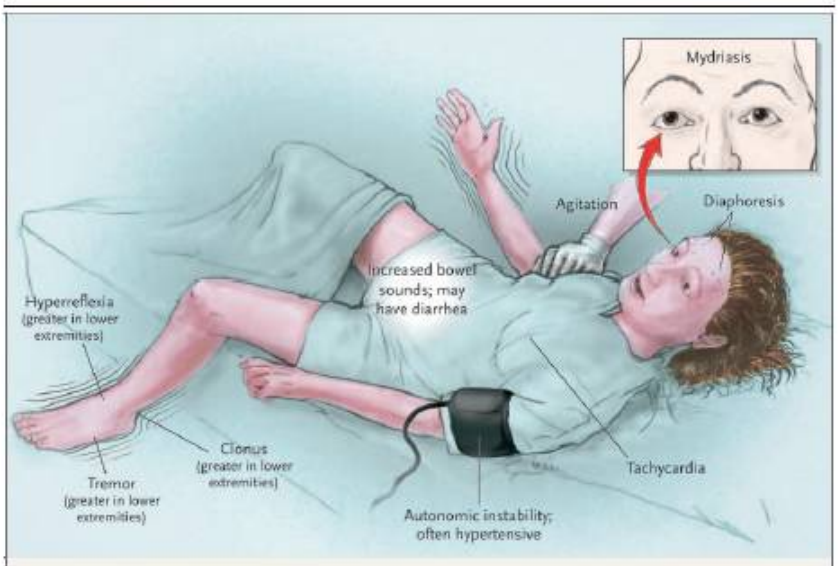

Figure 2. Findings in a Patient with Moderately Severe Serotonin Syndrome.
Hyperkinetic neuromuscular findings of tremor or clonus and hyperreflexia should lead the clinician to consider the diagnosis of the serotonin syndrome.

drenergic CNS hyperactivity may play a critical role, since the degree to which CNS norepinephrine concentrations are increased in the serotonin syndrome may correlate with the clinical outcome.[33,35,36] Other neurotransmitters, including *N*-methyl-D-aspartate (NMDA) receptor antagonists and γ-aminobutyric acid (GABA), may affect the development of the syndrome, but the role of these agents is less clear.[33,37] Dopaminergic receptors have been implicated, but this association may arise from pharmacodynamic interactions, direct interactions between serotonin and dopamine receptors, other mechanisms, or a misdiagnosis of the serotonin syndrome as the neuroleptic malignant syndrome.[26,33,38,39]

DIAGNOSIS

No laboratory tests confirm the diagnosis of the serotonin syndrome. Instead, the presence of tremor, clonus, or akathisia without additional extrapyramidal signs should lead clinicians to consider the diagnosis, which must be inferred from the patient's history and physical examination. When obtaining the patient's history, clinicians should inquire about the use of prescription and over-the-counter drugs, illicit substances, and dietary supplements, since all of these agents have been implicated in the development of the serotonin syndrome. The evolution of symptoms and their rate of change should also be reviewed. Physical examination should include a focused assessment of deep-tendon reflexes, clonus, and muscle rigidity, in addition to an evaluation of the size and reactivity of the pupils, the dryness of the oral mucosa, the intensity of bowel sounds, skin color, and the presence or absence of diaphoresis.

Although several diagnostic criteria have been developed, we prefer the decision rules described in Figure 4.[2,11,14,40] These rules, when compared with the original diagnostic criteria, are simpler, more sensitive (84 percent vs. 75 percent), and more specific (97 percent vs. 96 percent) for diagnosing the serotonin syndrome.[1,2] Clonus (inducible, spontaneous, and ocular) is the most important finding in establishing the diagnosis of the serotonin syndrome.[2,27,41] Clinicians should always be aware

