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Protocol Title: A Randomized, Open-Label, Phase 3 Study to Evaluate Efficacy and Safety of Pembrolizumab (MK-3475) plus Epacadostat vs Standard of Care (Sunitinib or Pazopanib) as First-Line Treatment for Locally Advanced or Metastatic Renal Cell Carcinoma (mRCC) (KEYNOTE-679/ECHO-302)

Protocol Number: 679-06/ECHO-302-06 / NCT03260894

Compound Number: MK-3475/INCB024360

Execution of Study:

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

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Global Sponsor of the Study:

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Regulatory Agency Identifying Number(s):

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Approval Date: 15-Jun-2018

MSD Signatory

Typed Name: Date
Title:

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

Investigator Signatory

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

Typed Name: Date
Title:

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment 06

Overall Rationale for the Amendment:

The external data monitoring committee (eDMC) analysis of the KEYNOTE-252/ECHO-301 melanoma blinded clinical trial, a Phase 3 study evaluating epacadostat in combination with pembrolizumab in participants with unresectable or metastatic melanoma determined that the study did not meet the pre-specified endpoint of improvement in progression-free survival for the combination of pembrolizumab and epacadostat compared to pembrolizumab and placebo. The eDMC further determined that the overall survival endpoint is not expected to reach statistical significance. These results are specific to melanoma, and cannot be extrapolated to other tumor types. Of note, there were no new safety concerns with the pembrolizumab plus epacadostat combination compared to pembrolizumab monotherapy. Given that there is no confirmed lack of efficacy of pembrolizumab plus epacadostat in other tumor types, the Sponsor and MSD consider interruption of study treatment unnecessary in KEYNOTE-679/ECHO-302. Enrollment to this study was permanently stopped on 02-MAY-2018 as a strategic decision. For participants who are considered to be obtaining ongoing clinical benefit, continued study treatment will be at the discretion of the investigator, after a discussion with the participant of the observed results from KEYNOTE-252/ECHO-301.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
Throughout	Addition of notes to inform sites that enrollment into the trial is permanently stopped and to clarify that after the first imaging assessment, disease monitoring will be performed as per standard of care (SoC).	Given the external data monitoring committee (DMC) review of the results of KEYNOTE 252/ECHO-301, a strategic decision was made to permanently stop enrollment as of 02-MAY-2018. Participants will be given the option to discontinue from the study or continue study treatment. The study will remain open so that participants still on study will have continued access to study treatment and to allow collection of preliminary efficacy data in this RCC indication. All efficacy procedures and endpoints after Week 12 are no longer being assessed. 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.

Section # and Name	Description of Change	Brief Rationale
1. Synopsis 4. Objectives/ Hypotheses and Endpoints 5.1.1 Study Diagram 5.4.1.1 Efficacy Endpoints 9.2.1 Tumor Imaging and Assessment of Disease 8.1 Discontinuation of Study Treatment 9.10.3.3 Survival Follow-up 10.1 Statistical Analysis Plan Summary	Changed primary endpoint from comparison of PFS (as assessed by blinded, independent central review ([BICR]) and OS between treatment arms to estimation of ORR (as assessed per RECIST 1.1 by the investigator) for each treatment arm after last protocol-defined scan. PFS, DOR, and OS were removed as endpoints. iRECIST will no longer be used as a response assessment criterion.	ORR is a reasonable endpoint for efficacy evaluation, given the reduction in the length of efficacy data collection. No confirmation of progressive disease (PD) or survival follow-up will be required.
1. Synopsis 4. Objectives/Hypotheses and Endpoints 5.1 Overall Design 5.2 Number of Participants 10.5.2 Efficacy Analysis Populations 10.4.1.2 Secondary	Removed all secondary efficacy endpoints and hypotheses.	PFS, OS, and DOR will no longer be followed in this study.

Section # and Name	Description of Change	Brief Rationale
1. Synopsis 2.1 Initial Treatment [redacted]	[redacted]	[redacted]
1. Synopsis 5.1 Overall Design 5.2 Number of Participants 10.Statistical Analysis Plan Summary	Reduced study population from 630 to 130.	As of 02-MAY-2018, enrollment was stopped. At that time there were 101 participants randomized and 46 participants in screening. Subjects in screening are allowed to continue through screening procedures.
1. Synopsis 5.1 Overall Design	On-study imaging will occur at the Week 12 (± 7 days) visit and be assessed by the investigator rather than by the central vendor. Subsequent imaging will be performed per Standard of Care (SoC) and only the date of subsequent scans will be recorded in the eCRF.	Change in primary endpoint to ORR does not require following up patients with imaging to assess PFS, DOR, and OS endpoints.
1. Synopsis Appendix 1, Committee Structure, Data Monitoring Committee	Removed interim analyses for efficacy.	No longer applicable given the design change. Only safety review is now planned for the Data Monitoring Committee.

Section # and Name	Description of Change	Brief Rationale
2. Schedule of Activities (SoA)	Adjusted SoA to provide for the collection of study efficacy measurements up to the first on-study imaging at Week 12 (± 7 d).	Survival follow up will no longer be monitored. Once the Week 12 (± 7 days) imaging is completed, participants will be followed up for safety through the 30-day safety follow-up using standard of care procedures.
2. Schedule of Activities (SoA)	Adjusted columns and simplified table layout to reflect study changes: • Removed Survival Follow-up Column and Row • Consolidated visits starting after Week 12 (Cycle 3 onward) • Updated notes to align with changes in the SoA in regard to timing of visits and procedures to be done per SoC.	Simplified SoA to reflect reduced scope of the trial.
2. Schedule of Activities	Updated note for the 12-lead electrocardiogram to add "and DC".	Clarification that all participants will have an ECG at discontinuation.
2. Schedule of Activities	Added to note for tissue sample. "May use archival tissue sample that was obtained prior to screening period as part of the participant's standard care."	Alignment with other Merck-Incyte collaboration protocols.
3.2 Background	Updated reference to the Investigator's Brochure (IB) to refer to the current version.	The IB is updated regularly, so reference to a specific version will become outdated.

Section # and Name	Description of Change	Brief Rationale
5.1 Study Design 7.8 Second Course Phase 8.1 Discontinuation of Study Treatment 9.10.4 Second Course Phase	Added duration for pembrolizumab of 17.5 cycles for Initial Treatment and 8.5 cycles for Second Course	Clarification.
5.3.1 Clinical Criteria for Early Study Termination	Updated with template language regarding early termination.	Correction of omission.
7.1 Treatments Administered	Added "as pazopanib hydrochloride" to description of treatments in Table 5	Clarification
7.2.1 Dose Modification for Immune-related Adverse Events: Table 6	Added that, in case of recurrent Grade 3 colitis, participants will permanently discontinue treatment and Management with corticosteroid text applied to all toxicity grades	To align with KEYTRUDA® Summary of Product Characteristics (SmPC) and Company Core Data Sheet (CCDS) Consistency and alignment with current clinical information for pembrolizumab and epacadostat
7.2.4 Interruptions Unrelated to Adverse Events	Added bolded text: Dosing interruptions are permitted **for situations other than treatment-related AEs, such as** in the case of medical/surgical events or logistical reasons not related to study treatment (eg, elective surgery, unrelated medical events, participant vacation, or holidays).	Clarification.

Section # and Name	Description of Change	Brief Rationale
7.6.2 Administration and Compliance of Oral Study Treatment (Epacadostat, Sunitinib, or Pazopanib)	Removed text specifying that Second Course C1D1 administration of epacadostat being given at study site.	Clarification
7.7.2 Prohibited Medications and Measures	#8 - Mefenamic acid, removed from listed prohibited UGT1A9 inhibitors	Alignment with current clinical information for epacadostat
7.8 Second Course Phase (Retreatment)	Removed "verified by BICR" from the PD criterion for entry into second course.	Blinded, independent central verification is no longer to be required in this trial.
8.2 Withdrawal from the Study	Removed text allowing for remaining on study after treatment discontinuation for survival follow-up.	Survival after discontinuation from treatment will no longer be tracked in the study.
9.1.9 Timing of Dose Administration	Added that "fasting state" means fasting for 8 to 12 hours.	Clarification
9.8.3 Distribution of Participant Reminder Cards and/or Participant Diaries	Corrected Day 15 to Day 22.	Correction to align with SoA.
9.1.9.1.2 Timing of Dose Administration of Epacadostat	Added (ie, 8-12 hr fasting) to clarify "fasting state"	Clarification

Section # and Name	Description of Change	Brief Rationale
9.2.1 Tumor Imaging and Assessment of Disease Appendix 6	No imaging beyond the Week 12 scan will be collected for the trial. Bone scans after Week 12 will not be collected. iRECIST will no longer be used to assess response. Imaging done after Week 12 will be performed per SoC and assessed locally. Investigators wishing to continue to treat after PD are to consult with the Merck Clinical Director. Participants who enter the Second Course only will be followed up for safety.	Reflects the change in primary endpoint to ORR and the reduced scope of the study.
9.10.1 Screening	Laboratory tests are to be done 14 days prior randomization (not first dose).	Alignment with schedule of activities.
9.10.3.1 Safety Follow-up Visit 9.10.3.2 Survival Follow-up 9.10.3.3.1 Survival Status Monitoring	Updated to indicate that this is the last visit, after which the participant will have completed the trial.	Updated now that survival follow-up has been omitted.
9.10.3.2 Follow-up Visits	Updated to reflect change in tumor imaging.	Imaging will be per SoC after the Week 12 assessment.
10.1 Statistical Analysis Plan Summary	[redacted]	[redacted]
10.1 Statistical Analysis Plan Summary 10.4.1 Efficacy Endpoints	Updated ORR from a key secondary endpoint to primary endpoint; Removed PFS, OS endpoints.	ORR is now the primary efficacy endpoint; there are no secondary efficacy endpoints.

Section # and Name	Description of Change	Brief Rationale
10.1 Statistical Analysis Plan Summary 10.6.1 Statistical Methods for Efficacy Analyses 10.6.2 Statistical Methods for Safety Analyses	Removed statistical methods for analysis of PFS and OS; and to use the Clopper–Pearson exact method to estimate ORR. Revised approach to analyzing safety data from tiered approach to summarization by descriptive statistics within group.	Updated to be aligned with updated objectives of the study.
10.7 Interim Analyses	Updated the Interim and Final Analysis Section to specify no interim efficacy analyses and final analysis will be performed after all randomized participants have had an opportunity to have 1 post baseline scan. eDMC will perform safety review per DMC charter.	Updated to be aligned with updated objectives of the study.
10.8 Multiplicity	Multiplicity adjustment methods were deleted.	No longer applicable.
10.9 Sample Size and Power Calculations	Sample size and power section was revised to reflect the change in endpoint and reduced sample size.	Updated to be aligned with updated objectives of the study.
10.10 Subgroup Analyses	Subgroup analyses were deleted.	No longer needed given the limited sample size.
2. Schedule of Activities Appendix 4: Clinical Laboratory Tests	Removed references to central laboratory.	Only local laboratories will be used as of this amendment.
Throughout	Correction of typographical, editorial and formatting errors.	Minor edits, not detailed.

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1. Synopsis

Protocol Title:

A Randomized, Open-Label, Phase 3 Study to Evaluate Efficacy and Safety of Pembrolizumab (MK-3475) plus Epacadostat vs Standard of Care (Sunitinib or Pazopanib) as First-Line Treatment for Locally Advanced or Metastatic Renal Cell Carcinoma (mRCC) (KEYNOTE-679/ECHO-302)

Short Title:

Pembrolizumab (MK-3475) plus Epacadostat vs SoC in mRCC

Objectives/Hypotheses and Endpoints:

NOTE: As of Amendment 06, the primary endpoint of the study will be ORR by Response Evaluation Criteria in Solid Tumors (RECIST 1.1) as assessed by the investigator after completion of the first protocol-defined efficacy imaging assessment. A secondary endpoint will examine the safety and tolerability in participants treated with pembrolizumab plus epacadostat and in those treated with sunitinib or pazopanib as standard of care (SoC). All other efficacy endpoints will no longer be analyzed.

This study will enroll participants with locally advanced/metastatic renal cell carcinoma (mRCC) with a clear cell component. Participants must not have received prior systemic therapy for their mRCC.

Objective/Hypothesis	Endpoint
Primary	
• Objective: To estimate the objective response rate (ORR) as measured per RECIST 1.1 by investigator determination of pembrolizumab plus epacadostat and standard of care (SoC) (sunitinib or pazopanib)	• ORR is defined as the proportion of participants who have a best response of complete response (CR) or partial response (PR)
Secondary	
• Objective: To evaluate the safety and tolerability of pembrolizumab plus epacadostat and SoC	• Safety and tolerability of the treatment regimens as measured by the following: o Number of participants experiencing adverse events (AEs) o Number of participants discontinuing study treatment due to AEs

Overall Design:

Study Phase	Phase III
Clinical Indication	Treatment of locally advanced/metastatic renal cell carcinoma (mRCC)
Population	Participants with locally advanced/metastatic renal cell carcinoma (mRCC) with clear cell component. Participants must not have received prior systemic therapy for their mRCC.
Study Type	Interventional
Type of Design	Randomized, parallel-group, active comparator
Type of Control	Active control without placebo
Study Blinding	Unblinded Open-label
Estimated Duration of Trial	The study is estimated to require approximately 5 years from the time the first participant signs the informed consent until the last participant's last study-related phone call or visit.

Number of Participants:

Approximately 630 participants will be enrolled.

Note: Originally, approximately 630 participants were to be enrolled, but as of Amendment 06 on 02-MAY-2018, enrollment was permanently stopped. It is estimated that by the time the strategic decision was made to stop enrollment that 130 participants will be randomized in this study.

Treatment Groups and Duration:

Treatment Groups	Group 1: Pembrolizumab 200 mg intravenously (IV) every three weeks (Q3W) plus epacadostat 100 mg orally (PO) twice daily (bid) continuously Group 2 (SoC): Sunitinib 50 mg PO once daily (6-week cycles; 4 weeks on treatment followed by 2 weeks off treatment) or pazopanib 800 mg PO once daily continuously As of Amendment 06, after the participant completes Week 12 imaging, participants can choose to discontinue from the study or continue study treatment as per protocol, if they are considered to receive clinical benefit and after discussion with the investigator.

Duration of Participation	Each participant will participate in the study from the time the participant signs the informed consent form through the final contact. After a screening period of up to 28 days, each eligible participant will be assigned to receive study treatment until disease progression, unacceptable AEs, intercurrent illness that prevents further administration of treatment, Investigator's decision to withdraw the participant, noncompliance with study treatment or procedural requirements, or administrative reasons requiring cessation of treatment. Participants in Group 1 will receive a maximum of 35 administrations of pembrolizumab (approximately 2 years). Participants in Group 1 who stop study treatment (for reasons other than disease progression or intolerability) with SD or PR after receiving 35 infusions of pembrolizumab or participants who stop study treatment after attaining a CR (with a minimum of 8 infusions of pembrolizumab and at least 2 infusions beyond the date when initial CR was declared) may be eligible for up to 17 additional infusions (approximately 1 year) of pembrolizumab plus epacadostat upon experiencing radiographic disease progression. Please refer to Section 7.8 for complete set of rules regarding eligibility for retreatment. After the end of treatment, each participant will be followed for the occurrence of AEs and spontaneously reported pregnancy, as described under Section 9.3. Subjects who discontinue for reasons other than CR or completion of 35 infusions with SD or better will discontinue from the study after Safety Follow-up Visit and have post treatment follow up imaging for disease status monitoring performed per local standards.

Study governance considerations are outlined in Appendix 1. A list of abbreviations used in this document can be found in Appendix 5.

2. Schedule of Activities (SoA)

2.1 Initial Treatment Phase

As of Amendment 06, after Week 12 assessment, participants can choose to discontinue from the study or continue study treatment as per protocol after participant discussion with the investigator and if they are receiving clinical benefits. For those participants remaining in the study, procedures are simplified. The SoA has been amended to show only the required assessments.

Table 1 Schedule of Study Activities for Initial Treatment Phase

	Screening	Treatment Cycles (6-Week Cycles)						EOT	Post-Treatment Safety Follow-up[b]	Notes
Study Period		**C1**			**C2**		**C3 onwards**	**DC**		**Assessments/procedures are to be performed on Day 1 and Day 22 prior to the first dose of treatment for each cycle unless otherwise specified.**
Days		**1**	**8[a]**	**22**	**1**	**22**			**30 Days Post-Last Dose**	
Scheduling Window (Days):	**–28 to –1**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**		**At DC**	**+7** **Follow-up**	**Participants who discontinue study treatment for whatever reason will proceed directly to EOT and Safety Follow-up.**
Administrative Procedures										
Informed Consent	X									May be obtained up to 42 days prior to C1D1. Participants do not need to be reconsented if consent was obtained greater than 42 days prior to C1D1
Inclusion/Exclusion Criteria	X									
Participant ID Card Issued	X									
Demographics	X									
Medical History	X									
RCC Disease History	X									
Smoking History	X									
Prior/Concomitant Medications	X	X	X	X	X	X	X	X	X	
Randomize participant in IVRS/IWRS	X									

Study Period	Screening	Treatment Cycles (6-Week Cycles)						EOT	Post-Treatment Safety Follow-up[b]	Notes
		C1			C2		C3 onwards	DC		**Assessments/procedures are to be performed on Day 1 and Day 22 prior to the first dose of treatment for each cycle unless otherwise specified.**
Days		1	8[a]	22	1	22			30 Days Post-Last Dose	
Scheduling Window (Days):	–28 to –1	± 3	± 3	± 3	± 3	± 3		At DC	+7 Follow-up	**Participants who discontinue study treatment for whatever reason will proceed directly to EOT and Safety Follow-up.**
International Metastatic Renal Cell Carcinoma Database Consortium (IMDC)	X									
Serotonin Syndrome Information Card		X								
Post-study Anti-cancer Therapy Status								X	X	
Clinical Assessments and Procedures										
Review Adverse Events	X	X	X	X	X	X	X	X	X	See Section 9.3.1 for time period and frequency of reporting.
Full Physical Examination	X							X		
Directed Physical Examination		X	X	X	X	X	X		X	
Vital Signs	X	X	X	X	X	X	X	X	X	Height at Screening only. Obtain predose.
12-Lead ECG with QTc Measurement	X	X		X				X		At Screening and DC for all participants. At select centers, perform on C1D1 and C1D22 predose and at 2 h (±15 min) after morning dose of epacadostat.
ECOG Status	X	X		X	X	X	X		X	Perform during screening, within 14 d prior to randomization
Karnofsky Performance Status (KPS)	X									Perform during screening, within 14 d prior to randomization

	Screening	Treatment Cycles (6-Week Cycles)						EOT	Post-Treatment Safety Follow-up[b]	Notes
Study Period		**C1**			**C2**		**C3 onwards**	**DC**		**Assessments/procedures are to be performed on Day 1 and Day 22 prior to the first dose of treatment for each cycle unless otherwise specified.**
Days		**1**	**8[a]**	**22**	**1**	**22**			**30 Days Post-Last Dose**	
Scheduling Window (Days):	**–28 to –1**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**		**At DC**	**+7** **Follow-up**	**Participants who discontinue study treatment for whatever reason will proceed directly to EOT and Safety Follow-up.**
Laboratory Procedures/ Assessments – Analysis Performed by Local Laboratory										
Pregnancy Test – Urine or Serum β-HCG	X									WOCBP require negative test within 72 h prior to randomization. Test monthly (ie, before each cycle) if required by local regulations.
Hepatitis B & C	X									At Screening within 14 days prior to randomization. Hepatitis B surface antigen, HBV-DNA, HCV-RNA (or HCV antibody if HCV-RNA is not the local SoC). If this testing was conducted per SoC within 42 days prior to randomization, testing does not need to be repeated.
HIV Testing	X									Not required unless mandated by local health authority.
PT/INR and aPTT/PTT	X									At Screening within 14 days prior to randomization. Participants receiving coumarin-based anticoagulants should have more frequent INR monitoring - weekly for first 4 weeks after initiation of therapy or per standard or per standard of care and upon DC of epacadostat.
CBC With Differential	X		X	X	X	X	X	X	X	At Screening within 14 days prior to randomization. For Group 2 only: Assess as per SoC after the Week 12 imaging.
Chemistry	X		X	X	X	X	X	X	X	
T3/FT3, FT4, and TSH	X			X		X	X	X	X	At Screening within 14 days prior to randomization. Perform Q6W from C1D22 onwards (C1D22, C2D22, C3D22…) throughout treatment period. For Group 2 only: Assess as per SoC after the Week 12 imaging.
Urinalysis	X			X		X	X	X	X	At Screening within 14 days prior to randomization. Perform Q6W from C1D22 through C4D22. Perform Q12W thereafter, starting at C6D22 (C6D22, C8D22, C10D22…) throughout treatment. For Group 2 only: Assess as per SoC after the Week 12 imaging.

