Official Protocol Title:	A Phase 1 Study of MK-1697 in Participants with Advanced Solid Tumors
NCT number:	NCT03515824
Document Date:	23-May-2019

Title Page

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Protocol Title: A Phase 1 Study of MK-1697 in Participants with Advanced Solid Tumors

Protocol Number: 001-03

Compound Number: MK-1697

Sponsor Name and Legal Registered Address:

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
(hereafter referred to as the Sponsor or MSD)

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

Regulatory Agency Identifying Number(s):

IND NUMBER: 141943

EudraCT NUMBER: To Be Determined

Approval Date: 23 May 2019

Sponsor Signatory

Typed Name:
Title:

Date

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

Investigator Signatory

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

Typed Name:
Title:

Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
MK-1697-001-03	23-May-2019	To respond to FDA review comments
MK-1697-001-02	29-Nov -2018	To change the target population for the Part B expansion cohorts, and other minor changes as requested by regulatory authorities.
MK-1697-001-01	10-Jul-2018	To add a 24-hour inpatient observation period for participants treated at the first dose level of MK-1697 and other minor changes as requested by regulatory authorities.
MK-1697-001-00	21-Feb-2018	Original Protocol

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment 001-03

Overall Rationale for the Amendment:

This amendment was initiated to align with the response to FDA review comments.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities 5.1 Inclusion Criteria 8.9 Biomarkers 8.11.1 Screening Phase	Removed the 90-day restriction for tumor tissue sample	Define tumor tissue collection as recent rather than new.
4.2.1.6 Planned Exploratory Biomarker Research	Revised MSI testing description	Clarified biomarker collection for participants with CRC in Part B
6.6.1 Definition of Dose-Limiting Toxicity	Revised to align with Merck standard DLT definition	Clarified that in order to be considered a DLT, a given AE must be attributed to study intervention.
7.1 Discontinuation of Study Treatment 8.1.1.1 General Informed Consent 8.2.2 iRECIST Assessment of Disease	Deleted text related to Sponsor-approved treatment continuation and treatment beyond confirmed progressive disease.	Clarified that treatment beyond confirmed progression is not an option in this trial. Clarified that an addendum informed consent form will be signed at the initial radiographic disease progression, and treatment will end if progression is confirmed.

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1. Protocol Summary

1.1 Synopsis

Protocol Title:

A Phase 1 Study of MK-1697 in Participants with Advanced Solid Tumors

Short Title:

A Phase 1 Study of MK-1697 in Participants with Advanced Solid Tumors

Objectives/Hypotheses and Endpoints:

In male/female participants with advanced solid tumors that have not responded to conventional therapies:

Objective/Hypothesis	**Endpoint**
Primary	
• Objective: To determine the safety and tolerability and to establish a preliminary recommended Phase 2 (RP2D) dose of MK-1697	• Dose-limiting toxicity (DLT) • Adverse event (AE) • Discontinuing study intervention due to an AE
Secondary	
• Objective: To evaluate the pharmacokinetics (PK) of MK-1697	• PK parameters including area under the curve (AUC), maximum concentration (C_{max}), and minimum concentration (C_{min})
• Objective: To evaluate the objective response rate (ORR) as assessed by the investigator based on Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) and iRECIST following administration of MK-1697	• Objective response is a confirmed complete response (CR) or partial response (PR)

Overall Design:

Study Phase	Phase 1b
Clinical Indication	Treatment of advanced solid tumors
Population	Part A: Participants with advanced/metastatic solid tumor who have received, or been intolerant to, or been ineligible for all treatments known to confer clinical benefit. Part B: Participants with the following tumor types that are naïve to anti-PD-1/PD-L1 therapy: • HNSCC that is considered incurable by local therapies. Participants should have progressed after receiving platinum-containing systemic therapy. Systemic therapy given as part of multimodal treatment for locally advanced disease is allowed. The eligible primary tumor locations are oropharynx, oral cavity, hypopharynx, and larynx. Participants may not have a primary tumor site of nasopharynx (any histology). • CRC originating in either the colon or rectum that is locally advanced unresectable or metastatic (ie, Stage IV) and that has received, and progressed on, all available standard-of-care therapies including fluoropyrimidine, oxaliplatin, and irinotecan. Participants with known MSI-high or MMR-deficient CRC (as determined by PCR, IHC, or a validated NGS panel, eg. Foundation Medicine or MSKImpact) are excluded from participating in this study.
Study Type	Interventional
Type of Design	Single arm, multi-site, dose escalation and confirmation
Type of Control	No treatment control
Study Blinding	Unblinded Open-label
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 4 years from the time the first participant signs the informed consent until the last participant's last study-related telephone call or visit.

Number of Participants:

A maximum of approximately 122 participants will be enrolled.

Treatment Groups and Duration:

Treatment Groups	Part A: Dose Level 1 (DL1) – 20 mg of MK-1697 every 3 weeks (Q3W) as intravenous (IV) infusion DL2 – 65 mg of MK-1697 Q3W as IV infusion DL3 – 200 mg of MK-1697 Q3W as IV infusion Part B: MK-1697 at the preliminary RP2D Q3W as IV infusion
Duration of Participation	Each participant will participate in the study from the time the participant signs the informed consent form (ICF) through the final protocol-specified contact. After a screening phase of 28 days, each participant will be assigned to receive study treatment until disease progression is radiographically documented and, when clinically appropriate, confirmed by the site per modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics (iRECIST), 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 or administrative reasons requiring cessation of treatment, pregnancy of the participant, the participant withdraws consent, or until the participant has received 35 administrations of MK-1697 (approximately 2 years). After the end of treatment, each participant will be followed for the occurrence of AEs and spontaneously reported pregnancy as described under Section 8.4. Participants who discontinue for reasons other than radiographic disease progression will have post-treatment follow-up imaging for disease status until disease progression is documented radiographically per RECIST 1.1, and confirmed by the site per iRECIST, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. All participants will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study.

Study Governance:

Study Governance Committees	There are no governance committees in this study.

A list of abbreviations used in this document can be found in Appendix 6.

1.2 Schema

The study design is depicted in Figure 1.

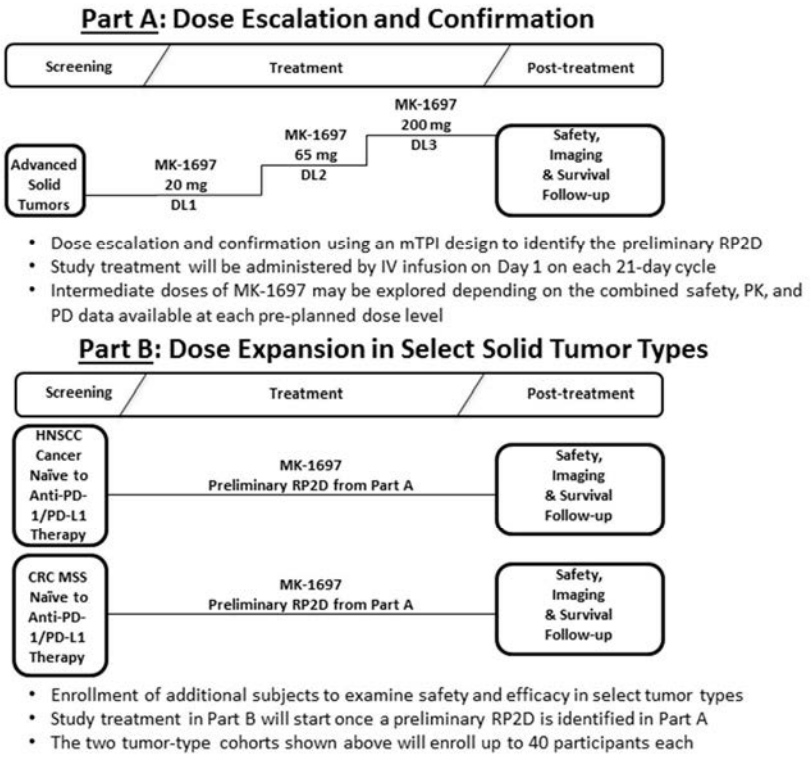

Figure 1 Study Diagram

1.3 Schedule of Activities (SoA)

Trial Period:	**Screening Phase**	**Treatment Phase (3-Week Cycles)**															**End of Treatment / Discontinuation**	**Post-Treatment Phase**			**Notes**
Treatment Cycle/Title:	**Screening**	**1**					**2**				**3**				**4**	**5 to 35**		Safety Follow-up	Imaging Follow-up	Survival Follow-up	All procedures and assessments are to be performed prior to administration of study treatment unless otherwise indicated.
Cycle Day:		**1**	**2**	**3**	**8**	**15**	**1**	**3**	**8**	**15**	**1**	**3**	**8**	**15**	**1**	**1**	**At time of treatment discon.**	30 days after last dose	Every 12 weeks	Every 12 weeks	
Scheduling Window (Days):	**-28 to -1**				**±3**	**± 3**	**+3**		**±3**	**± 3**	**±3**		**±3**	**± 3**	**± 3**	**± 3**	**+ 3**	**+ 14**	**± 7**	**± 7**	
Informed Consent	X																				
Informed Consent for Future Biomedical Research	X																				Optional
Participant Identification Card	X																				
Inclusion/Exclusion Criteria	X																				
Demographic and Medical History	X																				
Prior/Concomitant Treatment & Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Prior Oncology Treatment History	X																				
Treatment Allocation		X																			

Trial Period:	**Screening Phase**	**Treatment Phase (3-Week Cycles)**															**End of Treatment / Discontinuation**	**Post-Treatment Phase**			**Notes**
Treatment Cycle/Title:	**Screening**	**1**					**2**				**3**				**4**	**5 to 35**		Safety Follow-up	Imaging Follow-up	Survival Follow-up	All procedures and assessments are to be performed prior to administration of study treatment unless otherwise indicated.
Cycle Day:		**1**	**2**	**3**	**8**	**15**	**1**	**3**	**8**	**15**	**1**	**3**	**8**	**15**	**1**	**1**	**At time of treatment discon.**	30 days after last dose	Every 12 weeks	Every 12 weeks	
Scheduling Window (Days):	**-28 to -1**				**±3**	**± 3**	**+3**		**±3**	**± 3**	**±3**		**±3**	**± 3**	**± 3**	**± 3**	**+ 3**	**+ 14**	**± 7**	**± 7**	
Portacath (or similar device) Insertion*	X																				* Applies only to doses <65 mg, which require administration directly into a central vein. Only perform if participant does not have central venous access (eg, portacath, Hickman line, or PICC line) currently inserted. Only perform after all other screening procedures/assessments have been performed and participant has been determined to be eligible for the study.