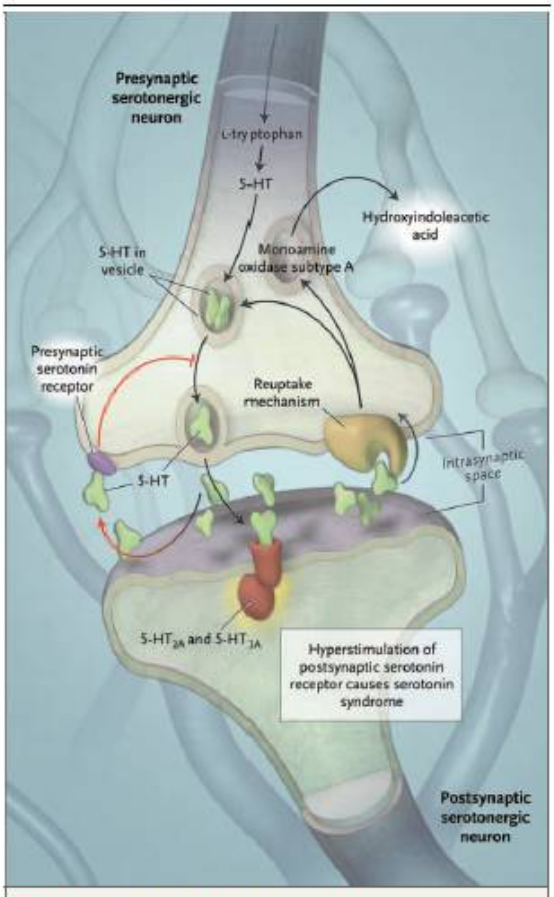

Figure 3. Serotonin Biosynthesis and Metabolism.
Serotonin is produced in presynaptic neurons by hydroxylation and decarboxylation of L-tryptophan. Serotonin is then incorporated into vesicles, where it resides until it is needed for neurotransmission. After axonal stimulation, serotonin is released into the intrasynaptic space; presynaptic serotonin receptors function as a feedback loop to inhibit exocytosis of vesicles (shown in red). Serotonin then binds to postsynaptic receptors to effect neurotransmission. A reuptake mechanism returns serotonin to the cytoplasm of the presynaptic neuron, where it is reintroduced into vesicles. Serotonin is then metabolized by monoamine oxidase subtype A to hydroxyindoleacetic acid.

that hyperthermia and hypertonicity occur in life-threatening cases, but muscle rigidity may mask the highly distinguishing findings of clonus and hyperreflexia and therefore cloud the diagnosis.[2,42]

The differential diagnosis includes anticholinergic poisoning, malignant hyperthermia, and the neuroleptic malignant syndrome, each of which can be readily distinguished from the serotonin syndrome on clinical grounds and on the basis of the medication history (Table 2). Patients with the anticholinergic syndrome have normal reflexes and show the "toxidrome" of mydriasis; agitated delirium; dry oral mucosa; hot, dry, erythematous skin; urinary retention; and an absence of bowel sounds. Hyperactive bowel sounds — along with neuromuscular abnormalities, diaphoresis, and normal skin color — distinguish the serotonin syndrome from the anticholinergic toxidrome.[2]

Malignant hyperthermia is a pharmacogenetic disorder characterized by increasing concentrations of end-tidal carbon dioxide, hypertonicity, hyperthermia, and metabolic acidosis. The disorder occurs within minutes after exposure to inhalational anesthetic agents.[43] On physical examination, the skin is often mottled, with cyanotic areas contrasting with patches of bright red flushing.[43] The rigor mortis–like rigidity of skeletal muscles and hyporeflexia that are seen in malignant hyperthermia further distinguish this condition from the serotonin syndrome.[43]

The neuroleptic malignant syndrome is an idiopathic reaction to dopamine antagonists, a condition that is defined by a slow onset, bradykinesia or akinesia, "lead pipe" muscular rigidity, hyperthermia, fluctuating consciousness, and autonomic instability.[44] Signs and symptoms of the neuroleptic malignant syndrome typically evolve during several days, in contrast to the rapid onset and hyperkinesia of the serotonin syndrome. Knowledge of the precipitating drug also helps in distinguishing between syndromes: dopamine antagonists produce bradykinesia, whereas serotonin agonists produce hyperkinesia.[45]