	Screening	Treatment Cycles (6-Week Cycles)						EOT	Post-Treatment Safety Follow-up[b]	Notes
Study Period		C1			C2		C3 onwards	DC		**Assessments/procedures are to be performed on Day 1 and Day 22 prior to the first dose of treatment for each cycle unless otherwise specified.**
Days		1	8[a]	22	1	22			30 Days Post-Last Dose	**Participants who discontinue study treatment for whatever reason will proceed directly to EOT and Safety Follow-up.**
Scheduling Window (Days):	–28 to –1	± 3	± 3	± 3	± 3	± 3		At DC	+7 Follow-up	
[redacted]										

	Screening	Treatment Cycles (6-Week Cycles)						EOT	Post-Treatment Safety Follow-up[b]	Notes
Study Period		**C1**			**C2**		**C3 onwards**	**DC**		**Assessments/procedures are to be performed on Day 1 and Day 22 prior to the first dose of treatment for each cycle unless otherwise specified.**
Days		**1**	**8[a]**	**22**	**1**	**22**			**30 Days Post-Last Dose**	
Scheduling Window (Days):	**–28 to –1**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**		**At DC**	**+7** **Follow-up**	**Participants who discontinue study treatment for whatever reason will proceed directly to EOT and Safety Follow-up.**
Efficacy Measurements										
Imaging – chest, abdomen, pelvis	X	X					Per SoC	X[c]		Perform within 28 d prior to randomization Baseline CAP CT/MRI to be performed in all participants within 28 days prior to randomization. Imaging assessment will be performed at 12 weeks (±7 days) after randomization. Thereafter imaging is to be performed as per SoC for the disease and local guidelines; Only the date of subsequent scans needs to be entered into the eCRF
Imaging – bone scan	X	X					Per SoC	X[c]		Perform within 28 d prior to randomization. After randomization, bone scan will be performed if positive at baseline, at 12 weeks (±7 days) then as per local SoC. Schedule should be followed regardless of treatment delays. Only the date of subsequent scans needs to be entered into the eCRF.
Imaging – brain	X						Per SoC	X[c]		MRI preferred Performed during screening for participants with brain metastasis to ensure participant is stable (according to Exclusion Criterion 5). Only the date of subsequent scans needs to be entered into the eCRF.

Study Period	Screening	Treatment Cycles (6-Week Cycles)						EOT	Post-Treatment Safety Follow-up[b]	Notes
		C1			C2		C3 onwards	DC		**Assessments/procedures are to be performed on Day 1 and Day 22 prior to the first dose of treatment for each cycle unless otherwise specified.**
Days		1	8[a]	22	1	22			30 Days Post-Last Dose	**Participants who discontinue study treatment for whatever reason will proceed directly to EOT and Safety Follow-up.**
Scheduling Window (Days):	–28 to –1	± 3	± 3	± 3	± 3	± 3		At DC	+7 Follow-up	
Study Medication Administration and/or Dispensing										
Pembrolizumab Infusion		X		X	X	X	X			Pembrolizumab will be administered Q3W (D1 and D22 of each cycle)
Epacadostat dispensed		X		X	X	X	X			Morning dose of epacadostat dosed in clinic on C1D1 and C2D1 prior to the pembrolizumab infusion. At all other times, epacadostat to be self-administered approximately Q12H.
Sunitinib dispensed		X			X		X			
Pazopanib dispensed		X			X		X			
Assess Compliance		X		X	X	X	X			For oral study medications
[redacted]										

Notes:
a. Cycle 1 Day 8 (W2) applies ONLY to Group 2/SoC arm.
b. If Discontinuation Visit occurs ≥30 days from last dose of study treatment, a Safety Follow-up Visit is not required.
c. Only applicable if a participant discontinues study treatment before Week 12.

Abbreviations: AE= adverse event; aPTT=activate partial thromboplastin time; CBC=complete blood count; $C^{XD}X$= Cycle X Day X; d= days; DC= discontinuation; ECG= electrocardiogram; ECOG = Eastern Cooperative Oncology Group; [redacted] EOT= end of treatment; [redacted]; HBV / HCV= hepatitis B/C virus; HIV=human immunodeficiency virus; ICF= informed consent form; ID= identification; INR=international normalized ratio; IVRS/IWRS= Interactive voice/web response system; min= minutes; NSAE= non-serious adverse event; PD= progressive disease; [redacted]; PT=prothrombin time; PTT=partial thromboplastin time; Q= every; [redacted]; SAE= serious adverse event; SoC= standard of care; wk= weeks; WOCBP= women of child-bearing potential.

2.2 Second Course (Retreatment)

As of Amendment 06, for participants remaining in the study who are eligible for the Second Course Phase, procedures are simplified. The SoA has been amended and assessments no longer required have been deleted. Disease assessments will be performed by the sites as per SoC for the disease and local guidelines.

Table 2 Schedule of Study Activities for Second Course (Retreatment)

	Treatment Cycles (6-week cycles)		EOT	Post-treatment	Notes
Study Period	**C1 onward**		**DC**	**Safety Follow-up[a]**	
Days	**D1**	**D22**	**At DC**	**30 Days Post Last Dose**	
Scheduling Window (Days):	**± 3**	**± 3**	**NA**	+7	
Administrative Procedures					
Eligibility Criteria	X				
Concomitant Medications	X	X	X	X	
Subsequent Antineoplastic Therapy Status			X	X	
Clinical Assessments and Procedures					
Review Adverse Events	X	X	X	X	Report all AEs (NSAEs and SAEs) occurring within 90 days after the last dose of study treatment, or 30 days after the last dose of study treatment if a new anti-cancer therapy is initiated, whichever is earlier.
Full Physical Examination	X		X		
Directed Physical Examination	X	X		X	Perform as per SoA except at C1D1, when a full physical exam is to be performed.
Vital Signs	X	X	X	X	Obtain predose.
12-Lead ECG with QTc Measurement	X		X		Perform within 14 d prior to second course C1D1.
ECOG Status	X	X	X	X	Both ECOG and KPS are performed within 14 d prior to second course C1D1. Only ECOG is performed after second course C1D1.
Karnofsky Performance Status	X				

	Treatment Cycles (6-week cycles)		EOT	Post-treatment	Notes
Study Period	**C1 onward**		**DC**	**Safety Follow-up[a]**	
Days	**D1**	**D22**	**At DC**	**30 Days Post Last Dose**	
Scheduling Window (Days):	**± 3**	**± 3**	**NA**	**+7**	
Study Medication Administration and/or Dispensing					
Pembrolizumab Infusion	X	X			Pembrolizumab will be administered Q3W (D1 and D22 of each second course cycle)
Epacadostat	X	X			Epacadostat is dosed in clinic on second course C1D1 prior to pembrolizumab infusion; self-administered thereafter.
Assess Compliance	X	X			For epacadostat
Laboratory Procedures / Assessments: Analysis Performed by Local Laboratory					
Pregnancy Test – Urine or Serum β-HCG	X				WOCBP require negative test within 72 h prior to second course C1D1. Test monthly if required by local regulations.
PT/INR and aPTT/PTT	X				Within 14 d prior to second course C1D1. Participants receiving coumarin-based anticoagulants should have more frequent INR monitoring - weekly for first 4 wk after initiation of therapy and upon DC of epacadostat.
CBC With Differential	X	X	X	X	Within 14 d prior to second course C1D1.
Chemistry	X	X	X	X	
T3/FT3, FT4, and TSH	X		X	X	Within 14 d prior to second course C1D1. Perform Q6W from C2D1 onwards (C2D1, C3D1, C4D1…) through the treatment period.
Urinalysis	X		X	X	Within 14 d prior to second course C1D1. Perform Q6W from C1D1 to C4D1). Perform Q12W thereafter, starting at C6D1 (C6D1, C8D1, C10D1…) throughout treatment period.
Efficacy Measurements					
Tumor Imaging (chest, abdomen and pelvis [CAP] CT/MRI)	X	As per SoC			Perform within 28 d prior to second course C1D1. Imaging to be performed as per local SoC for the disease and local guidelines, only the date of scans performed as per SoC needs to be documented in the eCRF.
Bone Scan	X	As per SoC			

Notes:
a. If second course Discontinuation visit occurs ≥30 days from last dose of study treatment, a second course Safety Follow-up Visit is not required.
Abbreviations: AE=adverse event; aPTT=activate partial thromboplastin time; CBC=complete blood count; CXDX= Cycle X Day X; d= days; DC= discontinuation; ECG= electrocardiogram; ECOG = Eastern Cooperative Oncology Group; ECG = electrocardiogram; [redacted]; EOT= end of treatment; H or h= hours; HBV / HCV= hepatitis B/C virus; HIV=human immunodeficiency virus; ICF=informed consent form; ID= identification; INR=international normalized ratio; min= minutes; NA= not applicable; NSAE= non-serious adverse event; PD= progressive disease; [redacted]; PT=prothrombin time; PTT=partial thromboplastin time; Q= every; SAE= serious adverse event; SoC= standard of care; wk= week(s); WOCBP= women of child-bearing potential.

3. Introduction

3.1 Study Rationale

Because of toxicities with TKIs, and inevitable relapse or disease progression with current therapies, there is unmet medical need for safe and effective combination therapies for clear-cell RCC. Both indoleamine 2, 3-deoxygenase 1 (IDO1) and programmed cell death 1 (PD-1) receptor have been shown to suppress T-cell-mediated antitumor immunity, and IDO1 and the PD-1 ligand (PD-L1) have been shown to be co-expressed in multiple cancer types and to correlate with poor prognosis. Combined inhibition of both pathways may therefore lead to increased efficacy.

Recently, nivolumab received approval by the US Food and Drug Administration (FDA) to treat patients with advanced RCC who have received prior anti-angiogenic therapy. Nivolumab is an immune checkpoint inhibitor targeting programmed cell death protein 1 (PD-1). The approval was based on data from a randomized Phase III open-label study in patients with advanced RCC following prior treatment with targeted therapy. Nivolumab demonstrated statistically significant improvement in the primary endpoint of OS versus everolimus during the planned interim analysis (median 25.0 months versus 21.8 months; HR: 0.73 (98.5% Confidence Interval [CI]: 0.57 to 0.93; P=.002 met the pre-specified significance P≤.0148). The ORR was 25% for nivolumab versus 5% for everolimus (odds ratio 5.98; 95% CI: 3.68 to 9.72; P<.001). PFS was not significantly improved with a median PFS 4.6 months for nivolumab versus 4.4 months for everolimus (HR: 0.88; 95% CI: 0.75 to 1.03; P=.11) [Motzer, R. J., et al 2015]. Additionally, a Phase 1a open-label, single arm study of atezolizumab in 70 subjects with advanced RCC was completed in which 61 of the subjects had received previous systemic therapies. Overall survival reached a median of 28.9 months (95% CI, 20.0 months to not reached) and PFS reached a median of 5.6 months (95% CI 3.9 to 8.2 months) [McDermott, D. F., et al 2016].

Response data for participants with RCC from the ongoing Phase 2 study (INCB 24360-202/KEYNOTE-037) is encouraging with a high ORR that exceeds monotherapy with PD-1 inhibitors and appears durable based on Phase 1 responders, thus warranting a further investigation. The present study will examine the combination of pembrolizumab plus epacadostat versus SoC (sunitinib or pazopanib) in participants with confirmed metastatic RCC with clear-cell histology who have not previously received systemic therapy for RCC.

3.2 Background

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

3.2.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades [Disis, M. L. 2010]. The inability of the immune system to control tumor growth does not appear to result from an inability to recognize the tumor as foreign. Tumor cells have been shown to evade immune destruction despite displaying recognizable antigens on their surface and despite the presence of high avidity T-cells that are specific for these antigens [Boon, T. 1996] [Ercolini, A. M., et al 2005]. Histologic evaluation of many human cancers shows extensive infiltration by inflammatory and immune cells [Galon, J., et al 2006], suggesting that the immune system responds less effectively to malignancy. These observations have led to the hypothesis that dominant mechanisms of immune tolerance or immune suppression are responsible for the immune system's inability to effectively respond in a way that consistently results in rejection.

The PD-1 receptor is an immunoglobulin superfamily member shown to negatively regulate antigen receptor signaling upon engagement of its ligands PD-L1 and/or PD-L2 [Greenwald, R. J., et al 2005], [Okazaki, T., et al 2001]. The PD-1 pathway represents a major immune control switch, which can be exploited by tumor cells to overcome active T-cell immune surveillance. Expressed on the surface of activated T-cells under healthy conditions, the function of the PD-1 receptor is to down-modulate unwanted or excessive immune/autoimmune responses. A variety of cancers have been demonstrated to express abundant levels of PD-1 ligands, unlike healthy organs. The observed correlation of clinical prognosis with PD-L1 expression in multiple cancers suggests that the PD-1/PD-L1 pathway plays a critical role in tumor evasion and is thus an attractive target for therapeutic intervention.

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

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

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

IDO1-driven oxidation of tryptophan results in a strong inhibitory effect on the development of T-cell-mediated responses by blocking T-cell activation and inducing T-cell apoptosis [Mellor, A. L., et al 2003]. Both the reduction in local tryptophan levels and the production of tryptophan catabolites that are inhibitory to cell proliferation contribute to the immunosuppressive effects [Frumento, G., et al 2002]. IDO1 activity also promotes the differentiation of naive T-cells to cells with a regulatory phenotype (Treg) [Fallarino, F., et al 2006]. 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 [Zou, W. 2006], 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 conception from the maternal immune system [Munn, D. H., et al 1998]. A critical role for IDO1 in immunomodulation has been confirmed in numerous animal models, including models of allograft tolerance, inflammation, and cancer [Mellor, A. L. 2004]. While IDO1 inhibition can exacerbate disease in models of autoimmune disorders [Mellor, A. L. 2004], IDO1 null mice show no evidence of susceptibility to developing spontaneous autoimmunity or alterations in immune system development [Mellor, A. L., et al 2003], suggesting that IDO1 inhibition, in a therapeutic setting, may produce minimal side effects in participants without pre-existing autoimmune conditions.

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

Based on studies examining serum levels of tryptophan and kynurenine, IDO1 appears to be chronically activated in participants with cancer, and IDO1 activation correlates with more extensive disease [Huang, L., et al 2010], [Weinlich, G., et al 2007]. IDO1 has subsequently been found to be overexpressed by a wide variety of human tumor cell types as well as by the dendritic cells that localize to the tumor-draining lymph nodes [Liu, X., et al 2010]. Increased expression of IDO1 in tumor cells has been shown to be an independent prognostic variable for reduced OS in participants with melanoma, ovarian, colorectal, and pancreatic cancers [Okamoto, A., et al 2005], [Brandacher, G., et al 2006], [Ino, K., et al 2006], [Nakamura, T., et al 2007], [Witkiewicz, A., et al 2008]. Together, these results suggest that the IDO1 pathway is a key regulatory element responsible for the induction and maintenance of tumor immune tolerance. Small molecule inhibitors of IDO1 may provide an innovative and tractable method to treat advanced malignancies in combination with chemotherapeutics and/or immunotherapy-based strategies.

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

3.2.2 Ongoing Studies

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

KEYNOTE-252/ECHO-301:

KEYNOTE-252/ECHO-301 is an ongoing Phase 3, randomized, double-blind, placebo-controlled study of pembrolizumab in combination with epacadostat or placebo in participants with unresectable or metastatic melanoma. The dual primary endpoints of the study are progression free survival (PFS) per RECIST 1.1 as assessed by central imaging and overall survival (OS). The external data monitoring committee (eDMC) concluded that study did not meet the primary objective of improving PFS in the combination compared to pembrolizumab monotherapy during a second interim analysis. There were no safety concerns for the combination pembrolizumab plus epacadostat relative to the findings on the phase 1/2 KEYNOTE-037. The study remains open so that participants still on study will have continued access to open-label pembrolizumab.

3.3 Benefit/Risk Assessment

It cannot be guaranteed that participants in clinical studies will directly benefit from treatment during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine.

Given initial data observed in KEYNOTE-037 suggesting improved efficacy of pembrolizumab in combination with epacadostat and an overall safety profile comparable to anti-PD-1 monotherapy, the addition of epacadostat to established treatments represents a rational and promising first line therapeutic option in patients with mRCC.

[redacted]

The IDO1 inhibitor epacadostat has several ongoing clinical studies in combination with immune-targeted agents, such as anti–PD-1 and anti–PD-L1. A study with epacadostat and an anti–CTLA-4 antibody has recently completed (INCB 24360-201). In an ongoing Phase 1/2 study (INCB 24360-202/KEYNOTE-037), the safety, efficacy, and tolerability of the combinations of epacadostat 25 mg BID, 50 mg BID, and 100 mg BID with pembrolizumab 2 mg/kg IV Q3W and epacadostat 300 mg BID with pembrolizumab 200 mg IV Q3W were evaluated in participants including, but not limited to, Stage 3B, IV or recurrent non-small cell lung cancer (NSCLC), melanoma, urothelial carcinoma (UC), renal cell carcinoma (RCC), endometrial adenocarcinoma (EA), triple negative breast cancer (TNBC), squamous cell carcinoma of the head and neck (SCCHN), microsatellite-instability (MSI), colorectal

cancer (CRC), and diffuse large B-cell lymphoma (DLBCL). In the Phase 1 dose-escalation part, epacadostat 50 mg BID, 100 mg BID, and 300 mg BID with pembrolizumab 200 mg IV Q3W was evaluated. As of 27-FEB-2017, a total of 294 participants were enrolled in Phase 2 and received ≥ 1 dose of epacadostat and pembrolizumab. Preliminary data show that the most common (≥10%) all-grade drug-related adverse events (DRAEs) were fatigue, rash, nausea, and pruritus. Grade ≥3 DRAEs were observed in 18% (most common: increased lipase [4%] and rash [3%]). There was 1 treatment-related death due to respiratory failure which was secondary to aspiration pneumonia. [Hamid, O., et al 2017].