Trial Period:	**Screening Phase**	**Treatment Phase (3-Week Cycles)**															**End of Treatment / Discontinuation**	**Post-Treatment Phase**			**Notes**
Treatment Cycle/Title:	**Screening**	**1**					**2**				**3**				**4**	**5 to 35**		Safety Follow-up	Imaging Follow-up	Survival Follow-up	All procedures and assessments are to be performed prior to administration of study treatment unless otherwise indicated.
Cycle Day:		**1**	**2**	**3**	**8**	**15**	**1**	**3**	**8**	**15**	**1**	**3**	**8**	**15**	**1**	**1**	**At time of treatment discon.**	30 days after last dose	Every 12 weeks	Every 12 weeks	
Scheduling Window (Days):	**-28 to -1**				**±3**	**± 3**	**+3**		**±3**	**± 3**	**±3**		**±3**	**± 3**	**± 3**	**± 3**	**+ 3**	**+ 14**	**± 7**	**± 7**	
MK-1697 Administration		X					X				X				X	X					An optional 24-hour inpatient observation period may be performed following MK-1697 administration on C1D1 for the first dose level.
Efficacy Procedures																					
Tumor Imaging and Response Assessment	X														X	X	X		X		Every 9 weeks (±7 days) during Treatment Phase. After 54 weeks, every 12 weeks (±7 days). Calculated from the first dose of study treatment and not adjusted for delays in treatment.

Trial Period:	**Screening Phase**	**Treatment Phase (3-Week Cycles)**															**End of Treatment / Discontinuation**	**Post-Treatment Phase**			**Notes**
Treatment Cycle/Title:	**Screening**	**1**					**2**				**3**				**4**	**5 to 35**		Safety Follow-up	Imaging Follow-up	Survival Follow-up	All procedures and assessments are to be performed prior to administration of study treatment unless otherwise indicated.
Cycle Day:		**1**	**2**	**3**	**8**	**15**	**1**	**3**	**8**	**15**	**1**	**3**	**8**	**15**	**1**	**1**	**At time of treatment discon.**	30 days after last dose	Every 12 weeks	Every 12 weeks	
Scheduling Window (Days):	**-28 to -1**				**±3**	**± 3**	**+3**		**±3**	**± 3**	**±3**		**±3**	**± 3**	**± 3**	**± 3**	**+ 3**	**+ 14**	**± 7**	**± 7**	
Medical Photography (cutaneous lesions, if applicable)	X														X	X	X		X		Every 9 weeks (±7 days) during Treatment Phase. After 54 weeks, every 12 weeks (±7 days). Calculated from the first dose of study treatment and not adjusted for delays in treatment.
Survival Status		<----------														---------->				X	After investigator determined PD or start of new anticancer treatment. In addition, upon Sponsor request, participants may be contacted for survival status at any time during the course of the study.

Trial Period:	**Screening Phase**	**Treatment Phase (3-Week Cycles)**															**End of Treatment / Discontinuation**	**Post-Treatment Phase**			**Notes**
Treatment Cycle/Title:	**Screening**	**1**					**2**				**3**				**4**	**5 to 35**		Safety Follow-up	Imaging Follow-up	Survival Follow-up	All procedures and assessments are to be performed prior to administration of study treatment unless otherwise indicated.
Cycle Day:		**1**	**2**	**3**	**8**	**15**	**1**	**3**	**8**	**15**	**1**	**3**	**8**	**15**	**1**	**1**	**At time of treatment discon.**	30 days after last dose	Every 12 weeks	Every 12 weeks	
Scheduling Window (Days):	**-28 to -1**				**±3**	**± 3**	**+3**		**±3**	**± 3**	**±3**		**±3**	**± 3**	**± 3**	**± 3**	**+ 3**	**+ 14**	**± 7**	**± 7**	
Safety Procedures																					
Full physical examination	X	X					X				X				X	X	X	X			Every 3rd cycle after C4 (C7, C10, C13…)
Height	X																				
Weight	X	X					X				X				X	X	X	X			
Directed Physical Examination			X		X	X			X	X			X	X		X					Symptom directed. When a full exam is not performed.
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			Heart rate, respiratory rate, blood pressure, and temperature.
12-lead electrocardiograph (ECG)	X																				As clinically indicated after screening.
Tumor Markers (as clinically indicated)	X	X					X				X				X	X	X				Specific tumor markers (eg, CEA, CA-125, CA-19-9) are to be obtained as clinically indicated.

Trial Period:	**Screening Phase**	**Treatment Phase (3-Week Cycles)**															**End of Treatment / Discontinuation**	**Post-Treatment Phase**			**Notes**
Treatment Cycle/Title:	**Screening**	**1**					**2**				**3**				**4**	**5 to 35**		Safety Follow-up	Imaging Follow-up	Survival Follow-up	All procedures and assessments are to be performed prior to administration of study treatment unless otherwise indicated.
Cycle Day:		**1**	**2**	**3**	**8**	**15**	**1**	**3**	**8**	**15**	**1**	**3**	**8**	**15**	**1**	**1**	**At time of treatment discon.**	30 days after last dose	Every 12 weeks	Every 12 weeks	
Scheduling Window (Days):	**-28 to -1**				**±3**	**± 3**	**+3**		**±3**	**± 3**	**±3**		**±3**	**± 3**	**± 3**	**± 3**	**+ 3**	**+ 14**	**± 7**	**± 7**	
Eastern Cooperative Oncology Group (ECOG) Performance Status	X	X					X				X				X	X	X	X			
Urine Pregnancy Test (Serum β-Human Chorionic Gonadotropin [β-hCG] if required) (WOCBP only)	X	X															X	X			Screening: perform within 72 hours prior to first dose of study treatment.
Human immunodeficiency virus (HIV), hepatitis B and C screen status (per site SOP)	X																				Acceptable to be based on history unless testing is required by local regulation.
Urinalysis	X	X					X				X				X						Screening: perform within 7 days of treatment allocation.

Trial Period:	**Screening Phase**	**Treatment Phase (3-Week Cycles)**															**End of Treatment / Discontinuation**	**Post-Treatment Phase**			**Notes**
Treatment Cycle/Title:	**Screening**	**1**					**2**				**3**				**4**	**5 to 35**		Safety Follow-up	Imaging Follow-up	Survival Follow-up	All procedures and assessments are to be performed prior to administration of study treatment unless otherwise indicated.
Cycle Day:		**1**	**2**	**3**	**8**	**15**	**1**	**3**	**8**	**15**	**1**	**3**	**8**	**15**	**1**	**1**	**At time of treatment discon.**	30 days after last dose	Every 12 weeks	Every 12 weeks	
Scheduling Window (Days):	**-28 to -1**				**±3**	**± 3**	**+3**		**±3**	**± 3**	**±3**		**±3**	**± 3**	**± 3**	**± 3**	**+ 3**	**+ 14**	**± 7**	**± 7**	
Hematology	X	X	X		X	X	X		X	X	X		X	X	X	X	X	X			Screening: perform within 7 days of treatment allocation.
Prothrombin (PT)/International Normalized Ratio (INR) and activated partial thromboplastin time (aPTT)	X																				Consider ongoing testing for participants on routine warfarin treatment. Perform within 7 days of treatment allocation.
Comprehensive Chemistry Panel	X	X	X		X	X	X		X	X	X		X	X	X	X	X	X			Screening: perform within 7 days of treatment allocation.
Thyroid Function (triiodothyronine [T3] or free T3 [FT3], free thyroxine [FT4], and thyroid stimulating hormone [TSH])	X	X									X					X	X	X			Every other cycle (C5, C7, C9…)

Trial Period:	**Screening Phase**	**Treatment Phase (3-Week Cycles)**															**End of Treatment / Discontinuation**	**Post-Treatment Phase**			**Notes**
Treatment Cycle/Title:	**Screening**	**1**					**2**				**3**				**4**	**5 to 35**		Safety Follow-up	Imaging Follow-up	Survival Follow-up	All procedures and assessments are to be performed prior to administration of study treatment unless otherwise indicated.
Cycle Day:		**1**	**2**	**3**	**8**	**15**	**1**	**3**	**8**	**15**	**1**	**3**	**8**	**15**	**1**	**1**	**At time of treatment discon.**	30 days after last dose	Every 12 weeks	Every 12 weeks	
Scheduling Window (Days):	**-28 to -1**				**±3**	**± 3**	**+3**		**±3**	**± 3**	**±3**		**±3**	**± 3**	**± 3**	**± 3**	**+ 3**	**+ 14**	**± 7**	**± 7**	
Lipase and Amylase	X	X					X				X				X	X	X	X			
Gamma-glutamyl transferase (GGT)	X																				Perform within 7 days of treatment allocation, and as clinically indicated after screening.
AE/SAE review	X	X	←													X	X	X			
Cytokine Panel	X	X	X				X				X				X	X					Cycles 1-6 only. Part A only.

Trial Period:	**Screening Phase**	**Treatment Phase (3-Week Cycles)**															**End of Treatment / Discontinuation**	**Post-Treatment Phase**			**Notes**
Treatment Cycle/Title:	**Screening**	**1**					**2**				**3**				**4**	**5 to 35**		Safety Follow-up	Imaging Follow-up	Survival Follow-up	All procedures and assessments are to be performed prior to administration of study treatment unless otherwise indicated.
Cycle Day:		**1**	**2**	**3**	**8**	**15**	**1**	**3**	**8**	**15**	**1**	**3**	**8**	**15**	**1**	**1**	**At time of treatment discon.**	30 days after last dose	Every 12 weeks	Every 12 weeks	
Scheduling Window (Days):	**-28 to -1**				**±3**	**± 3**	**+3**		**±3**	**± 3**	**±3**		**±3**	**± 3**	**± 3**	**± 3**	**+ 3**	**+ 14**	**± 7**	**± 7**	
Pharmacokinetics/Pharmacodynamics/Future Biomedical Research/Biomarkers																					
Blood for Genetic Analysis		X																			
Blood for MSI Status Test	X																				Testing is applicable only for the Part B CRC expansion cohort.
Peripheral Blood for PD-1 Target Engagement		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			Day 1 of Cycles 1-4, 6, 8: Collect samples predose (within 24 hours prior to dosing), after infusion (+10 min), and 2h after start of infusion (±10 min). Day 1 of every 4 cycles thereafter (C12, C16…): Only collect predose (within 24 hours prior to dosing).
Serum for Total sLAG-3		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Serum for MK-1697 Pharmacokinetics		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			

Trial Period:	**Screening Phase**	**Treatment Phase (3-Week Cycles)**															**End of Treatment / Discontinuation**	**Post-Treatment Phase**			**Notes**
Treatment Cycle/Title:	**Screening**	**1**					**2**				**3**				**4**	**5 to 35**		Safety Follow-up	Imaging Follow-up	Survival Follow-up	All procedures and assessments are to be performed prior to administration of study treatment unless otherwise indicated.
Cycle Day:		**1**	**2**	**3**	**8**	**15**	**1**	**3**	**8**	**15**	**1**	**3**	**8**	**15**	**1**	**1**	**At time of treatment discon.**	30 days after last dose	Every 12 weeks	Every 12 weeks	
Scheduling Window (Days):	**-28 to -1**				**±3**	**± 3**	**+3**		**±3**	**± 3**	**±3**		**±3**	**± 3**	**± 3**	**± 3**	**+ 3**	**+ 14**	**± 7**	**± 7**	
Peripheral Blood for Immunophenotyping		X			X	X	X			X	X			X	X						
Blood for circulating tumor DNA		X					X				X				X	X					
Serum for Anti-MK-1697 Antibodies		X					X				X				X	X		X			Collected within 24 hours prior to dosing of Cycles 1-4, 6, 8, and every 4 cycles thereafter (C12, C16…).
Blood for RNA Analysis		X					X				X				X	X	X				Cycles 1-5 and at treatment discontinuation.
Blood for Plasma Biomarker Analyses		X					X				X				X	X	X				
Blood for Serum Biomarker Analyses		X					X				X				X	X	X				