MANAGEMENT

Management of the serotonin syndrome involves the removal of the precipitating drugs, the provision of supportive care, the control of agitation, the administration of 5-HT_{2A} antagonists, the control of autonomic instability, and the control of hyperthermia.[45] Many cases of the serotonin syndrome typically resolve within 24 hours after the initiation of therapy and the discontinuation of serotonergic drugs, but symptoms may persist in patients taking drugs with long elimination half-lives, active metab-

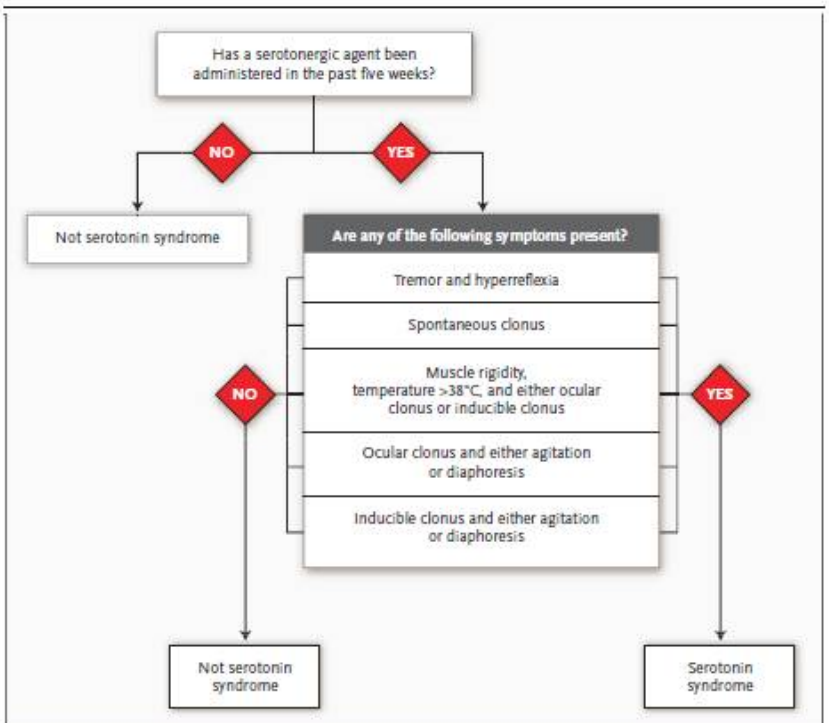

Figure 4. Algorithm for Diagnosis.
The neuromuscular features of clonus and hyperreflexia are highly diagnostic for the serotonin syndrome, and their occurrence in the setting of serotonergic drug use establishes the diagnosis. Clinicians should be aware that muscle rigidity can overwhelm other neuromuscular findings and mask the diagnosis. Criteria adapted from Dunkley.[2]

olites, or a protracted duration of action. Supportive care, comprising the administration of intravenous fluids and correction of vital signs, remains a mainstay of therapy. However, an abrupt deterioration in the condition of a patient who has been conservatively treated indicates the need for an immediate, aggressive response.[1,2,45]

The intensity of therapy depends on the severity of illness. Mild cases (e.g., with hyperreflexia and tremor but no fever) can usually be managed with supportive care, removal of the precipitating drugs, and treatment with benzodiazepines. Moderately ill patients should have all cardiorespiratory and thermal abnormalities aggressively corrected and may benefit from the administration of 5-HT_{2A} antagonists. Hyperthermic patients (those whose temperature is more than 41.1°C) are severely ill and should receive the above therapies as well as immediate sedation, neuromuscular paralysis, and orotracheal intubation.

Control of agitation with benzodiazepines is essential in the management of the serotonin syndrome, regardless of its severity. Benzodiazepines such as diazepam improve survival in animal models and blunt the hyperadrenergic component of the syndrome.[37,45] Physical restraints are ill-advised and may contribute to mortality by enforcing isometric muscle contractions that are associated with severe lactic acidosis and hyperthermia.[46] If physical restraints are used, they must be rapidly replaced with chemical sedation.