As of 27-FEB-2017, available efficacy data for participants enrolled in the renal cell carcinoma cohort (INCB 24360-202/KEYNOTE-037) was reviewed (Table 3). Among the 19 evaluable renal cell participants who received ≤ 1 prior lines of therapy, the objective response rate (ORR) was 47% and disease control rate (DCR) was 58%, which includes 1 complete response (CR) per RECIST v1.1 as determined by investigator [Lara, P. N. Jr., et al 2017]. These preliminary data suggest improved efficacy of the epacadostat plus pembrolizumab combination compared to monotherapy with anti-PD-1/PD-L1 agents in RCC as observed in other studies, and this forms the basis for initiating the proposed Phase 3 study.

Table 3 Efficacy of Epacadostat in Combination with Pembrolizumab in Renal Cell Carcinoma Patients that Received ≤1 Prior Lines of Therapy

Evaluable participants[a]	**Renal cell carcinoma (n=19)**
ORR (CR+PR), n (%)	**9 (47)**
CR	1
PR	8
SD	2
DCR (CR+PR+SD), n (%)	**11 (58)**
PD	8

CR=complete response; DCR=disease control rate; ORR=objective response rate; PD=progressive disease; PR=partial response; SD=stable disease.

[a] Evaluable participants included any participant with ≥ 1 post baseline response assessment or who had been discontinued from the study or died before response could be assessed.

Additionally, as noted in Gangadhar et al (2017), Smith et al, (2017), and in Hamid et al (2017), respectively, incremental increases in response rates from the same study have been observed when epacadostat is combined with pembrolizumab across a range of tumor types including NSCLC (in both high and low-expressing PD-L1 tumors), urothelial, and head and neck cancer [Gangadhar, T. C., et al 2017] [Smith, D. C., et al 2017] [Hamid, O., et al 2017]. These increases in ORR and totality of the data including the RCC cohort have proven durable in the ongoing INCB 24360-202 study and provide rationale for further study in larger patient populations in a Phase 3 setting.

The use of MAOIs is prohibited during the study, and all participants will be monitored for SS symptoms. Participants will be provided with an informative simplified leaflet describing the signs and potential symptoms of SS, along with instructions to seek immediate medical care if any of these signs or symptoms is observed.

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 co-expressed in multiple cancer types and to correlate with poor prognosis. Combined inhibition of both pathways may, therefore, lead to increased efficacy. Preclinical and clinical data indicate that these pathways are important in melanoma as well as in other cancers, including renal cell carcinoma.

Additional details regarding specific benefits and risks for participants participating in this clinical trial may be found in the current Investigator's Brochures (IBs) and the ICF.

4. Objectives/Hypotheses and Endpoints

NOTE: As of Amendment 06, the primary endpoint of the study will be ORR based on RECIST 1.1 as assessed by the investigator. All other efficacy endpoints, including imaging, will no longer be collected or performed after the first imaging assessment at Week 12. This section has been updated accordingly.

This study will enroll participants with locally advanced/metastatic renal cell carcinoma (mRCC) with clear cell component. Participants must not have received prior systemic therapy for their mRCC.

Objective/Hypothesis	Endpoint
Primary	
• Objective: To estimate the objective response rate (ORR) as measured per RECIST 1.1 by investigator determination of pembrolizumab plus epacadostat and SoC (sunitinib or pazopanib)	• ORR is defined as the proportion of participants who have a best response of complete response (CR) or partial response (PR).
Secondary	
• Objective: To evaluate the safety and tolerability of pembrolizumab plus epacadostat and SoC	• Safety and tolerability of the treatment regimens as measured by the following: o Number of participants experiencing adverse events (AEs) o Number of participants discontinuing study treatment due to AEs
[redacted]	

5. Study Design

5.1 Overall Design

NOTE: Enrollment was terminated on 02-MAY-2018. As of Amendment 06, all protocol-defined study efficacy procedures will discontinue after the first on-study imaging at Week 12 (± 7); thereafter participants will be assessed for efficacy as per SoC for the disease and local guidelines. Safety procedures will continue as per protocol for all participants continuing study treatment. The last study visit is the Safety Follow-up Visit. This section has been updated accordingly.

This is a randomized, open-label, parallel group, Phase 3 study to evaluate the efficacy and safety of pembrolizumab plus epacadostat compared to sunitinib or pazopanib in participants with locally advanced/metastatic renal cell carcinoma (mRCC) with clear cell component who have not received prior systemic therapy for their mRCC.

Approximately 130 eligible participants will be stratified by the following: 1) International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk categories (favorable versus intermediate versus poor [see Appendix 9]) [Ko, J. J., et al 2015], 2) Investigator's intended choice of comparator (sunitinib versus pazopanib [determined prior to randomization]) and 3) geographical region [US, CA and Western EU versus Rest of the World (ROW)] then randomly assigned 1:1 to one of two treatment groups.

- Group 1: Pembrolizumab 200 mg intravenously (IV) every three weeks (Q3W) plus epacadostat 100 mg orally (PO) twice daily (BID) continuously
- Group 2 (SoC): Sunitinib 50 mg PO once daily (6-week cycles; 4 weeks on treatment followed by 2 weeks off treatment) OR pazopanib 800 mg PO once daily continuously

During the treatment period, participants will have routine clinical visits for administration of or obtaining study treatment, monitoring safety and well-being, and assessing changes in disease status. Key safety assessments include physical examinations, vital signs, electrocardiography (ECG), safety laboratory assessments. Participants will also be assessed for the occurrence of AEs and spontaneously reported pregnancy. [redacted]

Participants are required to submit a newly obtained core or excisional biopsy or archival tissue. The tumor tissue must have been obtained prior to randomization and after the latest systemic treatment for RCC.

Required imaging assessments include computed tomography (CT) and/or magnetic resonance imaging (MRI) for chest, abdomen, and pelvis (CAP) and bone scans. A CT or MRI of CAP will be performed for all participants at baseline and on-study, according to the Schedule of Assessments (SoA) in Section 2. Bone scans will be performed for all participants at baseline. If the baseline bone scan is positive, on-study bone scans will be required according to the SoA. Brain imaging will be required according to the exclusion

criteria in Section 6.2 for participants, with a prior history of brain metastases in order to ensure that there is no evidence of progression prior to randomization.

Participants in Group 1 may receive treatment for up to 35 infusions (17.5 cycles) of pembrolizumab plus epacadostat (approximately 2 years) if protocol-specified criteria for discontinuation from treatment have not been met. Participants in Group 2 may receive treatment for an unlimited number of cycles provided that protocol-specified criteria for discontinuation from treatment have not been met.

After the end of treatment, participants will be followed up for safety, according to Table 1 in the SoA in Section 2.

Participants who discontinue treatment for a reason other than disease progression (eg, toxicity) will discontinue from the study after Safety Follow-ups per the Schedule of Activities in Section 2 and Section 9.3.

Participants in Group 1 who stop study treatment (for reasons other than disease progression or intolerability) with SD or PR after receiving 35 infusions of pembrolizumab, or participants who stop study treatment after attaining a CR (with a minimum of 8 infusions of pembrolizumab and at least 2 infusions beyond the date when initial CR was declared) may be eligible for up to 17 additional infusions of pembrolizumab (approximately 1 year) plus epacadostat upon experiencing radiographic disease progression. Please refer to Section 7.8 for complete set of rules regarding eligibility for retreatment.

Participants who discontinue treatment for a reason other than attaining a CR or completing 35 infusions of pembrolizumab (e.g. disease progression, toxicity, etc) will discontinue from the study after Safety Follow-ups per the Schedule of Activities in Section 2 and Section 9.3.

There is no interim analysis in this study. During the course of the study, Data Monitoring Committee (DMC) will perform one safety review based on the DMC charter.

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

5.1.1 Study Diagram

The overall study design is illustrated in Figure 1.

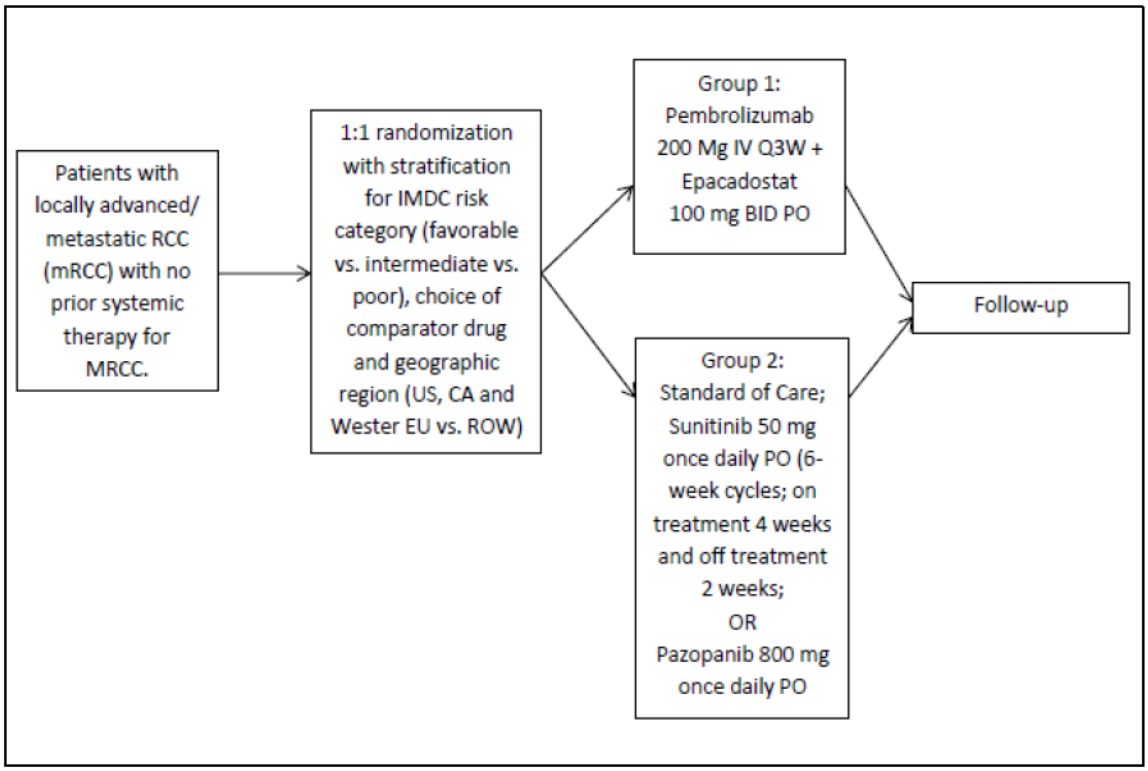


Figure 1 Overall Study Design

CA = Canada; BID = twice a day; EU = European Union; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; IV = intravenous; mRCC = metastatic renal cell carcinoma; PO = by mouth; Q3W = every 3 weeks; ROW = rest of world; US = United States

Note: As of Amendment 06, progression-free survival and overall survival will not be followed up.

5.2 Number of Participants

As of 02-MAY-2018, enrollment in this trial was stopped. It is estimated by the time the strategic decision was made on 02-MAY-2018 to permanently stop enrollment that approximately 130 participants will be randomized into the study.

5.3 Beginning and End of Study Definition

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

5.3.1 Clinical Criteria for Early Study Termination

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

5.4 Scientific Rationale for Study Design

5.4.1 Rationale for Endpoints

5.4.1.1 Efficacy Endpoints

NOTE: As of global Amendment 06, this study will use ORR based on RECIST 1.1 as assessed by the investigator. Transmission of images for central review is no longer required. All other efficacy endpoint assessments will no longer be collected. This section has been amended accordingly.

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

This study will use ORR based on RECIST 1.1 criteria, as assessed by the investigator. ORR is an acceptable measure of clinical benefit for a late stage study that demonstrates superiority of a new antineoplastic therapy. The final determination of radiologic progression will be based on the local site investigator/radiology assessment.

5.4.1.1.1 Response Evaluation Criteria in Solid Tumors, Version 1.1

RECIST 1.1 will be used by the investigator when determining eligibility and when assessing images for primary efficacy measures. Although traditional RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, this protocol has implemented a modification to RECIST 1.1 to allow a maximum of 10 target lesions in total and 5 per organ. This will be termed as RECIST 1.1 throughout the protocol. Further details are found in Section 9.2.1.5.

5.4.1.1.2 Modified RECIST for Immune-based Therapeutics (iRECIST)

Note: As per Amendment 06, this section is no longer applicable; iRECIST data will no longer be entered into the CRF. Participants with radiographic disease progression as determined by RECIST 1.1 will discontinue from the study treatment and be followed for safety monitoring, as detailed in Section 9.3; no confirmatory scans are required. The investigator should consult with the MSD Clinical Director if he/she chooses to continue treatment after initial radiographic PD.

RECIST 1.1 will be adapted to account for the unique tumor response characteristics seen following treatment with pembrolizumab (Section 9.2.1.6). Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and patients treated with

pembrolizumab may manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions.

Thus, standard RECIST 1.1 may not provide an accurate response assessment of immunotherapeutic agents, such as pembrolizumab. Based on an analysis of participants with melanoma enrolled in KEYNOTE-001 (KN001), 7% of evaluable participants experienced delayed or early tumor pseudo-progression. Of note, participants who had progressive disease (PD) by RECIST 1.1 but not by the immune-related response criteria [Wolchok, J. D., et al 2009] had longer overall survival than participants with PD by both criteria [Hodi, F. S., et al 2014]. Additionally, the data suggest that RECIST 1.1 may underestimate the benefit of pembrolizumab in approximately 15% of participants. These findings support the need to apply a modification to RECIST 1.1 that takes into account the unique pattern of atypical responses in immunotherapy and enables treatment beyond initial radiographic progression, if the participant is clinically stable.

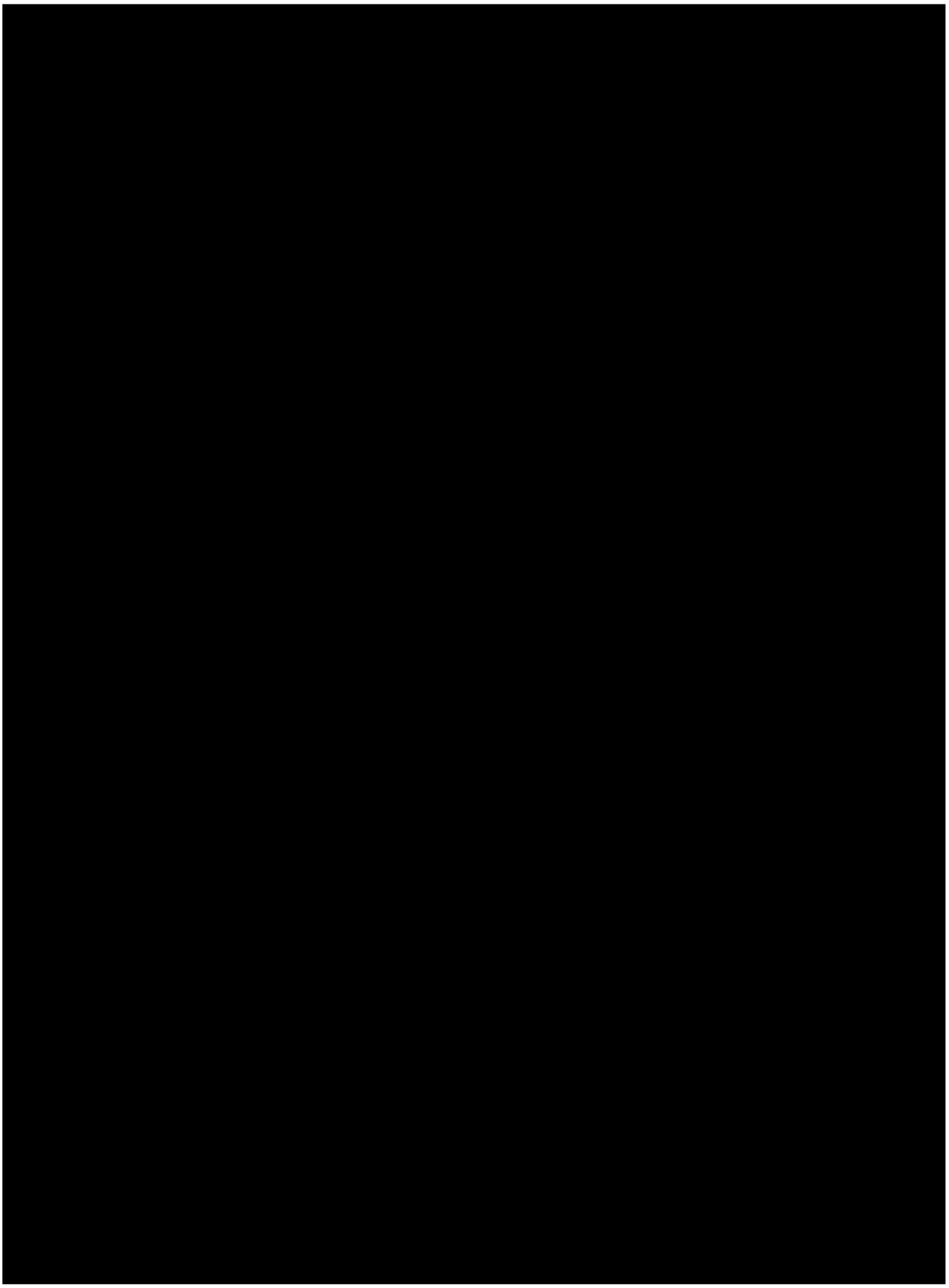
Modified RECIST 1.1 for immune-based therapeutics (iRECIST) assessment has been developed and published by the RECIST Working Group, with input from leading experts from industry and academia, along with participation from the US Food and Drug Administration and the European Medicines Agency [Seymour,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

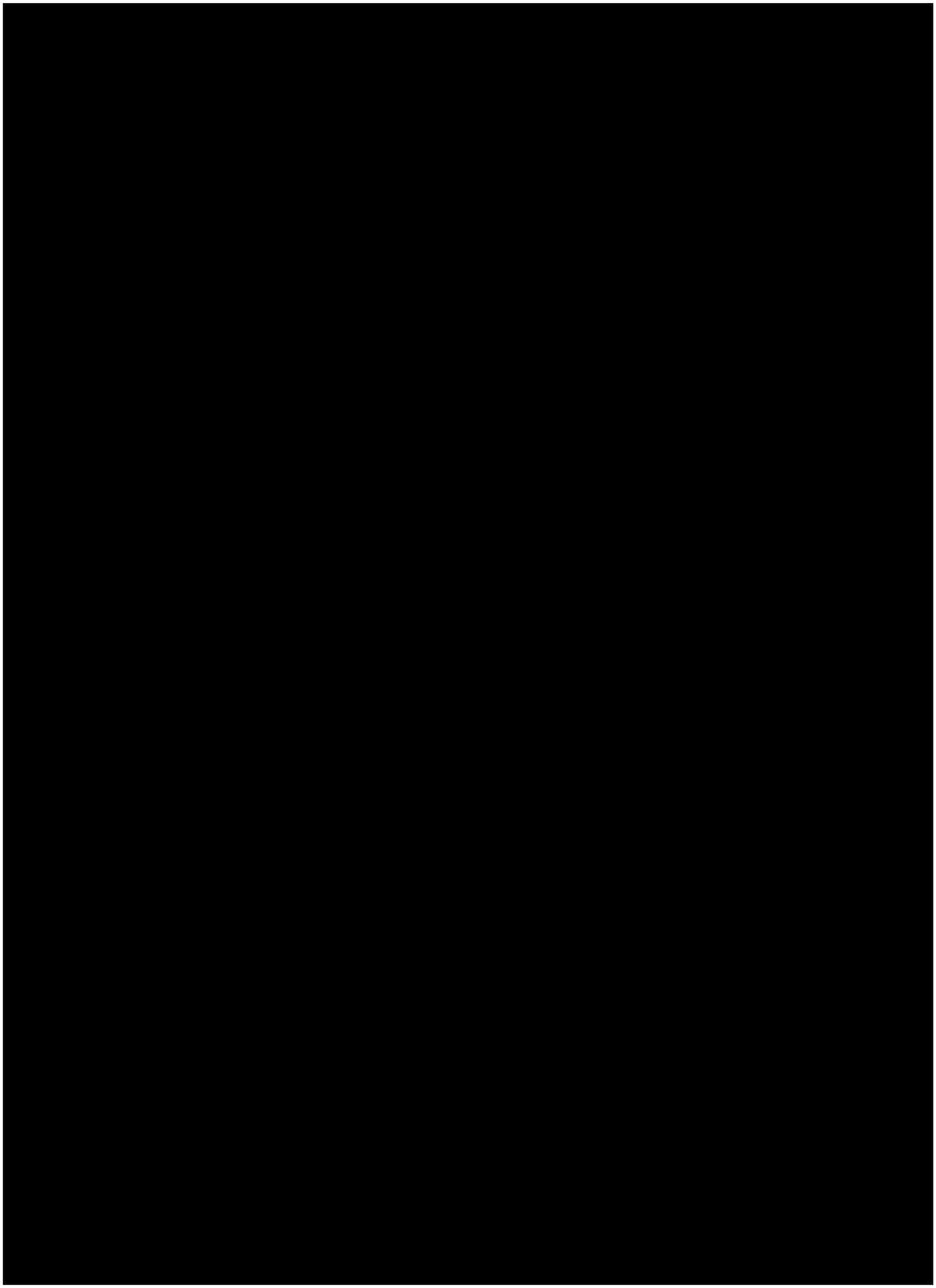
Refer to Section 9.2.1.6 and Appendix 6 for details on iRECIST.