Trial Period:	**Screening Phase**	**Treatment Phase (3-Week Cycles)**															**End of Treatment / Discontinuation**	**Post-Treatment Phase**			**Notes**
Treatment Cycle/Title:	**Screening**	**1**					**2**				**3**				**4**	**5 to 35**		Safety Follow-up	Imaging Follow-up	Survival Follow-up	All procedures and assessments are to be performed prior to administration of study treatment unless otherwise indicated.
Cycle Day:		**1**	**2**	**3**	**8**	**15**	**1**	**3**	**8**	**15**	**1**	**3**	**8**	**15**	**1**	**1**	**At time of treatment discon.**	30 days after last dose	Every 12 weeks	Every 12 weeks	
Scheduling Window (Days):	**-28 to -1**				**±3**	**± 3**	**+3**		**±3**	**± 3**	**±3**		**±3**	**± 3**	**± 3**	**± 3**	**+ 3**	**+ 14**	**± 7**	**± 7**	
Tumor Tissue Collection																					
Archival and/or Recently Obtained Tumor Tissue Collection	X																				This tumor sample may have been collected at any point prior to the first dose of treatment. For subjects in Part B with HNSCC (of oropharyngeal origin, only), HPV testing by p16 IHC, polymerase chain reaction (PCR), or fluorescent in situ hybridization is required before or during screening.

Trial Period:	**Screening Phase**	**Treatment Phase (3-Week Cycles)**															**End of Treatment / Discontinuation**	**Post-Treatment Phase**			**Notes**
Treatment Cycle/Title:	**Screening**	**1**					**2**				**3**				**4**	**5 to 35**		Safety Follow-up	Imaging Follow-up	Survival Follow-up	All procedures and assessments are to be performed prior to administration of study treatment unless otherwise indicated.
Cycle Day:		**1**	**2**	**3**	**8**	**15**	**1**	**3**	**8**	**15**	**1**	**3**	**8**	**15**	**1**	**1**	**At time of treatment discon.**	30 days after last dose	Every 12 weeks	Every 12 weeks	
Scheduling Window (Days):	**-28 to -1**				**±3**	**± 3**	**+3**		**±3**	**± 3**	**±3**		**±3**	**± 3**	**± 3**	**± 3**	**+ 3**	**+ 14**	**± 7**	**± 7**	
Tumor Biopsy	X								X												Required for first 10 participants in each expansion cohort of Part B. Cycle 2 biopsy may be collected between Days 8 and 15. An optional biopsy will be performed within 4 weeks after disease progression for participants in each expansion cohort of Part B who achieved either a CR, PR, or SD while participating in the study.

2. Introduction

MK-1697 is a novel small bispecific nanobody that binds to both programmed cell death protein 1 (PD-1) and lymphocyte-activation gene 3 (LAG-3), inhibitory immuno-modulatory receptors (IMRs). This is a first-in-human, dose-escalation, and dose-finding study to assess the safety, tolerability, and preliminary efficacy of MK-1697.

2.1 Study Rationale

Because of the roles of PD-1 and LAG-3 on both effector T-cell proliferation and activation, and on the suppressor activity of regulatory T cells (T_{regs}), the dual antagonism of these checkpoint molecules on both T cell populations may potentially increase antitumor activity [Goldberg, M. V. 2011] [Huang, C. T., et al 2004]. Additionally, both LAG-3 and PD-1 monoclonal antibodies (mAbs) are under clinical evaluation for a wide variety of solid tumor indications, and PD-1/PD-L1 mAbs have been approved for the treatment of a number of solid tumor indications. Therefore, Part A of the study will enroll participants with advanced solid tumors.

In Part B of the study, participants who are anti-PD-1/PD-L1 treatment-naïve and who have the following tumor types will be enrolled:

1) HNSCC that is considered incurable by local therapies. Participants should have progressed after receiving platinum-containing systemic therapy. Systemic therapy given as part of multimodal treatment for locally advanced disease is allowed. The eligible primary tumor locations are oropharynx, oral cavity, hypopharynx, and larynx. Participants may not have a primary tumor site of nasopharynx (any histology).

2) CRC originating in either the colon or rectum that is locally advanced unresectable or metastatic (ie, Stage IV) and that has received, and progressed on, all available standard-of-care therapies including fluoropyrimidine, oxaliplatin, and irinotecan. Participants with known MSI high or MMR deficient CRC (as determined by PCR, IHC, or a validated NGS panel, eg. Foundation Medicine or MSKImpact) are excluded from participating in this study.

These tumor types were selected based on the known expression of LAG-3 in these tumors [Jie, H. B., et al 2013] as well as the Sponsor's experience with co-administration of anti-PD-1 and anti-LAG-3 mAbs in participants with these tumor types. Additionally, since it is believed that therapies targeting LAG-3 might have potential antitumor activity in the MSS setting, this study will enroll participants that are naïve to anti-PD-1/PD-L1 therapy in the HNSCC and CRC cohorts.

Squamous cell cancer of the head and neck (HNSCC) was chosen based on high expression of LAG-3 and known response to PD-1 therapy. An anti-PD-1/PD-L1 treatment-naïve population is being assessed for both expansion cohorts in Part B. There is scientific evidence that the expression of alternate immune checkpoints including LAG-3 may increase after PD-1 blockade, promoting resistance to PD-1 therapy [Huang, R. Y., et al 2017]. Co-blockade with LAG-3 and PD-1 may overcome resistance in some tumors.

The intention of the anti-PD-1/PD-L1 treatment-naïve HNSCC expansion cohort is to determine if MK-1697 improves upon the response rates observed with pembrolizumab monotherapy in this population. Results from Keynote-055 demonstrated an objective response rate of 18% in anti-PD-1/PD-L1 treatment-naïve HNSCC patients that had progressed on at least 2 prior lines of therapy [Bauml, J., et al 2017].

MSS CRC was chosen based on high expression of LAG-3, little to no responsiveness to PD-1 monotherapy [O'Neil, B. H., et al 2017], and high unmet medical need. Response rates for regorafenib and TAS-102, approved agents in 3L CRC, have an OS benefit of 2 months and ~1-2% ORR. The intention of this expansion cohort is to determine if MK-1697 improves on the response rates observed for 3L standard of care therapies.

2.2 Background

Refer to the IB for detailed background information on MK-1697. This is a first-in-participant study.

2.2.1 Pharmaceutical and Therapeutic Background

MK-1697 is a bispecific nanobody that binds to both PD-1 and LAG-3. A nanobody is a novel class of therapeutic proteins based on single-domain V_{HH} antibody fragments that contain the unique structural and functional properties of naturally-occurring heavy chain only antibodies. The nanobody technology was developed following the discovery that camelidae (eg, camels, llamas, and alpacas) have functional antibodies constituted of heavy chains only and lack light chains. The cloned and isolated V_{HH} have full antigen binding capacity and are very stable. The current bispecific PD-1/LAG-3 nanobody (MK-1697) is composed of an anti-PD-1 module, an anti-LAG-3 module, and an anti-albumin module (to extend the nanobody's half-life) with all modules connected by linkers. PD-1 and LAG-3 are inhibitory IMRs that modulate the magnitude of effector T cell proliferation and activation. Both also have a role in the suppressor activity of T_{regs}. PD-1 is expressed on activated CD8+ and CD4+ T cells, CD4+ T_{regs}, exhausted T cells, B-cells, and at lower levels on monocytes [Francisco, L. M., et al 2010]. LAG-3 is expressed on activated CD8+ and CD4+ T-cells, CD4+ T_{regs}, exhausted T cells, as well as on natural killer cells and a subset of tolerogenic plasmacytoid dendritic cells [Gagliani, N., et al 2013] [Huard B, Gaulard P, Faure F, Hercend T, Triebel F. 1994] [Workman CJ, Wang Y, El Kasmi KC, Pardoll DM, Murray PJ 2009]. Due to their proposed roles on both effector T cells and T_{regs}, simultaneous blockade of PD-1 and LAG-3 on both cell populations has the potential to enhance anti-tumor immunity [Goldberg, M. V. 2011] [Huang, C. T., et al 2004].

Nonclinical tumor model data and human tumor immunology data support a combination immunotherapy approach with dual blockade of both the PD-1 and LAG-3 checkpoints with a bispecific PD-1/LAG-3 nanobody candidate. Studies using surrogate nanobodies have demonstrated that the bispecific PD-1/LAG-3 nanobody candidate may have potential greater efficacy than the corresponding cocktail of two mAbs [Woo, S. R., et al 2010] [Goding, S. R., et al 2013].

2.3 Benefit/Risk Assessment

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

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

3. Objectives/Hypotheses and Endpoints

In male/female participants with advanced solid tumors that have not responded to conventional therapy:

Objective/Hypothesis	Endpoint
Primary	
• Objective: To determine the safety and tolerability and to establish a RP2D of MK-1697	• Dose-limiting toxicity (DLT) • Adverse event (AE) • Discontinuing study intervention due to an AE
Secondary	
• Objective: To evaluate the PK of MK-1697	• PK parameters including AUC, C_{max}, and C_{min}
• Objective: To evaluate the ORR as assessed by the investigator based on RECIST 1.1 and iRECIST following administration of MK-1697	• Objective response is a confirmed CR or PR
Tertiary/Exploratory	
• Objective: To evaluate the development of circulating anti-MK-1697 antibodies following administration of MK-1697	• Antidrug antibody (ADA) levels
• Objective: To evaluate target engagement and pharmacodynamics through biomarker evaluation	• Total soluble LAG-3 (sLAG-3) • PD-1 receptor occupancy
• Objective: To evaluate progression-free survival (PFS) as assessed by investigator based on RECIST 1.1 and iRECIST and overall survival (OS) following administration of MK-1697	• PFS is time from the first dose of study medication to the first documented disease progression or death due to any cause, whichever occurs first • OS is the time from the first dose of study medication to death due to any cause

Objective/Hypothesis	Endpoint
• Objective: To identify molecular (genomic, metabolic and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of MK-1697. • Objective: To understand the association of human leukocyte antigen (HLA) type to the development of immune response to MK-1697	• Germline genetic variation, genetic (DNA) mutations from tumor, tumor and blood RNA variation, proteomics and IHC, and other biomarkers

4. Study Design

4.1 Overall Design

This is a first-in-human, multisite, worldwide, open-label study of MK-1697 in participants with a histologically or cytologically confirmed diagnosis of an advanced/metastatic solid tumor who have received, or been intolerant to, or been ineligible for all treatments known to confer clinical benefit (Part A) or with the specific tumor types described in Section 5.1 – Inclusion Criteria (Part B).

This study will evaluate the safety, tolerability, and preliminary efficacy of MK-1697. There are 2 parts in this study: dose escalation and confirmation (Part A) and cohort expansion (Part B).