Pharmacologically directed therapy involves the

Table 2. Manifestations of Severe Serotonin Syndrome and Related Clinical Conditions.

Condition	Medication History	Time Needed for Condition to Develop	Vital Signs	Pupils	Mucosa	Skin	Bowel Sounds	Neuromuscular Tone	Reflexes	Mental Status
Serotonin syndrome	Proserotonergic drug	<12 hr	Hypertension, tachycardia, tachypnea, hyperthermia (>41.1°C)	Mydriasis	Sialorrhea	Diaphoresis	Hyperactive	Increased predominantly in lower extremities	Hyperreflexia, clonus (unless masked by increased muscle tone)	Agitation, coma
Anticholinergic "toxidrome"	Anticholinergic agent	<12 hr	Hypertension (mild), tachycardia, tachypnea, hyperthermia (typically 38.8°C or less)	Mydriasis	Dry	Erythema, hot and dry to touch	Decreased or absent	Normal	Normal	Agitated delirium
Neuroleptic malignant syndrome	Dopamine antagonist	1–3 days	Hypertension, tachycardia, tachypnea, hyperthermia (>41.1°C)	Normal	Sialorrhea	Pallor, diaphoresis	Normal or decreased	"Lead-pipe" rigidity present in all muscle groups	Bradyreflexia	Stupor, akinetic mutism, coma
Malignant hyperthermia	Inhalational anesthesia	30 min to 24 hr after administration of inhalational anesthesia or succinylcholine	Hypertension, tachycardia, tachypnea, hyperthermia (can be as high as 46.0°C)	Normal	Normal	Mottled appearance, diaphoresis	Decreased	Rigor mortis–like rigidity	Hyporeflexia	Agitation

administration of 5-HT_{2A} antagonists.[7,45] Cyproheptadine is the recommended therapy for the serotonin syndrome, although its efficacy has not been rigorously established.[7,45] Treatment of the serotonin syndrome in adults may require 12 to 32 mg of the drug during a 24-hour period, a dose that binds 85 to 95 percent of serotonin receptors.[47] Clinicians should consider an initial dose of 12 mg of cyproheptadine and then 2 mg every two hours if symptoms continue. Maintenance dosing involves the administration of 8 mg of cyproheptadine every six hours. Cyproheptadine is available only in oral form, but tablets may be crushed and administered by nasogastric tube. Atypical antipsychotic agents with 5-HT_{2A}–antagonist activity may be beneficial in treating the serotonin syndrome. The sublingual administration of 10 mg of olanzapine has been used successfully, but its efficacy has not been rigorously determined.[48] Clinicians desiring a parenteral agent should consider the intramuscular administration of 50 to 100 mg of chlorpromazine.[45] Even though chlorpromazine is an outdated therapy that has been replaced in psychiatric practice by newer agents, its use may nonetheless be considered in severe cases.[45]

Control of autonomic instability involves stabilization of fluctuating pulse and blood pressure. Hypotension arising from MAOI interactions should be treated with low doses of direct-acting sympathomimetic amines (e.g., norepinephrine, phenylephrine, and epinephrine). Direct agonists do not require intracellular metabolism to generate a vasoactive amine, but their concentration in the synapse is regulated by catecholamine-O-methyl transferase. Indirect agents such as dopamine are metabolized to epinephrine and norepinephrine. Under normal conditions, monoamine oxidase limits the intracellular concentration of these metabolites. When inhibited, however, monoamine oxidase cannot control the amount of epinephrine and norepinephrine produced, and an exaggerated hemodynamic response may ensue. Patients in whom hypertension and tachycardia develop, either as a result of pressor therapy or from poisoning itself, should be treated with short-acting agents such as nitroprusside and esmolol.