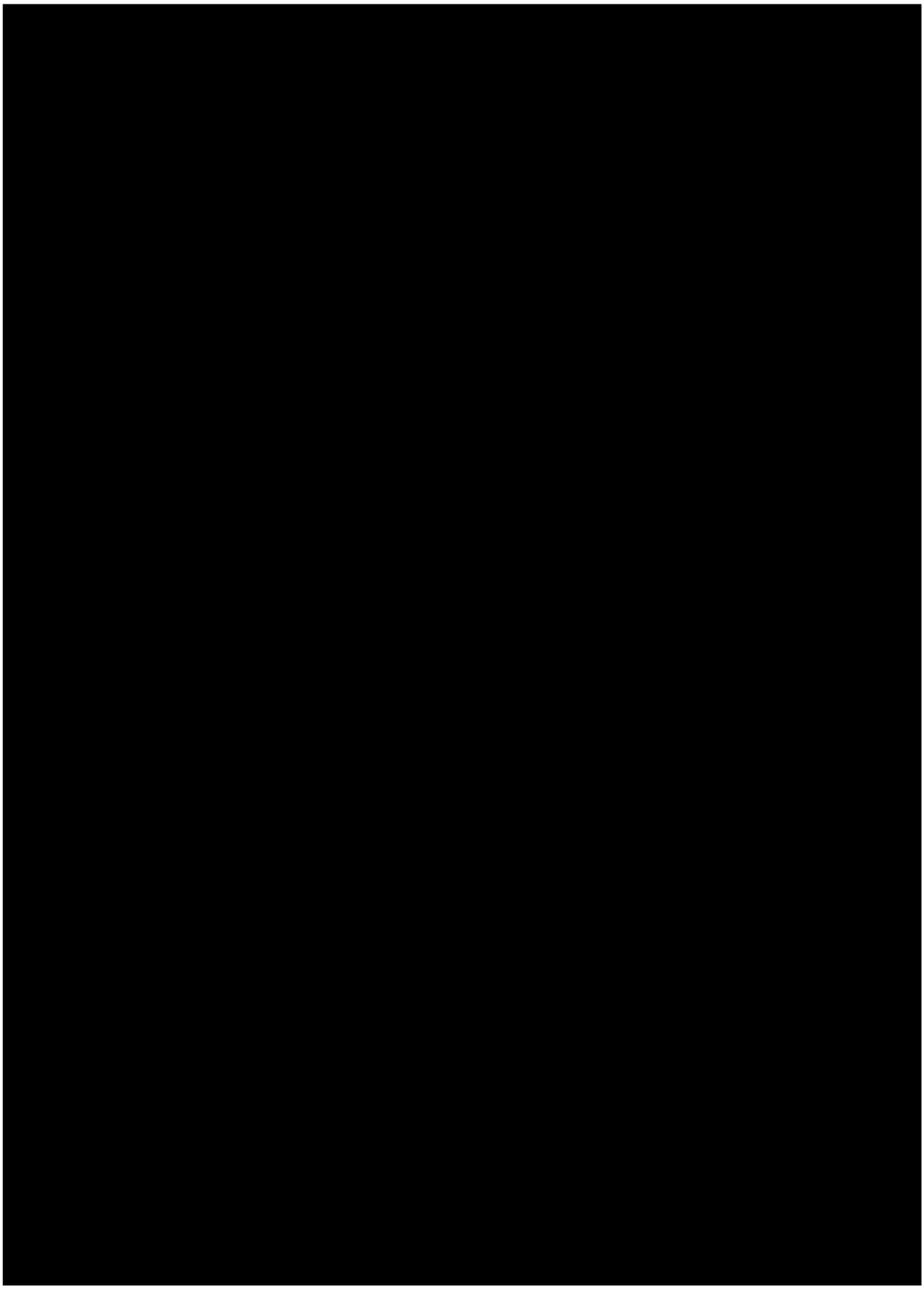
5.4.1.2 Safety Endpoints

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

[redacted]







5.4.2 Rationale for the Use of Comparators

Sunitinib and pazopanib are selected as reference therapies in this study in first-line treatment of participants with mRCC. Sunitinib is the most frequently tyrosine kinase inhibitors (TKI) used as first-line treatment for advanced RCC and has a well characterized safety profile; therefore, sunitinib is selected as a control for the study. Sunitinib is currently the TKI comparator for several ongoing RCC registration studies. Pazopanib, as an approved standard of care in this same setting, is warranted to be used in the control arm. Furthermore, in the first-line setting, clinicians often prescribe one of the VEGFR-TKIs, sunitinib or pazopanib [Malouf, G. G., et al 2016], with some variation depending on geography and availability.

Pazopanib has been demonstrated to be noninferior to sunitinib with similar PFS and OS durations, but with a better toxicity profile [Motzer, R. J., et al 2013]. The choice of either pazopanib or sunitinib allows physicians to determine which comparator is the best treatment option for their patient and potentially improves compliance based upon optimal management of the toxicity profiles. Stratification will occur by choice of comparator drug (either pazopanib or sunitinib) such that equal numbers of favorable-risk, intermediate-risk, and poor-risk participants will be randomized to each therapy on the SoC (control) arm. This strategy will help insure that there is not an imbalance between the 2 components of the SoC arm that may unfavorably bias the results from the use of either TKI.

5.5 Justification for Dose

[redacted]

5.5.2 Rationale for a Fixed Dose of Pembrolizumab

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

- 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 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and NSCLC, covering different disease settings (treatment naïve, previously treated, PD-L1 enriched and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W (KN001 B2, KN001 D, KN002, KN010 and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 B3, KN001 F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat-dose/exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (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 participant covariates on exposure, has shown that the fixed dosing provides similar control of PK variability as weight-based dosing; with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose.

Supported by these PK characteristics, and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

5.5.3 Rationale for Dose of Sunitinib

The dose for sunitinib is 50 mg orally once daily, with or without food (6-week cycles; 4 weeks on treatment followed by 2 weeks off treatment). This dose was selected because it is the approved dosage of sunitinib in advanced RCC.

5.5.4 Rationale for Dose of Pazopanib

The dose for pazopanib is 800 mg orally once daily without food (at least 1 hour before or 2 hours after a meal). This dose was selected because it is the approved dosage of pazopanib in advanced RCC.

6. Study Population

Male/female participants of at least 18 years of age with histologically confirmed locally advanced /metastatic renal cell carcinoma (mRCC) with clear cell component will be enrolled in this trial.

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

6.1 Inclusion Criteria

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

Type of Participant and Disease Characteristics

1. Has histologic confirmation of locally advanced or metastatic RCC (Stage IV per American Joint Committee on Cancer) with a clear cell component with or without sarcomatoid features.
2. Must not have received any prior systemic therapy for their mRCC.
3. Have measurable disease per RECIST 1.1 as determined by the site. Tumor lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
4. Have provided archival tumor tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated. The tumor tissue must have been obtained prior to randomization and after the latest systemic treatment for RCC.
5. Have a Karnofsky performance status of $\geq$ 70 within 14 days prior to randomization. (See Appendix 10).

Demographics

6. Male/female participants who are at least 18 years of age on the day of signing the informed consent.

Male participants:

7. A male participant must agree to use contraception, as detailed in Appendix 2 of this protocol, during the treatment period and for at least 120 days after the last dose of pembrolizumab and epacadostat and up to 180 days after last dose of SoC agents and refrain from donating sperm during this period.

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

Female participants:

8. A female participant is eligible to participate if she is not pregnant (see Appendix 2), not breastfeeding, and at least one of the following conditions applies:

   a) Not a woman of childbearing potential (WOCBP), as defined in Appendix 2

   OR

   b) A WOCBP who agrees to follow the contraceptive guidance in Appendix 2 during the treatment period and for at least 120 days after the last dose of pembrolizumab and epacadostat and up to 180 days after last dose of SoC agents. Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the participant.

Informed Consent

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

Laboratory Values

10. Have adequate organ function as defined in the following table (Table 4). Specimens must be collected within 14 days prior to randomization.

Table 4 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/μL
Platelets	≥100 000/μL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks prior to randomization.
Renal	
Creatinine OR Measured or calculated creatinine clearance (Creatinine clearance (CrCl) should be calculated per institutional standard) (GFR may also be used in place of creatinine or CrCl)	≤1.5 × ULN OR ≥30 mL/min for participant with creatinine levels >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN (If there is no institutional range for the direct bilirubin, the direct bilirubin should be <40% of the total bilirubin. In no case should the total bilirubin exceed 3 x ULN)
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT) OR PTT (PTT may be performed if the local lab is unable to perform aPTT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

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

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

6.2 Exclusion Criteria

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

Medical Conditions

1. Has a history of severe hypersensitivity reaction (eg, generalized rash/erythema, hypotension, bronchospasm, angioedema or anaphylaxis) to study treatments or their excipients.
2. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (doses exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior the first dose of study treatment. Corticosteroid use as premedication for IV contrast prophylaxis is permitted.
3. Has an active autoimmune disease that has required systemic treatment in past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered systemic treatment.
4. Has a known additional malignancy that has progressed or has required active systemic treatment in the last 3 years. Note: participants with curatively treated basal cell carcinoma of the skin, superficial bladder cancer, squamous cell carcinoma of the skin, curatively resected in situ cervical cancer and curatively resected in situ breast cancer are not excluded.
5. Has known active central nervous system metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable (ie, without evidence of progression for at least 4 weeks by repeat imaging) (note that the repeat imaging should be performed during study screening), clinically stable, and have not required steroids for at least 14 days before first dose of study treatment.
6. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.
7. Has an active infection requiring systemic therapy.
8. Has a known history of human immunodeficiency virus (HIV) infection. No HIV testing is required unless mandated by local health authority.
9. Has a known history of or is positive for active Hepatitis B (HBsAg reactive) or has active Hepatitis C (HCV RNA). Note: Testing must be performed to determine eligibility.
    a) HBV DNA must be undetectable and HBsAg negative at Screening visit.
    b) Hepatitis C Ab testing is allowed for screening purposes in countries where HCV RNA is not part of SoC. In these cases, HCV antibody positive participants will be excluded.

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

10. Has any history of SS after receiving serotonergic drugs.
11. Has a history of a gastrointestinal condition or procedure that in the opinion of the Investigator may affect oral drug absorption.
12. Has a history of any of the following cardiovascular conditions within 12 months prior to randomization: myocardial infarction, unstable angina pectoris, cardiac angioplasty or stenting, coronary/peripheral artery bypass graft, Class III or IV congestive heart failure per New York Heart Association (NYHA), cerebrovascular accident or transient ischemic attack, or NYHA Class III or IV congestive heart failure (CHF) (see Appendix 11). Medically controlled arrhythmia stable on medication is permitted.
13. Has a history of deep vein thrombosis or pulmonary embolism within 6 months of screening.
14. Poorly controlled hypertension (defined as systolic BP $\geq$ 150 mm Hg or diastolic BP $\geq$ 90 mm Hg). Initiation or adjustment of antihypertensive medication(s) is permitted prior to randomization.
15. Has a history or presence of an abnormal electrocardiogram (ECG) that, in the Investigator's opinion, is clinically meaningful. Screening QTc interval > 480 msec is excluded (corrected by Fridericia or Bazett formula). In the event that a single QTc is > 480 msec, the participant may enroll if the average QTc for 3 ECGs is < 480 msec.
16. WOCBP who has a positive urine pregnancy test within 72 hours before the first dose of study treatment. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

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

17. Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 120 days after the last dose of pembrolizumab and epacadostat and up to 180 days after last dose of chemotherapeutic agents.

Prior/Concomitant Therapy

18. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti PD-L2 agent, with epacadostat or any anti-IDO1 agent, or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137).
19. Has received prior therapy with vascular endothelial growth factor (VEGF)/VEGF receptors (VEGFR) or mechanistic target of rapamycin (mTOR) targeting agents in locally advanced/metastatic setting.
    Note: Prior neoadjuvant/adjuvant therapy for RCC with those agents is acceptable if completed > 12 months prior to randomization.

20. Has received prior systemic anti-cancer therapy including investigational agents within 4 weeks prior to randomization.

    Note: Participants must have recovered from all AEs due to previous therapies to ≤Grade 1 or baseline. Participants with ≤Grade 2 neuropathy may be eligible.

21. If participant received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting study treatment.

22. 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 are live attenuated vaccines and are not allowed.

23. Has received therapy with a monoamine oxidase inhibitor (MAOI) or UGT1A9 inhibitor within 21 days prior to randomization, or anticipates requiring one of these prohibited medications during the treatment phase. Examples of medications in these classes are found in Section 7.7.2.

24. Has current use (within 7 days of randomization) or anticipated need for treatment with drugs or foods that are known strong cytochrome P450 (CYP3A4/5) inhibitors including, but not limited to, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, voriconazole, and grapefruit or grapefruit juice. Note: The topical use of these medications, such as 2% ketoconazole cream, is allowed.

25. Current use of any prohibited medication as described in Section 7.7.2 – Prohibited Medications or Therapies.

Prior/Concurrent Clinical Study Experience

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

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

Other Exclusions

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

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

6.3 Lifestyle Restrictions

6.3.1 Meals and Dietary Restrictions

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

Participants receiving pazopanib should take their dose without food (at least 1 hour before or 2 hours after a meal).

There are no restrictions for pembrolizumab, epacadostat, and sunitinib with respect to timing of meals relative to dosing.

6.3.2 Caffeine, Alcohol, and Tobacco Restrictions

There are no restrictions for participants in this study with regard to caffeine, alcohol, or tobacco.

6.3.3 Contraception

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

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

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

Definitions of WOCBP and standards for adequate contraception are outlined in Appendix 2.

6.3.4 Pregnancy

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

6.3.5 Use in Nursing Women

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

6.4 Screen Failures

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

6.5 Participant Replacement Strategy

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

7. Treatments

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

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

7.1 Treatments Administered

The study treatments to be used in this trial are outlined below in Table 5.

Table 5 Study Treatments During Treatment Phase

Drug	Dose / Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use	Sourcing
Pembrolizumab	200 mg dose/ 25 mg/mL solution for infusion	Q3W	IV infusion	Days 1 and 22 of each 6-week cycle for up to 35 infusions	Experimental (Group 1)	Central
Epacadostat	100 mg dose/ 100 mg or 25 mg tablets	BID	Oral	Continuous, twice daily dosing each 6-week cycle	Experimental (Group 1)	Central
Sunitinib (as sunitinib malate) [a, b]	50 mg dose/ 12.5 mg, 25 mg, 37.5 mg, or 50 mg, capsules	QD	Oral	6-week cycles (4 weeks on treatment, once daily, followed by 2 weeks off treatment)	Treatment of cancer (Group 2)	Local or Central
Pazopanib [b] (as pazopanib hydrochloride)	800 mg dose/ 200 mg or 400 mg tablets	QD	Oral	Continuous once daily dosing each 6-week cycle	Treatment of cancer (Group 2)	Local or Central

[a] Dosing on a 2-week on, 1-week off schedule is not permitted.
[b] May receive treatment for an unlimited number of cycles provided that protocol-specified criteria for discontinuation from treatment have not been met.

All products indicated in Table 5 will be provided centrally by MSD or locally by the trial site, subsidiary, or designee, depending on local country operational or regulatory requirements. Every attempt should be made to source these supplies from a single lot/batch number.

Refer to section 9.1.8 for details regarding administration of the study treatment.

Pembrolizumab will be administered on an outpatient basis at the study site by study site staff.

Epacadostat will be dispensed every 3 weeks and will be administered in the clinic on Cycle 1 Day 1 and Cycle 1 Day 22 following blood draws. For all other doses, epacadostat will be self-administered by the patient.

Sunitinib and pazopanib will be dispensed every 6 weeks and will be self-administered by the participant.

7.2 Dose Modifications (Escalation/Titration/Other)

Doses of epacadostat, sunitinib, and pazopanib may need to be decreased due to toxicity or interrupted and restarted after recovery of laboratory values or AEs.

Pembrolizumab may be interrupted, and no dose modifications are permitted.

7.2.1 Dose Modification for Immune-related Adverse Events

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

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

Table 6 summarizes the irAE dose modification actions for pembrolizumab and epacadostat. Of note, participants who require dose reduction of epacadostat due to AEs will remain at the lower dose, summarized in Table 7. Re-escalation of epacadostat is not permitted.

In cases where pembrolizumab dosing is held, dosing for epacadostat must also be held. Upon improvement of the irAE to Grade 0 or 1, study treatment many resume according to Table 6. The Investigator may elect to resume both pembrolizumab and epacadostat or pembrolizumab monotherapy; however, epacadostat monotherapy is not permitted.

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 treatment hold.

Table 6 Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab or Epacadostat

Immune-related AEs	Toxicity Grade or Conditions (CTCAE v4.0)	Study Treatment	Action Taken with Study Treatment	irAE Management with Corticosteroid and/or Other Therapies	Monitor and Follow-up
Pneumonitis	Grade 2	Pembrolizumab	Withhold until Grade 0-1	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections.
		Epacadostat	Withhold until Grade 0-1 Once resolved to Grade 0-1, may restart: Related: Reduce by 1 dose level. Not Related: Same dose level.		
	Grade 3 or 4, or recurrent Grade 2	Pembrolizumab	Permanently discontinue		
		Epacadostat	Permanently discontinue		

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

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

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

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

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

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

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

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

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

General Instructions:

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

NOTES:

a. Withhold OR permanently discontinue pembrolizumab or epacadostat at the discretion of the investigator.
b. For participants with Grade 3 or 4 immune-related endocrinopathy where withholding of pembrolizumab and epacadostat is required, pembrolizumab and epacadostat may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).
c. Participants with Grade 3 rash in the absence of desquamation, no mucosal involvement, does not require systemic steroids, and resolves to Grade 1 within 14 days does not have to hold study treatment.