In Part A of the study, a modified Toxicity Probability Interval (mTPI) design [Ji, Y. and Wang, S.-J. 2013] will be used to identify a preliminary RP2D of MK-1697. Three predetermined dose levels of MK-1697 will be evaluated: 20 mg, 65 mg, and 200 mg. Intermediate or higher dose levels of MK-1697 may be explored depending on the combined safety, PK, and pharmacodynamics data available at each preplanned dose level.

During dose escalation, 3 to 6 participants will be initially enrolled to receive MK-1697. Treatment allocation will be accomplished by nonrandom assignment and controlled via an interactive voice response system/integrated web response system (IVRS/IWRS). Enrollment at the next dose level (DL) will begin once all participants in the current DL complete DLT evaluation and a dose-escalation decision has been made. Each subsequent dose level will proceed the same way. The final number of participants enrolled in Part A will depend on the safety data (number of DLTs observed), and what dose is ultimately identified as the preliminary RP2D using the mTPI design.

During dose escalation, a minimum of 3 participants are required at each dose level, and up to 6 participants may be initially enrolled at each dose level. At least 72 hours must pass between when the first and second participants receive study treatment in Cycle 1 of each new dose level. Additionally, participants treated at the first dose level may undergo, at the

investigator's discretion, a 24-hour observation period following administration of MK-1697 on Cycle 1, Day 1. This inpatient observation on Cycle 1, Day 1 may also be performed for participants treated at higher dose levels of MK-1697 at the discretion of the investigator and/or per local Institutional Review Board, Ethics Review Committee, and/or Health Authority requirement. As shown in Table 4, based on the mTPI design, the number of participants who are enrolled at a dose level, but are not yet fully evaluable for DLT assessment, may not exceed the number of remaining participants who are at risk of developing a DLT before the dose would be considered unacceptably toxic.

Part A will end after 14 participants have been treated at any of the selected doses (which may include intermediate or higher dose levels) and the decision based on Table 4 is to stay (or escalate, if at the highest dose level). The pool adjacent-violators algorithm [Ji, Y. and Wang, S.-J. 2013] will be used to estimate the DLT rates across doses under the assumption of monotonicity between DLT rates and dose levels. The totality of the data (including safety, PK, pharmacodynamics, and efficacy) will be considered before deciding on the preliminary RP2D to carry forward to Part B. Either a fixed or weight-based dose may be chosen as the preliminary RP2D.

In Part B, participants with select advanced solid tumors will be enrolled in expansion cohorts based on tumor type to further evaluate the safety and efficacy of MK-1697 at the preliminary RP2D defined in Part A. Up to 40 participants will be enrolled into each tumor-type cohort as described in Section 5.1 – Inclusion Criteria. Additional doses of MK-1697 may also be explored in Part B. The final RP2D for future studies will be confirmed using all available safety information (including early and late toxicities from Parts A and B), as well as PK and pharmacodynamics data and preliminary efficacy assessments. Additional expansion cohorts may be added by the Sponsor at a later point, in which case the protocol will be amended to add these cohorts.

Preliminary efficacy will be evaluated using ORR assessed by the investigator based on RECIST 1.1 as a secondary objective. Progression-free survival based on RECIST 1.1 as assessed by the investigator and OS will be evaluated as exploratory objectives. ORR and PFS will be also assessed by iRECIST per investigator.

Although in this study there will not be any formal hypothesis testing, an interim look at the data may be conducted to enable future trial planning and dosing decisions. In Part B, the efficacy data will be assessed after the first ~15 participants become evaluable in each of the select solid tumor expansion cohorts. If no responses are observed in a given cohort, enrollment in this cohort may be stopped early.

Participants will be monitored carefully for the development of AEs, and for clinical and/or radiographic evidence of disease progression according to RECIST 1.1. However, iRECIST will be used by the investigator for treatment decisions. In participants who have initial evidence of radiological progressive disease (PD) by RECIST 1.1, it will be at the discretion of the investigator whether to continue a participant on study treatment until repeat imaging is obtained. This clinical judgment decision should be based on the participant's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Participants may continue to receive study treatment until tumor assessment is repeated ≥4 weeks later in order to confirm progressive disease by iRECIST per site assessment.

Adverse events will be evaluated by the investigator, according to criteria outlined in the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE), version 4.0, to establish the safety and tolerability of MK-1697 as per the primary objective of this study.

There will be no intraparticipant dose escalation for participants enrolled in this study. The definition of DLTs and criteria for dose modification of MK-1697 are outlined in Section 6.6.1 and Section 6.6, respectively.

Participants may receive study treatment for up to 35 cycles (approximately 24 months). Participants will be treated until PD, unacceptable toxicity, intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw treatment, participant withdrawal of consent, pregnancy of the participant, noncompliance with trial treatment or procedure requirements, participant completes treatment, or administrative reasons requiring cessation of treatment, at which point they will be discontinue study treatment.

Once a participant discontinues from any part of the study, they will be treated at the discretion of the physician.

All participants will be followed for at least 90 days after their last dose of MK-1697 for AE and SAE monitoring. Participants with an ongoing AE of Grade >1 at the time of treatment discontinuation will be followed until resolution of the AE to Grade 0-1, until considered stable by the treating physician, or until beginning a new anticancer therapy, whichever occurs first.

Participants who discontinue treatment for reasons other than confirmed PD will have posttreatment follow-up for disease status (including imaging) until PD, initiating a new anticancer therapy, withdrawing consent for study participation, or becoming lost to follow-up.

After confirmed PD, each participant will be contacted by telephone every 12 weeks (84±7 days) for survival until withdrawal of consent to participate in the study, becoming lost to follow up, death, or end of the study, whichever occurs first.

Specific procedures to be performed during the study, as well as their prescribed times and associated visit windows, are outlined in the Schedule of Activities (SoA), Section 1.3. Details of each procedure are provided in Section 8.

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

Secondary and exploratory objectives for this trial are to evaluate the antitumor activity of MK-1697 in participants with several types of advanced solid malignancies, as detailed in Section 5.1 (Inclusion Criteria). Tumor response will be assessed using both RECIST 1.1 and iRECIST by investigator review. Antitumor activity will be measured through such endpoints as the ORR, PFS, and OS which are further described in Section 9.4.1.

iRECIST accounts for the unique tumor response characteristics seen with immunotherapeutic agents. iRECIST was developed and published by the RECIST Working Group, with input from leading experts from industry and academia, along with participation from the US Food and Drug Administration and European Medicines Agency.

Immunotherapeutic agents such as MK-1697 may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard RECIST may, thus, not provide an accurate response assessment of immunotherapeutic agents. These findings support the need to apply a modification to RECIST 1.1 that takes into account the unique patterns of atypical response in immunotherapy and enables treatment beyond initial radiographic progression, if the participant is clinically stable.

The unidimensional measurement of target lesions, qualitative assessment of nontarget lesions, and response categories are identical to RECIST 1.1, until progression is seen by RECIST 1.1. If a participant is clinically stable, additional imaging may be performed to confirm radiographic progression. In this study, iRECIST will be used by investigators to assess tumor response and progression and make treatment decisions. Additional information on iRECIST can be found in Section 8.2.2.

4.2.1.2 Safety Endpoints

The primary objective of this trial is to characterize the safety and tolerability of MK-1697 in participants with advanced solid tumors. The primary safety analysis will be based on participants who experience toxicities as defined by CTCAE Version 4.0 criteria and DLTs further defined in Section 6.6.1. Safety will be assessed by quantifying the toxicities and grades of toxicities experienced by participants who have received MK-1697.

For AEs, attribution to drug, time-of-onset, duration of the event, its resolution, and any concomitant medications administered will be recorded. AEs that will be analyzed include, but are not limited to, all AEs, SAEs, fatal AEs, and laboratory changes.

4.2.1.3 Pharmacokinetic Endpoints

A secondary objective of this trial is to characterize the PK profile of MK-1697 following administration. The serum concentrations of these agents will serve as the primary readout for the PK, and these data will be used to derive PK parameters (such as AUC, C_{min}, and C_{max}) of MK-1697. Furthermore, the results of these analyses will be used in conjunction with the safety, pharmacodynamics, and other exploratory endpoint data to help assess future dosing strategies for MK-1697.

4.2.1.4 Antidrug Antibody Endpoint

An exploratory objective of this trial is to characterize the formation of ADAs against MK-1697. The formation of ADAs can potentially confound drug exposures at therapeutic doses and prime for subsequent infusion-related toxicity. ADA response at the beginning of each cycle will be determined to understand drug metabolism, exposure, and safety. The incidence

of antidrug antibodies and neutralizing antidrug antibodies will be evaluated and summarized over time by dose. Correlations between the presence/absence of positivity for ADAs and PK and pharmacodynamics markers, activity, and safety of MK-1697 will be explored.

4.2.1.5 Pharmacodynamic Endpoints

Exploratory objectives in this trial are to evaluate receptor (target) engagement and serum cytokines.

4.2.1.5.1 Target Engagement

Target engagement of MK-1697 will be assessed through total soluble LAG-3 (sLAG-3) and PD-1 receptor occupancy.

The frequency of surface LAG-3+ cells in human, NHP, and mouse peripheral blood is negligible by flow cytometry which precludes the use of cell surface LAG-3 receptor binding or receptor availability assays for target engagement. Soluble LAG-3 present in the serum, however, presents an alternative method to assess target engagement of the LAG-3 component of MK-1697 by measuring total (free and bound) serum LAG-3 levels.

Target engagement of the PD-1 portion of MK-1697 can be assessed by measuring the binding of MK-1697 to the PD-1 receptor in peripheral blood.

4.2.1.5.2 Serum for Cytokine Testing

Because treatment with MK-1697 can result in immune stimulation and resulting potential for cytokine release, serum cytokines will be monitored to provide supplementary information to assist in the evaluation of any safety events (eg, IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13 and TNF-α).

4.2.1.6 Planned Exploratory Biomarker Research

Cancer immunotherapies represent an important and novel class of antitumor agents. However, the mechanism of action of these exciting new therapies is not completely understood and much remains to be learned regarding how best to leverage these new drugs in treating patients. Thus, to aid future patients, it is important to investigate the determinants of response or resistance to cancer immunotherapy and other treatments administered, as well as determinants of AEs in the course of our clinical studies. These efforts may identify novel predictive/PD biomarkers and generate information that may better guide single-agent and combination therapy with immuno-oncology drugs. To identify novel biomarkers, biospecimens (ie, blood components, tumor material) will be collected to support analyses of cellular components (eg, protein, DNA, RNA, metabolites) and other circulating molecules. Investigations may include but are not limited to:

Germline (blood) genetic analyses (eg, SNP analyses, whole exome sequencing, whole genome sequencing)

This research may evaluate whether genetic variation within a clinical study population correlates with response to the treatment(s) under evaluation. If genetic variation is found to

predict efficacy or adverse events, the data might inform optimal use of therapies in the patient population. Furthermore, it is important to evaluate germline DNA variation across the genome in order to interpret tumor-specific DNA mutations. Finally, microsatellite instability (MSI) may be evaluated, as this is an important tumor type-agnostic biomarker predictive of response to PD-1 blockade. For all subjects with CRC enrolled in Part B, MSI testing may be performed to confirm local tumor testing results.