Control of hyperthermia involves eliminating excessive muscle activity. Although benzodiazepines have a beneficial effect in moderate cases, in severely ill patients with hyperthermia (a temperature of more than 41.1°C) immediate paralysis should be induced with nondepolarizing agents such as ve-

curonium, followed by orotracheal intubation and ventilation. Clinicians should avoid succinylcholine because of the risk of arrhythmia from hyperkalemia associated with rhabdomyolysis. Recent case reports have shown that premature termination of neuromuscular paralysis was associated with a recrudescence of hyperthermia.[49] There is no role for antipyretic agents in the management of the serotonin syndrome; the increase in body temperature is due to muscular activity, not an alteration in the hypothalamic temperature set point.

Potential pitfalls for clinicians include misdiagnosis of the serotonin syndrome, a failure to comprehend its rapidity of progression, and adverse effects of pharmacologically directed therapy. The diagnosis may be clouded by the presence of severe muscle rigidity that obscures myoclonus and hyperreflexia. If the correct diagnosis is not obvious, a prudent course is to withhold antagonist therapy and provide aggressive supportive care, sedation with benzodiazepines, and, if necessary, intubation and paralysis.[7] Because of the speed with which the condition of patients declines, physicians should anticipate the need for aggressive therapy before clinical indications are reached.

Therapies such as propranolol, bromocriptine, and dantrolene are not recommended.[7,45] Propranolol, a 5-HT_{1A} antagonist with a long duration of action, may cause hypotension and shock in patients with autonomic instability. Furthermore, propranolol can abolish tachycardia that can be used to determine the duration and effectiveness of therapy.[2] Bromocriptine, a dopamine agonist, and dantrolene are not useful therapies; case reports citing their use probably involved a misdiagnosis of another condition as the serotonin syndrome.[7,35,45] Bromocriptine has been implicated in the development of the serotonin syndrome, and its use in patients in whom the neuroleptic malignant syndrome is misdiagnosed may worsen serotonergic signs.[27,50] According to one report, the administration of bromocriptine and dantrolene to a patient with the serotonin syndrome caused an abrupt increase in temperature, culminating in death.[39] This finding is supported by the observation that dantrolene has no effect on survival in animal models.[34,35]

Antagonist therapy with the use of cyproheptadine and chlorpromazine may have unintended effects. The dosage of cyproheptadine used to treat the serotonin syndrome may cause sedation, but this effect is a goal of therapy and should not deter clinicians from using the drug. Chlorpromazine is an outmoded drug that has been associated with severe orthostatic hypotension and has been thought to aggravate hyperthermia. Patients who require acute parenteral therapy for the serotonin syndrome are often hypertensive and are not ambulatory, so that the risk of orthostatic hypotension is minimized. Hyperthermia in response to neuroleptic administration is an idiopathic response; the normal outcome is hypothermia. Nonetheless, chlorpromazine should not be administered to a patient with hypotension or the neuroleptic malignant syndrome, since the drug could potentially exacerbate clinical findings.

PREVENTION

The serotonin syndrome can be avoided by a combination of pharmacogenomic research, the education of physicians, modifications in prescribing practices, and the use of technological advances. The application of pharmacogenomic principles can potentially protect patients at risk for the syndrome before the administration of serotonergic agents. Once toxicity occurs, consultation with a medical toxicologist, a clinical pharmacology service, or a poison-control center can identify proserotonergic agents and drug interactions, assist clinicians in anticipating adverse effects, and provide valuable clinical decision-making experience. The avoidance of multidrug regimens is critical to the prevention of the serotonin syndrome. If multiple agents are required, however, computer-based ordering systems and the use of personal digital assistants can detect drug interactions and decrease reliance on memory in drug ordering. Post-marketing surveillance linked to physician education has been proposed to improve awareness of the serotonin syndrome.[10]