When indicated by Table 6 to mitigate irAEs, the dose of epacadostat must be reduced using the dosing levels outlined in Table 7. Once reduced, re-escalation of epacadostat is not permitted.

Table 7 Dose Level Adjustments of Epacadostat

Starting Dose of Epacadostat	**Dose Level -1**	**Dose Level -2**
	First reduction of epacadostat	Second reduction of epacadostat
100 mg BID	50 mg BID	25 mg BID

Dose Level -2 is the lowest dose of epacadostat in this protocol. Refer to the general instructions in Table 6 for guidance regarding the re-occurrence of an AE when a participant has had their epacadostat dose reduced to dose level -2.

7.2.2 Infusion Reaction Dose Modifications

Pembrolizumab may cause severe or life threatening infusion-reactions, including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab-associated infusion reaction are provided in Table 8.

Table 8 Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

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

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

7.2.3 Procedures for Participants Exhibiting Serotonin Syndrome

There is a rare chance that epacadostat could cause an increase in serotonin levels in the brain that might trigger SS [Boyer EW, Shannon M. 2005], when administered in combination with other serotonergic agents. This syndrome has been most closely associated with the use of MAOIs, meperidine, linezolid, or methylene blue; all of these agents are prohibited during the study (Section 7.7.2).

Selective serotonin reuptake inhibitors (SSRIs) and selective serotonin/norepinephrine reuptake inhibitors (SNRIs) are permitted in the study. Serotonin syndrome usually manifests with autonomic changes, mental status changes, and neurological findings. These mild, moderate, and severe signs and symptoms of SS (summarized in Table 9) should be evaluated in the context of possible comorbid conditions as well.

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

- Immediately interrupt study treatment administration.
- Immediately interrupt any SSRI or SNRI administration.

- Provide appropriate medical management of the participant until all signs/symptoms are resolved (eg, IV fluids and/or sympathomimetic amines for hypotension, benzodiazepines for agitation, administration of 5-hydroxytryptamine antagonists such as cyproheptadine).
- If etiologies other than SS are excluded, pembrolizumab administration may be resumed unless other AE management guidelines apply for the specific event.
- If participant chooses to remain on study treatment, restart treatment with epacadostat 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 participant chooses to withdraw from study treatment, or must restart treatment with SSRI or SNRI, the participant should be scheduled for a follow-up visit. Treatment with SSRI or SNRI may be initiated 2 weeks after resolution of signs and symptoms of SS.
- If a participant had experienced moderate or severe unconfounded SS in the opinion of the investigator, without concomitant SSRI or SNRI usage, or serotonergic concomitant medications, only pembrolizumab administration may be resumed; epacadostat treatment should be permanently discontinued.

Table 9 Signs and Symptoms of Serotonin Syndrome

Seriousness	Autonomic signs	Neurological signs	Mental status	Other
Mild	Afebrile or low-grade fever Tachycardia Mydriasis Diaphoresis or shivering	Intermittent tremor Akathisia Myoclonus Mild hyperreflexia	Restlessness Anxiety	
Moderate	Increased Tachycardia Fever (up to 41 ^{0}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)

Seriousness	Autonomic signs	Neurological signs	Mental status	Other
Severe	Temperature often more than 41^{0}C (Secondary to increased tone)	Increased muscle tone (lower limb > upper) Spontaneous clonus Substantial myoclonus or hyperreflexia	Delirium Coma	As above

Boyer EW, Shannon M. The serotonin syndrome. New Engl J Med 2005;352: 1112-1120.

7.2.4 Interruptions Unrelated to Adverse Events

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

7.2.5 Dose Modifications for SoC Group Participants

7.2.5.1 Modifications for Sunitinib

Dose modifications in 12.5-mg steps may be applied based on individual safety and tolerability. Dose interruptions may be required based on individual safety and tolerability. Dose reductions are required with concomitant use of CYP 3A4 inhibitors such as ketoconazole (see Section 7.7.2, Restricted Medications). See the full prescribing information or SmPC for sunitinib for additional details on dose adjustments.

7.2.5.2 Modifications for Pazopanib

Dose modifications in 200 mg steps may be applied based on individual safety and tolerability. Dose interruptions may be required based on individual safety and tolerability. Dose reductions are required with concomitant use of CYP 3A4 inhibitors such as ketoconazole (see Section 7.7.2, Restricted Medications). See the full prescribing information or SmPC for pazopanib for additional details on dose adjustments.

7.3 Method of Treatment Assignment

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

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

Treatment allocation/randomization will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). There are 2 study treatment arms. Participants will be assigned randomly in a 1:1 ratio to pembrolizumab plus epacadostat or standard of care (sunitinib or pazopanib).

7.3.1 Stratification

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

1. IMDC risk category (favorable versus intermediate versus poor)
2. Physician's intended choice of comparator drug (sunitinib versus pazopanib [determined prior to randomization])
3. Geographical region (US, CA and Western Europe versus ROW)

   NOTE: The geographical regions are defined in detail by country in the IVRS manual.

7.4 Blinding

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

7.5 Preparation/Handling/Storage/Accountability

7.5.1 Dose Preparation

Details on preparation and administration of IV pembrolizumab are provided in the Pharmacy Manual. Epacadostat, sunitinib, and pazopanib are oral tablets.

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

7.5.2 Handling, Storage and Accountability

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

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

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

For all trial sites, the local country MSD personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

The trial site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by MSD.

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

7.6 Treatment Compliance

7.6.1 Administration and Compliance of Pembrolizumab

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

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

7.6.2 Administration and Compliance of Oral Study Treatment (Epacadostat, Sunitinib, or Pazopanib)

Participants will take their dose of epacadostat in the morning and evening, approximately 12 hours apart without regard to food. If the morning or evening dose is missed by more than 4 hours, that dose should be skipped and the next scheduled dose should be taken at the usual time. Participants will self-administer epacadostat except on Cycle 1 Day 1 (C1D1) and Cycle 1 Day 22 (C1D22), when the morning dose will be given at the study site clinic prior to the pembrolizumab infusion.

The administration schedule for sunitinib is daily for each 6-week series (on treatment for 4 weeks, followed by 2 weeks off treatment), and for pazopanib is daily for each 6-week series).

Participants will be instructed to bring all study treatments with them to the study visits in order for site personnel to conduct tablet counts to assess study treatment accountability. Investigators and their staff should evaluate compliance at each visit, and take appropriate steps to optimize compliance.

7.7 Concomitant Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medication or vaccination specifically prohibited, discontinuation from study therapy or vaccination may be required. The investigator should discuss any questions regarding this with the MSD Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or

the participant's primary physician. However, the decision to continue the participant on study treatment requires the mutual agreement of the investigator, MSD, and the participant.

7.7.1 Acceptable Concomitant Therapies

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

Palliative and supportive care is permitted during the course of the study for underlying medical conditions and management of symptoms. Surgery for tumor control is not permitted during the study. Palliative radiotherapy may be permitted to a limited number of lesions if considered medically necessary by the treating physician after consultation with the MSD Clinical Director. Study treatment should be held during the course of palliative radiotherapy and should be resumed no earlier than the next scheduled administration of study treatment. The specifics of the radiation treatment, including the location, will be recorded.

All concomitant medications received within 30 days before the first dose of study treatment through the Safety Follow-up Visit should be recorded. After the Safety Follow-up Visit, record all medications taken for SAEs and ECIs. If a participant enters into second course therapy, all concomitant medications received within 30 days before the first dose of second course treatment should be recorded. Following second course therapy Safety Follow-up Visit, record all medications taken for SAEs and ECIs.

7.7.2 Prohibited Medications or Therapies

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

If a study participant must receive a medication prohibited for concomitant use with epacadostat during the study treatment period, treatment with epacadostat must be interrupted or discontinued. Examples of such medications include MAO inhibitors and UGT1A9 inhibitors. Participants may continue on treatment with pembrolizumab after consultation with MSD.

Listed below are specific restrictions for concomitant therapy or vaccination:

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

- Antineoplastic systemic chemotherapy or biological therapy not specified in this protocol.

  - Note: denosumab is permitted.
- Immunotherapy not specified in this protocol.
- Investigational agents other than epacadostat and pembrolizumab.
- Any chronic immunological-suppressive treatment for any reason other than the management of adverse events, as described in Section 7.2 (Note: Inhaled or topical steroids are allowed, and systemic steroids or replacement doses of steroids at doses ≤ 10 mg/day prednisone or equivalents are allowed, and immune suppressants are allowed as prophylaxis for contrast allergy for imaging procedures.)
- Oncologic surgery for tumor control.
- Radiation therapy for disease control.
  - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the Investigator's discretion, provided the lesions were not previously defined by the site as target lesions.
- Live vaccines within 30 days prior to the first dose of study treatment and while participating in the study.
  - Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chickenpox, yellow fever, nasal seasonal flu, nasal H1N1 flu, rabies, BCG, and typhoid.

- **Participants in Group 1 Receiving pembrolizumab plus epacadostat**
  - Any MAOI or drug associated with significant MAO inhibitory activity agents is prohibited from 21 days before starting study treatment through 2 weeks after the final dose of epacadostat has been taken.
    - Including, but not limited to, hydrazines (example phenelzine), meperidine, caroxazone, linezolid, echinopsidine, methylene blue, furazolidone, tranylcypromine, brofaromine, metralindole, minaprine, moclobemide, pirlindole, toloxatone, lazabemide, pargyline, rasagiline, selegiline.

- Any UGT1A9 inhibitor, including, but not limited to acitretin, amitriptyline, androsterone, cyclosporine, dasatinib, diclofenac, diflunisal, efavirenz, erlotinib, flutamide, gefitinib, gemfibrozil, glycyrrhetinic acid, glycyrrhizin, imatinib, imipramine, ketoconazole (systemic), linoleic acid supplements, mycophenolic acid, niflumic acid, nilotinib, phenobarbital, phenylbutazone, phenytoin, probenecid, quinidine, ritonavir, sorafenib, sulfinpyrazone, valproic acid, and verapamil.

  Note: Ketoconazole 2% topical cream is allowed.

- **Participants in Group 2 Receiving sunitinib**
  - Strong CYP 3A4 inhibitors such a ketoconazole may increase sunitinib plasma concentrations. Selection of an alternate concomitant medication with no or minimal enzyme inhibition potential is recommended. A dose reduction for sunitinib to a minimum of 37.5 mg daily should be considered if strong CYP 3A4 inhibitors must be used. See Appendix 7 for listings of CYP inhibitors/inducers. Refer also to the prescribing information or SPC of sunitinib for complete information.
- **Participants in Group 2 Receiving pazopanib**
  - Avoid use of strong CYP 3A4 inhibitors such as ketoconazole with pazopanib. If co-administration is warranted reduce the dose of pazopanib to 400 mg. See Appendix 7 for listings of CYP inhibitors/inducers. Refer also to the prescribing information or SPC of pazopanib for complete information.
  - Agents that raise gastric pH should be used with caution with pazopanib. Consider short acting antacids in place of proton pump inhibitors or H2 receptor antagonists, and separate antacid administration from pazopanib dosing by several hours.

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

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

  There are no prohibited therapies during the Post-Treatment Follow-up Phase.

7.7.3 Restricted Medications

Group 1 (pembrolizumab plus epacadostat only): Use of coumarin-based anticoagulants (eg, warfarin [Coumadin]), Previscan (fluindione), and vitamin K antagonists are discouraged. Low-dose coumarin-based anticoagulants, eg, warfarin 1 mg is acceptable; however, doses that increase the INR are discouraged. If an alternative cannot be used, the INR should be monitored closely (weekly for the first 4 weeks after initiation of therapy and upon discontinuation of epacadostat).

7.7.4 Rescue Medications and Supportive Care

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

7.8 Second Course Phase (Retreatment)

All participants in Group 1 who stop study treatment with SD or better may be eligible for up to an additional 17 infusions (approximately 1 year) of pembrolizumab plus epacadostat if they progress after stopping study treatment from the initial treatment phase. This retreatment is termed the Second Course Phase of the study and is only available if the study remains open and the participant meets the following conditions:

Either

- Stopped study treatment after attaining a CR by the local investigator per RECIST 1.1, and,
  - Was treated for at least 4 cycles of study treatment (each cycle is 6 weeks and includes 2 infusions of pembrolizumab) before discontinuing therapy.
  - Received at least 2 infusions of pembrolizumab beyond the date when the initial CR was declared.

OR

- Had SD, PR, or CR and stopped study treatment after completion of 35 infusions of pembrolizumab plus 17.5 cycles of epacadostat (approximately 2 years) for reasons other than disease progression or intolerability.

- AND
  - Experienced a radiographic disease progression per RECIST 1.1 after stopping initial treatment, ,
  - No new anticancer treatment was administered after the last dose of study treatment, and
  - The participant meets all of the safety parameters listed in the inclusion criteria and none of the safety parameters listed in the exclusion criteria, and
  - The study is ongoing.

Participants who enter the Second Course Phase (Retreatment) will be re-treated at the same dose frequency as when they last received the combination of pembrolizumab plus epacadostat. Treatment will be administered for up to an additional 17 infusions of pembrolizumab (approximately 1 year) using the revised Second Course Phase Schedule of Activities in Section 2.2.

7.9 Treatment After the End of the Study

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

7.10 Clinical Supplies Disclosure

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

8. Discontinuation/Withdrawal Criteria

8.1 Discontinuation of Study Treatment

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

As certain data on clinical events beyond study treatment discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study treatment. Therefore, all participants who discontinue study treatment prior to completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 2 - Schedule of Activities (SoA) and Section 9.10.3 – Discontinued Participants Continuing to be Monitored in the Study.

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

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

- The participant or participant's legally acceptable representative requests to discontinue study treatment.
- Radiographic disease progression per RECIST 1.1The investigator should consult with the Merck Clinical Director if he/she chooses to continue treatment after initial radiographic PD.
- Unacceptable adverse experiences as described in Section 7.2.
- The participant has a medical condition or personal circumstance which, in the opinion of the Investigator and/or MSD, placed the participant at unnecessary risk from continued administration of study treatment.
- The participant has a confirmed positive serum pregnancy test.
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active systemic treatment.
- Completion of 35 infusions of pembrolizumab (approximately 2 years)
    - Discontinuation of treatment may be considered for participants who have attained a confirmed CR by local Investigator assessment and have been treated for at least 8 infusions (at least 24 weeks) and received at least 2 infusions beyond the date when the initial CR was declared. These participants may be eligible for second course treatment described in Section 7.8.
- The study is terminated by the Sponsor.
- The study is terminated by the local health authority, IRB, or IEC.

- The occurrence of unacceptable toxicity not caused by the underlying malignancy will be presumed to be related to study treatment and will require that all study treatment be permanently discontinued. Unacceptable toxicity is defined as follows:
    - Occurrence of an AE that is related to the study treatment that, in the judgment of the investigator or MSD's medical monitor, compromises the participant's ability to continue study-specific procedures or is considered to not be in the participant's best interest.
    - An AE requiring more than 2 dose reductions of epacadostat. Participants may continue on pembrolizumab monotherapy treatment.
    - Persistent AE requiring a delay of therapy for more than 12 weeks unless a greater delay has been approved by MSD.

A participant **may** be discontinued from study treatment(s) or reference therapies as follows:

- If, during the course of the study, a participant is found not to have met eligibility criteria, the medical monitor, in collaboration with the investigator, will determine whether the participant should be withdrawn from the study.

For participants who are discontinued from study treatment but continue to be monitored in the trial, all visits and procedures, as outlined in the SoA, should be completed.

8.2 Withdrawal from the Study

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

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

Specific details regarding procedures to be performed at the time of withdrawal from the study are outlined in Section 9.1.10. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 8.3.

8.3 Lost to Follow up

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

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, phone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

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

NOTE: As of Amendment 06, this section is no longer applicable. There will be no additional efforts to contact participants who are lost to follow-up.

9. **Study Assessments and Procedures**

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The Investigator is responsible for assuring that procedures are conducted by appropriately qualified or trained staff. Delegation of trial site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Additional evaluations/testing may be deemed necessary by the investigator and/or MSD for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

9.1 Administrative and General Procedures

9.1.1 Informed Consent

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

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

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

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

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

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

9.1.2 Inclusion/Exclusion Criteria

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

9.1.3 Participant Identification Card

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

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

9.1.4 Serotonin Syndrome Information Card

On Cycle 1 Day 1, participants in Group 1 will be given an information card listing signs and symptoms of SS. This information card instructs participants to seek immediate medical care if any of the listed symptoms are observed.

9.1.5 Medical History

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

Comprehensive medical history pertaining to RCC will also be collected. This includes the diagnosis, histopathology, and prior treatment (including radiation and surgery).

9.1.6 Prior and Concomitant Medications Review

9.1.6.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement and record prior medication taken, including antibiotics, by the participant within 30 days of the first dose of study treatment.

9.1.6.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study through the Safety Follow-up visit. After the Safety Follow-up Visit, if participants are eligible for second course of treatment, record new medications started during the Second Course Phase through the Second Course Safety Follow-up Visit.

9.1.7 Assignment of Screening Number

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

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

Specific details on the screening visit requirements (screening/rescreening) are provided in Section 9.10.1.

9.1.8 Assignment of Treatment/Randomization Number

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

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

9.1.9 Treatment Administration

Administration of pembrolizumab will be witnessed by the investigator and/or study staff. Administration of epacadostat will be witnessed by the investigator and/or study staff for the morning dose on C1D1 and C1D22 (and Second Course C1D1 if applicable). All other doses of epacadostat will be self-administered.

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

9.1.9.1 Timing of Dose Administration

9.1.9.1.1 Timing of Dose Administration of Pembrolizumab

Study Treatment should begin within 3 days of randomization.

Study treatment with pembrolizumab should be administered at each treatment visit after all procedures/assessments have been completed as detailed in the SoA (Section 2). At C1D1 and C1D22, pembrolizumab should be administered after all procedures/assessments have been completed and epacadostat dose has been taken in the clinic.

Pembrolizumab will be administered on an outpatient basis. Study treatment of pembrolizumab may be administered up to 3 days before or after the scheduled visit due to administrative reasons (except for C1D1, where the dosing window is on the date of randomization or up to 3 days after randomization).

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

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

9.1.9.1.2 Timing of Dose Administration of Epacadostat

The dose of epacadostat in this study is 100 mg twice daily. Epacadostat will be taken twice daily, once in the morning and once in the evening, approximately 12 hours apart without regard to food.

On C1D1 and C1D22, the morning dose of epacadostat will be given at the clinic prior to the infusion of pembrolizumab and after all procedures/assessments have been completed, as detailed in the SoA (Section 2). [redacted]

All other doses of epacadostat will be self-administered without regard to food.

If the morning or evening dose of epacadostat is missed by more than 4 hours, that dose should be skipped and the next scheduled dose should be taken at the usual time. If the participant vomits after taking a tablet, the dose should not be readministered; the next scheduled dose should be taken at the usual time.

The participant must be instructed in the handling of study treatment as follows:

- To store the study treatment at room temperature and tightly closed to avoid moisture.
- To only remove from the study treatment bottle/kit the number of tablets needed at the time of administration.
- To make every effort to take doses on schedule.
- To report any missed doses.

- If the participant vomits after taking study treatment, the participant should not take another dose.
- To keep study treatment in a safe place and out of reach of children.
- To bring all used and unused study treatment kits to the site at each visit.