Genetic (DNA) analyses from tumor

The application of new technologies, such as next generation sequencing, has provided scientists the opportunity to identify tumor-specific DNA changes (ie, mutations, methylation status, microsatellite instability). Key molecular changes of interest to immuno-oncology drug development include the mutational burden of tumors and the clonality of T-cells in the tumor microenvironment. Increased mutational burden (sometimes referred to as a 'hyper-mutated' state) may generate neo-antigen presentation in the tumor microenvironment. To conduct this type of research, it is important to identify tumor-specific mutations that occur across all genes in the tumor genome. Thus, genome-wide approaches may be used for this effort. Note that in order to understand tumor-specific mutations, it is necessary to compare the tumor genome with the germline genome. Microsatellite instability may also be evaluated as this is an important biomarker for some cancers (ie, colorectal cancer). Circulating tumor DNA and/or RNA may also be evaluated from blood samples.

Tumor and blood RNA analyses

Both genome-wide and targeted messenger RNA (mRNA) expression profiling and sequencing in tumor tissue and in blood may be performed to define gene signatures that correlate to clinical response to treatment with immunotherapies and/or other treatments administered. Immunotherapies induce a response in tumors that likely reflects an inflamed/immune phenotype. Specific immune-related gene sets (ie, those capturing interferon-gamma transcriptional pathways) may be evaluated and new signatures may be identified. Individual genes related to the immune system may also be evaluated (eg, IL-10). MicroRNA profiling may also be pursued as well as exosomal profiling.

Proteomics and immunohistochemistry (IHC) using blood or tumor

Tumor and blood samples from this study may undergo proteomic analyses (eg, PD-L1 IHC). PD L1 protein level in tumor sections, assessed by IHC, has been shown to correlate with response to immunotherapy in patients with NSCLC, and an in vitro diagnostic (IVD) device has been developed for use with immunotherapy in NSCLC. Preliminary data indicates that this association may also be true in additional cancer types (ie, triple negative breast cancer, head and neck, and gastric). Additional tumor or blood-derived proteins may also correlate with response to immunotherapy. Therefore, tumor tissue may be subjected to proteomic analyses using a variety of platforms that could include but are not limited to immunoassays and liquid chromatography/mass spectrometry. This approach could identify novel protein biomarkers that could aid in patient selection for immunotherapy and/or treatments.

Peripheral Blood Mononuclear Cell (PBMC) Phenotypic Analysis

Phenotypic characterization and enumeration of immune suppressive cells (eg, myeloid-derived suppressor cells [MDSC], T_{regs}) and activated/proliferating T-cell subsets (eg, Ki67, human leukocyte antigen – antigen D related [HLA-DR]) circulating in blood collected at pre- and posttreatment time points may be assessed by flow cytometry as a potential pharmacodynamic biomarker downstream of target engagement.

Other biomarkers

In addition to expression on the tumor tissue, PD-L1 and other tumor derived proteins can be shed from tumor and released into the blood. Assays such as enzyme-linked immunoassay (ELISA) that measure proteins may also be evaluated from blood samples. Correlation of these biomarkers with response to immunotherapy and/or treatments may identify new approaches for predictive biomarkers in blood, representing a major advance from today's reliance on assessing tumor biomarkers. This research would serve to develop such assays for future clinical use.

Other molecular changes of interest include the subtype of T-cells in the tumor microenvironment. The T-cell repertoire from tumor tissue and blood components may be evaluated.

4.2.1.7 Future Biomedical Research

The Sponsor will conduct future biomedical research on specimens for which consent was provided during this study. This research may include genetic analyses (DNA), gene expression profiling (ribonucleic acid [RNA]), proteomics, metabolomics (serum, plasma) and/or the measurement of other analytes, depending on which specimens are consented for future biomedical research.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main study) and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for future biomedical research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that participants receive the correct dose of the correct drug/vaccine at the correct time. The details of this future biomedical research substudy are presented in Appendix 2.

4.3 Justification for Dose

4.3.1 Starting Dose for This Study

The starting dose for this study is 20 mg (0.3 mg/kg in an approximately 70 kg participant) of MK-1697 Q3W. This dose was determined based on an integrated analysis approach of all nonclinical dosing data. More information can be found in the IB. A 2-compartment PK model with linear and nonlinear clearance components was used to predict the anticipated serum-exposure profiles of MK-1697 in humans for a variety of doses. These predicted

exposures were then compared to the exposures observed in the nonhuman primate (NHP) toxicology studies The NOAEL in a 4-week toxicology study in Rhesus monkeys was estimated as 10 mg/kg given once weekly. The predicted maximum serum concentration (C_{max}) of the starting 20 mg dose level in humans provides an approximately 31- to 60-fold safety margin relative to the C_{max} observed in Rhesus monkeys in 2 independent studies at the NOAEL (Table 1). In addition, the anticipated exposure in humans at the 20 mg starting dose based on AUC comparison provides an approximately 20- to 44-fold safety margin to the AUC at steady state ($AUC_{0-\tau}$) observed in Rhesus monkeys at the NOAEL (Table 1).

Table 1 Predicted Pharmacokinetic Parameters in Humans at the Starting Dose and the Relative Fold Differences to these Parameters at the NOAEL in Rhesus Monkeys

PK parameter	Units	Rhesus monkey NOAEL (10 mg/kg /week)	Study #1		Study #2	
			Human (0.3 mg/kg)	Fold increase of human prediction over NOAEL in Rhesus monkeys	Human (0.3 mg/kg)	Fold increase of human prediction over NOAEL in Rhesus monkeys
C_{max}	nmol/L (nM)	7901	132	59.8	255	30.9
AUC[3,4]	nM day	23570	536	43.9	1210	19.4

Additionally, the 20 mg starting dose of MK-1697 is predicted to achieve >90% whole body occupancy in humans, as shown in Table 2. Based on previous Sponsor experience, this level of saturation is expected to be sufficient to elicit antitumor efficacy.

Table 2 Whole Body Target Saturation Corresponding To Predicted Maximum Concentration upon MK-1697 Dosing in Human

MK-1697 dose (mg/kg)	Predicted C_{max} in humans (nmol/L)		Predicted whole body target occupancy[1] (%)	
	Study #1	Study #2	Study #1	Study #2
0.1	43.5	83.9	78.5	87.6
0.3	132	255	91.7	95.5
1	457	906	97.5	98.7
3	1460	2820	99.2	99.6
10	5000	9550	99.8	99.9

[1] The % whole body target occupancy was calculated as (C_{max} / (C_{max} + Km)) * 100.

Additionally, results from the Sponsor's MK-4280-001 study, combining an anti-LAG-3 mAb (MK-4280) with pembrolizumab, have shown this combination to be well-tolerated. No DLTs were observed in any participants (N=47) treated with escalating doses of MK-4280 (ranging from 7 mg to 700 mg) either as monotherapy or in combination with pembrolizumab.

A fixed-dosing strategy, as opposed to weight-based dosing, is proposed for this study. Prior Sponsor experience has demonstrated that fixed-dosing can provide similar control of PK variability as weight-based dosing for monoclonal antibodies. Additionally, fixed-dosing has many advantages such as reduced dosing complexity and less potential for dosing errors.

Based on all of these assessments, the FIH starting dose of 20 mg (equivalent to 0.3 mg/kg in an approximately 70 kg participant) of MK-1697 Q3W is proposed.

4.3.2 Maximum Dose/Exposure for This Study

The higher planned doses for this study are 65 mg and 200 mg of MK-1697 Q3W. These were determined as half-log increases over the starting dose, rounded for ease of administration. These doses correspond approximately to 1 mg/kg and 3 mg/kg doses in a 70 kg participant. As shown in Table 2, the maximum dose of 200 mg corresponds to a >99% predicted whole body target occupancy. The predicted whole-body target saturation appears to plateau at this dose and, as such, this is proposed as the highest dose for the study. Additionally, as shown in Table 3, this maximum dose still provides an approximately 2.8- to 5.4-fold safety margin relative to the C_{max} observed in Rhesus monkeys at the NOAEL.

Table 3 Predicted Pharmacokinetic Parameters in Humans at the Highest Planned Dose and the Relative Fold Differences to these Parameters at the NOAEL in Rhesus Monkeys

PK parameter	Units	Rhesus monkey NOAEL (10 mg/kg /week)	Study #1		Study #2	
			Human (3 mg/kg)	Fold increase of human prediction over NOAEL in Rhesus monkeys	Human (3 mg/kg)	Fold increase of human prediction over NOAEL in Rhesus monkeys
C_{max}	nmol/L (nM)	7901	1460	5.4	2820	2.8

4.3.3 Rationale for Dose Interval and Study Design

The starting dose and dosing interval for MK-1697 are based on an integration of nonclinical, toxicological, PK and pharmacodynamics data. Dose escalation and confirmation will use a modified toxicity probability interval (mTPI) approach to identify a preliminary RP2D.

4.3.3.1 Dose Finding Using a Modified Toxicity Probability Interval Design

In Part A of this study, an mTPI design [Ji Y, Li Y, Bekele BN 2007] with a target toxicity rate of about 30% will be used to determine the RP2D of MK-1697.

Three predetermined dose levels of MK-1697 will be assessed: 20 mg (DL1), 65 mg (DL2), and 200 mg (DL3). Intermediate doses of MK-1697 may be used if one of the predetermined doses is deemed toxic and the immediate lower dose is deemed too low for potential efficacy. All dose-escalation decisions will be made based on the frequency of DLT(s) and will be

made in collaboration between the Sponsor and the investigators after the DLT observation period (ie, 21 days after the dose on Day 1 of the treatment cycle) of the last participant enrolled at each dose level is completed.

Treatment allocation will be accomplished by nonrandom assignment as described in Section 6.3.1 – Method of Treatment Assignment. An observation period of at least 72 hours will occur between treatment initiation in the first 2 participants enrolled within each dose level. Each new dose level will open for enrollment once the 21-day DLT observation period of the previous dose level is completed and decision is made to escalate the dose.

In Table 4, the number of participants treated is indicated in the columns and the number of participants who experience at least 1 DLT is indicated in the rows. Dosing decisions include: escalate to the next higher dose (E), stay at the current dose (S), deescalate to the next lower dose (D), and deescalate to a lower dose and never test this dose again (ie, unacceptably toxic dose; DU).

During dose escalation, a minimum of 3 participants are required at each dose. Depending on accrual rate, 3 to 6 participants may be initially enrolled at each new dose until the last of those participants completes the 21-day DLT observation period.

Based on the mTPI design, the number of participants who are enrolled at a dose but are not yet fully evaluable for DLT assessment may not exceed the number of remaining participants who are at risk of developing a DLT before the dose would be considered unacceptably toxic (DU). To determine how many more participants can be enrolled at a dose level, one can count steps in a diagonal direction (down and to the right) from the current cell to the first cell marked DU.

