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Protocol Title: A Phase 3 Randomized, Double-Blind Clinical Study of Pembrolizumab + Epacadostat vs Pembrolizumab + Placebo as a Treatment for Recurrent or Progressive Metastatic Urothelial Carcinoma in Patients who have Failed a First-Line Platinum-containing Chemotherapy Regimen for Advanced/Metastatic Disease (KEYNOTE-698/ECHO-303)

Protocol Number: 698-03/ECHO-303-03 / NCT03374488

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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Wilmington, Delaware, 19803, U.S.A.

Regulatory Agency Identifying Number(s):

IND NUMBER: 133,761

EudraCT NUMBER: 2017-002310-31

Approval Date: 12-Jun-2018

MSD Signatory

Typed Name: Date
Title:

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

Investigator Signatory

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

Typed Name: Date
Title:

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment 03

Overall Rationale for the Amendment:

The external data monitoring committee (eDMC) analysis of the KEYNOTE-252/ECHO-301 melanoma blinded clinical study, a Phase 3 study evaluating epacadostat in combination with pembrolizumab in participants with unresectable or metastatic melanoma, determined that the study did not meet the pre-specified endpoint of improvement in progression-free survival for the combination of pembrolizumab and epacadostat compared to pembrolizumab and placebo. The eDMC further determined that the overall survival endpoint is not expected to reach statistical significance. These results are specific to melanoma, and cannot be extrapolated to other tumor types. Of note, there were no new safety concerns with the pembrolizumab 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-672/ECHO-307 and KEYNOTE-698/ECHO-303. Enrollment in both studies 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 results from KEYNOTE-252/ECHO-301.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
1. Synopsis 2.1 Initial Treatment Phase SoA	Addition of notes that the study will be unblinded after last participant completes first imaging assessment for efficacy analysis; participants may choose to discontinue from the study or continue open-label study treatment as per protocol.	Given the results for pembrolizumab + epacadostat treatment from the melanoma study KEYNOTE-252/ECHO-301, as of 02-MAY-2018 enrollment was permanently stopped in KEYNOTE 698/ECHO-307. 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 UC indication.

Section # and Name	Description of Change	Brief Rationale
		Efficacy procedures after Week 9 are no longer being mandated. Where deletion of text could cause confusion, due to the design of the study to date, the text has been left unchanged and a note has been added.
2.2 Second Course Phase (Retreatment) SoA	Addition of note that procedures are simplified, SoA updated accordingly; disease assessment will be performed by the investigator per local SoC guidelines.	
3.2.3 Ongoing Clinical Studies	KEYNOTE-252/ECHO-301 related text inserted.	
5.1 Overall Design	Inserted note that enrollment was stopped. All efficacy procedures will discontinue after Week 9; thereafter performed as per local standard of care (SoC). The study will be unblinded after the last participant completes their Week 9 imaging assessment for efficacy analysis.	
5.1.1 Study Diagram	Figure 1 - Addition of footnote that the study will be unblinded after the last participants completes the Week 9 imaging assessment for efficacy analysis; that participants can chose to discontinue from the study or continue treatment as per protocol after discussion with the investigator and that no placebo will be administered after unblinding. The last study visit will be the Safety FU visit.	

Section # and Name	Description of Change	Brief Rationale
5.2 Number of Participants	Addition of note that as of 02-MAY-2018 enrollments was stopped and that 85 participants will be randomized in the study.	
7.1 Treatments Administered	Addition of note that participants that continue study treatment after unblinding will no longer be dispensed epacadostat placebo.	
7.2.2 Second Course Phase Retreatment	Addition of note that as of Amendment 03, disease assessment will be performed by the investigator per local SoC guidelines; placebo will not be administered after unblinding. This section has been updated accordingly Changed imaging requirements from confirmed to evaluated by investigator. Deleted reference to placebo, and specified pembrolizumab monotherapy.	
7.4 Blinding	Addition of text that the study will be unblinded after the last participant completes the Week 9 imaging assessment for efficacy analysis and that after unblinding for participants continuing study treatment the participant, study site personnel, Sponsor and MSD or designee will be informed of the study treatment they receive	

Section # and Name	Description of Change	Brief Rationale
7.9 Clinical Supplies Disclosure	Additional of text that the emergency unblinding call center should only be used in cases of emergency (see Section 9.1.11).	
9.1.11 Participant Blinding/Unblinding	Revision of text for emergency unblinding specifying principal investigator, site personnel, and Sponsor personnel may be unblinded so that the appropriate follow-up medical care can be provided to the participant. Addition of text that the study will be unblinded after the last participant completes the Week 9 imaging assessment for efficacy analysis and that at the time of unblinding every effort will be made to have all pending data entered into the eCRFs before the site is unblinded.	
9.2.1 Tumor Imaging and Assessment of Disease	Addition of note that central review of imaging and iRECIST is no longer applicable. Section updated accordingly.	
9.2.1.1 Initial Tumor Imaging	Addition of note that central review of imaging is no longer applicable. Section updated accordingly.	
9.2.1.2 Tumor Imaging During the Study	Addition of note that central review of imaging and iRECIST is no longer applicable. No further imaging will be required after the Week 9 imaging assessment for efficacy analysis. Section updated accordingly.	

Section # and Name	Description of Change	Brief Rationale
	Inserted text that any further imaging for disease assessments will be performed per local SoC guidelines; any further imaging for disease assessments will be performed by site investigator/radiology assessment as per local SoC guidelines; only the date of scans performed as per SoC needs to be documented in the eCRF	
9.2.1.3 End of Treatment and Follow-up Tumor Imaging	Addition of note that there is no protocol specified imaging after the Week 9 assessment for efficacy analysis. Section updated accordingly. Removal of reference to iRECIST Addition of clarification that end-of-treatment (EOT) scan will be performed for participants who discontinue study treatment before the first scheduled on-study imaging for efficacy analysis	
9.2.1.4 Second Course Phase Tumor Imaging	Addition of note that the text in this section is no longer applicable; disease assessment will be performed by the investigator per local SoC guidelines; results will not be collected, only the date of scans performed as per SoC needs to be documented in the eCRF.	

Section # and Name	Description of Change	Brief Rationale
9.8.1 Tumor Tissue Collection	Addition of text to clarify that a participant's PD-L1 status will not be disclosed to investigative sites or study participants after the study is unblinded	
1. Synopsis 4. Objectives/ Hypotheses and Endpoints	Addition of notes to clarify the secondary efficacy endpoint of ORR based on RECIST 1.1 by investigator determination will become the primary endpoint; safety endpoint updated to align with current guidance; all other efficacy endpoints will no longer be collected after Week 9. ORR and safety objectives and endpoints reworded. All other efficacy objectives/endpoints deleted.	The study scope has been reduced to collect preliminary efficacy data for combination treatment in this UC indication. Where deletion of text could cause confusion, due to the design of the study to date, the text has been left unchanged and a note has been added
2.1 Initial Treatment Phase	Imaging/bone scan assessments after Week 9 changed to as per SoC; only the date of scans performed as per SoC needs to be documented in the eCRF. Deleted footnotes regarding follow-up visits.	
2.2 Second Course Phase	Changed collection timing of tumor imaging, bone scans to as per SoC; only the date of scans performed as per SoC needs to be documented in the eCRF. Deleted row for PROs and footnotes regarding follow-up visits.	

Section # and Name	Description of Change	Brief Rationale
5.1 Overall Design	Inserted note that the primary objective will evaluate the endpoint of ORR based on RECIST 1.1, as assessed by the investigator; all other efficacy endpoints will no longer be collected. Deleted reference to BICR, PFS, DCR, DOR and iRECIST.	
5.4.1.1 Efficacy Endpoints	Addition of note that the primary endpoint will be ORR based on RECIST 1.1 as assessed by the investigator; transmission of images for central review is no longer required. After the Week 9 imaging, all other efficacy endpoints will no longer be collected or performed. Deletion of all text relating to PFS, OS, DCR, DOR	
5.4.1.1.2 Modified RECIST for Immune-based Therapeutics (iRECIST)	Addition of note that this section is no longer applicable; iRECIST data will no longer be collected. Participants with radiographic disease progression as determined by RECIST 1.1 will discontinue from the study and be followed for safety monitoring, as detailed in Section 9.3; no confirmatory scans are required.	
5.4.1.3 Rationale for Patient Reported Outcomes 9.2.2 Patient Reported Outcomes	Addition of note that PROs will no longer be collected after the first on-study imaging assessment at Week 9.	

Section # and Name	Description of Change	Brief Rationale
9.2.1.6 iRECIST Assessment of Disease Appendix 7	Addition of note that this section is no longer applicable; iRECIST data will no longer be collected. Participants with radiographic disease progression as determined by RECIST 1.1 will discontinue from the study and be followed for safety monitoring, as detailed in Section 9.3; no confirmatory scans are required.	
10. Statistical Analysis Plan	Whole section revised to reflect changes in objectives and endpoints.	
1. Synopsis	Deletion of text relating to follow-up of participants that discontinue treatment for reasons other than disease progression.	The final visit in the study will be the Safety Follow-up Visit. There will be no follow-up for survival status. Participants currently in follow-up or in survival follow-up are considered to have completed the study. However, standard safety reporting should continue, as applicable.
2.1 Initial Treatment Phase & 2.2 Second Course Phase (Retreatment) SoAs	Deletion of columns for Follow-up and Survival Follow-up. Deletion of row for survival status assessment.	
5.1 Overall Design	Addition of note that the last study visit is the Safety Follow-up Visit. Deletion of text relating to follow up imaging for participants that discontinue treatment for reasons other than disease progression.	
8.2 Withdrawal from the Study	Deletion of text indicating that participants who discontinue/withdraw should be encouraged to continue to be followed for Survival status	

Section # and Name	Description of Change	Brief Rationale
8.3 Lost to Follow-up	Addition of a note that this is no longer applicable. There will be no additional efforts to contact participants who are lost to follow-up.	
9.2.1.3 End of Treatment and Follow-up Tumor Imaging	Deletion of text relating to imaging follow-up after treatment discontinuation for reasons other than disease progression.	
9.9.5.1 Safety Follow-up Visit	Addition of note that the last study visit is the Safety Follow-up Visit. Added text that participants currently in follow-up or in survival follow-up are considered to have completed the study; these participants are not required to attend any further visits. Assessment and recording of AEs will be performed as per Section 9.3.	
9.2.3 Survival Follow-up	Addition of a note that this section is no longer applicable. Participants currently in survival follow-up are considered to have completed the study. Assessment and recording of AEs will be performed as per Section 9.3.	

Section # and Name	Description of Change	Brief Rationale
9.9.5.2 Follow-Up Visits	Addition of a note that this section is no longer applicable. Participants currently in post-treatment follow-up are considered to have completed the study once they have attended the Safety Follow-up Visit. Assessment and recording of AEs will be performed as per Section 9.3.	
9.9.5.3 Survival Follow-up	Addition of a note that this section is no longer applicable. Participants currently in Survival Follow-up are considered to have completed the study; these participants will no longer be contacted for survival information. Assessment and recording of AEs will continue as per Section 9.3.	
9.9.5.4 Survival Status	Addition of a note that this section is no longer applicable; survival data is no longer being collected.	
5.1 Overall Design	Replaced text relating to interim analysis with text that there is no interim analysis and eDMC will perform one safety review based on the DMC charter.	There is no formal efficacy IA following the reduce scope of the study. eDMC will conduct a safety review as per the DMC charter.
Section 12, Appendix 1	Data Monitoring Committee –text referencing interim data replaced with safety data. Deletion of text regarding interim analysis of data.	

Section # and Name	Description of Change	Brief Rationale
1. Synopsis 5.4.2 Rationale for the Use of Comparator/Placebo	Addition of note that the study will be unblinded after the last participant completes Week 9 imaging. Participants on the pembrolizumab plus placebo arm who want to continue study treatment as per protocol and are considered to receive clinical benefit will no longer receive placebo.	No longer necessary to continue with placebo after unblinding and collection of efficacy data.
1. Synopsis 9.9.1 Screening 9.3.7 Events of Clinical Interest (ECI)	Screening phase window of up to 42 day changed to *approximately* 42 days Insertion of additional text for reporting requirements of ECIs "or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier".	Alignment with other ongoing pembrolizumab + epacadostat studies
2.1 Initial Treatment Phase	In SoA tumor imaging notes: changed "Baseline CAP CT/MRI to be performed in all participants within 28 days of randomization" to "within 28 days prior to randomization" 12 lead ECG row: cross reference to notes Note added for T3/FT3, FT4, and TSH row: Total T3 is preferred but free T3 is acceptable. Sites only need to report either Total T3 or free T3. Note added to SoA for archival tissue.	Correction and clarification of timing of procedures

Section # and Name	Description of Change	Brief Rationale
2.2 Second Course Retreatment	Inserted footnote cross reference into header rows Updated notes for all labs to indicate that pretreatment labs should be taken 14 days prior to second course Cycle 1 Inserted row for 12-Lead ECG with QTc Measurement	
2.1 Initial Treatment Phase 2.2 Second Course Phase (Retreatment Phase) 9.9.2 Treatment Period	Added that epacadostat will be dosed twice daily (approximately Q12H)	Alignment with current clinical information for current epacadostat IB
3.3.1 Benefit/Risks for Epacadostat	Change an uncommon risk of IDO1 inhibition to a potential concern of IDO1 inhibition.	
6.2 Exclusion Criteria	Criteria# 21 - note removed. Melatonin and propofol removed from exclusion criteria.	
7.7.2 Prohibited Concomitant Medications	#7 - melatonin supplements removed. #8 - mefenamic acid and propofol removed from listed prohibited UGT1A9 inhibitors. Note relating to Propofol deleted.	

Section # and Name	Description of Change	Brief Rationale
7.2.1.1 Procedures for Participants Exhibiting Serotonin Syndrome (SS) 9.3.7 Events of Clinical Interest (ECI)	Addition of following procedure of participants exhibiting signs/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/placebo treatment should be permanently discontinued. Serotonin syndrome added as an ECI	
7.2.1 Dose Modification for Immune-related AEs	Table 3 – added that, in case of recurrent Grade 3 colitis, participants will permanently discontinue treatment and Management with corticosteroid text applied to all toxicity grades Table 3 - note #4 – inserted clarification on grade of AE to which note applies	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
7.5.1 Dose Preparation	Addition of reference to pharmacy manual for preparation of epacadostat in cases where a participant is unable to swallow or has a feeding tube.	Request [redacted]

Section # and Name	Description of Change	Brief Rationale
7.6.1 Administration and Compliance of Pembrolizumab	Removal of text requiring consultation with Sponsor for interruptions from the protocol-specified treatment plan for more than 12 weeks between pembrolizumab doses for nondrug-related or administrative reasons	Consistency and alignment with current clinical information for pembrolizumab
7.2.1.3 Dose Interruptions Unrelated to Adverse Events	Added that dose interruptions are permitted "for situations other than treatment-related AEs."	Clarification
7.6.2 Administration and Compliance of Epacadostat or Matching Placebo	Removal text specifying that of Second Course C1D1 administration of epacadostat /placebo being given at study site.	
9.1.12 Calibration of Equipment	Updated equipment calibration language.	Textual revisions were applied to clarify investigator responsibility for calibration and maintenance of study equipment.
9.9.5.1 Safety Follow-up Visit	Updated Safety Follow-up Visit language.	To remove conflict for reporting AEs/SAEs
Throughout	Correction of typographical, editorial and formatting errors.	Correction and consistency

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1. Synopsis

Protocol Title:

A Phase 3 Randomized, Double-Blind Clinical Study of Pembrolizumab + Epacadostat vs Pembrolizumab + Placebo as a Treatment for Recurrent or Progressive Metastatic Urothelial Carcinoma in Patients who have Failed a First-Line Platinum-containing Chemotherapy Regimen for Advanced/Metastatic Disease (KEYNOTE-698/ECHO-303)

Short Title:

Phase 3 Study of Pembro with/without Epacadostat in 2L Urothelial Carcinoma

Objectives/Hypotheses and Endpoints:

In male/female participants of at least 18 years of age with histologically confirmed diagnosis of advanced/unresectable or metastatic urothelial carcinoma (UC) that has recurred or progressed following one prior line of platinum-containing chemotherapy for advanced/metastatic disease:

NOTE: As of Amendment 03, the primary endpoint of the study will be objective response rate (ORR) based on Response Evaluation Criteria in Solid Tumors (RECIST 1.1) as assessed by the investigator. A secondary endpoint will evaluate the safety and tolerability of participants treated with pembrolizumab plus epacadostat versus those treated with pembrolizumab plus placebo. All other endpoints, including imaging, will no longer be collected or performed after the imaging assessment at Week 9. This section has been amended accordingly.