9.1.9.1.3 Timing of Dose Administration of Sunitinib

Sunitinib will be self-administered during each 6-week treatment cycle. Each 6-week treatment cycle is broken up into 4 weeks on treatment followed by 2 weeks off treatment. During the 4-week treatment period, sunitinib should be taken once daily (50 mg) without regard to food. Sunitinib should be taken at approximately the same time each day. Dosing on a 2-week on, 1-week off schedule is not permitted.

9.1.9.1.4 Timing of Dose Administration of Pazopanib

For each 6-week treatment cycle, pazopanib will be self-administered (800 mg) once daily without food (at least 1 hour before or 2 hours after a meal). Pazopanib should be taken at approximately the same time each day.

9.1.10 Withdrawal/Discontinuation

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

When a participant withdraws from participation in the trial, all applicable activities scheduled for the discontinuation visit should be performed at the time of withdrawal. Any adverse events which are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 9.3 - Adverse Events.

9.1.11 Participant Blinding/Unblinding

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

9.1.12 Calibration of Critical Equipment

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

Critical Equipment for this trial includes:

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

9.2 Efficacy Assessments

9.2.1 Tumor Imaging and Assessment of Disease

Note: As of Amendment 06, the endpoint of the study will be ORR by Response Evaluation Criteria in Solid Tumors (RECIST 1.1) as assessed by the investigator after completion of the first protocol-defined imaging assessment, which is scheduled at Week 12 (±7 days). Thus, submission of images for blinded independent central review (BICR) is no longer required.

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

Participant eligibility will be determined using local assessment (Investigator assessment) based on RECIST 1.1. Treatment should continue until PD has been determined per site assessment.

9.2.1.1 Initial Tumor Imaging

Note: As of Amendment 06, all text in this section relating to transmission of images to the central imaging vendor for retrospective review is no longer applicable and has been updated accordingly.

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

Tumor imaging performed as part of routine clinical management are acceptable for use as screening tumor imaging if they are of diagnostic quality and performed within 28 days prior to the date of randomization.

Mandatory tumor imaging for all participants at Screening includes CAP imaging and a bone scan. Participants with a history of brain metastases may participate provided they are radiologically stable according to the exclusion criteria documented in Section 6.2.

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

9.2.1.2 Tumor Imaging During the Study

Note: As of Amendment 06, central review of images and iRECIST are no longer applicable. After the first on-study imaging assessment at Week 12, further imaging will be performed as per local SoC guidelines however the data will not be collected. This section has been updated accordingly.

The first on-study imaging assessment of CAP should be performed at 12 weeks (±7 days) from the date of randomization. No further imaging is mandated; any further imaging for disease assessments will be performed by site investigator/radiology assessment as per SoC for the disease and local guidelines; only the date of scans performed as per SoC needs to be documented in the eCRF.

If the first bone scan is positive at baseline, bone scans should be performed per SoC, according to local guidelines; the results will NOT be collected. The timing of imaging assessments should follow calendar days from randomization and should not be adjusted for delays in cycle starts.

The investigator should consult with the MSD Clinical Director if he/she chooses to continue treatment after initial radiographic PD.

9.2.1.3 End of Treatment and Follow-up Tumor Imaging

Note; As per Amendment 06, there is no protocol specified imaging after the Week 12 assessment for efficacy analysis. This section has been updated accordingly.

For participants who discontinue study treatment before the Week 12 imaging assessment for efficacy analysis, tumor imaging should be performed at the time of treatment discontinuation (±4 week window). If a previous image was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory. For participants who discontinue study treatment due to documented disease progression, this is the final required tumor imaging.

9.2.1.4 Second Course Phase Tumor Imaging

Note: As per Amendment 06, this section is no longer applicable; only safety assessments will be performed during Second Course retreatment. Disease assessment in this period will be performed by the investigator only per SoC for the disease and local guidelines. Disease assessments will not be collected in the CRFs.

Tumor imaging (CAP and bone scan) must be performed within 28 days prior to restarting treatment with pembrolizumab + epacadostat. Before a participant may enter Second Course Phase, BICR verification of PD must have occurred. The PD imaging may also be used as the Second Course baseline imaging if it is within 30 days prior to restarting treatment and otherwise meets the baseline standards outlined in the Site Imaging Manual.

Local reading (Investigator assessment with site radiology reading) will be used to determine eligibility. All second course imaging should be submitted to the central imaging vendor for quality control, storage, and possible retrospective review, though BICR-verification of PD will not occur during Second Course phase.

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

For participants with positive bone scan entering second course, the first on-study bone scan should be performed at 24 weeks (±7 days) after the restart of treatment. Subsequent tumor imaging should be performed every 24 weeks (±7 days), at weeks or more frequently if clinically indicated.

All imaging should be transmitted to the central imaging vendor, though BICR-verification of PD will not occur during Second Course phase.

Per iRECIST (Section 9.2.1.6), if tumor imaging shows initial PD, tumor assessment should be repeated 4 to 8 weeks later in order to confirm PD, with the option of continuing treatment while awaiting radiologic confirmation of progression. Participants who obtain confirmatory imaging do not need to undergo scheduled tumor imaging if it is less than 4 weeks later and may wait until the next scheduled imaging time point, if clinically stable.

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

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

For participants who discontinue Second Course study treatment without documented PD, every effort should be made to continue monitoring disease status by radiologic imaging according to the schedule that the participant was on during treatment until the start of new anticancer treatment, disease progression, pregnancy, death, or the end of the study, whichever occurs first. For these participants, the next imaging would occur at the discontinuation visit, and then 12 weeks later. If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory. The timing of Second Course follow-up visits (Section 2.2) should be scheduled to coincide with the participant's follow-up imaging. Once imaging is complete (eg, PD, new anti-neoplastic therapy), the participant enters into Survival Follow-Up.

9.2.1.5 RECIST 1.1 Assessment of Disease

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

9.2.1.6 iRECIST Assessment of Disease (Group 1)

Note: As per Amendment 06, this section is no longer applicable; iRECIST will no longer be applied in this clinical study. Participants with radiographic disease progression as determined by RECIST 1.1 by investigator assessment will discontinue from the study treatment; no confirmatory scans are required. However, if the participant is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered following consultation with the Merck Clinical Director. The final study visit will be the 30-day Safety Follow-up Visit. Assessment of AEs will be recorded and reported per Section 9.3.

iRECIST is based on RECIST 1.1, but adapted to account for the unique tumor response seen with immunotherapeutic drugs. iRECIST will be used by the Investigator to assess tumor response and progression, and make treatment decisions. When clinically stable, participants should not be discontinued until progression is confirmed by the Investigator, working with local radiology, according to the rules outlined in Appendix 6. This allowance to continue treatment despite initial radiologic PD takes into account the observation that some participants can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. These data will be captured in the clinical database.

Clinical stability is defined as the following:

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

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

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

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

If a participant has confirmed radiographic progression (iCPD) as defined in Appendix 6, study treatment should be discontinued; however, if the participant is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered following consultation with MSD. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 2 and submitted to the central imaging vendor.

A description of the adaptations and iRECIST process is provided in Appendix 6, with additional detail in the iRECIST publication [Seymour, L., et al 2017]. A summary of imaging and treatment requirements after first radiologic evidence of progression is provided in Table 10 and illustrated as a flowchart in Figure 2.

Table 10 Imaging and Treatment After First Radiologic Evidence of PD

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

BICR = blinded independent central review; iCPD = iRECIST confirmed progressive disease; iCR = iRECIST complete response; iPR=iRECIST partial response; iRECIST = modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; iSD = iRECIST stable disease; iUPD = iRECIST unconfirmed progressive disease; MSD = Merck, Sharp & Dohme; PD = progressive disease; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors 1.1.

Note: If progression has been centrally verified, further management is by the site, based on iRECIST. Any further imaging should still be submitted to the central imaging vendor, but no rapid review will occur.

If RECIST 1.1 disease progression has not been centrally verified; ideally the site should continue treatment. Whether or not treatment continues, imaging should be collected and submitted to the central imaging vendor with VOP request until RECIST 1.1 progression is verified by BICR.]

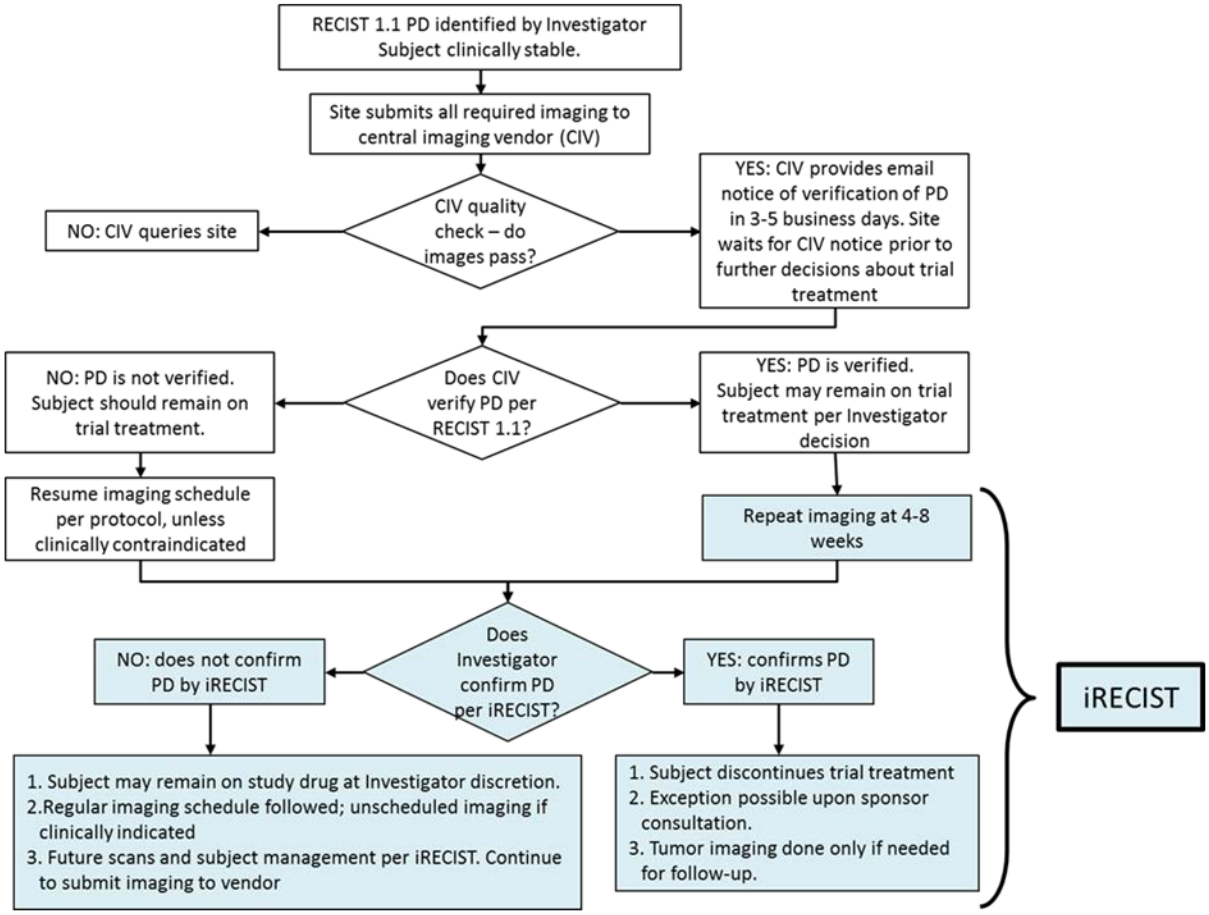


Figure 2 Imaging and Treatment for Clinically Stable Group 1 Participants after First Radiologic Evidence of PD Assessed by the Investigator

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

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

Progression of the cancer under study is not considered an adverse event as described in Section 9.3.5 – Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs, and Appendix 3.

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

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

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

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

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

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

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

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

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

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

All initial and follow-up AEs, SAEs and other reportable safety events will be recorded and reported to MSD or designee within the timeframes as indicated in Table 11.

Table 11 Reporting Time Periods and Timeframes for Adverse Events and Other Reportable Safety Events

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

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

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

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs and other reportable safety events including pregnancy and exposure during breastfeeding, ECI, Cancer and Overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). In addition, the investigator will make every attempt to follow all non-serious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

9.3.4 Regulatory Reporting Requirements for SAE

- Prompt notification (within 24 hours) by the investigator to MSD of SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The Sponsor and MSD have a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, ie, per International Conference on Harmonisation (ICH) Topic E6 (R1) Guidelines for Good Clinical Practice.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and MSD policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAE) from MSD will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

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

Efficacy endpoints, as outlined in this section, will not be reported to MSD, as described in Section 9.3.1.

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

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

9.3.6 Pregnancy and Exposure During Breastfeeding

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

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

9.3.7 Events of Clinical Interest (ECI)

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

Events of clinical interest for this trial include:

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

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

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

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

3. serotonin syndrome. The signs and symptoms of SS are described in Section 7.2.3, Table 9.

9.4 Treatment of Overdose

In this study, an overdose of pembrolizumab is defined as any dose higher than ≥1000 mg (5 times the dose), and for epacadostat, any daily dose ≥1000 mg. An overdose of the SoC treatments is defined as administration of more than the protocol-specified dose, ie, > 50 mg for sunitinib, and >800 mg for pazopanib.

In the event of an overdose, appropriate supportive treatment should be provided, if clinically indicated. The investigator should contact MSD, and additional monitoring of the participant for AEs/SAEs and laboratory abnormalities should be considered. Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with MSD based on the clinical evaluation of the participant. The participant may resume study treatment at the discretion of the investigator (refer to SoC labeling for more details). Information regarding the quantity of the excess dose should be documented in the eCRF.

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

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

All reports of overdose with and without an AE must be reported by the investigator within 24 hours to MSD either by electronic media or paper. Electronic reporting procedures can be found in the electronic data collection data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

9.5 Safety

Details regarding specific safety procedures/assessments to be performed in this study are provided below. The total amount of blood/tissue to be drawn/collected over the course of the study (from pre-study to post-study visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant can be found in the Procedure Manual.

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

9.5.1 Physical Examinations

9.5.1.1 Full Physical Examination

The Investigator or qualified designee will perform a full physical examination as per institutional standard during the Screening period. Clinically significant abnormal findings should be recorded as medical history. The time points for full physical examinations are described in Section 2. After the first dose of study treatment, new clinically significant abnormal findings should be recorded as AEs. A full physical examination should also be performed at the discontinuation visit and, if applicable, at the Second Course Cycle 1 Day 1 and Second Course discontinuation visit.

9.5.1.2 Directed Physical Examination

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

9.5.2 Vital Signs

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

9.5.3 Electrocardiograms

Baseline ECGs will be obtained at Screening, with additional ECGs obtained at treatment discontinuation and as clinically indicated for all participants. At SELECT centers only, additional ECGs will also be obtained at C1D1 predose and approximately 2 hours (±15 minutes) after the first dose of epacadostat, and C1D22 predose and approximately 2 hours (±15 minutes) after administration of epacadostat.

The ECG measurement should always be performed prior [redacted]

Clinically significant abnormal findings observed prior to signing the ICF should be recorded as medical history. Clinically significant abnormal findings observed after signing the ICF should be recorded as an AE. An ECG should also be performed within 14 d prior to the second course Cycle 1 Day 1 to confirm continuing eligibility.

The 12-lead ECGs will be interpreted by the Investigator at the site and will be used for immediate participant management. The decision to include or withdraw a participant from the study based on an ECG flagged as "Abnormal, Clinically Significant" is the responsibility of the Investigator, in consultation with the MSD medical monitor, as appropriate. The Fridericia (preferred) or Bazett correction method for calculating QTc will be used and recorded in the electronic case report form (eCRF).

9.5.4 Clinical Safety Laboratory Assessments

Refer to Appendix 4 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All protocol-required laboratory assessments, as defined in Appendix 4, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate eCRF.

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

9.5.4.1 Laboratory Safety Evaluations (Hematology, Chemistry, Urinalysis)

Laboratory tests for hematology, chemistry, and urinalysis are specified in Appendix 4. Refer to SoA for the timing of laboratory assessments. For Group 2 only, safety laboratory assessments may be done per SoC after the Week 12 imaging assessment.

9.5.4.2 Pregnancy Test

All women who are being considered for participation in the study, and who are not surgically sterilized or postmenopausal (as defined in Appendix 2), must be tested for pregnancy within 72 hours of the first dose of study treatment. Monthly pregnancy testing should be conducted as per local regulations, where applicable. If a urine test is positive or not evaluable, a serum test will be required. Participants must be excluded/discontinued from the study treatment in the event of a positive or borderline-positive test result.

9.5.5 Performance Assessments

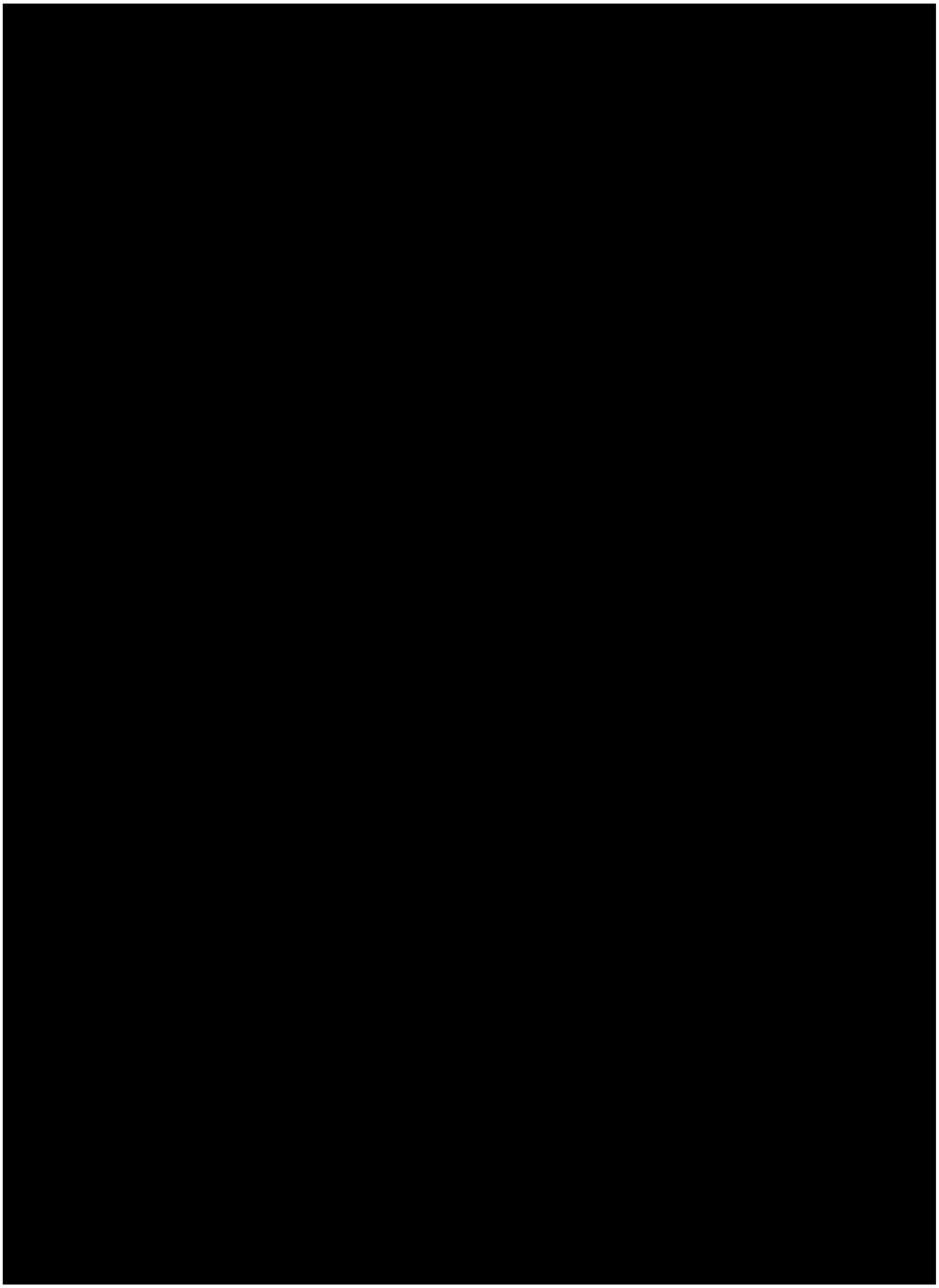
As both ECOG and Karnofsky performance scores are collected at Screening, it is important for these values to not contradict.