For example, if 3 participants are enrolled at a dose and none of them develops a DLT, then the dose can be escalated to the next level without further expansion. If 1 out of the first 3 participants develops a DLT, no more than an additional 3 participants may be enrolled at this dose level until additional DLT data are available since this dose would be considered unacceptably toxic if all 3 of the additional participants experience a DLT (ie, 4 out of 6 total participants). If 2 out of the first 3 participants at a given dose level develop a DLT, the dose will be deescalated to the next lower level. If 3 out of the first 3 participants at a given dose level develop a DLT, this dose will be considered unacceptably toxic and the dose will be deescalated and never re-escalated to that dose again. These same principles (see Table 4) will be applied whether 3, 4, 5, or 6 participants are initially enrolled in that dose level.

Dose escalation and confirmation will end after 14 participants have been treated at any of the selected doses (including intermediate or higher dose levels) and the decision based on Table 4 is to stay (or escalate if at the highest pre-determined dose level). If dose escalation proceeds to the highest dose level, the dose will be considered acceptably safe (and therefore Part B enrollment may begin) once the DLT period has been completed for enough participants (out of 14 total) such that, even if all remaining participants experienced a DLT, the mTPI table would still call for a ‘stay’ or ‘escalate’ decision. For example, if there was 0 DLTs with 12 participants enrolled at the highest dose, even if participants 13 and 14 both had DLTs, the mTPI decision would still be to stay at the highest dose.

The pool-adjacent-violators algorithm that forces the DLT rate estimates to be nondecreasing with dose levels and pools adjacent violators for weighted estimates by sample size will be used to estimate the DLT rates for each dose level.

The totality of the data will be considered when determining the preliminary RP2D to be used in Part B. In the event that a RP2D cannot be determined based on the totality of data collected from the dose escalation part of the study (ie, the MTD is not reached, high variability is seen with PK profiles, or target engagement cannot be confirmed), up to 2 doses of MK-1697 may be tested in a subset of the expansion part of the study, at the Sponsor's discretion.

Note that while 30% was the target toxicity rate used to generate the guidelines in Table 4, the observed rates of participants with DLTs at any given dose level may be slightly above or below 30%.

Table 4 Dose-finding Rules per mTPI Design

	Number of Participants Evaluable for DLT at Current Dose											
Number of Participants with at Least 1 DLT	3	4	5	6	7	8	9	10	11	12	13	14
0	E	E	E	E	E	E	E	E	E	E	E	E
1	S	S	S	E	E	E	E	E	E	E	E	E
2	D	S	S	S	S	S	S	S	E	E	E	E
3	DU	DU	D	S	S	S	S	S	S	S	S	S
4		DU	DU	DU	D	D	S	S	S	S	S	S
5			DU	DU	DU	DU	DU	D	S	S	S	S
6				DU	DU	DU	DU	DU	DU	D	S	S
7					DU	DU	DU	DU	DU	DU	DU	D
8						DU	DU	DU	DU	DU	DU	DU
9							DU	DU	DU	DU	DU	DU
10								DU	DU	DU	DU	DU
11									DU	DU	DU	DU
12										DU	DU	DU
13											DU	DU
14												DU

E = Escalate to the next higher dose
S = Stay at the current dose
D = De-escalate to the next lower dose
DU = The current dose is unacceptably toxic
Target toxicity rate = 30%
Flat non-informative prior Beta (1,1) is used as a prior and ε1=ε2=0.03[Ji Y, Li Y, Bekele BN 2007].

4.4 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 telephone-call or visit, withdraws from the study or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

4.4.1 Clinical Criteria for Early Study Termination

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

1. Incidence or severity of adverse drug reactions in this or other trials suggest a potential health hazard to participants
2. Plans to modify or discontinue the development of the trial drug
3. Poor adherence to protocol and regulatory requirements
4. Quality or quantity of data recording is inaccurate or incomplete

Ample notification will be provided in the event of Sponsor decision to no longer supply MK-1697.

5. Study Population

Male/Female participants of at least 18 years of age with advanced solid tumors will be enrolled in this study.

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

5.1 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. **Part A** - Have a histologically- or cytologically-confirmed advanced/metastatic solid tumor by pathology report and have received, or been intolerant to, or been ineligible for all treatments known to confer clinical benefit.

2. **Part B** – Have 1 of the following histologically or cytologically confirmed tumor types confirmed by pathology report and are anti-PD-1/PD-L1-treatment-naïve:

    a. HNSCC that is considered incurable by local therapies. Participants should have progressed after receiving platinum-containing systemic therapy. Systemic therapy given as part of multimodal treatment for locally advanced disease is allowed. The eligible primary tumor locations are oropharynx, oral cavity, hypopharynx, and larynx. Participants may not have a primary tumor site of nasopharynx (any histology).

b. CRC originating in either the colon or rectum that is locally advanced unresectable or metastatic (ie, Stage IV) and that has received, and progressed on, all available standard-of-care therapies including fluoropyrimidine, oxaliplatin, and irinotecan.

3. Have measurable disease by RECIST 1.1 as assessed by the local site investigator/radiology. Target lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.

4. Submit an evaluable baseline tumor sample for analysis (either an archival or recently obtained tumor sample). Details pertaining to tumor tissue submission can be found in the Laboratory Manual.

5. Have a performance status of 0 or 1 on the ECOG Performance Scale

6. Have central venous access (eg, portacath, Hickman line, or peripherally inserted central catheter [PICC] line) currently inserted or be considered medically fit for (in the opinion of the investigator and/or treating surgeon) and willing to undergo the insertion of such a device.

   Note: This Inclusion Criterion only applies to participants who are being considered for enrollment at a dose level that requires administration into a central vein. See the Laboratory Manual and Pharmacy Manual for more details on dose levels to which this applies.

7. Demonstrate adequate organ function as defined by Table 5 (labs to be obtained within 7 days of treatment initiation)

Table 5 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[1]
Renal	
Creatinine OR Measured or calculated[2] 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
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)
Coagulation	
INR or PT aPTT (PTT may be substituted)	≤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); GFR=glomerular filtration rate; ULN=upper limit of normal.

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

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

Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations.

Demographics

Male participants:

8. A male participant must agree to use a contraception as detailed in Appendix 3 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:

9. A female participant is eligible to participate if she is not pregnant (see Appendix 3), not breastfeeding, and at least one of the following conditions applies:
   a.) Not a woman of childbearing potential (WOCBP) as defined in Appendix 3
   OR
   b.) A WOCBP who agrees to follow the contraceptive guidance in Appendix 3 during the treatment period and for at least 120 days after the last dose of study treatment.

Informed Consent

10. Be ≥ 18 years of age on the day of signing the ICF

11. The participant (or legally acceptable representative if applicable) provides written informed consent for the study. The participant may also provide consent for future biomedical research. However, the participant may participate in the main study without participating in future biomedical research.

5.2 Exclusion Criteria

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

Medical Conditions

1. Has a history of a second malignancy, unless potentially curative treatment has been completed with no evidence of malignancy for 3 years.

   Note: The time requirement does not apply to participants who underwent successful definitive resection of basal cell carcinoma of the skin, superficial bladder cancer or *in situ* cervical cancer, or other *in-situ* cancers.

2. Has clinically active central nervous system (CNS) metastases and/or carcinomatous meningitis. Participants with previously-treated brain or meningeal metastases may participate and be eligible for treatment provided they are stable and asymptomatic (without evidence of progression by magnetic resonance imaging (MRI) scan of the brain separated by at least 4 weeks after treatment), have no evidence of new or enlarging brain metastases, are evaluated within 4 weeks prior to first study treatment administration, and are off immunosuppressive doses of systemic steroids at least 2 weeks prior to enrollment.

3. Has had a severe hypersensitivity reaction to treatment with any monoclonal antibody and/or components of the study treatment.

4. Has an active infection requiring therapy.

5. Has a history of interstitial lung disease.

6. Has a history of (noninfectious) pneumonitis that required steroids or current pneumonitis.

7. Has an active autoimmune disease that has required systemic treatment in the past 2 years (ie, with use of disease-modifying agents, corticosteroids, or immunosuppressive drugs) except vitiligo or resolved childhood asthma/atopy. Replacement therapy, such as thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, is not considered a form of systemic treatment and is allowed. Use of nonsystemic steroids is permitted.

8. Participants with known human immunodeficiency virus (HIV) and/or Hepatitis B or C infections, or known to be positive for Hepatitis B antigen (HBsAg)/ Hepatitis B virus (HBV) DNA or Hepatitis C Antibody or RNA.

9. 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, make administration of the study treatments hazardous or make it difficult to monitor adverse effects such that it is not in the best interest of the participant to participate, in the opinion of the treating investigator

10. Has a history or current evidence of severe cardiovascular disease, ie, arrhythmias requiring chronic treatment, congestive heart failure (New York Heart Association [NYHA] Class III or IV) or symptomatic ischemic heart disease.

11. Has a known psychiatric or substance abuse disorder that would interfere with the participant's ability to cooperate with the requirements of the trial.

12. 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.

13. Has not fully recovered from any effects of major surgery without significant detectable infection. Surgeries that required general anesthesia must be completed at least 2 weeks before first study treatment administration. Surgery requiring regional/epidural anesthesia must be completed at least 72 hours before first study treatment administration and participants should be recovered.

14. Has known MSI high or MMR deficient colorectal cancer (as determined by PCR, IHC, or a validated NGS panel [eg. Foundation Medicine or MSKImpact]). If a participant's MSI status is unknown, a paired blood sample for MSI in addition to biomarker testing is required to determine MSI status retrospectively (for the CRC expansion cohort only).

15. A WOCBP who has a positive urine pregnancy test within 72 hours before the first dose of study treatment. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

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

Prior/Concomitant Therapy

16. Has had chemotherapy, definitive radiation, or biological cancer therapy within 4 weeks (2 weeks for palliative radiation) prior to the first dose of study therapy, or has not recovered to CTCAE Grade 1 or better from any adverse events that were due to cancer therapeutics administered more than 4 weeks earlier (this includes participants with previous immunomodulatory therapy with residual immune-related adverse events). Participants receiving ongoing replacement hormone therapy for endocrine immune-related adverse events will not be excluded from participation in this study.

    Note: Participants with ≤ Grade 2 neuropathy may be eligible after consultation with the Sponsor.

    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.

17. Has received prior therapy with an anti-LAG-3 agent.

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

19. Has undergone a prior stem cell or bone marrow transplant within the last 5 years.

    Note: Participants who have had a transplant greater than 5 years ago are eligible as long as there are no symptoms of graft-versus-host disease (GVHD).

20. Is expected to require any other form of antineoplastic therapy while on study.

Prior/Concurrent Clinical Study Experience

21. 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.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

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

5.3.2 Contraception

MK-1697 may have adverse effects on a fetus in utero. Refer to Appendix 3 for approved methods of contraception.

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 this study, participants of childbearing potential must adhere to the contraception requirement (Appendix 3) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of study medication. If there is any question that a participant of childbearing potential will not reliably comply with the requirements for contraception, that participant should not be entered into the study.

5.3.3 Pregnancy

If a participant inadvertently becomes pregnant while on treatment with MK-1697, 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 the Sponsor without delay and within 24 hours if the outcome is a serious adverse experience (eg, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study Investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. 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 the Sponsor and followed as described in Section 8.4.