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12.9 List of Abbreviations

Abbreviation/Term	Definition
AACR	American Association for Cancer Research
ADA	Anti-Drug Antibodies
AE	Adverse Event
AJCC	American Joint Committee on Cancer
ALT	Alanine Aminotransferase
APS	Allred proportion score
aPTT	Activated Partial Thromboplastin Time
ASaT	All Subjects as Treated
AST	Aspartate Aminotransferase
BCG	Bacillus Calmette–Guérin vaccine
BID	twice daily
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CI	Confidence Interval
CL	Clearance
CNS	Central Nervous System
CR	Complete Response
CRP	C-reactive protein
CrCl	Calculated Creatinine Clearance
CSR	Clinical Study Report
CT	Computed Tomography
Ctrough	serum minimum concentration
CTCAE	Common Toxicity Criteria for Adverse Events
CTFG	Clinical Trial Facilitation Group
CTLA-4	Cytotoxic T-Lymphocyte-Associated Antigen-4
DC	dendritic cell
DCR	disease control rate
DKA	diabetic ketoacidosis
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DOR	Duration of Response
DTIC	Dacarbazine
ECG	Electrocardiogram
ECI	Events of Clinical Interest
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eDMC	external Data Monitoring Committee
EOC	Executive Oversight Committee
[redacted]	[redacted]
EOT	end of treatment
[redacted]	[redacted]
ERC	Ethics Review Committee
EU	European Union
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act

Abbreviation/Term	Definition
FDAMA	Food and Drug Administration Modernization Act
FFPE	Formalin-fixed, paraffin-embedded
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	Gastrointestinal
H&N	Head and neck
HBsAg	Hepatitis B surface Antigen
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
[redacted]	[redacted]
IA1	interim analysis 1
IA2	interim analysis 2
IA3	interim analysis 3
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDO1	indoleamine 2,3 dioxygenase-1
IEC	independent ethics committee
Ig	immunoglobulin
IHC	Immunohistochemistry
IL-2	interleukin-2
INR	International Normalized Ratio
irAEs	Immune-related Adverse Events
IRB	Institutional Review Board
irRECIST	Immune related Response Evaluation Criteria in Solid Tumors (Modification of RECIST 1.1)
ITT	Intent To Treat
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Integrated Web Response System
Kg	Kilogram
LDH	Lactate Dehydrogenase
LFT	liver function test
MAOI	monoamine oxidase inhibitors
mcL	Microliters
MEL	Melanoma
mg	Milligram
mg/kg	Milligram per Kilogram
mL	milliliter
MRI	Magnetic Resonance Imaging
MSD	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
MSI	Microsatellite Instability
MTD	maximum tolerated dose
n/a or N/A	Not Applicable
NCI	National Cancer Institute
NCCN	National Comprehensive Cancer Network

Abbreviation/Term	Definition
NSAID	Non-Steroidal Anti-inflammatory Drug
NSCLC	Non-Small Cell Lung Cancer
ORR	Overall Response Rate
OS	Overall Survival
PD	pharmacodynamic or progressive disease
PD-1	Programmed Death Receptor-1
PD-L1	Programmed cell Death Ligand 1
PET	positron emission tomography
PFS	Progression Free Survival
PIN	Personal Identification Number
PK	Pharmacokinetic
po	Oral Administration
PR	Partial Response
PRO	Patient Reported Outcomes
PT	Prothrombin Time
Q3W	Every 3 Weeks
Q9W	Every 9 Weeks
QALYs	quality adjusted life years
QoL	Quality of Life
RCC	Renal Cell Carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RMST	Restricted Mean Survival Time
RNA	Ribonucleic Acid
SAC	Scientific Advisory Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCC	squamous cell carcinoma
SCCHN	squamous cell carcinoma of the head and neck
SD	Stable Disease
SNP	single nucleotide polymorphism
SNRI	serotonin/norepinephrine reuptake inhibitors
SOP	Standard Operating Procedures
SS	serotonin syndrome
sSAP	supplemental Statistical Analysis Plan
SIM	Site Imaging Manual
SSRI	serotonin reuptake inhibitors
T3	Total triiodothyronine
T4	Free thyroxine
TCC	transitional cell carcinoma
TNBC	Triple negative breast cancer
Treg	regulatory T cell
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
US	United States
V	Volume of distribution
WHO	World Health Organization
[redacted]	[redacted]

12.10 R Code for Calculations of Sample Size and Monitoring Boundaries for Progression-Free Survival

The sample size for this study is driven primarily by the enrollment and follow-up required to have the specified power (~98%) to detect a true hazard ratio (pembrolizumab + epacadostat versus pembrolizumab + placebo) for progression-free survival of 0.65:1.00.