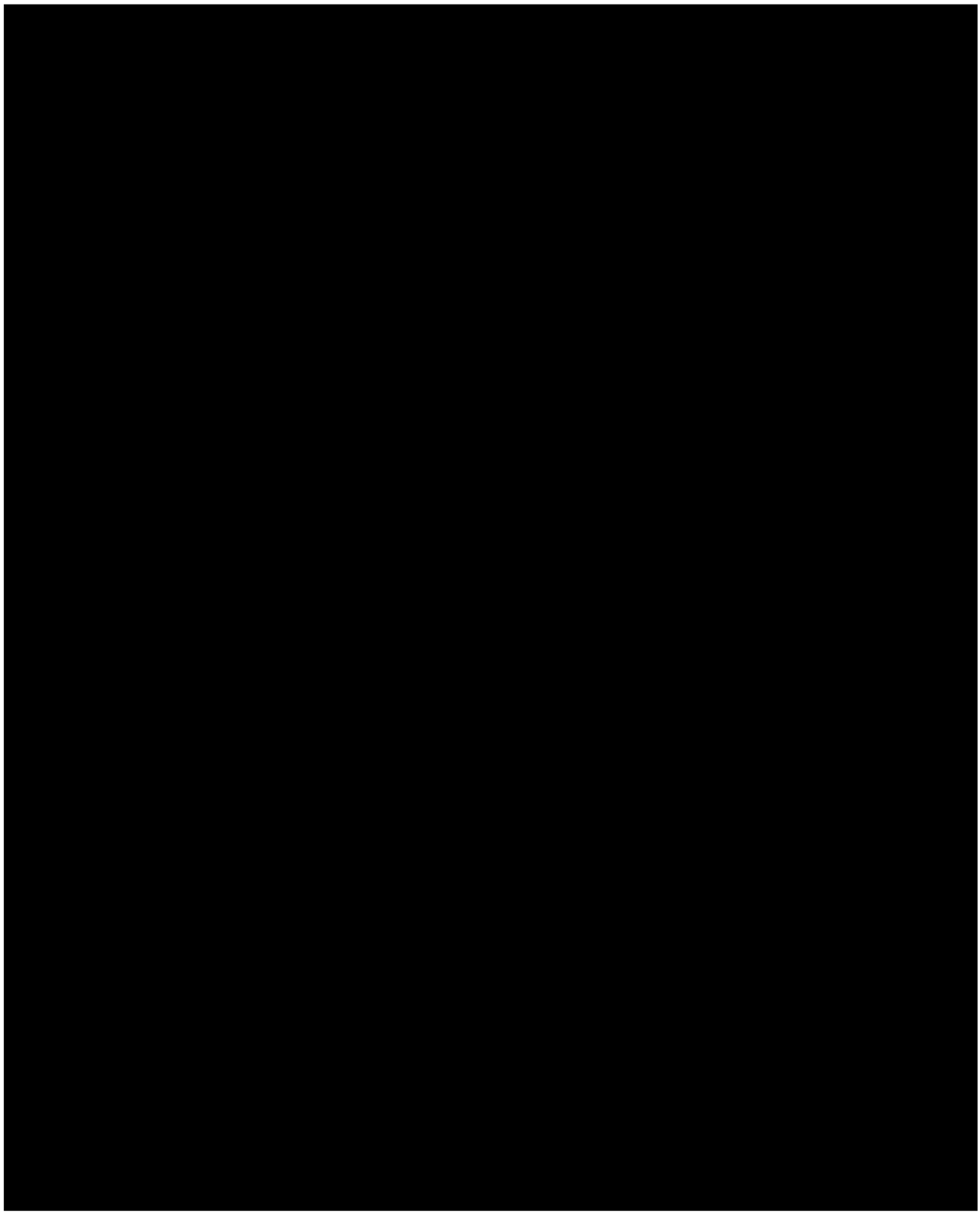
9.5.5.1 Eastern Cooperative Oncology Group Performance Scale

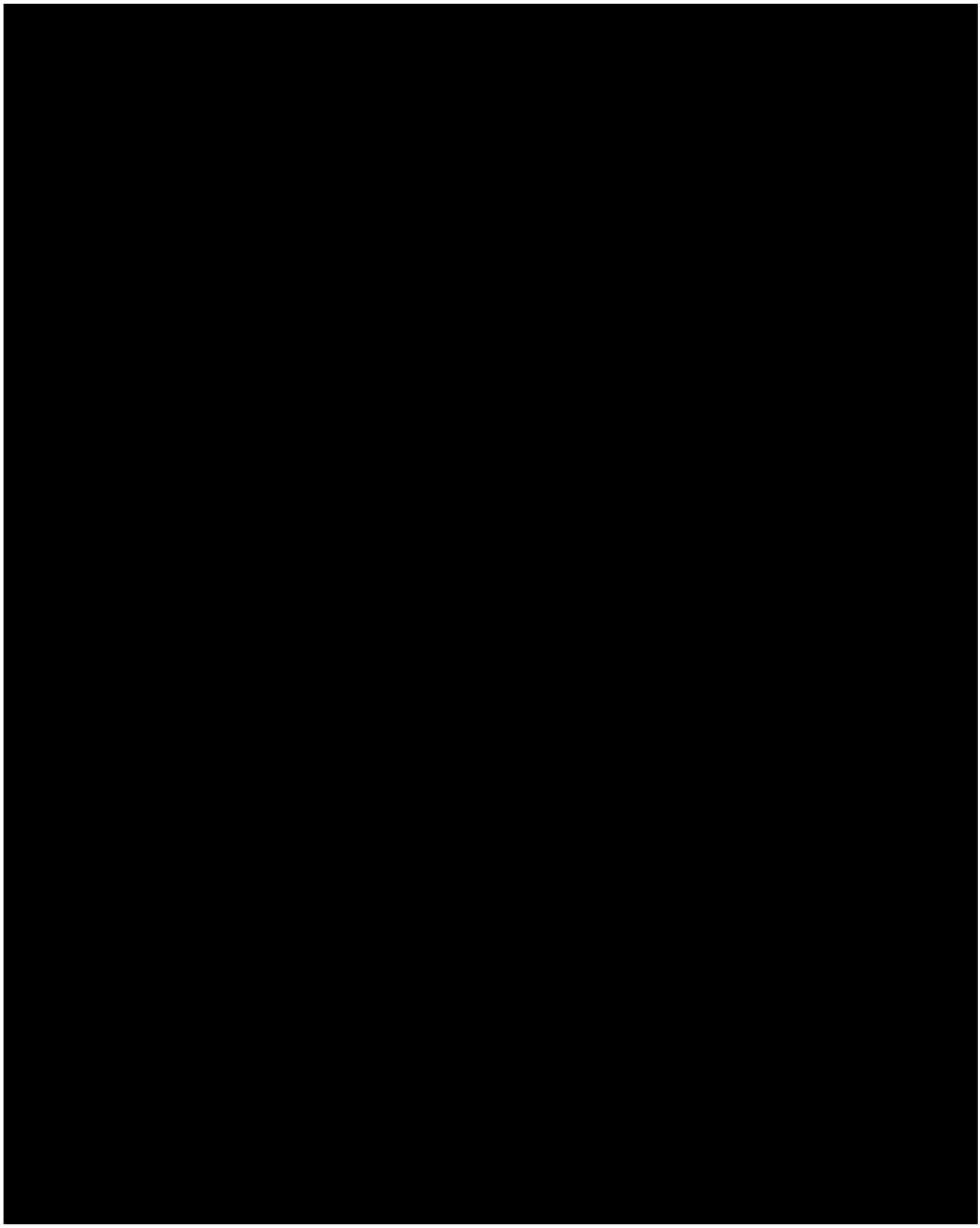
The investigator or qualified designee will assess ECOG status (see Appendix 9) at Screening, prior to the administration of each dose of study treatment and during the follow-up period, as specified in the SoA (Section 2).

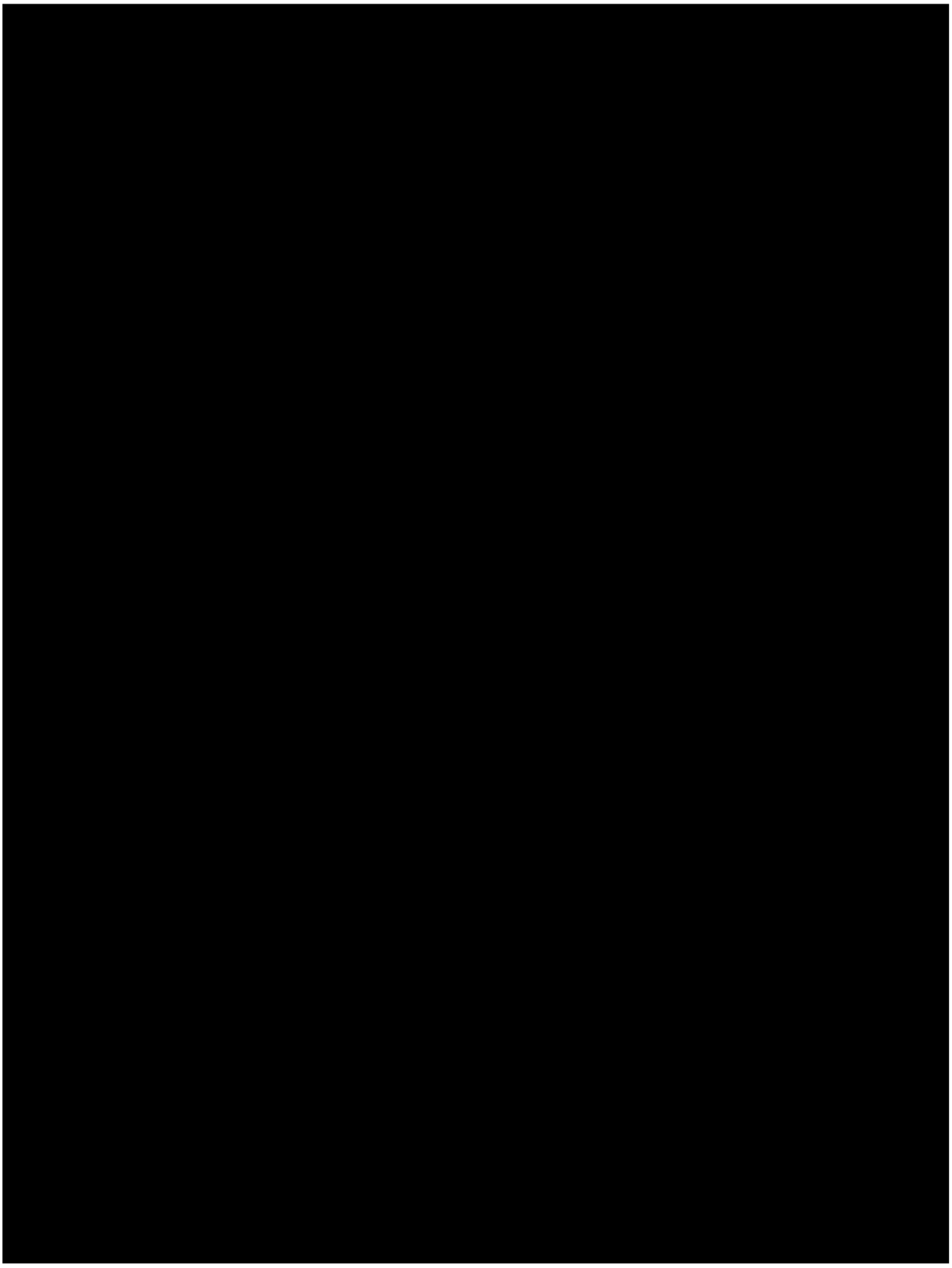
9.5.5.2 Karnofsky Performance Score

Karnofsky performance scores (see Appendix 10) will be required at Screening to evaluate eligibility and for stratification purposes. The score must be assessed by a medically qualified individual and recorded in the eCRF.









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9.10 Visit Requirements

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

9.10.1 Screening

Potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Sections 6.1 and 6.2. Screening procedures may be repeated after consultation with MSD.

Written consent must be obtained prior to performing any protocol-specific procedure. Results of a test performed prior to the participant signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the protocol-specified time frame. The following screening procedures must be performed, as specified:

- Laboratory tests are to be performed within 14 days prior to randomization . An exception is hepatitis testing, which may be done up to 42 days prior to the first dose of study treatment.
- Evaluation of ECOG and KPS is to be performed within 14 days prior to the first dose of study treatment before randomization.
- For women of reproductive potential, a urine or serum pregnancy test will be performed within 72 hours prior to randomization. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory).
- Archival tumor sample collection is not required to be obtained within 28 days prior to the first dose of study treatment, but must be submitted prior to randomization. Newly obtained tumor tissue must be obtained and submitted prior to randomization.

9.10.2 Treatment Period Visit

Treatment visit requirements are outlined in the SoA (Section 2).

Treatment with pembrolizumab will occur every 21 days (Days 1 and 22 of each 6-week cycle) for up to 35 administrations (approximately 2 years).

Epacadostat will be dosed BID every 12 hours (Q12H) during the treatment phase. Treatment may continue until the last day of the last cycle of pembrolizumab, unless a discontinuation criterion is met.

Sunitinib and Pazopanib will continue until protocol-specified criteria for treatment discontinuation are met.

9.10.3 Discontinued Participants Continuing to be Monitored in the Study

9.10.3.1 Safety Follow-up Visit

NOTE: As of Amendment 06, the Safety Follow-up Visit will be the last visit in the study. This section has been amended accordingly.

The mandatory Safety Follow-up Visit should be conducted approximately 30 days after the last dose of study treatment or before the initiation of a new anticancer treatment, whichever comes first. If the participant has a discontinuation visit ≥30 days after the last dose of study treatment, the Safety Follow-up visit is not required.

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

Participants who enter Second Course retreatment with pembrolizumab plus epacadostat may have up to two Safety Follow-up Visits, one after the Initial Treatment Period and one after the Second Course Treatment.

9.10.3.2 Follow-up Visits

NOTE: As of Amendment 06, this section is no longer applicable. Participants currently in post-treatment follow-up are considered to have completed the study once they have attended the Safety Follow-up Visit. Disease assessment will continue as per local SoC guidelines; assessment and recording of AEs will be performed as per Section 9.3.

Participants who discontinue study treatment for a reason other than PD will have imaging assessments per SoC. Every effort should be made to collect information regarding disease status until the start of new anti-cancer therapy, disease progression, pregnancy, death, the end of study, or if the participant begins retreatment as detailed in Section 7.8. Information regarding post-study anticancer treatment will be collected if new treatment is initiated.

Participants who are eligible to receive retreatment with pembrolizumab plus epacadostat (see Section 7.8) will move from the Follow-Up Phase to the Second Course Phase when they experience disease progression.

9.10.3.3 Survival Follow-up

NOTE: As of Amendment 06, this section is no longer applicable. Participants currently in survival follow-up are considered to have completed the study; these participants will no longer be contacted for survival information. Assessment and recording of AEs will continue as per Section 9.3.

Participants who experience confirmed disease progression or start a new anticancer therapy, will move into the Survival Follow-Up Phase and should be contacted by telephone approximately every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the trial, whichever occurs first.

Participants may withdraw their consent at any time from any or all portions of the study. Participants who withdraw consent for treatment and/or imaging are encouraged to remain on the non-invasive Survival Follow-Up portion of the study. The only procedures associated with this phase are telephone contacts to assess survival status and the current state of the participant's mRCC. The non-invasive nature and societal benefit of Survival Follow-Up should be explained to the participant by the site staff, particularly when discontinuing treatment and imaging.

9.10.3.3.1 Survival Status Monitoring

NOTE: As of Amendment 06, this section is no longer applicable; survival data is no longer being collected.

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

9.10.3.4 Unscheduled Visits

Unscheduled visits may be held at any time at the investigator's discretion, and appropriate clinical and laboratory measurements may be performed based on AEs or other findings. Unscheduled visits will be recorded in the eCRFs.

9.10.4 Second Course Phase

Participants who consent to enter the Second Course Phase will be retreated at the same combination, dose level, and frequency as when they last received the combination of pembrolizumab plus epacadostat. Chemotherapy will not be dosed in Second Course Phase.

Pembrolizumab will be dosed every 21 days (Days 1 and 22 of each 6-week cycle) for up to 17 administrations of pembrolizumab (approximately 1 year). Epacadostat will be dosed BID (Q12H) during the Second Course Phase. Treatment may continue until a discontinuation criterion is met.

10. Statistical Analysis Plan

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with International Conference on Harmonisation Guideline E9). [redacted]

10.1 Statistical Analysis Plan Summary

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

Study Design Overview	This is a randomized, open-label, multicenter Phase III study to evaluate the efficacy and safety of pembrolizumab + epacadostat compared to SoC (sunitinib or pazopanib monotherapy) in participants with confirmed unresectable, advanced or metastatic RCC with a clear-cell component who have not received prior systemic therapy for advanced or metastatic RCC.
Treatment Assignment	Approximately 130 participants will be randomized 1:1 into the following two treatment arms: pembrolizumab 200 mg IV Q3W + epacadostat 100 mg PO BID or SoC (sunitinib 50 mg PO QD or pazopanib 800 mg PO QD). Stratification factors are provided in Section 7.3.1.
Analysis Populations	Efficacy: Intention-to-Treat Safety: All Participants as Treated
Primary Endpoints	Objective Response Rate (ORR) per RECIST 1.1, as assessed by investigator
Key Secondary Endpoints	Not Applicable (N/A)
Statistical Methods for Key Efficacy Analyses	ORR will be estimated within each treatment arm with 95% confidence intervals (CI) using Clopper-Pearson exact method based on binomial distribution [Clopper, C. J. and Pearson, E. S. 1934].
Statistical Methods for Key Safety Analyses	Counts and percentages of participants with AEs will be provided by treatment group.
Interim and Final Analyses	There is no interim analysis for efficacy. Final analysis will be performed after all randomized participants had an opportunity to have one post-baseline imaging scan. During the course of the study, DMC safety review will be conducted per DMC charter.
Multiplicity	Since this is an estimation study, there will be no multiplicity adjustment.
Sample Size and Power	The sample size is approximately 130. With approximately 65 participants per treatment arm, the 95% CIs for ORR estimate are expected to be (19.9%, 43.4%) or (28.0%, 52.9%) when the ORR rate is approximately 31% or 40%, respectively.