5.3.4 Use in Nursing Women

It is unknown whether MK-1697 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.

5.4 Number of Participants

The total number of participants enrolled will depend on the frequency of DLTs observed in Part A and on which expansion cohorts (if any) discontinue enrollment early in Part B. For planning purposes and under the assumption that 3 doses will be tested during Part A with up to 14 participants in each of the 3 dose levels, followed by 2 expansion cohorts in Part B with up to 40 participants each, we assume an approximate maximum sample size of 122 participants. See Section 9.9 for a more thorough description of sample size and power calculations.

5.5 Screen Failures

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

5.6 Participant Replacement Strategy

In order to adequately evaluate the safety of the doses administered in this study, all participants enrolled in the dose escalation phase must meet the criteria for evaluability for Cycle 1. Participants are considered nonevaluable and will be replaced if:

- They are allocated but not treated
- They discontinue from the trial prior to completing all the safety evaluations for reasons other than treatment-related adverse events
- They receive less than 75% of the total MK-1697 infusion in Cycle 1 (eg, if the infusion had to be discontinued due to an infusion reaction) and did not experience a DLT

Participants who are nonevaluable will be replaced unless accrual to the expansion cohort has stopped. Nonevaluable participants will not be counted toward the total number of participants in the expansion cohort for DLT evaluation.

If a participant experiences a DLT in Cycle 1, trial treatment may be discontinued following discussion between the sponsor and investigator. However, if the participant is deriving clinical benefit from the trial treatment, the participant may be allowed to continue after discussion between the Sponsor and the investigator.

6. 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 the Sponsor] will be packaged to support enrollment as required. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Treatments Administered

The study treatment to be used in this study is outlined below in Table 6.

Table 6 Study Treatment

Study Treatment Name	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period	Use	IMP/NIMP	Sourcing
MK-1697	Solution for Infusion	10 mg/mL	**Part A:** 20 mg 65 mg 200 mg **Part B:** Preliminary RP2D	IV infusion	Q3W for up to 35 cycles	Experimental	IMP	Provided centrally by the Sponsor
Definition Investigational Medicinal Product (IMP) and Non- Investigational Medicinal Product (NIMP) is based on guidance issued by the European Commission. Regional and/or Country differences of the definition of IMP/NIMP may exist. In these circumstances, local legislation is followed.								

All supplies indicated in Table 6 will be provided per the 'Sourcing' row depending upon local country operational requirements. Every attempt should be made to source these supplies from a single lot/batch number where possible (eg, not applicable in the case where multiple lots or batches may be required due to the length of the study etc.).

Refer to Section 8.1.8 for details regarding administration of the study treatment.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each participant. The rationale for selection of doses to be used in this study is provided in Section 4.3.

6.2.2 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 study sites, the local country Sponsor 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 study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product (if applicable) as per local guidelines unless otherwise instructed by the Sponsor.

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.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Method of Treatment Assignment

Participants participating in this study will be allocated by nonrandom assignment.

6.3.1.1 Stratification

In Part A of the study, no stratification based on age, sex or other characteristics will be used.

In Part B of the study, treatment allocation/randomization will be stratified according to the following factors:

1. Tumor type

6.3.2 Blinding

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

6.4 Treatment Compliance

Interruptions from the protocol specified treatment plan for ≥12 weeks require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

6.5 Concomitant Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medication or vaccination specifically prohibited, discontinuation from study treatment may be required. The investigator should discuss any questions regarding this with the Sponsor 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, the Sponsor and the participant.

Listed below are specific concomitant therapies and vaccinations prohibited during the course of the study:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents not specified in this protocol
- Radiation therapy

  Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the Investigator’s discretion.

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

- Prolonged therapy with systemic glucocorticoids (>7 days) for any purpose other than the management of AEs as described in Section 6.6. Brief, limited use of systemic corticosteroids (≤7 days) are permitted where such use is considered standard of care (eg, for COPD exacerbation). The use of physiologic doses of corticosteroids (ie, prednisone 5 to 7.5 mg daily) may be approved after consultation with the Sponsor. The use of local steroids 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 study.

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

All concomitant medications received within 28 days prior to the first dose of study treatment and up to 30 days after the last dose of study treatment should be recorded. Concomitant medications administered 30 days after the last dose of study treatment should be recorded for SAEs and events of clinical interest (ECIs) as defined in Section 8.4.

6.5.1 Supportive Care

AEs associated with immunomodulatory agents such as MK-1697 may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of MK-1697 treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on clinical study data for pembrolizumab, most irAEs were reversible and could be managed with interruptions of study treatment, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, or skin biopsy may be included as part of the evaluation.

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 6.6, Table 7. 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 MK-1697.

Note: If after the evaluation of the event, it is determined not to be related to MK-1697, the Investigator does not need to follow the treatment guidance. Refer to Table 7 in Section 6.6 for guidelines regarding dose modification and supportive care.

6.6 Dose Modification

Dose modification and toxicity management guidelines for irAEs associated with MK-1697 are provided in Table 7.

Table 7 Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with MK-1697

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 MK-1697 has been withheld, MK-1697 can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. MK-1697 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.

Immune-related AEs	**Toxicity grade or conditions (CTCAEv4.0)**	**Action taken to MK-1697**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue		

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to MK-1697	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to MK-1697	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Guillain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

1. Withhold or permanently discontinue MK-1697 is at the discretion of the investigator or treating physician.

NOTES:

For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of MK-1697 is required, MK-1697 may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

All Grade 1 AEs should be treated with appropriate supportive care, but treatment should not be withheld or discontinued, unless stated otherwise.

Dose modification and toxicity management of infusion-reactions related to MK-1697

Immuno-modulators such as MK-1697 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 MK-1697-associated infusion reaction are provided in Table 8.

Table 8 MK-1697 Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment.**	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of MK-1697 with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further study drug 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		

6.6.1 Definition of Dose-Limiting Toxicity

All toxicities will be graded using NCI-CTCAE Version 4.0 based on the investigator assessment.

The DLT window of observation will be during Cycle 1.

The occurrence of any of the following toxicities during Cycle 1 will be considered a DLT, if assessed by the investigator to be possibly, probably, or definitely related to study intervention administration:

- Grade 4 non-hematologic toxicity (not laboratory)
- Grade 4 hematologic toxicity lasting at least 7 days, except thrombocytopenia, which is a DLT as follows:
    - Grade 4 thrombocytopenia of any duration
    - Grade 3 thrombocytopenia if associated with clinically significant bleeding
- Any Grade 3 or higher nonhematologic clinical AE should be considered a DLT, except for the following: Grade 3 fatigue lasting ≤3 days and Grade 3 rash without use of corticosteroids or anti-inflammatory agents per standard of care. Grade 3 nausea, vomiting, or diarrhea lasting greater than 72 hours, despite use of anti-emetics, anti-diarrheals, or other supportive care, should be considered a DLT.
- Any Grade 3 or Grade 4 non-hematologic laboratory value, if
    - Clinically significant medical intervention is required to treat the participant, or
    - The abnormality leads to hospitalization, or
    - The abnormality persists for more than 1 week, or
    - The abnormality results in a Drug-induced Liver Injury (DILI)
- Grade 3 or Grade 4 febrile neutropenia
    - Grade 3 is defined as absolute neutrophil count (ANC) <1000/mm^3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than 1 hour

- Grade 4 is defined as ANC <1000/mm^3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than 1 hour, with life-threatening consequences and urgent intervention indicated

- Any treatment-related toxicity that caused the participant to discontinue treatment during Cycle 1
- Missing >25% of the intended MK-1697 dose as a result of drug-related AE(s) during the first cycle
- Grade 5 toxicity
- Any treatment-related toxicity that causes a greater than 2-week delay in initiation of Cycle 2.

6.7 Treatment After the End of the Study

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

6.8 Clinical Supplies Disclosure

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

7. Discontinuation of Study Treatment and Participant Withdrawal

7.1 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 1.3 and Section 8.11.3.

Participants may discontinue study treatment at any time for any reason or be discontinued 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 the Sponsor if study treatment is inappropriate, the study 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 8.1.9.

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 interrupts study treatment administration for more than 12 consecutive weeks (unless Sponsor approval to continue – See Section 6.4)
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study treatment.
- The participant has a confirmed positive serum pregnancy test.
- The participant has confirmed radiographic disease progression as outlined in Section 8.2.2.
- The participant experiences any progression or recurrence of any malignancy, or any occurrence of another malignancy, that requires active treatment.
- The participant demonstrates noncompliance with study treatment or procedure requirements.
- The participant experiences recurrent Grade 2 pneumonitis.
- The participant completes 35 treatments (approximately 2 years) with MK-1697.
- The participant experiences an overdose, and after consultation with the Sponsor (Section 8.5).

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

Discontinuation from study treatment is "permanent." Once a participant is discontinued, he/she shall not be allowed to restart study treatment.

7.2 Participant 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, as well as specific details regarding withdrawal from future biomedical research are outlined in Section 8.1.9.1. 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 7.3.

7.3 Lost to Follow-up

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

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.

- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone 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 missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.

8. 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 study 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 the Sponsor 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.

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, is described in detail in the accompanying Laboratory Manual.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General Procedures

8.1.1 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 study or future biomedical research. If there are changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or qualified designee must ensure the appropriate consent is in place.

8.1.1.1 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 study.

The initial ICF, any subsequent revised written ICF and any written information provided to the participant must receive the Institutional Review Board/Independent Ethics Committee's (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 study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's dated signature or by the participant's legally acceptable representative's dated signature.

The participant or his/her legally acceptable representative will be asked to sign consent at the point of initial radiographic disease progression.

Specifics about a study and the study 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 Sponsor requirements.

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or qualified designee will explain the future biomedical research consent to the participant, answer all of his/her questions, and obtain written informed consent before performing any procedure related to the future biomedical research substudy. A copy of the informed consent will be given to the participant.

8.1.2 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.

8.1.3 Participant Identification Card

All participants will be given a Participant Identification Card identifying them as participants in a research study. The card will contain study 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.

8.1.4 Medical History

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

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use and record prior medication taken by the participant within 28 days before the first dose of study medication. Additionally, the investigator or qualified designee will review and record all prior treatment and medication the participant has received for the indication they are enrolled into the trial for.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study.

8.1.6 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 treatment allocation. 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 8.11.1.

8.1.7 Assignment of Treatment/Randomization Number

All eligible participants will be allocated, by nonrandom assignment, 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.

8.1.8 Treatment Administration

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

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

8.1.8.1 Timing of Dose Administration

MK-1697 will be administered as an IV infusion Q3W. The reason for any variability in administration of MK-1697 outside of the protocol-specified window should be documented in the participant's chart and recorded on the electronic case report forms (eCRFs).

Every effort should be made to begin the first dose of study treatment on the day of allocation, but if this is not achieved, study treatment should be initiated no later than 3 days from the date of allocation. All subsequent cycles of study treatment may be administered up to 3 days before or 3 days after the scheduled Day 1 of each cycle due to administrative reasons per the investigator's judgement (Cycle 2 treatment may be administered up to 3 days *after* the scheduled Day 1, only). All study treatments will begin on Day 1 of each cycle after all predose study procedures and assessments have been completed except as otherwise indicated in Section 1.3 – Schedule of Activities.