Objective/Hypothesis	Endpoint
Primary	
• **Objective:** To estimate the ORR of pembrolizumab plus epacadostat and pembrolizumab plus placebo based on RECIST 1.1 by investigator determination.	• ORR - defined as the proportion of participants in the analysis population who have a best response of complete response (CR) or partial response (PR).
Secondary	
• **Objective:** To evaluate the safety and tolerability of pembrolizumab plus epacadostat versus pembrolizumab plus placebo.	• Adverse events (AEs) • Study drug discontinuations due to AEs

Overall Design:

Study Phase	Phase III
Clinical Indication	A second-line (2L) treatment of patients with advanced/unresectable or metastatic urothelial carcinoma
Population	Adult participants with advanced/unresectable or metastatic urothelial carcinoma
Study Type	Interventional
Type of Design	Randomized, parallel-group, multi-site, double-blind As of Amendment 03, the study will be unblinded after the last participant completes Week 9 imaging assessment for efficacy analysis.
Type of Control	Active Control
Study Blinding	Double-blind Note: As of Amendment 03, the study will be unblinded when the last participants completes Week 9 imaging; any continuation of study treatment will be unblinded/open-label and as per protocol.
Estimated Duration of Trial	The study is estimated to require approximately 36 months from the time the first participant signs the informed consent until the last participant's last study-related visit.

Number of Participants:

Originally, approximately 648 participants were to be enrolled, but as of Amendment 03, on 02-MAY-2018 enrollment was permanently stopped. It is estimated that by the time the strategic decision was made to stop enrollment that 85 participants will be randomized in this study.

Treatment Groups and Duration:

Treatment Groups	1. Pembrolizumab 200 mg intravenous (IV) every 3 weeks (Q3W) + epacadostat 100 mg PO BID continuously 2. Pembrolizumab 200 mg IV Q3W + placebo PO BID continuously As of Amendment 03, the study will be unblinded after the last participant completes Week 9 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. Note: Participants assigned to the pembrolizumab plus placebo arm will receive pembrolizumab without placebo after unblinding.
Duration of Participation	Each participant will participate in the study from the time the participant signs the informed consent form (ICF) through the final protocol-specified contact. After a screening phase of approximately 42 days, each participant will be assigned to receive study treatment until disease progression, unacceptable adverse event(s) (AEs), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the participant, noncompliance with study treatment or procedure requirements, administrative reasons requiring cessation of treatment, or until the participant has received 35 administrations of pembrolizumab (approximately 2 years). Participants who stop study treatment after receiving 35 administrations of pembrolizumab for reasons other than disease progression or intolerability, or participants who attain a complete response (CR) and stop study treatment may be eligible for up to 17 additional administrations (approximately 1 year) of pembrolizumab with epacadostat/matching placebo upon experiencing disease progression. After the end of treatment, each participant will proceed to Safety Follow-up and be followed for the occurrence of AEs and spontaneously reported pregnancy as described under Section 9.3.

Study governance considerations are outlined in Appendix 1. A list of abbreviations used in this document can be found in Appendix 6.

2. Schedule of Activities (SoA)

2.1 Initial Treatment Phase

As of Amendment 03, the study will be unblinded after the last participant completes Week 9 imaging assessment for efficacy analysis. Participants can choose to discontinue from the study or continue study treatment as per protocol after discussion with the investigator and if they are receiving clinical benefit. For those participants remaining in the study, procedures are simplified. The SoA has been amended to show only the required assessments.

Study Period	Screening Phase	Treatment Cycles (3-Week Cycles)					EOT	Post Treatment	Notes
Treatment Cycle	Screening (Visit 1)	1	2	3	4	5 to 35	DC	Safety Follow-up[1]	Participants who discontinue study treatment for whatever reason will proceed directly to EOT and Safety Follow-up.
Scheduling Window (Days):	-42 to -1	+3	±3	±3	±3	±3	Time of DC	30 Days from the last dose (+7 days)	
Administrative Procedures									
Informed Consent Form	X								
Inclusion/Exclusion Criteria	X								
Participant Identification Card	X								
Demographics and Medical History	X								
Prior/Concomitant Meds	X	X	X	X	X	X	X	X	
Obtain Randomization Number and Study Drug Assignment using IVRS/IWRS	X								
Serotonin Syndrome Information Card		X							
Subsequent Anti-neoplastic Therapy Status							X	X	
Clinical Procedures / Assessments									
Review Adverse Events	X	X	X	X	X	X	X	X	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.

Study Period	Screening Phase	Treatment Cycles (3-Week Cycles)					EOT	Post Treatment	Notes
Treatment Cycle	**Screening (Visit 1)**	**1**	**2**	**3**	**4**	**5 to 35**	**DC**	**Safety Follow-up[1]**	**Participants who discontinue study treatment for whatever reason will proceed directly to EOT and Safety Follow-up.**
Scheduling Window (Days):	**-42 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**Time of DC**	**30 Days from the last dose (+7 days)**	
Full Physical Exam	X						X		
Directed Physical Exam		X	X	X	X	X		X	
Vital Signs, Height, and Weight	X	X	X	X	X	X	X		Height at Screening only.
12-Lead ECG with QTc Measurement	X	X*	X*				X		At Screening and DC for all participants. *At select centers, also perform on C1D1 and C2D1 at predose and 2 hr ± 15 mins after morning dose of epacadostat/placebo.
ECOG Performance Status	X	X	X	X	X	X	X		Perform within 14 days prior to randomization.
Laboratory Procedures / Assessments: Analysis Performed by Local Laboratory									
Pregnancy Test - Urine or Serum β-HCG	X								WOCBP require negative test within 72 hours prior to randomization. Test monthly (ie, before each cycle) if required by local regulations.
HIV testing	X								Not required unless mandated by local health authority.
PT/INR and aPTT	X								Perform 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 and upon DC of epacadostat/placebo).
CBC with Differential	X		X	X	X	X	X	X	Perform eligibility labs within 14 days prior to randomization. After Cycle 1, may collect up to 3 days prior to dosing.
Chemistry Panel	X		X	X	X	X	X	X	
Urinalysis	X		X		X	X	X	X	Perform within 14 days prior to randomization. Then every 2 cycles through Cycle 6, then every 6 cycles thereafter (Cycles 2, 4, 6, 12, 18, etc.).
Hepatitis B and C Serology	X								Hepatitis B surface antigen, HBV-DNA, HCV-RNA (or HCV antibody if HCV-RNA is not the local SOC). May use central laboratory only if local laboratory is not capable.

Study Period	Screening Phase	Treatment Cycles (3-Week Cycles)					EOT	Post Treatment	Notes
Treatment Cycle	**Screening (Visit 1)**	**1**	**2**	**3**	**4**	**5 to 35**	**DC**	**Safety Follow-up[1]**	**Participants who discontinue study treatment for whatever reason will proceed directly to EOT and Safety Follow-up.**
Scheduling Window (Days):	**-42 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**Time of DC**	**30 Days from the last dose (+7 days)**	
T3/FT3, FT4, and TSH	X		X		X	X	X	X	Perform within 14 days prior to randomization, then every 2 cycles (Cycles 2, 4, 6, 8, etc.). May use central laboratory only if local laboratory is not capable. Total T3 is preferred but free T3 is acceptable. Sites only need to report either Total T3 or free T3.

[redacted]

Study Period	Screening Phase	Treatment Cycles (3-Week Cycles)					EOT	Post Treatment	Notes
Treatment Cycle	**Screening (Visit 1)**	**1**	**2**	**3**	**4**	**5 to 35**	**DC**	**Safety Follow-up[1]**	**Participants who discontinue study treatment for whatever reason will proceed directly to EOT and Safety Follow-up.**
Scheduling Window (Days):	**-42 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**Time of DC**	**30 Days from the last dose (+7 days)**	
Efficacy Measurements									
Tumor Imaging (chest, abdomen and pelvis [CAP] CT/MRI	X				X	Per SoC	X*		Baseline CAP CT/MRI to be performed in all participants within 28 days prior to randomization. Imaging assessment will be performed at 9 weeks (±7 days) after randomization. Thereafter imaging is to be performed as per SoC for the disease and local guidelines; only the date of scans performed as per SoC needs to be documented in the eCRF. Schedule should be followed regardless of treatment delays. X*only applicable if a participants discontinues study treatment before Week 9.
Bone scan	X				X	Per SoC	X*		Baseline bone scan to be perform in all participants within 28 days prior to randomization; after randomization, bone scan will be performed if positive at baseline, at 9 weeks (±7 days) then as per local SoC; only the date of scans performed as per SoC needs to be documented in the eCRF. Schedule should be followed regardless of treatment delays. X*only applicable if a participants discontinues study treatment before Week 9.
Study Treatment Administration									
Pembrolizumab (MK-3475)		X*	X	X	X	X			*Cycle 1 treatment must be given within 3 days of randomization number assignment in IVRS/IWRS.
Epacadostat or Matching Placebo Dosed at Clinic		X	X						Morning dose of epacadostat or placebo dosed in clinic on C1D1 and C2D1 prior to the pembrolizumab infusion. At all other times, epacadostat or placebo to be self-administered approximately Q12H.
Epacadostat or Matching Placebo Dispensed		X	X	X	X	X			
Count and Collect Remaining Epacadostat or Matching Placebo			X	X	X	X	X		

Study Period	Screening Phase	Treatment Cycles (3-Week Cycles)					EOT	Post Treatment	Notes
Treatment Cycle	**Screening (Visit 1)**	**1**	**2**	**3**	**4**	**5 to 35**	**DC**	**Safety Follow-up[1]**	**Participants who discontinue study treatment for whatever reason will proceed directly to EOT and Safety Follow-up.**
Scheduling Window (Days):	**-42 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**Time of DC**	**30 Days from the last dose (+7 days)**	
Patient Reported Outcomes									
EuroQol (EQ)-5D-5L		X	X	X	X				All ePROs are to be performed prior to dosing every cycle for Cycle 1-4. EQ-5D-5L will be administered first, then EORTC QLQ-C30.
EORTC QLQ-C30		X	X	X	X				

General Notes:
1. If Discontinuation Visit occurs ≥30 days from last dose of study treatment, a Safety Follow-up Visit is not required.

Abbreviations: AE= adverse event(s); aPTT= activated partial thromboplastin time; β-HCG=beta-human chorionic gonadotropin; CBC = complete blood count; CXD1 = Cycle X Day 1; d = days; DC = discontinuation; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group, EORTC = European Organisation for Research and Treatment of Cancer, EOT = end of treatment; EQ-5D-5L = EuroQol 5-dimension, 5-level Questionnaire, HBV / HCV = hepatitis B/C virus, ; HIV= human immunodeficiency virus; hr/H = hours; ICF = informed consent form; ID = identification; IRB/IEC= Institutional Review Board/Independent Ethics Committee; IVRS/IWRS = interactive voice response system / integrated web response system, min = minutes; mos = months; PD = progressive disease; PRO = patient-reported outcomes: Q = every; QLQ-C30= Quality of Life Questionnaire Core 30; QTc= corrected QT interval; SAE= serious adverse event; SOC= standard of care; T3/FT3= free or total triiodothyronine; TSH= thyroid stimulating hormone; tx = treatment; wks = weeks; WOCBP = women of child-bearing potential.

2.2 Second Course Phase (Retreatment)

As of Amendment 03, 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.

Study Period	Treatment Cycles (3-Week-Cycles)		EOT	Post-Treatment	Notes:
Treatment Cycle	1	2 to 17	DC	Safety Follow-up[1]	
Scheduling Window (Days):	+3	±3	Time of DC	30 Days from last dose (+7 days)	
Administrative Procedures					
Eligibility Criteria	X				
Concomitant Meds Review	X	X	X	X	
Post-Study Anti-cancer Therapy Status			X	X	
Clinical Procedures / Assessments					
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 Exam	X			X	
Directed Physical Exam		X	X		
Vital Signs and Weight	X	X	X		
12-Lead ECG with QTc Measurement	X		X		Perform within 14 days prior to Second Course Cycle 1.
ECOG Performance Status	X	X	X		Perform within 14 days prior to Second Course Cycle 1.
Laboratory Procedures / Assessments: Analysis Performed by Local Laboratory					
Pregnancy Test - Urine or Serum β-HCG	X				WOCBP require negative test within 72 hours prior to Second Course Cycle 1. Test monthly (ie, each cycle) if required by local regulations.
PT/INR and aPTT	X				Perform within 14 days prior to Second Course Cycle 1. Participants receiving coumarin-based anticoagulants should have more frequent INR monitoring (weekly for first 4 weeks after initiation of therapy and upon DC of epacadostat/placebo).

Study Period	Treatment Cycles (3-Week-Cycles)		EOT	Post-Treatment	Notes:
Treatment Cycle	1	2 to 17	DC	Safety Follow-up[1]	
Scheduling Window (Days):	+3	±3	Time of DC	30 Days from last dose (+7 days)	
CBC with Differential	X	X	X	X	Perform within 14 days prior to Second Course Cycle 1. After Second Course Cycle 1, may collect up to 3 days prior to dosing.
Chemistry Panel	X	X	X	X	
Urinalysis	X	X*	X	X	Perform within 14 days prior to Second Course Cycle 1. *Urinalysis every 2 cycles through Cycle 5, then every 6 cycles thereafter (SC Cycles 1, 3, 5, 11, 17).
T3/FT3, FT4, and TSH	X	X*	X	X	Perform within 14 days prior to Second Course Cycle 1. *Every 2 cycles (SC Cycles 1, 3, 5, 7, etc.). May use central laboratory only if local lab is not capable.
Efficacy Measurements					
Tumor Imaging (chest, abdomen and pelvis [CAP] CT/MRI)	As per SoC				Imaging to be performed as per local SoC guidelines; only the date of scans performed as per SoC needs to be documented in the eCRF.
Bone Scan	As per SoC				
Study Treatment Administration					
Pembrolizumab (MK-3475)	X	X			
Epacadostat or Matching Placebo Dispensed and Dosed	X	X			Epacadostat to be self-administered approximately Q12H. Participants who restart treatment should resume at the same dose of epacadostat/matching placebo they were receiving prior to DC from first course.
Count and Collect Remaining Epacadostat or Matching Placebo		X	X		

General Notes:

1. If Discontinuation Visit occurs ≥30 days from last dose of study treatment, a Safety Follow-up Visit is not required.

Abbreviations: AE= adverse event(s); aPTT= activated partial thromboplastin time; β-HCG=beta-human chorionic gonadotropin; CBC = complete blood count; CXDX = Cycle X Day X; d = days; DC = Discontinuation Visit; ECOG= Eastern Cooperative Oncology Group; EOT = end of treatment; FT4= free thyroxine; H = hours; INR= international normalized ratio; PD= progressive disease; PS= performance status; PT=prothrombin time; Q = every; SC = Second Course (Phase); T3/FT3= free or total triiodothyronine; TSH= thyroid stimulating hormone; W = weeks; WOCBP = women of child-bearing potential.

3. Introduction

3.1 Study Rationale

The goal of cancer immunotherapy is to initiate or reinitiate a self-sustaining cycle of cancer immunity, enabling it to amplify and propagate. Cancer immunotherapies must overcome the negative feedback mechanisms that are inherent in most cancers to evade immune surveillance.

Bladder cancer was the first indication for which an immunotherapy was granted approval by the Food and Drug Administration (FDA) in 1990. Bacillus Calmette-Guérin (BCG) has been shown to be an effective agent for the treatment of superficial bladder cancer since its approval in 1990. Augmentation of BCG immunotherapy with interferon-α2b and other agents have emerged since then for patients who fail initial treatment [Kassouf, W. 2004] suggesting that bladder cancer may be a tumor type responsive to immunotherapy.

There is an unmet need in the advanced disease setting, since current chemotherapy regimens are toxic and provide limited benefit. There are reports of promising results with the immune checkpoint programmed cell death (PD-1) inhibitor, pembrolizumab (MK-3475) monotherapy, and other anti-PD-1 pathway agents in this patient population [Powles, T., et al 2014] [Kim, J. W., et al 2015]. The current approach will attempt to extend the number of participants who develop an immune response by targeting PD-1 with pembrolizumab, and the tryptophan-catabolizing enzyme indoleamine 2,3 dioxygenase-1 (IDO1) with epacadostat (formerly INCB024360). Both IDO1 and PD-1 have been shown to suppress T-cell-mediated antitumor immunity, and IDO1 and the PD-1 ligand, PD-L1, have been shown to be coexpressed in multiple cancer types and to correlate with poor prognosis. PD-L1 and IDO1 are gamma-interferon responsive genes that are often subverted in tandem by tumor cells. Combined inhibition of both pathways may therefore lead to greater suppression of antitumor immunity and to increased efficacy. Response data for participants with progressive metastatic urothelial carcinoma (UC) from the ongoing Phase 1/2 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 2 responders (see Section 3.2.1.8), thus warranting a further carefully controlled randomized study. The present study will examine the combination of pembrolizumab and epacadostat versus pembrolizumab plus placebo in participants with advanced/metastatic disease who have had progression or recurrence following a platinum-containing chemotherapy regimen.

3.2 Background

Refer to the current Investigator's Brochure (IB)/approved labeling for detailed background information on pembrolizumab (MK-3475) and epacadostat.

3.2.1 Pharmaceutical and Therapeutic Background

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) mAb with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with programmed cell death-ligand 1 (PD-L1) and programmed cell death-ligand 2 (PD-L2). Epacadostat 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 pembrolizumab IB and the current epacadostat IB.