As specified in Section 8.9, the statistical considerations assume a 12 month period for the 600 patient protocol-specified enrollment. PFS for the patients treated with the pembrolizumab + placebo regimen is assumed to follow a distribution with a "cure" rate of 30%, with PFS for the remaining 70% of patients following an exponential distribution with a median of 4.75 months. The true hazard ratio under the alternative hypothesis for PFS between the pembrolizumab + epacadostat combination and the pembrolizumab + placebo regimen is assumed to be 0.65.

Similarly, OS for patients treated with the pembrolizumab + placebo regimen is assumed to follow a distribution with a "cure" rate of 35%, with survival for the remaining 65% of patients following an exponential distribution with a median of 14 months. The true hazard ratio under the alternative hypothesis for OS between the pembrolizumab + epacadostat combination and the pembrolizumab + placebo regimen is assumed to be 0.70.

For the PFS and OS hypotheses, an exponential alpha-spending function with nu=0.75 (approximating an O'Brien-Fleming boundary) will be used. For PFS the cumulative alpha will be 1.25%; for OS the cumulative alpha will be 1.25% (if PFS superiority is not demonstrated) or 2.5% (if PFS superiority is demonstrated).

The R code generating the monitoring specifications for PFS is specified below. The R code generating the monitoring specifications for OS follows the same approach.

R code for specification of the PFS analysis plan

````
---
title: 'RETRED: REcurring (T)252 RE-Design'
output:
  word_document: default
  html_notebook: default
---
Note that sample size below is actually number of events for both designs.

# PFS design

```{r,echo=FALSE,message=FALSE,results='asis'}
library(gsDesign)
# PFS design
n.I <- c(331,420)
hr <- .65
alpha <- .0125
beta <- .0162
sfu <- sfExponential
sfupar <- .75
nfix <- nEvents(hr=hr,alpha=alpha,beta=beta)
PFSdesign <- gsDesign(n.fix=nfix,alpha=alpha,beta=beta,sfu=sfu,sfupar=sfupar,test.type=1,
                      k=2,timing=n.I[1]/n.I[2],endpoint="TTE",delta1=log(hr))
cat(summary(PFSdesign))
```

HR assumed for PFS power calculations is `r hr`.

```{r,echo=FALSE,message=FALSE}
gsBoundSummary(PFSdesign,deltaname="HR",logdelta=TRUE)
```

# OS design


```{r,echo=FALSE,message=FALSE,results='asis'}
# OS design
n.I <- c(100,200,293)
hr <- .7
alpha <- .0125
beta <- .214
sfu <- sfExponential
sfupar <- .75
nfix <- nEvents(hr=hr,alpha=alpha,beta=beta)
OSdesign <- gsDesign(n.fix=nfix,alpha=alpha,beta=beta,sfu=sfu,sfupar=sfupar,test.type=1,
                      k=3,timing=c(n.I[1],n.I[2])/n.I[3],endpoint="TTE",delta1=log(hr))
cat(summary(OSdesign))
```

HR assumed for OS power calculations is `r hr`.

```{r,echo=FALSE}
gsBoundSummary(OSdesign,deltaname="HR",logdelta=TRUE)
```
````

```
# no futility bound
test.type=1
```

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

13.2 Investigator

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 (including other manuals and documents referenced from this protocol). I agree to conduct the trial in accordance with generally accepted standards of Good Clinical Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse events as defined in Section 7.0 – TRIAL PROCEDURES (Assessing and Recording Adverse Events). I also agree to handle all clinical supplies provided by MSD and collect and handle all clinical specimens in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol and the referenced Investigator's Brochure is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the trial is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure or access by third parties.

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	