10.2 Responsibility for Analyses/In-House Blinding

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

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

Although the study is open label, analyses or summaries generated by randomized treatment assignment or actual treatment received will be limited and documented. Further documentation will be provided in the sSAP.

10.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 4 – Objectives/Hypotheses and Endpoints.

10.4 Analysis Endpoints

10.4.1 Efficacy Endpoints

10.4.1.1 Primary

10.4.1.1.1 Objective Response Rate (ORR) – RECIST 1.1 by Investigator

ORR is defined as the proportion of the participants in the analysis population who have best response of CR or PR.

10.4.2 Safety Endpoints

Safety endpoints are described in Section 5.4.1.2

10.5 Analysis Populations

10.5.1 Efficacy Analysis Population

The Intention-to-Treat (ITT) population will serve as the population for the primary efficacy analyses. All randomized participants will be included in this population. Participants will be analyzed in the treatment group to which they are randomized. Details on the approach to handling missing data are provided in Section 10.6.1 – Statistical Methods for Efficacy Analyses.

10.5.2 Safety Analysis Population

The All Participants as Treated (APaT) population will be used for the analysis of safety data in this study. The APaT population consists of all randomized participants who received at least 1 dose of study treatment. Participants will be analyzed in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the APaT population. For most participants, this will be the treatment group to which they are randomized. Participants who take incorrect study treatment for the entire treatment period will be included in the treatment group corresponding to the study treatment actually

received. Any participant who receives the incorrect study treatment for one cycle but receives the correct treatment for all other cycles will be analyzed according to the correct treatment group and a narrative will be provided for any events that occur during the cycle for which the participant is incorrectly dosed.

At least 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.

10.6 Statistical Methods

10.6.1 Statistical Methods for Efficacy Analyses

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

10.6.1.1 Objective Response Rate (ORR) – RECIST 1.1 by Investigator

For ORR, the point estimate and 95% CI will be provided using the exact binomial method proposed by Clopper and Pearson (1934). Participants in the analysis population without response data will be counted as non-responders.

10.6.2 Statistical Methods for Safety Analyses

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

Individual events and the broad AE categories consisting of the proportion of participants with any AE, a drug related AE, a serious AE, an AE which is both drug-related and serious, a Grade 3-5 AE, a drug related Grade 3-5 AE, a fatal AE, dose interruption due to an AE and discontinuation due to an AE, will be summarized by counts and percentages by treatment group (Table 14).

Table 14 Analysis Strategy for Safety Parameters

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

10.6.3 Summaries of Demographic and Baseline Characteristics

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

10.7 Interim Analyses

NOTE: As of Amendment 06, there will be no interim efficacy analysis. The eDMC will conduct safety review based on DMC charter.

10.8 Multiplicity

NOTE: As of Amendment 06, no hypothesis testing will be performed in this study. Therefore, no multiplicity adjustment is needed.

10.9 Sample Size and Power Calculations

The study will randomize participants in a 1:1 ratio into the pembrolizumab plus epacadostat and SoC arms. The primary objective is to estimate ORR for each treatment arm. The overall sample size of approximately 130 is based on the projected number of randomized participants when a strategic decision was made to redesign the study based on ORR as the primary endpoint.

With 65 participants per treatment arm, the 95% CIs for ORR estimate are expected to be (19.4%, 43.4%) or (28.0%, 52.9%) when the ORR rate is approximately 31% or 40%, respectively. The CIs for different observed response rates are listed below for 95% confidence level in Table 15.

Table 15 95% CIs for Different Observed Response Rates

Sample Size	Number of Participants with a Response	Observed Response Rate	95% CIs
65	20	~31%	(19.9%, 43.4%)
	23	~35%	(23.9%, 48.2%)
	26	40%	(28.0%, 52.9%)

10.10 Subgroup Analyses

Note: As of Amendment 06, this section is no longer applicable.

10.11 Compliance (Medication Adherence)

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

10.12 Extent of Exposure

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

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12. Appendices

Appendix 1: Study Governance Considerations

Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

Merck, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participant safety is the overriding concern in the design of clinical trials. In all cases, Merck clinical trials will be conducted in compliance with local and/or national regulations and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

To the extent scientifically appropriate, Merck seeks to publish the results of trials it conducts. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing. In such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues of multiplicity.

Merck's policy on authorship is consistent with the requirements outlined in the ICH-Good Clinical Practice guidelines. In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. Merck funding of a trial will be acknowledged in publications.

III. Participant Protection

A. IRB/IEC review

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

B. Safety

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

All participation in Merck clinical trials is voluntary. Participants are enrolled only after providing informed consent for participation. Participants may withdraw from a Merck trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

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

Financial Disclosure

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

The investigator/subinvestigator(s) agree, if requested by MSD in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor or MSD to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by MSD. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor and MSD in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

Data Protection

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

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

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

Confidentiality of Data

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

Confidentiality of Participant Records

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

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

Confidentiality of IRB/IEC Information

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

Committees Structure

Trial Steering Committee

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

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

The Trial Steering Committee will provide guidance on the operational aspects of the trial, evaluate recommendations from the Data Monitoring Committee (DMC) and make recommendations to the Executive Oversight Committee (EOC).

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

Joint Executive Oversight Committee

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

Data Monitoring Committee

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

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

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the Sponsor and MSD protocol team; meeting facilitation; the trial governance structure; and requirements for and proper

documentation of DMC reports, minutes, and recommendations will be described in the DMC charter that is reviewed and approved by all the DMC members.

Publication Policy

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

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

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

Compliance with Trial Registration and Results Posting Requirements

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

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

Compliance with Law, Audit and Debarment

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

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

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

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

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

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

Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to MSD or designee electronically (eg, laboratory data). The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

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

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

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

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

MSD or designee is responsible for the data management of this study, including quality checking of the data.

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

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

Source Documents

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

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

Study and Site Closure

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

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

Appendix 2: Contraceptive Guidance and Pregnancy Testing

Definitions

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP:

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

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

Contraception Requirements

Male Participants

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

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent.
- Use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in Table 16 when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.

- Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

Female Participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception that has a low user dependency consistently and correctly as described in Table 16 during the protocol-defined time frame in Section 6.1.

Table 16 Highly Effective Contraception Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen- containing) hormonal contraception [b, c] ○ Oral ○ Intravaginal ○ Transdermal ○ Injectable
• Progestogen-only hormonal contraception [b, c] ○ Oral ○ Injectable
Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen- only contraceptive implant [b, c] • Intrauterine hormone-releasing system (IUS) [b] • Intrauterine device (IUD) • Bilateral tubal occlusion
• **Vasectomized partner** A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
• **Sexual abstinence** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. a) Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly). b) If hormonal contraception efficacy is potentially decreased due to interaction with study treatment, condoms must be used in addition to the hormonal contraception during the treatment period and for at least 120 days after the last dose of pembrolizumab and epacadostat and up to 180 days after last dose of chemotherapeutic agents. c) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation.

Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test within 72 hours of randomization. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.

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

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

Definition of AE

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

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, or are considered clinically significant in the medical and scientific judgment of the investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. • For all reports of overdose (whether accidental or intentional) with an associated adverse event, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect." • Any new cancer (that is not a condition of the study). Note: Progression of the cancer under study is not a reportable event. Refer to Section 9.3.5 for additional details.

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

Definition of SAE

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

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening • The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.
d. Results in persistent or significant disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

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

f. Other important medical events:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

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

Additional Events Reported in the Same Manner as SAE

Additional Events Which Require Reporting in the Same Manner as SAE

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

Recording AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the Adverse Event case report forms/worksheets at each examination.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to MSD in lieu of completion of the AE CRF page.
- There may be instances when copies of medical records for certain cases are requested by MSD. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to MSD.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

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

Assessment of Causality

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by MSD to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the CRF.
- The investigator will submit any updated SAE data to MSD within 24 hours of receipt of the information.

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

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

• The primary mechanism for reporting to MSD will be the electronic data collection (EDC) tool.
  • Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
  • If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
  • Reference section 9.3.1 – Time Period and Frequency for Collecting AE and SAE and Other Reportable Safety Event Information for reporting time requirements
• The site will enter the SAE data into the electronic system as soon as it becomes available.
• After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
• If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
• Contacts for SAE reporting can be found in the Investigator Trial File Binder (or equivalent).

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

Appendix 4: Clinical Laboratory Tests

Note: As of Amendment 06, local laboratories will be used for screening tests and all other standard-of-care clinical laboratory tests.

- The tests detailed in Table 17 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 17 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology/Coagulation Factors	Platelet Count RBC Count Hemoglobin Hematocrit PT, INR, aPTT/PTT (PTT may be performed if the local lab is unable to perform aPTT)	WBC count with Differential:[a] Neutrophils Lymphocytes Monocytes Eosinophils Basophils	RBC Indices: MCV MCH %Reticulocytes	
Chemistry	Blood Urea Nitrogen (BUN)[b]	Potassium	Aspartate Aminotransferase (AST)/Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the upper limit of normal)
	Albumin	Bicarbonate or carbon dioxide[c]	Chloride	Phosphorous
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/Serum Glutamic-Pyruvic Transaminase (SGPT)	Total protein
	Glucose [Indicate if fasting, or nonfasting]	Calcium	Alkaline phosphatase	Lactate dehydrogenase
	Uric acid	Amylase	Lipase	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, occult blood, ketones, bilirubin, urobilinogen, nitrite, leukocytes • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests (performed locally unless not feasible to perform at the site)	• Serology – Hepatitis B surface antigen (HBsAg) – Hepatitis B virus deoxyribonucleic acid (HBV DNA) – Hepatitis C antibody (HCV) if HCV RNA is not the local SoC – Hepatitis C antibody ribonucleic acid (HCV RNA) • HIV RNA (only if required by local regulation)			

Laboratory Assessments	Parameters
Other tests during study	• Coagulation panel (prothrombin time [PT], activated partial thromboplastin time [aPTT] or partial thromboplastin time [PTT], International Normalized Ratio [INR]) • Endocrinology (T3/FT3, FT4, and thyroid stimulating hormone [TSH])
NOTES: Additional tests may be required, as agreed by the investigator and MSD, based on emerging safety data a. Absolute values must be provided for WBC differential laboratory results for lymphocytes and neutrophils b. Blood Urea Nitrogen is preferred; if not available, urea may be tested c. Perform if available as SoC in your region. Carbon dioxide may be either a measurement of CO2 or bicarbonate as an electrolyte.	

Investigators must document their review of each laboratory safety report.

Appendix 5: Abbreviations and Trademarks

Abbreviation	Definition
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
APaT	All Participants as Treated
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BCG	Bacillus Calmette-Guérin
BICR	blinded, independent, central review
BID	Twice a day
CA	Canada
CAP	Chest, abdomen, and pelvis
CFR	Code of Federal Regulations
CI	Confidence interval
CR	Complete response
CrCl	Creatinine clearance
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DC	Discontinuation
DCR	Disease control rate
DNA	Deoxyribonucleic acid
DOR	Duration of response
eDMC	External data monitoring committee
[redacted]	[redacted]
EOT	End of treatment
[redacted]	[redacted]
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration

Abbreviation	Definition
[redacted]	[redacted]
GCP	Good Clinical Practice
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HR	Hazard ratio
HRQoL	Health-related quality of life
IB	Investigators Brochure
IA	Interim analysis
iCPD	iRECIST Confirmed radiographic progression
ICF	Informed consent form
ICH	International Conference on Harmonisation
ID	Identification
IDO1	Indoleamine 2, 3-deoxygenase 1
IEC	Independent ethics committee
IHC	Immunohistochemistry
IMDC	International metastatic renal cell carcinoma database consortium
irAE	Immune-related adverse event
IRB	Institutional review board
iRECIST	Modified RECIST for Immune-based Therapeutics
iSD	iRECIST stable disease
ITT	Intention-to-treat
iUPD	iRECIST unconfirmed progressive disease
IV	Intravenous
IVRS	Interactive voice/web response system
KPS	Karnofsky Performance Status
MAOI	Monoamine oxidase inhibitors
mRCC	Metastatic Renal Cell Carcinoma
MRI	Magnetic resonance imaging
mRNA	Messenger RNA
MSD	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
NCI	National Cancer Institute
NSAE	Non-serious adverse event
NSCLC	Non-small cell lung cancer

Abbreviation	Definition
NYHA	New York Heart Association
ORR	Objective response rate
OS	Overall Survival
PD	Progressive disease
PD-1	Programmed cell death 1
PD-L1	PD-1 ligand
PD-L2	PD-2 ligand
[redacted]	[redacted]
PFS	Progression-free survival
PFS2	Progression after second line of therapy
PR	Partial Response
PK	Pharmacokinetic
PO	Per os (by mouth)
PT	Prothrombin time
PTT	Partial thromboplastin time
Q3W	Every 3 weeks
[redacted]	[redacted]
QoL	Quality of life
RCC	Renal Cell Carcinoma
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
RNA	Ribonucleic acid
ROW	Rest of World
SAE	Serious adverse event
SD	Stable disease
SAP	Statistical Analysis Plan
SoA	Schedule of Activities
SoC	Standard of care
SS	Serotonin syndrome
sSAP	Supplemental statistical analysis plan
SUSAR	Suspected unexpected serious adverse reaction
T1DM	Type 1 diabetes mellitus
TKI	Tyrosine-kinase inhibitors
Treg	T-cells with a regulatory phenotype
TTD	Time to deterioration

Abbreviation	Definition
ULN	Upper limit of normal
VEGF/ VEGFR	Vascular endothelial growth factor /VEGF receptors
WOCBP	Woman of child-bearing potential

Appendix 6: Description of the iRECIST Process for Assessment of Disease Progression

Note: As per Amendment 06, this section is no longer applicable; iRECIST data will no longer be collected. Participants with radiographic disease progression as determined by RECIST 1.1 will discontinue from the study and be followed for safety monitoring, as detailed in Section 9.3; no confirmatory scans are required.

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

Assessment and Decision at RECIST 1.1 Progression

For Group 1 participants who show evidence of radiological PD by RECIST 1.1 as determined by the Investigator, the Investigator will decide whether to continue a participant on study treatment until repeat imaging is obtained (using iRECIST for participant management (see Table 10 and Figure 2). This decision by the Investigator should be based on the participant's overall clinical condition. Clinical stability is defined as the following:

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

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

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

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

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

iRECIST defines new response categories, including iUPD (unconfirmed progressive disease) and iCPD (confirmed progressive disease). For purposes of iRECIST assessment,

the first visit showing disease progression according to RECIST 1.1 will be assigned a visit (overall) response of iUPD, regardless of which factors caused the progression.

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

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

Assessment at the Confirmatory Imaging

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

Confirmation of Disease Progression

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

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

Persistent iUPD

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

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

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

Resolution of iUPD

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

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

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

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

Management Following the Confirmatory Imaging

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

NOTE: If a participant has confirmed radiographic progression (iCPD) as defined above, but the participant is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered following consultation with MSD. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 2.

Detection of Progression at Visits After Pseudo-progression Resolves

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

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

- Non-target lesions
  - If non-target lesions have never shown unequivocal progression, their doing so for the first time results in iUPD.
  - If non-target lesions have shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of non-target lesions, taken as a whole.
- New lesions
  - New lesions appear for the first time
  - Additional new lesions appear
  - Previously identified new target lesions show an increase of ≥5 mm in the new lesion sum of diameters, from the nadir value of that sum
  - Previously identified non-target lesions show any significant growth

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

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

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

Appendix 7: Cytochrome P450 Inhibitors/Inducers

This appendix is not inclusive. For a comprehensive list please check with your pharmacy personnel.

University of Washington School of Pharmaceutics: Drug Interaction Database Program. 2002. http://www.druginteractioninfo.org. Accessed May 2015.

Potent CYP3A4 Inhibitors (yielding substrate > AUC 5)

Inhibitor	Therapeutic Class	AUC Ratio
Ketoconazole	Antifungal	15.9
Troleandomycin	Antibiotic	14.8
Itraconazole	Antifungal	10.8
Voriconazole	Antifungal	9.63
Mibefradil	Calcium channel blocker	8.86
Clarithromycin	Antibiotic	8.39
Posaconazole	Antifungal	6.23
Telithromycin	Antibiotics	6.2
Nefazodone	Antidepressant	5.44

Moderate CYP3A4 Inhibitors (yielding substrate ≥ 2 and < 5)

Inhibitor	Therapeutic Class	AUC Ratio
Erythromycin	Antibiotics	4.99
Fluconazole	Antifungal	4.93
Diltiazem	Calcium channel blocker	4.06
Aprepitant	Antiemetic	3.29
Casopitant	Antiemetic	3.13
Verapamil	Calcium channel blocker	2.92
Ciprofloxacin	Antibiotics	2.12

Appendix 8: IMDC Risk Categories

Assessments	Risk Factor
Baseline Karnofsky Performance Status	< 80%
Interval between initial diagnosis of RCC to start of first-line systemic treatment for advanced disease (*note for this study, date of randomization will be used as the start of first-line systemic treatment*)	< 1year
Baseline Hemoglobin	< Lower limit of normal
Baseline Platelet Count	> Upper limit of normal
Baseline Corrected Calcium[1]	> Upper limit of normal
Baseline Neutrophil	> Upper limit of normal
The IMDC risk group is determined by totaling the existing risk factors per subject.	
IMDC Risk Group	**IMDC Category**
Favorable	No risk factors
Intermediate	1 or 2 risk factors
Poor	3 or more risk factors

1. Corrected calcium can be calculated based on the following formula:
Corrected calcium (mg/dl) = 0.8 × [4.0 - subject's albumin (g/dl)] + subject's calcium (mg/dl).
A subject's corrected calcium will be compared with the upper limit of normal of institution serum calcium [Heng, D. Y., et al 2009].

Appendix 9: Eastern Cooperative Oncology Group Performance Scale

ECOG Performance Status

Developed by the Eastern Cooperative Oncology Group, Robert L. Comis, MD, Group Chair.*

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

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

Appendix 10: Karnofsky Score

100 – Normal; no complaints; no evidence of disease.

90 – Able to carry on normal activity; minor signs or symptoms of disease.

80 – Normal activity with effort; some signs or symptoms of disease.

70 – Cares for self; unable to carry on normal activity or to do active work.

60 – Requires occasional assistance, but is able to care for most of their personal needs.

50 – Requires considerable assistance and frequent medical care.

40 – Disabled; requires special care and assistance.

30 – Severely disabled; hospital admission is indicated although death not imminent.

20 – Very sick; hospital admission necessary; active supportive treatment necessary.

10 – Moribund; fatal processes progressing rapidly.

0 – Dead

References:

Karnofsky DA, Burchenal JH, The clinical evaluation of chemotherapeutic agents in cancer. In: Evaluation of Chemotherapeutic Agents, Maclead CM, ed. New York: Columbia University Press, 1949.

Schag CC, Heinrich RL, Ganz PA. Karnofsky performance status revisited: reliability, validity, and guidelines. J Clin Oncol 1984;2(3):187–93.

Appendix 11: New York Heart Association (NYHA) Functional Classification

Class	Functional Capacity: How a patient with cardiac disease feels during physical activity
I	Participants with cardiac disease but resulting in no limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain.
II	Participants with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.
III	Participants with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea or anginal pain.
IV	Participants with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort increases.

** As published in: The Criteria Committee of the New York Heart Association. (1994). Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. (9th ed.). Boston: Little, Brown & Co. pp. 253–256.*

Signature Manifest

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