3.2.1.1 Overview of Urothelial Carcinoma

Urothelial carcinoma, also known as transitional cell carcinoma (TCC) describes a range of tumors that arise from the urothelial endothelium, which includes the bladder, renal pelvis, ureter, and urethra. The worldwide incidence of bladder cancer exceeds 300,000 cases annually, [Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D 2011]. Urothelial carcinoma is the predominant histologic type of bladder cancer in the United States and Western Europe, where it accounts for approximately 90 percent of bladder cancers.

3.2.1.2 Treatment for Recurrent or Progressive Metastatic Urothelial Carcinoma

The majority of patients with TCC develop localized, non-invasive disease. However, approximately 25% of patients will have muscle-invasive disease and either present with or later develop metastases. Systemic chemotherapy is the standard approach for the initial treatment of patients with inoperable locally advanced or metastatic urothelial malignancies. The median survival with combination chemotherapy is approximately 14 to 15 months [von der Maase, H., et al 2005]. While this is superior to the estimated 6-month survival with metastatic disease prior to the development of modern chemotherapy regimens, the 5-year survival rate is approximately 15% with contemporary chemotherapy regimens. Second-line chemotherapy, usually as a single agent, has had only a limited role, with a modest increase in median overall survival (OS) was at best 6.9 months compared to best supportive care [Bellmunt, J., et al 2009].

A number of clinical and molecular characteristics have been shown to correlate with OS. Poor performance status and the presence of visceral (ie, pulmonary, liver, bone) metastases correlate with shortened survival in clinical trials. This was illustrated by an intergroup study that compared cisplatin alone with methotrexate, vinblastine, doxorubicin, and cisplatin in patients with metastatic disease [Loehrer, P. J. Sr., et al 1992]. The presence of bone or liver metastases and poor performance status were most predictive of poor response and survival. The presence of these unfavorable features was associated with median survival of 4 months, compared with 18 months in those patients without these features. No patients with liver or bone metastases and only one patient with a Karnofsky PS <80 percent survived past 6 years [Saxman, S. B., et al 1997]. Several subsequent reports confirmed the relationship between shortened survival and poor performance status or the presence of visceral metastases. In the second-line setting (patients with platinum-refractory TCC), multivariate analysis identified ECOG PS >1, hemoglobin level less than 10 g/dL and the presence of liver metastasis as the main adverse prognostic factors for OS [Bellmunt, J., et al 2010]. These factors illustrate that since bladder cancer is more often a disease of the elderly and infirm, many patients cannot benefit from modern cisplatin-based chemotherapy regimens, and other treatment options are needed for this large population of patients.

More effective and less toxic treatments are greatly needed in this patient population, and immunotherapy offers additional options for patients progressing after their initial systemic therapy. Treatment for bladder cancer has evolved over time to encompass not only traditional chemotherapy, but has been particularly impacted by the use of immunotherapy [Bellmunt, J., et al 2017]. The PD-1/PD-L1 inhibitors such as atezolizumab, pembrolizumab, nivolumab and durvalumab have demonstrated some activity in early clinical studies and are currently being evaluated in randomized clinical studies in patients with UC. These include studies as first- and second-line therapy and as well as in the adjuvant setting. Atezolizumab nivolumab,

durvalumab, and avelumab recently received accelerated approval from the US FDA for the treatment of advanced UC that has progressed during or after previous platinum-based chemotherapy. In addition, atezolizumab received accelerated approval from the US FDA for the treatment of advanced UC who were not eligible for cisplatin-containing chemotherapy.

On 18-May-2017, the FDA granted accelerated approval to pembrolizumab for patients with locally advanced or metastatic UC who were not eligible for cisplatin-containing chemotherapy, based on data from a multicenter, open-label, single-arm trial, KEYNOTE-052, investigating pembrolizumab in 370 patients. Also on 18-May-2017, the FDA granted regular approval to pembrolizumab for patients with locally advanced or metastatic UC with disease progression on or after platinum-containing chemotherapy. Approval was based on data from a multicenter, randomized, active-controlled trial, KEYNOTE-045. Patients were randomized to receive either pembrolizumab 200 mg every 3 weeks (Q3W) (n=270) or Investigator's choice of paclitaxel, docetaxel, or vinflunine [Bellmunt, J., et al 2017] [Keytruda® United States Package Insert [USPI], 2017].

3.2.1.3 Immune Surveillance and Neoplastic Transformation

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 the immune system by exploiting the immune checkpoint pathways that downregulate the immune response to avoid healthy tissue damage [Davies, M. 2014]. 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.

There are a number of inhibitory mechanisms that have been identified to be involved in tumor-mediated immune suppression and include expression of PD-L1, which can engage the inhibitory receptor PD-1 on activated T cells; the presence of the tryptophan-catabolizing enzyme IDO1, which exposes the exquisite sensitivity of T cells to tryptophan depletion and tryptophan metabolites; and infiltration with FoxP3+ regulatory T cells (T-reg), which can mediate extrinsic suppression of effector T-cell function. Therefore, agents that target these negative regulatory pathways and thereby allow the expansion of effector T cells present in the tumor may be beneficial in the clinic.

3.2.1.4 Inhibition of PD-1 as a Target for Cancer

The PD-1 receptor-ligand interaction is a major pathway stimulated by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an immunoglobulin (Ig) superfamily member related to CD28 and cytotoxic T-lymphocyte-associated antigen-4

(CTLA-4), which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [Talmadge, J. E., et al 2007] [Usubütün, A., et al 1998]. The mechanism by which PD-1 down modulates T-cell responses is similar to but distinct from that of CTLA-4, as both molecules regulate an overlapping set of signaling proteins [Hiraoka, N. 2010] [Nobili, C., et al 2008]. PD-1 has been shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T-regs, and natural killer cells [Hodi, F. S. and Dranoff, G. 2010] [Kloor, M. 2009]. Expression has also been shown during thymic development on CD4-CD8- (double negative) T cells as well as subsets of macrophages and dendritic cells [Hillen, F., et al 2008]. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including nonhematopoietic tissues as well as in various tumors [Lee, H. E., et al 2008] [Leffers, N., et al 2009] [Nishimura, H., et al 2000] [Nobili, C., et al 2008]. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various nonhematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments.

PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T cell function in peripheral tissues [Nobili, C., et al 2008]. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in participants with melanoma [Liotta, F., et al 2011]. This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

3.2.1.5 Activity of PD-1/PD-L1 Inhibitors in Urothelial Carcinoma

Several PD-1/PD-L1 checkpoint inhibitors have demonstrated activity in refractory UC. Atezolizumab (TECENTRIQ®) is an Fc-engineered, humanized, mAb that binds to PD-L1 and blocks interactions with the PD-1 and B7.1 receptors (TECENTRIQ® USPI, 2016). Atezolizumab received accelerated approval from the US FDA in May 2016 for the treatment of advanced UC that has progressed during or after previous platinum-based chemotherapy, either for metastatic disease or for progressive disease (PD) less than 12 months after adjuvant or neoadjuvant chemotherapy. An urothelial expansion cohort in a Phase I study provided initial evidence of the safety and efficacy [Powles, T., et al 2014]. Subsequently, IMvigor210, an open label Phase 2 study enrolled 310 participants with advanced urothelial cancer who were previously treated with platinum-based chemotherapy. Accelerated approval was based upon an ORR of 14.8% (95% confidence interval [CI] 11.1, 19.3) and prolonged duration of response (median DOR not reached) [Rosenberg, J. E., et al 2016].

Nivolumab (MDX-1106; OPDIVO) is a fully human IgG4 mAb that binds to PD-1 and blocks interaction with PD-L1 and PD-L2 and restores T-cell antitumor function [Brahmer, J. R., et al 2010]. Nivolumab received accelerated approval from the US FDA in February 2017 for the treatment of participants with locally advanced or metastatic UC who have disease progression during or following platinum-containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with a platinum-containing chemotherapy (OPDIVO®, 2017). In a Phase 1/2 study (CheckMate 032); the UC part of the study consisted of two treatment regimens: nivolumab monotherapy and nivolumab in combination with

ipilimumab. The study population is participants with advanced urothelial cancer who have progressed after ≥1 prior line of platinum-based chemotherapy. A total of 86 participants with UC were enrolled and 78 participants were treated with nivolumab 3 mg/kg as a monotherapy. With a minimum follow up of 9 months, the investigator-assessed ORR in the monotherapy group was 24.4% (95% CI 15.3-35.4). Median OS was 9.7 months (95% CI 7.3-16.2) [Sharma, P., et al 2016] In the Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg group, there were 104 participants treated and median OS was 10.2 months (95% CI 4.5-NR). In the Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg group, there were 26 participants treated and median OS was 7.3 months (95% CI 5.6-11.4).

Pembrolizumab is a humanized IgG4-kappa mAb that also binds to PD-1 and is approved for multiple indications. Additionally, pembrolizumab was granted breakthrough therapy designation in the US for the second line treatment of participants with locally advanced or metastatic UC with disease progression on or after platinum-containing chemotherapy. This application is based on a phase 3 study (KEYNOTE-045) where participants with advanced UC receive either pembrolizumab or investigator's choice of second-line chemotherapy following progression on a platinum-containing regimen. The results demonstrate a statistically significant OS advantage of pembrolizumab over chemotherapy and a lower rate of treatment-related adverse events (AEs) than chemotherapy [Bellmunt, J., et al 2017] [Bajorin, D. F., et al 2017].

Durvalumab (IMFINZI™) is a PD-L1 checkpoint inhibitor that received accelerated approval on 01-May-2017 for the treatment of patients with locally advanced or metastatic UC who have disease progression during or following platinum-containing chemotherapy or who have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. These studies indicate that immunotherapies are active and may offer improved efficacy over traditional chemotherapy in advanced UC. These data support the use of PD-1/PD-L1 inhibitors in this setting. However, the majority of participants do not derive a benefit as evidenced by the relatively low response rates (RR), and there remains a high unmet medical need for more efficacious therapies.

Avelumab (BAVENCIO®) (is also a PD-L1 checkpoint inhibitor that received accelerated approval on 09-May-2017 for patients with locally advanced or metastatic UC whose disease progressed during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy.

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

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

The expression and activity profiles of IDO1 are distinct from those of tryptophan dioxygenase, an enzyme predominantly expressed in liver that catalyzes the same enzymatic reaction as IDO1 and maintains proper tryptophan balance in response to dietary uptake. In contrast to tryptophan dioxygenase, IDO1 is expressed in a variety of tissues, with particularly high levels found in

areas of contact with potential sources of immune challenge (e.g., gut, respiratory tract, placenta, spleen), consistent with a role for regulating tryptophan metabolism in a local microenvironment [Mellor, A. L. 2004]. Within the immune system, IDO1 activity is specifically induced in cells such as 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 T-regs [Fallarino, F., et al 2006]. Since increased T-reg activity has been shown to promote tumor growth and T-reg depletion has been shown to allow an otherwise ineffectual antitumor immune response to occur [Zou, W. 2006], IDO1 expansion of T-regs may provide an additional mechanism whereby IDO1 could promote an immunosuppressive environment.

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

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

Based on studies examining serum levels of tryptophan and kynurenine, IDO1 appears to be chronically activated in participants with cancer, and IDO1 activation correlates with more extensive disease [Huang, L., et al 2010] [Weinlich, G., et al 2007]. IDO1 has subsequently been found to be overexpressed by a wide variety of human tumor cell types as well as by the dendritic cells that localize to the tumor draining lymph nodes [Uyttenhove, C., et al 2003]. Increased expression of IDO1 in tumor cells has been shown to be an independent prognostic variable for reduced OS in participants with melanoma, ovarian, colorectal, pancreatic, and bladder cancers [Brandacher, G., et al 2006] [Ino, K., et al 2006] [Nakamura, T., et al 2007] [Okamoto, A., et al 2005] [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 either alone or in combination with chemotherapeutics and/or immunotherapy-based strategies.

3.2.1.7 Combined Immune Checkpoint Inhibition

Blockade of immune inhibitory pathways is emerging as an important therapeutic modality for the treatment of cancer as evidenced by the clinical responses observed with antibodies to CTLA-4 and PD-1/PD-L1. Ipilimumab, a fully human, IgG1 mAb blocking CTLA-4, improved OS in participants with advanced melanoma [Hodi, F. S. and Dranoff, G. 2010]. Nivolumab, a fully human IgG4 antibody blocking PD-1, produced durable overall responses in participants with melanoma, renal cell cancer, and non-small cell lung cancer (NSCLC) [Hamid, O., et al 2013] [Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC. 2012] and [Wolchok, J.D., et al 2013]. Although these single agents have antitumor activity, multiple immune inhibitory mechanisms are present concurrently within the tumor microenvironment, suggesting that combination therapies may be required for optimal therapeutic effect [Quezada, S. A. 2013].

For example, CTLA-4 and PD-1 appear to play complementary roles in regulating adaptive immunity. Whereas PD-1 contributes to T-cell exhaustion in peripheral tissues, CTLA-4 inhibits at earlier points in T-cell activation. In preclinical models, combined blockade of PD-1 and CTLA-4 achieved more pronounced antitumor activity than blockade of either pathway alone [Curran, M. A., et al 2010] [Selby, M, et al 2013]. This was demonstrated in clinical studies evaluating participants with metastatic melanoma, and the combination of nivolumab and ipilimumab has since been approved by regulatory authorities for melanoma, and this combination continues to be investigated in a number of additional tumor types.

3.2.1.8 Combination of IDO1 Inhibitor with Checkpoint Inhibition

As described above, IDO1 is another negative regulatory mechanism that contributes to tumor-derived immune suppression. In preclinical models, IDO1 inhibition has been shown to synergize with blockade of either anti–CTLA-4 or anti–PD-1/PD-L1 in delaying tumor growth and increasing OS [Holmgaard, R. B., et al 2013] [Spranger, S., et al 2013]. This effect was shown to be T-cell dependent, leading to enhanced T-cell proliferation and interleukin-2 production within the tumor and to a marked increase in the effector-to-regulatory T-cell ratios in the tumors.

There are several ongoing clinical studies with the IDO1 inhibitor epacadostat 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 twice daily (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 with Stage 3B, IV or recurrent NSCLC, melanoma, TCC, renal cell carcinoma, endometrial adenocarcinoma or squamous cell carcinoma of the head and neck (SCCHN). 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 the Phase 2 portion, and received ≥ 1 dose of epacadostat and pembrolizumab. The most common (≥10%) all-grade treatment-related adverse events (TRAEs)

were fatigue, rash, nausea and pruritus [Hamid, O., et al 2017]. Grade ≥3 TRAEs were observed in 18% (most common: increased lipase [4%] and rash [3%]). There was one treatment-related death due to respiratory failure which was secondary to aspiration pneumonia.

As of 27-Feb-2017, available efficacy data for participants enrolled in the UC cohort (INCB 24360-202/KEYNOTE-037) was reviewed [Smith, D. C., et al 2017]. There were 40 evaluable participants with an ORR of 35% (14 of 40). Of these, there were 11 PRs and 3 CRs. At the time of the data cutoff all 10 of 14 responses were still ongoing. The disease control rate (DCR) was 53%, with 21 of 40 participants with CR, partial response (PR), or stable disease (SD) as their best objective response. Twelve of the 14 responders had received one prior treatment regimen. These results compare favorably to second-line therapy with pembrolizumab monotherapy in this setting, which has an ORR of 21.1% [Bellmunt, J., et al 2017].

3.2.2 Pre-clinical and Clinical Studies

Refer to the IBs for pembrolizumab and epacadostat for preclinical and clinical study data.

3.2.3 Ongoing Clinical Studies

Refer to the IB for pembrolizumab and epacadostat for ongoing clinical studies 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 OS. The external data monitoring committee (eDMC) concluded that the study did not meet the primary objective of improving PFS in the combination compared to pembrolizumab monotherapy during a second interim analysis. There were no new safety concerns. The study remains open so that participants still on study will have continued access to open-label pembrolizumab.

3.3 Benefit/Risk Assessment

3.3.1 Benefit/Risks for Epacadostat

Epacadostat, as a single therapy, had a predictable pharmacokinetic (PK) profile and acceptable safety profile, but limited single-agent efficacy in participants with solid tumors in the Phase 1 study of 52 participants (INCB 24360-101). The data showing the limited efficacy in solid tumors support that an epacadostat monotherapy arm is not warranted.

A potential concern of IDO1 inhibition is an increase in serotonin levels that could precipitate a cluster of AEs termed serotonin syndrome (SS) when administered alone or in combination with other serotonergic agents. This rare syndrome has been associated with some monoamine oxidase inhibitors (MAOIs) and combinations of serotonergic drugs [Boyer, E. W. 2005]. The clinical manifestations of SS range from barely perceptible to lethal; onset is rapid (within 12 hours of drug[s] administration). Nonclinical data suggest that SS is unlikely following treatment with either epacadostat alone or in combination with MAO inhibitors such as linezolid [Zhang, Y., et al 2016]. As of 27-Feb-2017, 2 of 958 participants treated across the epacadostat program have reported SS or symptoms of SS and both were mild in their severity and resolved.

Although the incidence of SS is uncommon, use of MAOIs are prohibited during the study, and all participants will be assessed for SS symptoms at an appropriate timeframe after dosing. Participants will be provided with an informative card describing the signs and symptoms of SS along with instructions to seek immediate medical care if any of these signs or symptoms are observed.

Additional details regarding specific benefits and risks of epacadostat for participants in this clinical study may be found in the accompanying current IB and ICF.

3.3.2 Benefit/Risks from Pembrolizumab

Pembrolizumab monotherapy has a positive benefit-risk profile and is well tolerated in multiple approved indications as detailed in the IB.

In the Phase 3 study, KEYNOTE-045, pembrolizumab versus chemotherapy, as second-line therapy for platinum-refractory advanced UC, was associated with significantly longer OS (10.3 months versus 7.4 months, respectively) and a lower rate of treatment-related AEs [Bellmunt, J., et al 2017] [Bajorin, D. F., et al 2017].

Due to the mechanism of action of pembrolizumab, immune-related AEs (irAEs) have been seen when used as monotherapy. The majority of the irAEs were mild to moderate in severity, manageable with appropriate care, and rarely required discontinuation of therapy. Infusion-related reactions are also possible following administration of pembrolizumab. Guidance for the management of irAEs and infusion-related reactions is in the protocol.

The Reference Safety Dataset (N=2799) comprises the locked safety data from studies KEYNOTE-001, -002, -006, and -010 [IB Edition 15 2017]. In that dataset, adverse events (AEs) were generally manageable and infrequently required discontinuation of pembrolizumab treatment. Additional details regarding specific benefits and risks for participants in this clinical study may be found in the accompanying current IB and Informed Consent Form.

3.3.3 Benefit/Risks for the Combination of Epacadostat and Pembrolizumab

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

Study INCB 24360-202 (KEYNOTE-037) is an ongoing Phase 1/2 study of epacadostat administered in combination with pembrolizumab. Phase 1 is being conducted in participants with advanced or metastatic solid tumors who have disease progression on at least 1 line of therapy for advanced or metastatic cancer (except melanoma). Phase 2 is conducted in participants with NSCLC, melanoma, TCC of the genitourinary tract, triple negative breast cancer, SCCHN, ovarian cancer, Diffuse Large B-Cell Lymphoma, clear cell renal cell cancer, gastric cancer, hepatocellular carcinoma, and microsatellite instability (MSI) high colorectal cancer.

Safety data is available on 294 participants from the Phase 2 portion of INCB 24360-202 (KEYNOTE-037) treated with the recommended Phase 2 dose of epacadostat 100 mg BID and pembrolizumab 200 mg Q3W. The most frequently reported (≥ 10%) treatment-related AEs of any grade were fatigue (29%), rash (17%), nausea (11%), and pruritus (10%). Rash includes the preferred terms rash, rash generalized, rash macular, rash maculopapular, and rash pruritic. Treatment-related AEs Grade ≥3 were observed in 18% of participants. The most common

treatment-related AEs Grade≥3 were increased lipase (4%) and rash (3%). There was one treatment-related death due to respiratory failure which was secondary to aspiration pneumonia.

Given initial data observed in KEYNOTE-037 suggesting improved efficacy of pembrolizumab with epacadostat and an overall safety profile comparable to anti-PD-1 monotherapy, this combination represents a rationale and promising option in participants with metastatic UC.

4. Objectives/Hypotheses and Endpoints

NOTE: As of Amendment 03, the primary endpoint of the study will be ORR based on RECIST 1.1 as assessed by the investigator. All other efficacy endpoints, including imaging, will no longer be collected or performed after the first imaging assessment at Week 9. This section has been updated accordingly.

In male/female participants of at least 18 years of age with histologically confirmed diagnosis of advanced/unresectable or metastatic UC that has recurred or progressed following one prior line of platinum-containing chemotherapy for advanced/metastatic disease:

Objective/Hypothesis	Endpoint
Primary	
• **Objective:** To estimate the objective response rate (ORR) of pembrolizumab plus epacadostat and pembrolizumab plus placebo based on RECIST 1.1 by investigator determination.	• ORR - defined as the proportion of participants in the analysis population who have a best response of complete response (CR) or partial response (PR).
Secondary	
• **Objective:** To evaluate the safety and tolerability of pembrolizumab plus epacadostat versus pembrolizumab plus placebo.	• Adverse events (AEs) • Study drug discontinuations due to AEs.
[redacted]	

[redacted]

5. Study Design

5.1 Overall Design

Note: Enrollment was stopped strategically on 02-MAY-2018. As of Amendment 03, all study efficacy procedures will discontinue after the first on-study imaging at Week 9 (± 7 days); thereafter participants will be treated as per SoC for the disease and local guidelines. The study will be unblinded after the last participant completes their Week 9 imaging assessment for efficacy analysis. Safety procedures will continue as per protocol for all participants continuing study treatment (eg, with either open-label pembrolizumab or pembrolizumab and epacadostat, if they are considered to be deriving clinical benefits). The last study visit is the Safety Follow-up Visit. This section has been updated accordingly.

This is a randomized, double-blind, placebo-controlled, parallel-group, multi-site, study of pembrolizumab plus epacadostat compared to pembrolizumab plus placebo, in participants with confirmed metastatic or locally advanced/unresectable UC (transitional cell or predominantly transitional cell histology) of the bladder, renal pelvis, ureter, or urethra that has recurred or progressed following one prior line of platinum-containing chemotherapy for advanced/metastatic disease. No additional lines of systemic treatment are allowed.

Approximately 648 eligible participants were to be randomized into the study but as of Amendment 03, on 02-MAY-2018 enrollment in the study was stopped. It is estimated by the time the strategic decision was made on 02-MAY-2018 to permanently stop enrollment that 85 participants will be randomized in this study.

Participants will be centrally randomized in a 1:1 ratio to receive either pembrolizumab 200 mg IV Q3W plus epacadostat 100 mg BID continuous dosing or pembrolizumab 200 mg IV Q3W plus matching epacadostat placebo. Prior to randomization, eligible participants will be stratified by the following 2 stratification factors: 1) Bellmunt score (0, vs 1 vs ≥2) and 2) PD-L1 expression from tumor tissue samples, based on CPS ≥10 versus CPS <10 per IHC, as assessed by the designated central laboratory. Prior to randomization, each participant must provide a newly obtained or archival formalin-fixed paraffin-embedded (FFPE) tumor biopsy for PD-L1 determination by immunohistochemistry (IHC) by a central laboratory. Participants with non-evaluable tumor tissue sample will be excluded.

Study treatment is defined as pembrolizumab + epacadostat or pembrolizumab + matching epacadostat placebo, and will be given for up to 35 cycles or until disease progression, unacceptable toxicity, or Investigator decision. Participants who discontinue treatment will

discontinue from the study after Safety Follow-up. Investigators will assess the images using RECIST 1.1 (see Section 9.2.1.5) to determine eligibility at screening as well as ORR after the first on-study imaging at Week 9. Tumor imaging will be site-assessed for PD and treatment discontinuation.

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.

There is no interim analysis in this study. During the course of the study, the external Data Monitoring Committee (eDMC) will perform 1 safety review based on the eDMC charter.

5.1.1 Study Diagram

The study design is depicted in Figure 1.

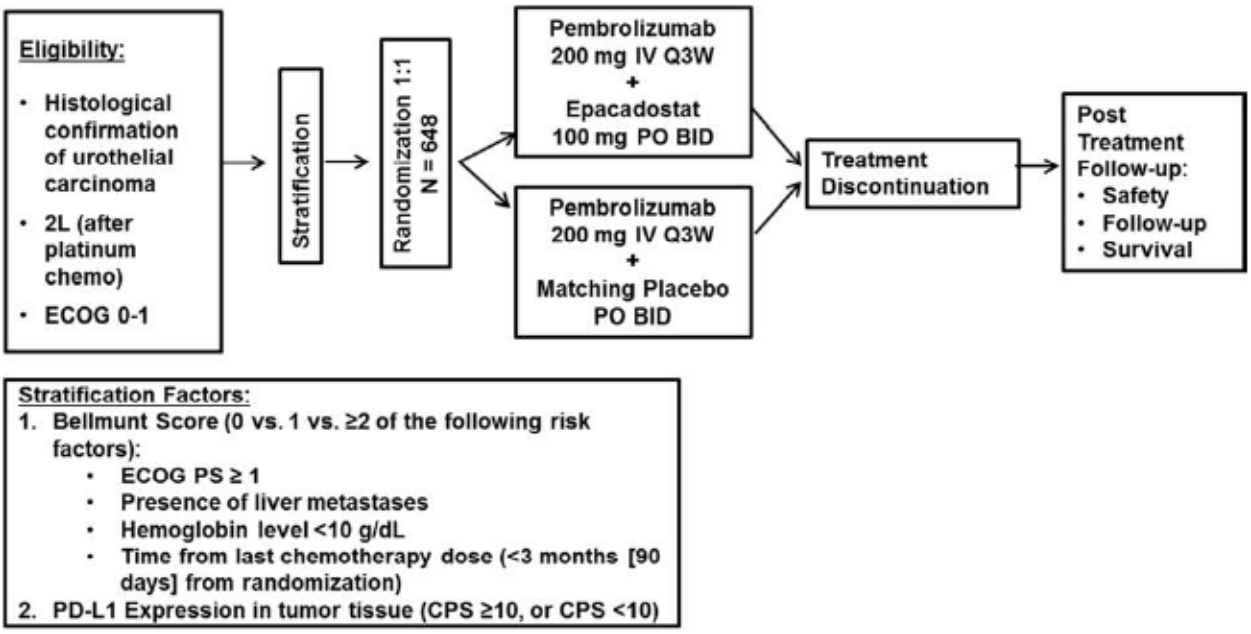


Figure 1 Study Design

NOTE: As of Amendment 03, the study will be unblinded after the last participant completes the Week 9 imaging assessment for efficacy analysis; participants can choose to discontinue from the study or continue study treatment as per protocol after discussion with the investigator and if they are deriving clinical benefits. No placebo will be administered after unblinding. The last study visit is the Safety Follow-up Visit.

BID= twice daily; CPS= combined positive score; ECOG PS= Eastern Cooperative Oncology Group; Performance Status; IV= intravenous; PO= orally; Q3W= every 3 weeks

5.2 Number of Participants

Originally, approximately 648 participants were to be randomized in this study but as of Amendment 03, on 02-MAY-2018 enrollment in the study was stopped. It is estimated that by the time the strategic decision was made on 02-MAY-2018 to permanently stop enrollment 85 participants will be randomized in this 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

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

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

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

5.4 Scientific Rationale for Study Design

The goal of cancer immunotherapy is to initiate or reinitiate a self-sustaining cycle of cancer immunity, enabling it to amplify and propagate. Cancer immunotherapies must overcome the negative feedback mechanisms that are inherent in most cancers to evade immune surveillance.

Bladder cancer was the first indication for which an immunotherapy was granted approval by the FDA in 1990. BCG has been shown to be an effective agent for the treatment of superficial bladder cancer since its approval in 1990. Augmentation of BCG immunotherapy with interferon-α2b and other agents have emerged since then for participants who fail initial treatment [Kassouf, W. 2004] suggesting that bladder cancer may be a tumor type responsive to immunotherapy.

Both IDO1 and PD-1 have been shown to suppress T-cell-mediated antitumor immunity, and IDO1 and the PD-1 ligand, PD-L1, have been shown to be coexpressed in multiple cancer types and to correlate with poor prognosis. PD-L1 and IDO1 are gamma-interferon responsive genes that are often subverted in tandem by tumor cells. Combined inhibition of both pathways may therefore lead to greater suppression of antitumor immunity and to increased efficacy. Response data for participants with progressive metastatic UC from the ongoing Phase 2 study (INCB 24360-202), 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 carefully controlled randomized study.

The FDA granted accelerated approval to pembrolizumab for patients with locally advanced or metastatic UC who were not eligible for cisplatin-containing chemotherapy based on data from a multicenter, open-label, single-arm trial, KEYNOTE-052, investigating pembrolizumab in 370 patients. The efficacy analysis showed an ORR of 29% (95% CI: 24, 34), with a complete response (CR) rate of 7 % and a PR rate of 22 %. The median DOR had not been reached (range: 1.4+ to 17.8+ months). The median follow-up time was 7.8 months (Keytruda® USPI, 2017).

The FDA granted regular approval to pembrolizumab for patients with locally advanced or metastatic UC with disease progression on or after platinum-containing chemotherapy. This approval is based on a phase 3 Study KEYNOTE-045 where participants receive either pembrolizumab or investigator's choice second-line chemotherapy following progression on a platinum-containing regimen.

In KEYNOTE-045, 542 participants (pembrolizumab, n= 270; chemotherapy, n=272) were enrolled as of the 18-Jan-2017 data cut-off for a planned survival analysis. The median follow-up was 18.5 months (range, 14.2-26.5) [Bajorin, D. F., et al 2017]. The median OS was significantly longer with pembrolizumab vs chemotherapy (10.3 vs 7.4 months; HR, 0.70; P< 0.001), and significance was maintained regardless of PD-L1 expression as measured by combined positive score ([CPS]; Hazard Ratio [HR]: CPS <1, 0.84; CPS ≥1, 0.59; CPS <10, 0.76; CPS ≥10, 0.57). OS benefit with pembrolizumab vs chemotherapy was seen regardless of age, ECOG PS, prior therapy, liver metastases, histology, and choice of chemo. The 18-month OS rate (95% CI) was 36.1% (30.1%-42.0%) with pembrolizumab vs 20.5% (15.2%-25.8%) with chemotherapy (Kaplan-Meier estimate). PFS was not different between arms. ORR was higher with pembrolizumab v chemo (21.1% vs 11.0%), and median (range) DOR was longer (not reached [1.6+ to 20.7+ month] vs 4.4 months [1.4+ to 20.3]). Responses lasted ≥12 months in 69% of participants treated with pembrolizumab vs 36% in participants treated with chemotherapy. Fewer participants experienced a treatment-related AE with pembrolizumab vs chemotherapy treatment (any Grade, 61.3% vs 90.2%; Grade ≥3, 16.5% vs 49.8%).

In KEYNOTE-052, an open-label, multicenter, Phase 2 study evaluating the efficacy and safety of pembrolizumab (200 mg Q3W) in first-line cisplatin-ineligible participants with unresectable or metastatic UC, the PD-L1 CPS-high cut point was determined to be ≥10 PD-L1 expression. In data presented at ASCO 2017, as of a 09-Mar-2017 data cutoff, subjects with PD-L1 CPS ≥10 demonstrated higher response rates (RR) with pembrolizumab monotherapy than participants with CPS <10 (ORR of 23% in CPS <10 subjects and 51% in subjects with CPS ≥10) [O'Donnell, P. H., et al 2017]. Moreover, complete responses were seen in 3% of CPS <10 subjects and 18% of those with CPS ≥10.

The present study will examine the combination of pembrolizumab and epacadostat versus pembrolizumab plus placebo in participants with advanced/metastatic UC who have had progression or recurrence following a platinum-containing chemotherapy regimen. OS, and PFS will be the objective endpoints. There is an unmet need in this setting, since current chemotherapy regimens are toxic and provide limited benefit. While the current monotherapy PD-1 therapies have shown promising activity, they have limited benefit given that the RR is low and only a small proportion of participants derive long term benefit.

5.4.1 Rationale for Endpoints

5.4.1.1 Efficacy Endpoints

NOTE: As of Amendment 03, the primary endpoint of the study will be ORR based on RECIST 1.1 as assessed by the investigator; transmission of images for central review is no longer required. After imaging at Week 9, all other efficacy endpoints, including imaging after the first on study scan at Week 9, will no longer be collected or performed. This section has been amended accordingly.

This study will use ORR based on RECIST 1.1 criteria as assessed by the Investigator as the primary endpoint. ORR is an acceptable measure of clinical benefit for a late stage study that demonstrates superiority of a new antineoplastic therapy. Images will be read by Investigators blinded to treatment assignment to minimize bias in the response assessments. The final determination of radiologic progression will be based on the local site Investigator/radiology assessment.

5.4.1.1.1 RECIST 1.1

RECIST 1.1 will be used by the Investigator when assessing images for primary efficacy measures and by the local site when determining eligibility (Section 9.1.2.5). 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.

Refer to Section 9.2.1.5 for details on RECIST 1.1.

5.4.1.1.2 Modified RECIST for Immune-based Therapeutics (iRECIST)

NOTE: As of Amendment 03, 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.

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

Thus, standard RECIST 1.1 may not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab. Based on an analysis of participants with melanoma enrolled in KEYNOTE-001, 7% of evaluable participants experienced delayed or early tumor pseudo-progression. Of note, participants who had PD by RECIST 1.1 but not by the immune-related response criteria [Wolchok, J. D., et al 2009] had longer OS than participants with PD by both criteria [Hodi, F. S., et al 2014]. Additionally, the data suggest that RECIST 1.1 may underestimate the benefit of pembrolizumab in approximately 15% of participants. These findings support the need to apply a modification to RECIST 1.1 that takes into account the unique 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 FDA and the European Medicines Agency (EMA) [Seymour, L., et al 2017]. The unidimensional measurement of target lesions, qualitative assessment of non-target lesions, and response categories are identical to RECIST 1.1, until progression is seen by RECIST 1.1. However, if a participant is clinically stable, additional

imaging may be performed to confirm radiographic progression. iRECIST will be used by Investigators to assess tumor response and progression, and make treatment decisions.

Refer to Section 9.2.1.6 for details on iRECIST.

5.4.1.2 Safety Endpoints

Safety parameters commonly used for evaluating investigational systemic anticancer treatments are included as safety endpoints including, but not limited to, the incidence of, causality, and outcome of AEs/serious adverse events (SAEs); and changes in vital signs and laboratory values. AEs will be assessed as defined by National Cancer Institute (NCI) CTCAE, Version 4.0.

5.4.1.3 Rationale for Patient Reported Outcomes

NOTE: As of Amendment 03, PROs will no longer be collected after the first on-study imaging assessment at Week 9.

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

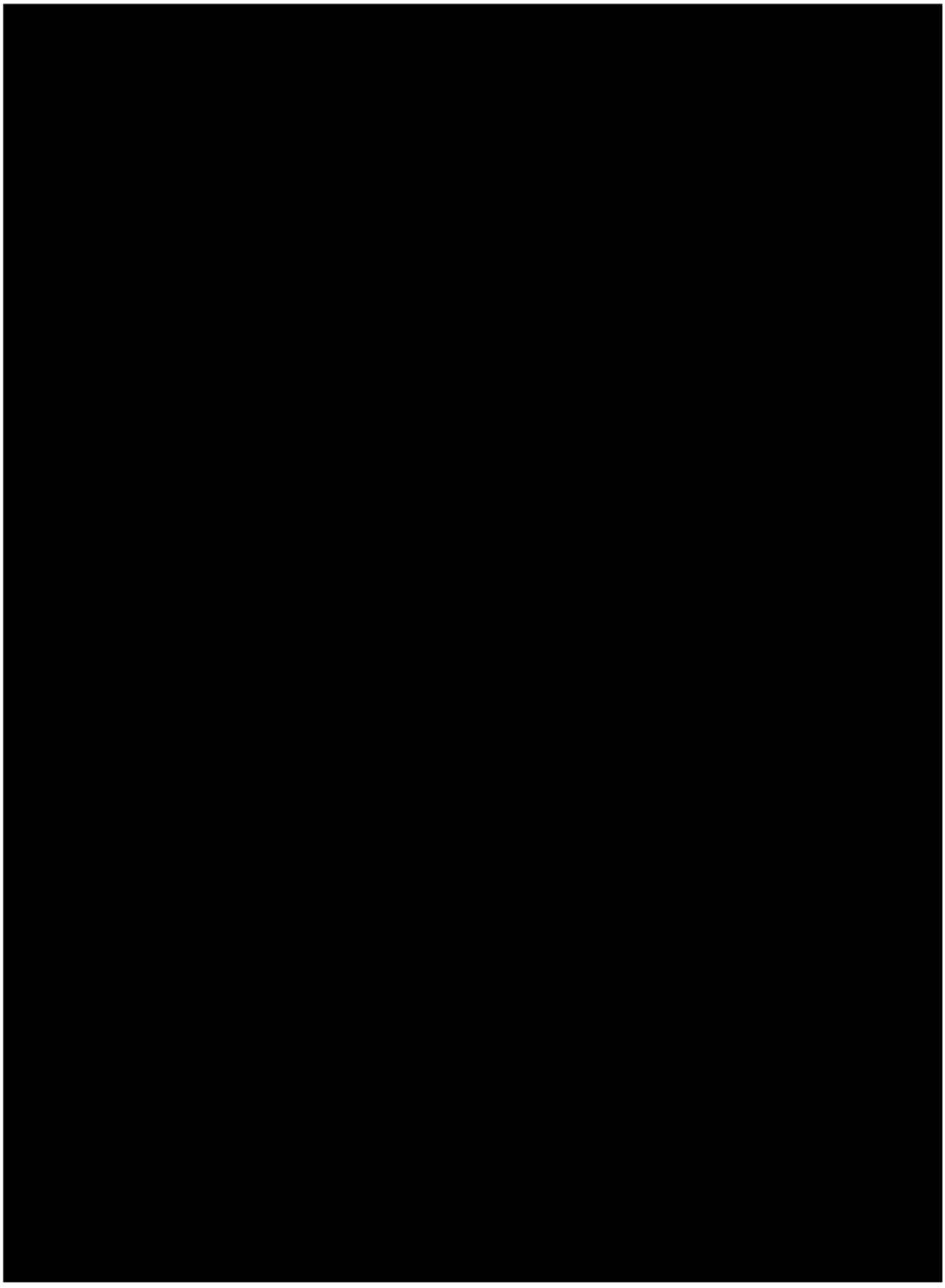
5.4.1.3.1 EORTC QLQ-C30

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

For the global health status/quality of life and function scales, a higher value indicates a better level of function; for symptom scales and items, a higher value indicates increased severity of symptoms. Mean change from baseline in global health status/quality of life scale of the EORTC QLQ-C30 will be evaluated as a tertiary objective.

5.4.1.3.2 EuroQol-5D-5L (EQ-5D-5L)

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



5.4.2 Rationale for the Use of Comparator/Placebo

In a phase 3 trial (KEYNOTE-045) where participants receive either pembrolizumab or investigator's choice second-line chemotherapy following progression on a platinum-containing regimen, there was a statistically significant OS advantage of pembrolizumab over chemotherapy (10.3 vs 7.4 months; HR, 0.70; P< 0.001) in 542 participants (pembrolizumab, n= 270; chemotherapy, n=272) enrolled as of the 18-Jan-2017 data cut-off for a planned survival analysis [Bajorin, D. F., et al 2017]. The 18-month OS rate (95% CI) was 36.1% (30.1%-42.0%) with pembrolizumab vs 20.5% (15.2%-25.8%) with chemotherapy (KM estimate). PFS was not different between arms. ORR was higher with pembrolizumab vs chemotherapy (21.1% vs 11.0%), and median (range) DOR was longer (not reached [1.6+ to 20.7+ month] vs 4.4 months [1.4+ to 20.3]). Responses lasted ≥12 months in 69% of participants treated with pembrolizumab vs 36% in participants treated with chemotherapy. Fewer participants experienced a treatment-related AE with pembrolizumab vs chemotherapy treatment (any grade, 61.3% vs 90.2%; Grade ≥3, 16.5% vs 49.8%).

In this study, pembrolizumab plus epacadostat will be compared to pembrolizumab plus placebo. The use of an epacadostat matching placebo in combination with pembrolizumab will ensure the objectivity of investigator-assessed progression for the pembrolizumab plus epacadostat combination versus pembrolizumab monotherapy, as well as any decisions to interrupt/discontinue therapy.

NOTE: As of Amendment 03, the study will be unblinded after the last participant completes their Week 9 imaging assessment.

5.5 Justification for Dose

5.5.1 Rationale for Dose and Regimen of Pembrolizumab

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

- Clinical data from 8 randomized studies demonstrating flat dose- and exposure- efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W),
- Clinical data showing meaningful improvement in benefit-risk including OS at 200 mg Q3W across multiple indications, and

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

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

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Secondly, a physiologically-based PK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

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

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

The dose for epacadostat for the current study was selected on the basis of having a well-tolerated safety profile as monotherapy and in combination with pembrolizumab, a robust objective response rate (ORR), durable DCRs, as well as providing optimal target inhibition of IDO1 based on nonclinical models. Doses of epacadostat of up to 700 mg BID as monotherapy have been well tolerated.

Doses of 25 mg BID to 300 mg BID of epacadostat in combination with pembrolizumab, nivolumab, durvalumab and atezolizumab are currently being evaluated in several ongoing Phase 2 studies. Doses of pembrolizumab 2 mg/kg and 200 mg flat dose have been studied in the ongoing Phase 1/2 study of pembrolizumab in combination with epacadostat. Reductions in tumor burden were seen in 14 of 19 evaluable participants across doses of 25 mg BID to 100 mg BID in combination with pembrolizumab 2 mg/kg and 200 mg flat dosing [Gangadhar, T. C., et

al 2015]. Objective responses were observed in all tumor types and the majority are durable; this combination has been well tolerated with rates of irAEs that are similar to pembrolizumab monotherapy and low rates of treatment discontinuation due to irAEs [Gangadhar, T. C., et al 2017] [Hamid, O., et al 2017].

[redacted]

[redacted] The overall experience of the epacadostat 100 mg BID dose in combination with pembrolizumab in study KEYNOTE-037 supports the selection of this dose in this Phase 3 study of epacadostat to be combined with IV pembrolizumab 200 mg Q3W.

6. Study Population

Male/Female participants of at least 18 years of age with progression or recurrence of urothelial cancer following one prior platinum-containing chemotherapy regimen for metastatic or inoperable locally advanced disease will be enrolled in this trial.

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

6.1 Inclusion Criteria

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

Type of Participant and Disease Characteristics

1. Have histologically-confirmed diagnosis of UC of the renal pelvis, ureter, bladder, or urethra, that is transitional cell, or mixed transitional/non-transitional (predominantly transitional) cell type.
2. Have progression or recurrence of UC following one prior platinum containing chemotherapy regimen for metastatic or unresectable locally advanced disease. No additional lines of systemic treatment are allowed.
    - Note: A participant who receives a neoadjuvant or adjuvant platinum-containing regimen following cystectomy for localized muscle-invasive UC is acceptable (without further systemic treatment), if recurrence/progression occurs ≤12 months following completion of therapy.
3. Have the presence of at least one measurable lesion by computed tomography (CT) or Magnetic Resonance Imaging (MRI) per RECIST 1.1 as determined by the investigator/ local radiology assessment.

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

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

4. Have provided an archival tumor tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated for PD-L1 analysis. A newly obtained biopsy is strongly preferred but not required if archival tissue is adequate for analysis. If submitting unstained cut slides, freshly cut slides should be submitted to the central laboratory within 14 days from when the slides are cut. Refer to Section 9.8.1 in the protocol for an explanation. PD-L1 status (CPS ≥10 or CPS <10) must be determined by the central laboratory prior to randomization. Participants will be excluded if PD-L1 status cannot be determined.

5. Have resolution of all toxicities and any toxic effect(s) of the most recent prior therapy to Grade 1 or less (except alopecia). Participants with ≤Grade 2 neuropathy are an exception and may enroll.

Demographics

6. Be ≥18 years of age on day of signing informed consent.

7. Eastern Cooperative Oncology Group (ECOG) performance status of 0-1 within 14 days prior to randomization.

Male participants:

8. A male participant must agree to use a contraception as detailed in Appendix 2 of this protocol during the treatment period and for at least 120 days after the last dose of study treatment and refrain from donating sperm during this period.

Female participants:

- 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 (corresponding to time needed to eliminate any study treatments (MK-3475 and epacadostat) after the last dose of study treatment.

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 1). Specimens must be collected within 14 days prior to randomization.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/µL
Platelets	≥100 000/µL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[a]
Renal	
Creatinine OR Measured or calculated[b] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN OR ≥30 mL/min for participant with creatinine levels >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN. If there is no institutional ULN, then direct bilirubin should be < 40% of the total bilirubin. In no case can total bilirubin exceed 3.0 x ULN.
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT) or partial thromboplastin time (PTT)[c]	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT 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.

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

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

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

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

6.2 Exclusion Criteria

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

Medical Conditions

1. Has urothelial carcinoma that is suitable for local therapy with curative intent.

2. Has presence of a gastrointestinal condition that in the opinion of the Investigator may affect drug absorption.
3. Has clinically significant cardiac disease, including unstable angina, acute myocardial infarction within 6 months from Day 1 of study drug administration, or New York Heart Association Class III or IV congestive heart failure. Medically controlled arrhythmia stable on medication is permitted.
4. Has a history or presence of an abnormal electrocardiogram (ECG) that, in the investigator's opinion, is clinically meaningful. Screening corrected QT interval (QTc) interval >480 msec is excluded (corrected by Fridericia formula or Bazett formula). In the event that a single QTc is >480 milliseconds, the participant may enroll if the average QTc for the 3 ECGs is <480 milliseconds.
5. 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. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior the first dose of study treatment.
7. Has a known additional malignancy that is progressing or has required active treatment within the past 3 years.
    - Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (eg, breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded. Participants with low-risk early stage prostate cancer defined as follows are not excluded; Stage T1c or T2a with a Gleason score ≤ 6 and prostatic-specific antigen (PSA) < 10 ng/mL either treated with definitive intent or untreated in active surveillance that has been stable for the past year prior to study allocation.
8. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable, ie, without evidence of progression for at least 4 weeks by repeat imaging, (note that repeat imaging should be performed during the study screening), clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of study treatment.
9. Has severe hypersensitivity ($\geq$Grade 3) to study treatment (pembrolizumab and epacadostat) and/or any of its excipients.
10. Has an active autoimmune disease that has required systemic treatment in past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.

11. Has known history of or is positive for active Hepatitis B (HBsAg reactive) or has active Hepatitis C (HCV RNA). Note: Testing must be performed to determine eligibility.
    - HBV DNA must be undetectable and HBsAg negative at screening visit.
    - 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.
    - Participants who have had definitive treatment for HCV are permitted if HCV RNA undetectable at Screening Visit.
12. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.
13. Has an active infection requiring systemic therapy.
14. Has a known history of human immunodeficiency virus (HIV) infection. HIV testing is not required unless mandated by local health authority.
15. Has known psychiatric or substance abuse disorders that would interfere with cooperating with the requirements of the study.
16. A WOCBP who has a positive urine pregnancy test within 72 hours before randomization (see Appendix 2). 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 subject to start receiving study treatment.

Prior/Concomitant Therapy

17. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti PD-L2 agent, IDO1 inhibitor, or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (eg, CTLA-4, OX 40, CD137), or any other antibody or drug targeting T-cell co-stimulatory pathways in the adjuvant or advanced/metastatic setting.
18. 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.
    - Note: If participant received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting study treatment.
19. Has received prior radiotherapy within 2 weeks of randomization. Participants must have recovered from all radiation-related toxicities (to Grade ≤1), and not require corticosteroids. A 1-week washout is permitted for palliative radiation (≤ 2 weeks of radiotherapy) to non-CNS disease.

20. Has received a live vaccine within 30 days prior to the first dose of study treatment. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, 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.
21. Has received therapy with a MAOI or UGT1A9 inhibitor within 21 days prior to starting treatment, or anticipates requiring one of these prohibited medications during the treatment phase. Examples of medications in these classes are found in Section 7.7.2.
22. Has any history of SS after receiving serotonergic drugs.

Prior/Concurrent Clinical Study Experience

23. 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

24. Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 120 days after the last dose of study treatment.

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.

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

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

6.3.3 Pregnancy

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

6.3.4 Use in Nursing Women

It is unknown whether pembrolizumab or epacadostat is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, 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 treatment(s) to be used in this trial are outlined below in Table 2.

Table 2 Study Treatment(s)

Study Treatment Name	Dosage Formulation	Unit Dose Strength(s)	Dosage Level	Route of Administration	Sourcing
Pembrolizumab	Solution for IV infusion	25 mg/mL	200 mg Q3W Day 1 of each cycle for up to 35 cycles	IV infusion	Provided centrally
Epacadostat or Placebo	Tablet	100 mg	100 mg BID continuously for up to 35 cycles	Oral	Provided centrally
Epacadostat or Placebo	Tablet	25 mg	25 mg or 50 mg* BID continuously for up to 35 cycles	Oral	Provided centrally

* Epacadostat or matching placebo may be reduced to 50 mg BID (Level -1) or 25 mg BID (Level -2) to mitigate immune-related AEs (irAEs), if indicated in Table 3.

BID=twice daily; IV=intravenous; Q3W=every 3 weeks.

All placebos were created by the Sponsor to match the active product.

All supplies indicated in Table 2 will be provided per the 'Sourcing' column depending upon local country operational requirements. Every attempt should be made to source these supplies from a single lot/batch number.

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

As of Amendment 03, participants who continue study treatment after unblinding will no longer be dispensed epacadostat placebo.

7.2 Dose Modification (Escalation/Titration/Other)

7.2.1 Dose Modification for Immune-related AEs

Dose modification and toxicity management for immune-related AEs associated with pembrolizumab and epacadostat or matching placebo should be managed as follows.

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

Table 3 summarizes the irAE dose modification actions for pembrolizumab and epacadostat/matching placebo. Of note, participants who require dose reduction of epacadostat/matching placebo due to AEs will remain at the lower dose, summarized in Table 4. Re-escalation of epacadostat or matching placebo is not permitted.

In cases where pembrolizumab dosing is held, dosing for epacadostat/matching placebo must also be held until pembrolizumab is resumed. Participants are allowed, however, to receive pembrolizumab monotherapy at the Investigator's discretion upon improvement of the irAE to Grade 0 or 1, unless discontinuation of both study treatments is specified in Table 3 (eg, if the toxicity was considered related to the combination therapy and not pembrolizumab monotherapy).

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

Table 3 Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab or Epacadostat/Matching Placebo

Immune-related AEs	Toxicity Grade or Conditions (CTCAEv4.0)	Study Medication	Action Taken with Study Medication	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 or matching placebo	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 or matching placebo	Permanently discontinue		
Diarrhea / colitis	Grade 2 or 3	Pembrolizumab	Withhold until Grade 0-1	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and
		Epacadostat or matching placebo	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 or matching placebo	Permanently discontinue		

Immune-related AEs	Toxicity Grade or Conditions (CTCAEv4.0)	Study Medication	Action Taken with Study Medication	irAE Management with Corticosteroid and/or Other Therapies	Monitor and Follow-up
					electrolytes should be substituted via IV infusion.
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 or matching placebo	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 or matching placebo	Permanently discontinue		
Type 1 diabetes mellitus (T1DM) or Hyperglycemia[a]	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 or matching placebo	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 (CTCAEv4.0)	Study Medication	Action Taken with Study Medication	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 or matching placebo	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[b]		
		Epacadostat or matching placebo	Withhold until Grade 0- 1 or permanently discontinue[b] Once resolved to Grade 0-1, may restart: Related: Reduce by 1 dose level. Not Related: Same dose level.		
Hyperthyroidism[a]	Grade 2	Pembrolizumab	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
		Epacadostat or matching placebo	Continue		
	Grade 3 or 4	Pembrolizumab	Withhold until Grade 0- 1 or permanently discontinue[b]		
		Epacadostat or matching placebo	Withhold until Grade 0- 1 or permanently discontinue[b]		

Immune-related AEs	Toxicity Grade or Conditions (CTCAEv4.0)	Study Medication	Action Taken with Study Medication	irAE Management with Corticosteroid and/or Other Therapies	Monitor and Follow-up
			Once resolved to Grade 0-1, may restart: Related: Reduce by 1 dose level. Not Related: Same dose level.		
Hypothyroidism[a]	Grade 2-4	Pembrolizumab	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
		Epacadostat or matching placebo	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 or matching placebo	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 or matching placebo	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 or matching placebo	Withhold until Grade 0		
	Grade 3 or 4	Pembrolizumab	Permanently discontinue		
		Epacadostat or matching placebo	Permanently discontinue		

Immune-related AEs	Toxicity Grade or Conditions (CTCAEv4.0)	Study Medication	Action Taken with Study Medication	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 or matching placebo	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.	• If toxicity does not resolve within 12 weeks of last dose, or cannot taper below 10 mg or less of prednisone or equivalent within 12 weeks, must permanently discontinue. • 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 or matching placebo	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	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper.	
		Epacadostat or matching placebo	Permanently discontinue		
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
		Epacadostat or matching placebo	May continue treatment with MSD Clinical Director approval		

Immune-related AEs	Toxicity Grade or Conditions (CTCAEv4.0)	Study Medication	Action Taken with Study Medication	irAE Management with Corticosteroid and/or Other Therapies	Monitor and Follow-up
	Grade 4	Pembrolizumab	Withhold until toxicity resolves to Grade 0-1		permanently discontinue unless approved by the medical monitor to continue. • If Grade 4 lipase/amylase elevation is asymptomatic and abdominal imaging suggests no pathology, study drug administration dosing may continue with medical monitor approval.
		Epacadostat or matching placebo	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.		
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 or matching placebo	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: Gullain-Barre Syndrome, encephalitis		
		Epacadostat or matching placebo	Withhold until Grade 0-1 Once resolved to Grade 0-1, may restart: Related: Reduce by 1 dose level.		

Immune-related AEs	Toxicity Grade or Conditions (CTCAEv4.0)	Study Medication	Action Taken with Study Medication	irAE Management with Corticosteroid and/or Other Therapies	Monitor and Follow-up
			Not Related: Same dose level. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Pembrolizumab	Permanently discontinue		
		Epacadostat or matching placebo	Permanently discontinue		

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/placebo have been withheld, pembrolizumab and epacadostat/placebo can be resumed after AE has been reduced to Grade 1 or 0, and corticosteroid has been tapered. Pembrolizumab and epacadostat/placebo 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 the study medical monitor.

NOTES:

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

b. Withhold OR permanently discontinue pembrolizumab + epacadostat/placebo at the discretion of the Investigator.

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 medication

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; DKA = diabetic ketoacidosis; IV = intravenous; irAE = infusion-related adverse events; T1DM = Type 1 diabetes mellitus

When indicated by Table 3 to mitigate irAEs, the dose of epacadostat or matching placebo must be reduced using the dosing levels outlined in Table 4. Once reduced, re-escalation of epacadostat or matching placebo is not permitted.

Table 4 Dose Level Adjustments for Epacadostat or Matching Placebo

Dose of Epacadostat or Matching Placebo	Dose Level -1	Dose Level -2
	First Reduction of Epacadostat or Placebo	Second Reduction of Epacadostat or Placebo
100 mg BID	50 mg BID	25 mg BID

BID= twice daily.

Dose Level -2 is the lowest dose of epacadostat in this protocol. Refer to the general instructions at the bottom of Table 3 for guidance regarding the re-occurrence of an AE when a participant has had their epacadostat dose reduced to dose level -2.

7.2.1.1 Procedures for Participants Exhibiting Serotonin Syndrome (SS)

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 use of MAOIs, meperidine, linezolid, or methylene blue; all of these agents are prohibited during the study.

Selective serotonin reuptake inhibitors (SSRIs) and serotonin/norepinephrine reuptake inhibitors (SNRIs) are permitted in the study. Serotonin syndrome usually manifests with autonomic changes, mental status changes, and neurological findings. These mild, moderate, and severe signs and symptoms of SS (summarized in Table 5) should be evaluated in the context of possible comorbid conditions as well.

The following procedures will be implemented if participant exhibit the signs/symptoms of SS (described in Table 5), 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 in the study, restart study treatment after the SSRI or SNRI has been discontinued, no sooner than after 5 half-lives have elapsed for the specific SSRI or SNRI in question, and after resolution of signs/symptoms of SS. The SSRI or SNRI dosing MAY NOT be restarted.
- If participant chooses to withdraw from the study, or must restart treatment with SSRI or SNRI, the participant should be scheduled for a follow-up visit. Treatment with SSRI or SNRI may be initiated 2 weeks after resolution of signs and symptoms of 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/placebo treatment should be permanently discontinued.

Table 5 Signs and Symptoms of Serotonin Syndrome

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

Source: [Boyer, E. W. 2005]

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

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

modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 6.

Table 6 Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., 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 (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study treatment**	Participant may be premedicated 1.5 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 (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further study treatment.**	No subsequent dosing

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

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

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous; NCI = National Cancer Institute; NSAIDs = nonsteroidal anti-inflammatory drugs; PO = oral.

7.2.1.3 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 therapy 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.

7.2.2 Second Course Phase (Retreatment)

NOTE: As of Amendment 03, disease assessment will be performed by the investigator per local SoC guidelines; placebo will not be administered after unblinding. This section has been updated accordingly.

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

Either

- Stopped initial treatment with study treatment after attaining CR evaluated by the local investigator based on RECIST 1.1, and
  - Was treated with at least 8 cycles of study treatment before discontinuing treatment, and
  - Received at least 2 treatments with pembrolizumab beyond the date when the initial CR was declared

OR

- Had SD, PR, or CR and stopped study treatment after completion of 35 cycles (approximately 2 years) of study treatment

AND

- Experienced radiographic disease progression verified by Investigator assessment based on RECIST 1.1 after stopping initial treatment, and
  - 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 will be retreated with the same combination, and epacadostat dose level as when they last received the combination of pembrolizumab plus epacadostat or pembrolizumab monotherapy in the initial treatment phase, unless a study-wide decision is otherwise announced by the DMC or Sponsor via an administrative memo. Note: If

epacadostat was discontinued it should not be restarted. Treatment will be administered for up to an additional 17 cycles (approximately 1 year) using the Second Course Phase SoA in Section 2.2.

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

7.3 Method of Treatment Assignment

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

7.3.1 Stratification

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

1. Bellmunt risk score of 0 vs 1 vs ≥2.

   The Bellmunt risk score for each participant is calculated by the presence of the total number of the following risk factors (each counts a score of 1) at baseline:

   - ECOG PS ≥ 1
   - Presence of liver metastases
   - Hemoglobin level < 10 g/dL
   - Time from last chemotherapy dose (<3 months [Note: 90 days will be used] from randomization)

2. PD-L1 expression from tumor tissue samples, based on CPS ≥10 vs CPS <10 per IHC assay, as assessed by the designated central laboratory

7.4 Blinding

The study is double-blinded using epacadostat and matching placebo, such that the participant, the study site personnel, and the Sponsor and MSD or designee do not know the identity of the treatment arm.

Note: As of Amendment 03, the study will be unblinded after the last participant completes the Week 9 imaging assessment for efficacy analysis. After unblinding, for participants who are benefiting from study treatment and continue study treatment after discussion with the investigator, the participant, study site personnel, Sponsor and MSD or designee will be informed of the study treatment they receive (eg, pembrolizumab or pembrolizumab in combination with epacadostat).

Pembrolizumab, which will be dosed to all participants in both treatment arms, will not be blinded.

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

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 and matching placebo are oral tablets and do not require preparation.

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

7.5.2 Handling, Storage and Accountability

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

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

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

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

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

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

7.6 Treatment Compliance

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

7.6.1 Administration and Compliance of Pembrolizumab

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

Pembrolizumab will be administered on an out-patient basis. Instructions for preparing and administering pembrolizumab are provided in the Pharmacy Manual.

7.6.2 Administration and Compliance of Epacadostat or Matching Placebo

Participants will take their dose of epacadostat or matching placebo 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. If the participant vomits after taking a tablet, the dose should not be re-administered until the next scheduled dose. Participants will self-administer epacadostat or matching placebo except on Cycle 1 Day 1 (C1D1), and Cycle 2 Day 1 (C2D1), when the morning dose will be given at the study site clinic prior to the pembrolizumab infusion.

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

7.7.1 Acceptable Concomitant Medications

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

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

All concomitant medications received within 28 days before the first dose of study treatment through the Safety Follow-up Visit should be recorded. After the Safety Follow-up Visit, record all medications taken for SAEs and ECIs as defined in Section 9.3. 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 as defined in Section 9.3.

7.7.2 Prohibited Concomitant Medications

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 (or placebo) 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:

1. Investigational agents other than pembrolizumab and epacadostat.
2. Any anti-cancer medications, including chemotherapy or biologic therapy other than the study treatments.
3. Immunotherapy not specified in this protocol.
4. Prolonged therapy with systemic glucocorticoids (>7 days) for any purpose other than to modulate symptoms from an AE, SAE, or ECI or for use as a pre-medication for chemotherapy or in participants with a known history of an IV contrast allergy administered as part of CT radiography. Brief, limited use of systemic corticosteroids (≤7 days) are permitted where such use is considered SOC (eg, for COPD exacerbation).

   Replacement doses of steroids (for example, prednisone 5 to 7.5 mg daily) are permitted while on study, as is the use of local steroids.
5. Radiation therapy or surgery:

   Note: Radiation therapy or surgery to a symptomatic solitary lesion is allowed. No pembrolizumab infusions are permitted during radiation therapy or procedure and epacadostat or matching placebo should be stopped the day treatment begins. Study treatment may be resumed as early as 1 week after treatment if the participant's symptoms are improving and not requiring corticosteroids for management. MSD consultation is required for study treatment restart after radiation therapy or surgery. If study treatment is not resumed within 12 weeks of completing treatment (radiation therapy or surgery), the participant should discontinue study treatment permanently.
6. Live attenuated vaccine within 30 days before the first dose of study treatment and while participating in the study.
   - Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines are live attenuated vaccines and are not allowed.
7. 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 or matching placebo has been taken.

- Including, but not limited to, hydrazines (example phenelzine), meperidine, caroxazone, linezolid, echinopsidine, methylene blue, furazolidon, tranylcypromine, brofaromine, metralindole, minaprine, moclobemide, pirlindole, toloxatone, lazbemide, pargyline, rasagiline, selegiline.

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

Note: Ketoconazole 2% topical cream is allowed.

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

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

All concomitant medications received within 28 days prior to the first dose of trial treatment and up to 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered 30 days after the last dose of trial treatment should be recorded for SAEs and events of clinical interest (ECIs) as defined in Section 9.3.7

7.7.3 Restricted Concomitant Medications

Use of coumarin-based anticoagulants (eg, warfarin) with epacadostat is discouraged. Low-dose warfarin (1 mg) is acceptable; however, other higher doses are discouraged. If an alternative to coumarin-based anticoagulants cannot be used, the international normalized ratio (INR) should be monitored closely (weekly for the first 4 weeks after initiation of therapy and upon discontinuation of epacadostat or matching placebo).

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 along with the dose modification guidelines in Section 7.2, Table 3. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the Investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab or epacadostat, the Investigator does not need to follow the treatment guidance. Refer to Table 3 in Section 7.2.1 for guidelines regarding dose modification and supportive care.

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

7.8 Treatment After the End of the Study

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

7.9 Clinical Supplies Disclosure

The emergency unblinding call center will use the treatment/randomization schedule for the trial to unblind participants and to unmask study treatment identity. The emergency unblinding call center should only be used in cases of emergency (see Section 9.1.11). In the event that the emergency unblinding call center is not available for a given site in this trial, the central electronic treatment allocation/randomization system (IVRS/IWRS) should be used in order to unblind participants and to unmask study treatment identity. MSD will not provide random code/disclosure envelopes or lists with the clinical supplies.

See Section 9.1.10, Participant Blinding/Unblinding, for a description of the method of unblinding a participant during the trial, should such action be warranted.

7.10 Standard Policies

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

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

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 - SoA and Section 9.9.5 – 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.
- 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.
- Participant chooses to discontinue study treatment and remains in the study to be followed for progression and survival.
- Participant has received 35 cycles (approximately 2 years) of treatment with pembrolizumab.
- The study is terminated by the sponsor.
- The study is terminated by the local health authority, IRB, or IEC.
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment.

  Note: Surgical excision of non-urothelial cancer is allowed. Refer to Section 7.7 – Concomitant Therapy for radiation and surgery allowed for urothelial cancer.
- The occurrence of unacceptable adverse experiences not caused by an underlying malignancy as described in Section 7.2.1.
- Persistent AE requiring a delay of therapy for more than 12 weeks unless a greater delay has been approved by MSD.
- Recurrent Grade 2 pneumonitis.

A participant **may** be discontinued from study treatment 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.

Participants may be allowed to begin study treatment again if deemed medically appropriate, following consultation with MSD. Following unblinding (necessary only in true medical emergencies) participants may be treated with pembrolizumab monotherapy, treatment with epacadostat/placebo is not allowed.

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 – Withdrawal/Discontinuation. 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

NOTE: As of Amendment 03, this section is no longer applicable. There will be no additional efforts to contact participants who are lost to follow-up.

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

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, phone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.
- Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The amount of missing data for the participant will be managed via the pre-specified data handling and analysis guidelines.

9. Study Assessments and Procedures

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

9.1.1.1 General Informed Consent

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

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

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

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

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

9.1.2 Inclusion/Exclusion Criteria

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

9.1.3 Participant Identification Card

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

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

9.1.4 Serotonin Syndrome Information Card

On C1D1, participants will also be given a SS information card listing signs and symptoms of SS. This information card also instructs participants to seek immediate medical care if any of these symptoms are observed.

9.1.5 Medical History

A medical history will be obtained by the investigator or qualified designee. The medical history will collect all active conditions and any condition diagnosed within the prior 10 years that the Investigator considers to be clinically significant. Details regarding the disease for which the participant has enrolled in this study will be recorded separately and not listed as medical history.

9.1.6 Prior and Concomitant Medications Review

9.1.6.1 Prior Medications

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

9.1.6.2 Concomitant Medications

The Investigator or qualified designee will record medication, if any, taken by the participant during the study through the Safety Follow-up visit. In addition, new medications started during the Second Course Phase through the Second Course Safety Follow-up visit should be recorded.

9.1.7 Assignment of Screening Number

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

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

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

9.1.8 Assignment of Treatment/Randomization Number

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

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

9.1.9 Treatment Administration

Administration of pembrolizumab will be witnessed by the investigator and/or study staff. Administration of epacadostat or matching placebo will be witnessed by the investigator and/or study staff for the morning dose on C1D1 and C2D1 (and Second Course C1D1 if applicable), but otherwise self-administered.

Study treatment should begin within 3 days of and as close as possible to the date on which the participant is allocated/assigned.

9.1.9.1 Timing of Dose Administration

9.1.9.1.1 Timing of Dose Administration of Pembrolizumab

Study treatment with pembrolizumab should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed in the SoA (Section 2). All study treatments will be administered on an outpatient basis.

Study treatment of pembrolizumab may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons except for C1D1, where window is + 3 days from randomization.

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

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

9.1.9.1.2 Timing of Dose Administration of Epacadostat

Epacadostat/matching placebo will be supplied as 100 mg tablets packaged in high-density polyethylene bottles. All tablet excipients comply with the requirements of the applicable compendial monographs (Ph Eur, USP/NF; refer to IB). Epacadostat/matching placebo 25 mg tablets are also available. Bottles of tablets should be stored at room temperature (15°C to 30°C/ 59°F to 86°F).

Participants will take their dose of epacadostat or matching placebo in the morning and evening, approximately 12 hours apart without regard to food. Participants will self-administer epacadostat or matching placebo except on C1D1 and C2D1, when the morning dose will be given at the study site clinic prior to the infusion of pembrolizumab. [redacted]

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. If the participant vomits after taking a tablet, the dose should not be re-administered until the next scheduled dose.

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.
- If a dose of epacadostat/matching placebo is missed by more than 4 hours, that dose should be skipped and the next scheduled dose should be administered at the usual time.

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

9.1.11 Participant Blinding/Unblinding

Participants whose treatment assignment has been unblinded by the investigator/delegate and/or non-study treating physician should continue to be monitored in the trial.

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

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

In the event that unblinding has occurred, the circumstances around the unblinding (eg, date, reason and person performing the unblinding) must be documented promptly, and the MSD Clinical Director notified as soon as possible. Once an emergency unblinding has taken place, the principal investigator, site personnel, and Sponsor personnel may be unblinded so that the appropriate follow-up medical care can be provided to the participant.

As of Amendment 03, the study will be unblinded when the last participant completes the Week 9 imaging assessment for efficacy analysis. At the time of unblinding every effort will be made to have all pending data entered into the eCRFs before the site is unblinded to the participant's treatment assignment. The site should ensure imaging data is entered in the

database prior to unblinding. Please refer to the CRF guidelines and contact the site monitor for operational details.

9.1.12 Calibration of Equipment

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

9.2 Efficacy Assessments

9.2.1 Tumor Imaging and Assessment of Disease

Note: As of Amendment 03, central review of imaging and iRECIST is no longer applicable. This section has been updated accordingly.

Tumor imaging is strongly preferred to be acquired by CT; imaging should include the chest, abdomen, and pelvis. For the abdomen and pelvis, contrast-enhanced MRI may be used when CT with iodinated contrast is contraindicated, or when local practice mandates it. MRI is the strongly preferred modality for imaging of 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.

All participants will have a baseline bone scan performed at screening. For participants with new symptoms suggestive of osseous metastasis, a bone scan should be obtained. Additionally, plain X-ray evaluation should be obtained for symptomatic sites with negative bone scan evaluations.

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

Treatment should continue until PD has been determined by Investigator assessed disease progression by RECIST 1.1.

9.2.1.1 Initial Tumor Imaging

Note: As of Amendment 03, central review of imaging is no longer applicable. This section 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.

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 03, central review of images and iRECIST are no longer applicable. After the first on-study imaging assessment at Week 9, 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 should be performed at 9 weeks (63 days ± 7 days) from the date of randomization. No further imaging is mandated; any further imaging for disease assessments will be performed by site investigator/radiology assessment as per local SoC guidelines; only the date of scans performed as per SoC needs to be documented in the eCRF. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. If the bone scan is positive at baseline, bone scans should be performed as per local SoC guidelines; the results will not be monitored, only the date of scans performed as per SoC needs to be documented in the eCRF.

9.2.1.3 End of Treatment and Follow-up Tumor Imaging

Note: As of Amendment 03, there is no protocol specified imaging after the Week 9 assessment for efficacy analysis. This section has been updated accordingly.

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

9.2.1.4 Second Course Phase Tumor Imaging

Note: As of Amendment 03, the text in this section is no longer applicable; disease assessment will be performed by the investigator per local SoC guidelines; results will not be collected, only the date of scans performed as per SoC needs to be documented in the eCRF.

Tumor imaging (including bone scan) must be performed within 28 days prior to restarting treatment with pembrolizumab + epacadostat/matching placebo. Local reading (Investigator assessment with site radiology reading) will be used to determine eligibility. Second Course imaging can be submitted to the central imaging vendor for quality control, storage, and possible retrospective review.

The first on-study imaging assessment should be performed at 12 weeks (84 days ± 7 days) after randomization. Subsequent tumor imaging should be performed every 12 weeks (84 days ± 7 days) or more frequently if clinically indicated.

Per RECIST 1.1 (Section 9.2.1.5) 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 than4 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 a new anticancer treatment, withdrawal of consent, death, or notification by the 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 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. For participants who discontinue study treatment due to documented disease progression, this is the final required tumor imaging.

For participants who discontinue Second Course study treatment without documented disease progression, every effort should be made to continue monitoring disease status by radiologic imaging every 12 weeks (84 days ± 7 days) until either the start of a new anticancer treatment, disease progression, death, or the end of the study, whichever occurs first.

9.2.1.5 RECIST 1.1 Assessment of Disease

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

9.2.1.6 iRECIST Assessment of Disease

Note: As of Amendment 03, this section is no longer applicable; iRECIST data will no longer be collected. Participants with radiographic disease progression as determined by RECIST 1.1 will discontinue from the study and be followed for safety monitoring, as detailed in Section 9.3; no confirmatory scans are required.

iRECIST is based on RECIST 1.1, but adapted to account for the unique tumor response seen with immunotherapeutic 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 7. 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. This 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 site-assessed first radiologic evidence of PD, and is not required to have repeat tumor imaging for confirmation of PD by iRECIST.

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

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

If a participant has confirmed radiographic progression (iCPD) as defined in Appendix 7, 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 the Sponsor. 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 iRECIST process is provided in Appendix 7, with additional details in the iRECIST publication [Seymour, L., et al 2017]. A summary of imaging and treatment requirements after first radiologic evidence of progression is provided in Table 7.

Table 7 Imaging and Treatment after First Radiologic Evidence of Progressive Disease

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD by RECIST 1.1 which has been verified by Investigator	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 imaging should occur according to the regular imaging schedule

iCPD = iRECIST confirmed progressive disease; iCR = iRECIST complete response; iRECIST = Modified Response Evaluation Criteria in Solid Tumors 1.1 for Immune-based Therapeutics; iSD = iRECIST stable disease; iUPD = iRECIST unconfirmed progressive disease; PD = progressive disease; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors 1.1.

Note: If progression has been verified by the Investigator, further management by the site should be based on iRECIST. Any further imaging should still be submitted to the central imaging vendor, for possible retrospective review.

9.2.2 Patient Reported Outcomes

Note: As of Amendment 03, PROs will no longer be collected after the first on-study imaging assessment at Week 9.

The EuroQoL EQ-5D and EORTC QLQ-C30 questionnaires will be administered by trained site personnel and completed electronically by participants in the following order: EuroQoL EQ-5D first, then EORTC QLQ-C30. The questionnaires should be administered prior to dosing at Cycle 1-4, then every 3rd cycle through 12 months (ie, Cycles 7, 10, 13, 16), then every 4th cycle after 12 months until EOT (ie, Cycles 20, 24, 28, 32), at Discontinuation, and at the 30-day Safety Follow-up Visit.

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

9.2.3 Survival Follow-up

NOTE: As of Amendment 03, 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.

Once a participant experiences Investigator-confirmed PD or starts a new anti-cancer therapy, the participant moves into the Survival Follow-Up Phase and should be contacted by telephone approximately every 12 weeks ± 7 days to assess survival status until death, withdrawal of consent, or the end of the study, whichever occurs first. Post-study treatments and the participant's response to them will also be collected.

If a participant withdraws consent for treatment and/or imaging, the participant should still be followed for survival unless they specifically withdraw their consent for survival follow-up. Participants should be encouraged to remain in the Survival Follow-Up Phase and sites should ensure the participant understands the non-invasive nature of this phase.

MSD will request survival status to be assessed at additional time points during the course of the study. For example, survival status may be requested prior to an external DMC safety review, efficacy interim analyses, and final analysis. All participants who are in the Follow-Up and Survival Follow-Up Phases and not known to have died prior to the request for these additional survival status time points will be contacted at that time.

9.3 Adverse Events (AE), Serious Adverse Events (SAE) 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 cancer under study is not considered an adverse event as described in 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 AE, SAEs and other reportable safety events for outcome according to Section 9.3.3.

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

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

All AEs, SAEs and other reportable safety events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event causes 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.
- All AEs meeting serious criteria, from the time of treatment allocation/randomization through 90 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy, whichever is earlier must be reported by the investigator.
- All pregnancies and exposure during breastfeeding, from the time of treatment allocation/randomization through 120 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy must be reported by the investigator.
- Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately to MSD if the event is considered to be drug-related.

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

All initial and follow-up AEs, SAEs and other reportable safety events will be recorded and reported to MSD or designee within the timeframes as indicated in Table 8.

Table 8 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 AE, SAE and other reportable safety events including pregnancy and exposure during breastfeeding, ECI, Cancer and Overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). In addition, the investigator will make every attempt to follow all non-serious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 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 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

Progression of cancer under study is not considered a reportable event.

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

9.3.6 Pregnancy and Exposure During Breastfeeding

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

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

9.3.7 Events of Clinical Interest (ECI)

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

Events of clinical interest for this trial include:

1. an overdose of study treatment, as defined in Section 9.4 – Treatment of Overdose, that is not associated with clinical symptoms or abnormal laboratory results.
2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

   *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).
3. serotonin syndrome. The signs and symptoms of serotonin syndrome are described in Section 7.2.1.1.

ECIs that occur after the consent form is signed but before treatment randomization must be reported by the Investigator to MSD if the event caused the participant to be excluded from the study or is the result of a protocol-specified intervention.

All ECIs that occur from the time of treatment randomization through 90 days following cessation of study treatment, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator to MSD within 24 hours of learning of the event.

9.4 Treatment of Overdose

For this study, an overdose is defined as any dose higher than ≥1000 mg (≥5 times the dose) of pembrolizumab or ≥1000 mg of epacadostat.

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

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

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

All reports of overdose with and without an AE must be reported by the investigator within 24 hours to MSD either by electronic media or paper. Electronic reporting procedures can be found in the electronic data capture (EDC) 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 trial 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 Study Procedures Manual.

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

9.5.1 Physical Examinations

9.5.1.1 Full Physical Examination

The Investigator or clinical designee will perform a full physical exam per institutional standard during the screening period, and discontinuation visit. Clinically significant abnormal findings should be recorded as medical history. Additional full physical exams should be performed as specified in the SoA (Section 2). After the first dose of study treatment new clinically significant abnormal findings should be recorded as AEs. A full physical should also be performed at the discontinuation visit and, if applicable, at the Second Course Cycle 1, and Second Course discontinuation visit.

9.5.1.2 Directed Physical Examination

For cycles that do not require a full physical exam per the SoA (Section 2), the Investigator or qualified designee will perform a directed physical exam as clinically indicated prior to dosing on Day 1 of each treatment cycle. 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 and prior to the administration of each dose of study treatment as specified in the SoA. Vital signs include

temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at Screening Visit only.

9.5.3 Electrocardiograms

Baseline ECGs will be obtained at screening, with additional ECGs obtained at EOT, and as clinically indicated for all participants. At select centers only, additional ECGs will also be obtained at C1D1 predose and approximately 2 hours (± 15 minutes) after the first dose of epacadostat, and C2D1 predose and approximately 2 hours (± 15 minutes) after administration of epacadostat. The ECG measurement should always be performed prior to the PK sample blood draw if both are scheduled at the same nominal planned time point. Clinically significant abnormal findings prior to signing consent should be recorded as medical history. Clinically significant abnormal findings after signing consent should be recorded as an AE.

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

9.5.4 Performance Assessments

9.5.4.1 Eastern Cooperative Oncology Group (ECOG) Performance Status

The Investigator or qualified designee will assess ECOG PS at screening (within 14 days prior to randomization); on Day 1 of each cycle, prior to the administration of each dose of pembrolizumab; and at EOT as specified in the SoA. The ECOG PS scale is described in Appendix 5.

9.5.5 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 CRF (eg, SLAB).
- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study treatment, every

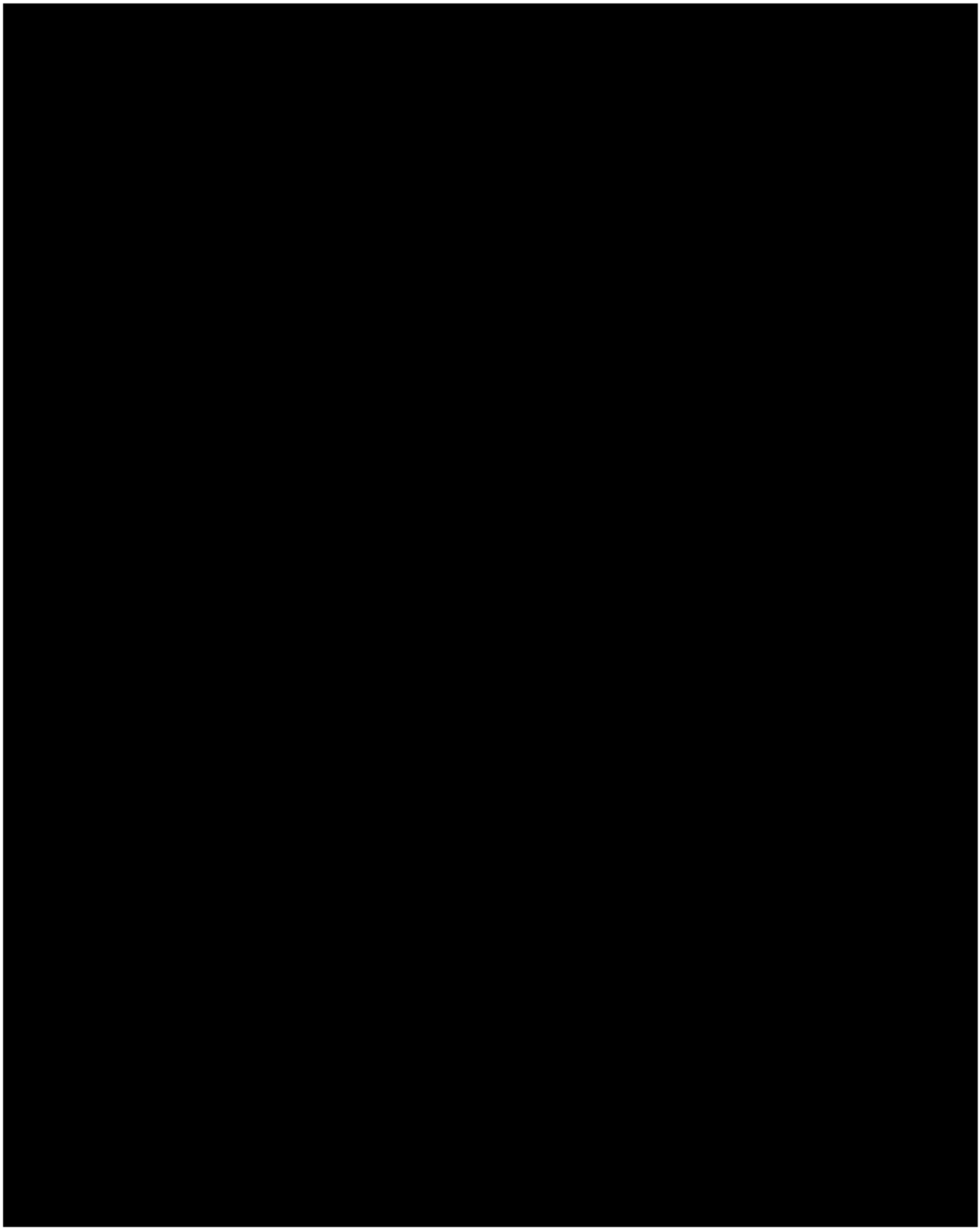
attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

9.5.5.1 Laboratory Safety Evaluations (Hematology, Chemistry, Urinalysis)

Laboratory tests for hematology, chemistry, and urinalysis are specified in Appendix 4. Refer to SoA for the timing of laboratory assessments.

9.5.5.2 Pregnancy Test

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



9.9 Visit Requirements

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

9.9.1 Screening

After a screening phase of approximately 42 days prior to treatment randomization, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 6.0. Screening procedures may be repeated after consultation with MSD.

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

procedures are to be completed within approximately 42 days prior to randomization except for the following:

- 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 randomization.
- Evaluation of ECOG is to be performed within 14 days prior to 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).
- Initial tumor imaging must be performed within 28 days prior to randomization.

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

9.9.2 Treatment Period

Visit requirements are outlined in the SoA (Section 2.0). Specific procedure-related details are provided in Section 9.9.

Treatment with pembrolizumab will occur every 21 days (1 cycle) for a maximum of 35 cycles (approximately 2 years).

Epacadostat or matching placebo will be dosed BID (approximately every 12 hours [Q12H]) during the treatment phase, until C35D21. Treatment will continue until C35D21, unless a discontinuation criterion is met (Section 8.1)

9.9.3 Second Course Phase (Retreatment)

Visit requirements for the Second Course Phase (Retreatment) are outlined in the Second Course Phase (Retreatment) SoA (Section 2.0).

9.9.4 Discontinuation Visit

If a decision is made that the participant will permanently discontinue study treatment, the Discontinuation Visit should be conducted at EOT. If the Discontinuation Visit coincides with a regular study visit, the EOT evaluations will supersede those of that scheduled visit. The participant should be encouraged to return for the Safety Follow-up visit.

9.9.5 Discontinued Participants Continuing to be Monitored in the Study

9.9.5.1 Safety Follow-Up

NOTE: As of Amendment 03, 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 occur 30 days (+ 7 days) after the last dose of study treatment or before the initiation of a new anticancer treatment, whichever comes first. Reasonable efforts should be made to have the participant return for the Safety Follow-up Visit and report any AEs that may occur prior to initiating new anticancer therapy. 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 are eligible for retreatment with the combination therapy or pembrolizumab (as described in Section 7.2.2) may have up to 2 Safety Follow-up visits, 1 after the treatment period and 1 after the Second Course Phase (Retreatment).

9.9.5.2 Follow-Up Visits

NOTE: As of Amendment 03, this section is no longer applicable. Participants currently in post-treatment follow-up are considered to have completed the study once they have attended the Safety Follow-up Visit; assessment and recording of AEs will be performed as per Section 9.3.

Participants who discontinue study treatment for a reason other than disease progression will move into follow-up and should be assessed every 9 weeks (63 ± 7 days) for the first 12 months (54 weeks) by radiologic imaging to monitor disease status then every 12 weeks (84 days ± 7 days) thereafter. The imaging assessment schedule continues if a participant discontinues treatment; if a participant has started the 12 week imaging, they will continue to be assessed every 12 weeks. Every effort should be made to collect information regarding disease status until the start of new antineoplastic therapy, disease progression, death, and end of the study, or if the participant begins retreatment as detailed in Section 7.2.2. Information regarding post-study antineoplastic treatment will be collected if new treatment is initiated.

Participants who are eligible to receive retreatment according to the criteria in Section 7.2.2 will move from the follow-up phase to the Second Course Phase (Retreatment) when they experience disease progression.

9.9.5.3 Survival Follow-up

NOTE: As of Amendment 03, 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 be performed as per Section 9.3.

Participants who experience disease progression by site assessment or start a new anti-cancer therapy will move into the Survival Follow-up Phase. Participants should be contacted by telephone approximately every 12 weeks (± 7 days) to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

9.9.5.4 Survival Status

NOTE: As of Amendment 03, 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 the MSD. For example, updated survival status may be requested prior to but not limited to an external Data Monitoring Committee (eDMC) review, interim and/or final analysis. Upon MSD notification, all participants who do not/will not have a scheduled study visit or study contact during the MSD defined time period will be contacted for their survival status (excluding participants that have a previously recorded death event in the collection tool).

9.9.5.5 Unscheduled Visits

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

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 Harmonization Guideline E9). [redacted]

10.1 Statistical Analysis Plan Summary

NOTE: As of Amendment 03, this section has been updated.

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

Study Design Overview	This is a randomized, double-blind, multicenter Phase III trial to evaluate the efficacy and safety of pembrolizumab plus epacadostat compared to pembrolizumab plus placebo in participants with UC of the renal pelvis, ureter, bladder, or urethra that is transitional cell type or mixed histology (predominantly transitional cell) type (KEYNOTE-698/ECHO-303).
Treatment Assignment	Approximately 85 participants will be randomized 1:1 to receive pembrolizumab + epacadostat or pembrolizumab + placebo. Stratification factors are provided in Section 7.3.1.
Analysis Populations	Efficacy: Intention-to-Treat (ITT) Safety: All Participants as Treated (APaT)
Primary Endpoints	Objective Response Rate (ORR) per RECIST 1.1 assessed by investigator determination
Statistical Methods for Key Efficacy Analyses	ORR will be estimated by treatment group with 95% CI calculated by the Clopper-Pearson exact method [Clopper, C. J. and Pearson, E. S. 1934]
Statistical Methods for Key Safety Analyses	Point estimates (count and percentage) by treatment group will be provided for safety endpoints.
Interim and Final Analyses	There will be no interim analysis. During the course of the study, DMC will perform 1 safety review based on the DMC charter. The final analysis will be performed after the last participant completes the Week 9 imaging assessment.
Multiplicity	There will be no multiplicity adjustment.
Sample Size and Power	Total sample size is approximately 85.

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.

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.

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

An eDMC will be convened to review accumulating safety data. The eDMC responsibilities and review schedules will be outlined in the DMC charter.

Blinding to treatment assignment will be maintained at all investigational sites until the last participant completes the first scheduled imaging (ie, Week 9) for efficacy analysis. Participant-level unblinding will be restricted to an external unblinded statistician and external unblinded scientific programmer performing the analysis, who will have no other responsibilities associated with the study. The extent to which individuals are unblinded with respect to the results will be documented. Additional logistical details, revisions to the above plan, and data monitoring guidance will be provided in the DMC Charter.

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

10.3 Hypotheses/Estimation

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

10.4 Analysis Endpoints

10.4.1 Efficacy Endpoint

10.4.1.1 Primary Endpoint

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

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

10.4.2 Safety Endpoints

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, SAEs, fatal AEs, laboratory tests, and vital signs as described in Section 9.5. Furthermore, specific events will be collected and designated as ECIs as described in Section 9.3.7.

10.5 Analysis Populations

10.5.1 Efficacy Analysis Population

The ITT population will serve as the population for the efficacy analysis. All randomized participants will be included in this population. Participants will be analyzed in the treatment group to which they are randomized.

10.5.2 Safety Analysis Population

The 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.

[redacted]

10.6 Statistical Methods

10.6.1 Statistical Methods for Efficacy Analyses

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

10.6.1.1 Objective Response Rate

The primary efficacy endpoint ORR is defined as the proportion of participants in the analysis population who have a best response of complete response (CR) or partial response (PR) based on RECIST 1.1 by investigator determination.

ORR will be estimated by treatment group. 95% CI for ORR will be provided using the Clopper-Pearson method.

10.6.2 Statistical Method for Safety Analysis

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

Individual events and the broad AE categories consisting of the proportion of participants with any AE, a drug-related AE, a serious AE, an AE which is both drug-related and serious, a Grade 3-5 AE, a drug related Grade 3-5 AE, a fatal AE, dose interruption due to an AE and discontinuation due to an AE, will be summarized by counts and percentages by treatment group (Table 11).

Table 11 Analysis Strategy for Safety Endpoints

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

10.6.3 Clinical Laboratory Tests

The clinical laboratory data will be analyzed using summary statistics (eg, means and frequencies), and no formal statistical comparisons among the treatments are planned. In addition, distributions of key laboratory parameters (including hemoglobin, neutrophils, and platelets) will be plotted over time; these values will also be classified into CTCAE toxicity grades and tabulated. Descriptive statistics and mean change from baseline will be determined for vital signs at each assessment time. Vital sign results will be reviewed for clinically notable abnormalities.

10.6.4 Summaries of Baseline Characteristics and Demographics

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

10.7 Interim Analyses

NOTE: As of Amendment 03, there will be no interim efficacy analysis. The eDMC will conduct safety review based on DMC charter.

10.8 Multiplicity

NOTE: As of Amendment 03, 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 pembrolizumab plus placebo arms. The primary objective is to estimate ORR for each treatment arm. The overall sample size of approximately 85 is based on the projected randomized participants when a strategic decision was made to redesign the study based on ORR as the primary endpoint.

With estimated 42 participants per treatment arm, Table 12 gives examples of ORR estimate and 95% CI, with different numbers of observed responders.

Table 12 ORR estimate and 95% CI

# of participant	# of responder	ORR	95% CI	CI Width
42	9	21.4%	(10.3%, 36.8%)	26.5%
42	10	23.8%	(12.0%, 39.4%)	27.4%
42	11	26.2%	(13.9%, 42.0%)	28.2%
42	12	28.6%	(15.7%, 44.6%)	28.9%

10.10 Subgroup Analyses

NOTE: As of Amendment 03, this section is no longer applicable.

10.11 Compliance (Medication Adherence)

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

10.12 Extent of Exposure

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

12.1 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 are suspected, the issues are promptly investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified and data disclosed accordingly.

B. Publication and Authorship

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

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

III. Participant Protection

A. IRB/IEC review

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

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

Financial Disclosure

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

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

Data Protection

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

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

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

Confidentiality of Data

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

Confidentiality of Participant Records

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

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

Confidentiality of IRB/IEC Information

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

Committees Structure

Trial Steering Committee

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

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

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

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

Joint Executive Oversight Committee

The Joint Executive Oversight Committee (EOC) comprises members of Sponsor and MSD Senior Management. The EOC will receive and decide upon any recommendations made by the 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 and regulatory authorities as a result of an audit or inspection to cure deficiencies in the trial documentation and worksheets/case report forms.

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

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

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

Source Documents

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

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

Study and Site Closure

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

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

12.2 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 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

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

Contraception Requirements

Male Participants

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

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

- Use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant.
  - The following are not acceptable methods of contraception:
    - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM).
    - Male condom with cap, diaphragm or sponge with spermicide.
    - Male and female condom cannot be used together.
  - Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

Female Participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 13 during the protocol-defined time frame in Section 6.1.

Table 13 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, corresponding to time needed to eliminate study treatment plus 30 days for study treatments with genotoxic potential after the last dose of study treatment. c) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation.

Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test within 72 hours of randomization. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required. Monthly pregnancy testing should be conducted as per local regulations where applicable.

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

12.3 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 placebo or active comparator product) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor or MSD for human use in this study.

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

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

Definition of SAE

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

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

e. Is a congenital anomaly/birth defect

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

f. Other important medical events:

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

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

Additional Events reported in the same manner as SAE

Additional Events which require reporting in the same manner as SAE

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

Recording AE and SAE

AE and SAE Recording

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

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.
- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.
  - Grade 1: Mild; asymptomatic or 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).

12.4 Appendix 4: Clinical Laboratory Tests

- The tests detailed in Table 14 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6.0 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 14 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit PT aPTT INR	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Chemistry	Blood Urea Nitrogen (BUN)	Potassium Urea[a]	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the upper limit of normal)
	Albumin	A measure of carbon dioxide (CO_2 or bicarbonate)[b]	Chloride	Phosphorous
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose [Indicate if fasting, or nonfasting]	Calcium	Alkaline phosphatase	
	Uric acid	Amylase	Lipase	
Routine	• Specific gravity			

Laboratory Assessments	Parameters
Urinalysis	• Glucose, protein, blood, and ketones, by dipstick • Microscopic examination (if blood or protein is abnormal) • Pregnancy test, as needed for women of childbearing potential (WOCBP) within 72 hrs before randomization
Other Tests	• Thyroid panel: thyroid-stimulating hormone (TSH), FT4, FT3/T3 • Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Serum β human chorionic gonadotropin (β-hCG) pregnancy test (as needed for WOCBP • Serology: o Hepatitis B surface antigen, HBV-DNA o HCV-RNA, HCV antibody (if HCV-RNA is not the local standard of care) o HIV-RNA (if required by local regulations)

Notes:

a Blood Urea Nitrogen is preferred; if not available urea may be tested.

b If available as SoC in your region. The carbon dioxide may be either a measurement of CO2 or bicarbonate as an electrolyte.

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; DNA = deoxyribonucleic acid; FT4 = free thyroxine; HCV = Hepatitis C Virus;; MCH = mean corpuscular hemoglobin; MCV= mean corpuscular volume; RBC = red blood cells; RNA = ribonucleic acid; RBC = red blood cells; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; SoC = Standard of Care; T3 = triothyronine; TSH = thyroid stimulating hormone (thyrotropin); WBC = white blood cells.

Investigators must document their review of each laboratory safety report.

Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

12.5 Appendix 5: ECOG Performance Status

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

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

12.6 Appendix 6: Abbreviations and Trademarks

Abbreviation/Term	Definition
2L	second line
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 (tuberculosis vaccine)
BICR	blinded independent central review
BID	twice daily
C1D1	Cycle 1 Day 1
CAP	chest, abdomen and pelvis
C2D1	Cycle 2 Day 1
CI	confidence interval
cLDA	constrained longitudinal data analysis
C_{max}	plasma maximum concentration
CNS	central nervous system
CPS	Combined Positive Score for PD-L1 positivity (combined expression of tumor cells and inflammatory markers)
CR	complete response
CrCl	creatinine clearance
CRF	case report form
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte-associated antigen-4
C_{trough}	plasma minimum concentration
DC	Discontinuation
DCR	disease control rate (CR, PR, and SD)
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	duration of response
ECI	events of clinical interest
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
eDMC	external Data Monitoring Committee
EMA	European Medicines Agency

Abbreviation/Term	Definition
EOC	Executive Oversight Committee
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
eEQ-5D	electronic EuroQol-5 Dimensions
EQ-5D	EuroQol-5 Dimensions
EOT	End of Treatment
ePRO	electronic patient-reported outcome
EU	European Union
EuroQol	European Quality of Life
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FFPE	formalin-fixed, paraffin-embedded
FSH	follicle stimulating hormone
FWER	familywise Type I error rate
GCP	Good Clinical Practice
H1	Hypothesis 1
H2	Hypothesis 2
HBsAG	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCG	human chorionic gonadotropin
HCV	Hepatitis C virus
HIV	human immunodeficiency virus
HR	hazard ratio
HRQoL	Health Related Quality of Life
HRT	hormonal replacement therapy
IB	Investigator's Brochure
iCPD	iRECIST confirmed progressive disease
ICF	informed consent form
ICH	International Conference on Harmonization
iCR	iRECIST complete response
IDO1	indoleamine 2,3-dioxygenase
IEC	Independent Ethics Committee
Ig	immunoglobulin
IHC	immunohistochemistry
INR	international normalized ratio
IRB	Institutional Review Board
irAE	immune-related adverse event
iRECIST	immune-based therapeutics RECIST
ITT	Intention-to-Treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system

Abbreviation/Term	Definition
IV	intravenous
IVRS	interactive voice response system
IWRS	integrated web response system
LAM	lactational amenorrhoea method
mAb	monoclonal antibody
MAOI	monoamine oxidase inhibitor
mg	milligram
mg/kg	milligram per kilogram
MK-3475 (formerly SCH90045)	Merck designation for pembrolizumab
mL	milliliter
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MSI	microsatellite instability
MSD	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
NA or N/A	not applicable
NCI	(US) National Cancer Institute
NSAID	nonsteroidal anti-inflammatory drugs
NSCLC	non-small cell lung cancer
ORR	Objective Response Rate
OS	overall survival
OTC	Over-the-Counter (non-prescription)
PD	progressive disease
PD-1	programmed cell death 1
PD-L1	programmed cell death-ligand 1
PD-L2	programmed cell death-ligand 2
pembro	pembrolizumab
PFS	progression-free survival
PH	proportional hazard
PI	Principal Investigator
PK	pharmacokinetic(s)
PR	partial response
PRO	patient-reported outcome
PS	Performance Status
PT	prothrombin time
PTT	partial thromboplastin time
PS	performance status
PSA	prostate-specific Antigen
Q12H	every 12 hours
Q2W	every 2 Weeks
Q3W	every 3 Weeks
QLQ	Quality of Life Questionnaire
QoL	Quality of Life

Abbreviation/Term	Definition
QTc	corrected QT interval
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RR	response rate
SAE	serious adverse event(s)
SAP	Statistical Analysis Plan
SD	stable disease
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SIM	Site Imaging Manual
SNRI	serotonin-norepinephrine reuptake inhibitor
SoA	Schedule of Activities
SOC	standard of care
SOP	Standard Operating Procedure
SS	serotonin syndrome
sSAP	supplemental Statistical Analysis Plan
SSRI	Selective serotonin reuptake inhibitor
T1DM	Type 1 diabetes mellitus
TCC	transitional cell carcinoma
TRAEs	treatment-related adverse events
T-reg	regulatory T-cell
TSH	thyroid-stimulating hormone
TTD	time to true deterioration
UC	urothelial carcinoma
ULN	upper limit of normal
US	United States
USPI	United States Package Insert
[redacted]	[redacted]
WOCBP	woman of child bearing potential

12.7 Appendix 7: Description of the iRECIST Process for Assessment of Disease Progression

Note: As of Amendment 03, this section is no longer applicable; iRECIST data will no longer be collected. Participants with radiographic disease progression as determined by RECIST 1.1 will discontinue from the study and be followed for safety monitoring, as detailed in Section 9.3; no confirmatory scans are required.

Assessment at Screening and Prior to RECIST 1.1 Progression

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

Assessment and Decision at RECIST 1.1 Progression

For 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 7). 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, including worsening of laboratory values
- 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 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 review.

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 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 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 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 initial iUPD 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].

Signature Manifest

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