8.1.8.2 Central Venous Access for MK-1697 Administration

All dose levels of MK-1697 below 65 mg require administration directly into a central vein due to the concentration of the supplied drug product and acceptable rate of infusion. See the accompanying Laboratory Manual and Pharmacy Manual for more information. If an enrolled participant does not have central venous access (eg, portacath, Hickman line, or PICC line) currently inserted, the participant should undergo a procedure to have such a device inserted. This should be done in accordance with the standard operating procedures of the local site. This procedure should not be performed until the participant has completed all other screening procedures/assessments and they have been determined to be eligible for the study.

8.1.9 Domiciling

An inpatient observation for at least 24 hours may be performed, at the Investigator's discretion, on Cycle 1, Day 1 for participants treated at the first dose level of MK-1697. If performed, participants will report to the clinical research unit on Cycle 1, Day 1 and will remain for inpatient observation for at least 24 hours. The inpatient observation period may also be extended to the higher dose levels of MK-1697 at the discretion of the Investigator, local Institutional Review Board, Ethics Review Committee, and/or Health Authority requirement.

8.1.10 Discontinuation and Withdrawal

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

When a participant withdraws from participation in the study, all applicable activities scheduled for the final study visit (ie, End of Treatment/Discontinuation as indicated in the SoA) should be performed (at the time of withdrawal). Any AEs which are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4 .

8.1.10.1 Withdrawal From Future Biomedical Research

Participants may withdraw their consent for future biomedical research. Participants may withdraw consent at any time by contacting the principal investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the participant's consent for future biomedical research will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the participant of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main study records) or the specimens have been completely anonymized, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for specimen withdrawal cannot be processed.

8.1.11 Participant Blinding/Unblinding

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

8.1.12 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.

8.2 Efficacy Assessments

8.2.1 Tumor Imaging and Assessment of Disease

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

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

8.2.1.1 Initial Tumor Imaging

Initial tumor imaging at screening must be performed within 28 days prior to the date of allocation.

Scans 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 allocation.

Participants with previously-treated brain metastases may participate provided they have stable brain metastases, ie, without evidence of progression by imaging (confirmed by magnetic resonance imaging (MRI) if MRI was used at prior imaging or confirmed by computed tomography (CT) imaging if CT used at prior imaging) for at least 4 weeks prior to the first dose of trial treatment. Any neurologic symptoms must have returned to baseline and participants must have no evidence of new or enlarging brain metastases and have not used steroids for brain metastases for at least 2 weeks prior to trial initiation as per local site assessment. This exception does not include carcinomatous meningitis, as participants with carcinomatous meningitis are excluded regardless of clinical stability.

8.2.1.2 Tumor Imaging During the Trial

The first on-study imaging assessment should be performed at 9 weeks (63 days ±7 days) from the date of allocation. Subsequent tumor imaging should be performed every 9 weeks (63 days ±7 days) or more frequently if clinically indicated. After 54 weeks, participants who remain on treatment will have imaging performed every 12 weeks (84 ±7 days). Imaging

timing should follow calendar days and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until disease progression, the start of new anticancer treatment, withdrawal of consent, or death, whichever occurs first.

Per RECIST 1.1, partial and complete response should be confirmed by a repeat tumor imaging assessment not less than 4 weeks from the date the response was first documented. The tumor imaging for confirmation of response may be performed at the earliest 4 weeks after the first indication of response, or at the next scheduled scan (ie, 9 weeks later), whichever is clinically indicated. Participants will then return to regular scheduled imaging, starting with the next scheduled imaging time point. Participants who obtain a confirmation scan do not need to undergo the next scheduled tumor imaging if it is <4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point.

Per iRECIST, disease progression should be confirmed by the site at least 4 weeks after first radiologic evidence of PD in clinically stable participants. Participants who have unconfirmed disease progression may continue on treatment at the discretion of the investigator until progression is confirmed provided they have met the conditions detailed in Section 8.2.2. Participants who obtain a confirmation scan do not need to undergo the next scheduled tumor imaging if it is <4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point if clinically stable. Participants who have confirmed disease progression as assessed by the site will discontinue the treatment.

8.2.2 iRECIST Assessment of Disease

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 investigator/local radiology reviewers to assess tumor response and progression, and to make treatment decisions. These data will be collected in the clinical database.

When feasible, participants should not be discontinued until progression is confirmed by the local investigator/radiology assessment. This allowance to continue treatment despite initial radiologic progressive disease (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. Participants who are deemed clinically unstable are not required to have repeat tumor imaging for confirmation of PD. Tumor flare includes any of the following scenarios:

- Worsening of existing target lesion(s)
- Worsening of existing nontarget lesion(s)
- Development of new lesion(s)

In participants who have shown initial evidence of radiological PD by RECIST 1.1 as determined by the site, it is at the discretion of the investigator whether to continue a participant on study treatment until repeat imaging is obtained (using iRECIST for participant management, see Table 9). This clinical judgment decision by the site investigator should be based on the participant's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Participants may receive study treatment and the

tumor assessment should be repeated ≥4 weeks later in order to confirm PD by iRECIST per site assessment. 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
- Absence of rapid progression of disease
- Absence of progressive tumor at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention

Any participant deemed clinically unstable should be discontinued from trial treatment at site-assessed first radiologic evidence of PD and is not required to have repeat imaging for PD confirmation.

In determining whether or not the tumor burden has increased or decreased per iRECIST, the local site investigator should consider all target and nontarget lesions, as well as any incremental new lesion(s).

Scenarios in which PD is not confirmed at repeat imaging if ALL of the following occur by iRECIST:

- Target lesion sum of diameters is <20% or <5 mm absolute increase compared with nadir
- Nontarget disease resulting in initial PD is stable or qualitatively improved
- New lesion resulting in initial PD is stable or qualitatively improved
- No incremental new lesion(s) since last evaluation
- No incremental new nontarget lesion progression since last evaluation

If repeat imaging does not confirm PD per iRECIST as assessed by the local site investigator and the participant continues to be clinically stable, treatment may continue and follow the regular imaging schedule.

Scenarios in which PD is confirmed at repeat imaging if ANY of the following occur by iRECIST:

- Target lesion sum of diameters remains ≥ 20% and at least 5 mm absolute increase compared to nadir
- Nontarget disease resulting in initial PD is qualitatively worse
- New lesion resulting in initial PD is qualitatively worse
- Additional new lesion(s) since last evaluation

- Additional new nontarget lesion progression since last evaluation

If repeat imaging confirms PD due to any of the scenarios listed above, participants will be discontinued from study therapy.

Additional details about iRECIST are referenced in Merck TIP Sheet for RECIST 1.1 and iRECIST.

Table 9 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	Repeat imaging at >4 weeks at site to confirm PD	May continue study treatment at the local site investigator's discretion while awaiting confirmatory tumor imaging by site by iRECIST.	Repeat imaging at >4 weeks to confirm PD per physician discretion only	Discontinue treatment
Repeat tumor imaging confirms PD by iRECIST at the local site	No additional imaging required	Discontinue treatment	No additional imaging required	N/A
Repeat tumor imaging shows iUPD by iRECIST per investigator assessment	Repeat imaging at >4 weeks at site to confirm PD. May occur at next regularly scheduled imaging visit	Continue study treatment at the investigator's discretion.	Repeat imaging at >4 weeks to confirm PD per investigator's discretion only	Discontinue treatment
Repeat tumor imaging shows SD, PR, or CR by iRECIST at the local site	Continue regularly scheduled imaging assessments	Continue study treatment at the local site investigator's discretion	Continue regularly scheduled imaging assessments	May restart study treatment if condition has improved and/or clinically stable per investigator's discretion. Next tumor image should occur according to the regular imaging schedule outlined in the protocol

8.2.3 Medical Photography of Cutaneous Lesions

For participants with cutaneous lesions where photography is clinically indicated, qualitative digital photography should be performed at the timepoints specified in the SoA. Cutaneous lesions are not considered measurable for the purposes of this trial but may be considered as non-target lesions for tumor assessments by the investigator. Information regarding submission and/or retention of the digital photographs is included in the SIM.

8.2.4 ECOG Performance Status

The investigator or qualified designee will assess ECOG status at screening, prior to the administration of each dose of trial treatment, and during the follow-up period as specified in the SoA.

8.3 Safety Assessments

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

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

8.3.1 Physical Examinations

8.3.1.1 Full Physical Exam

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

8.3.1.2 Directed Physical Exam

For visits that do not required a full physical exam per the SoA, the investigator or qualified designee will perform a directed physical exam as clinically indicated. New clinically significant abnormal findings should be recorded as AEs.

8.3.2 Vital Signs

The investigator or qualified designee will take vital signs at specified time points as indicated in the SoA. Vital signs include temperature, pulse, respiratory rate, and blood pressure. Additionally, height and weight will be measured as specified in the SoA.

8.3.3 Electrocardiograms

A standard 12-lead ECG will be performed using local standard procedures. The timing of ECGs is specified in the SoA. Clinically significant abnormal findings from the screening ECG should be recorded as medical history. Additional ECGs may be performed as

clinically necessary over the course of the study. Clinically significant abnormal findings for any ECGs performed after the first dose of study treatment should be recorded as AEs.

8.3.4 Clinical Safety Laboratory Assessments

Refer to Appendix 5 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 case report form (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 5, must be conducted in accordance with the Laboratory Manual and the SoA.

- If laboratory values from nonprotocol 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.

Details regarding specific laboratory 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 trial (from pre-trial to post-trial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant can be found in the Study Laboratory Manual. Refer to the SoA for the schedule of laboratory assessments.

8.3.4.1 Laboratory Safety Evaluations (Hematology, Chemistry, and Urinalysis)

Laboratory tests for hematology, chemistry, and urinalysis are specified in Appendix 5.

Laboratory tests for screening should be performed within 7 days prior to the first dose of study treatment. Exceptions are HIV, hepatitis and thyroid serologies, and lipase & amylase, which may be performed within 28 days prior to first dose. Predose laboratory safety tests can be conducted up to 72 hours prior to dosing.

Laboratory test results must be reviewed by the investigator or qualified designee and found to be acceptable prior to administration of each dose of trial treatment. Unresolved abnormal laboratory values that are drug-related AEs should be followed until resolution. Laboratory tests do not need to be repeated after the end of treatment if laboratory results are within normal range.

8.3.4.2 Pregnancy Testing

All women who are being considered for participation in the trial, and who are not surgically sterilized or postmenopausal, must be tested for pregnancy as described in the SoA. 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 serum test result.

8.4 Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Reportable Safety Events

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

Progression of the cancer under study is not considered an AE as described in Section 8.4.5 and Appendix 4.

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

The investigator, who is a qualified physician, and any designees are responsible for detecting, assessing, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AE, SAEs, and other reportable safety events for outcome according to Section 8.4.3.

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

- All AEs from the time of treatment allocation/randomization through 90 days following cessation of study treatment must be reported by the investigator.
- All AEs meeting serious criteria, from the time of treatment allocation/randomization through 90 days following cessation of study treatment must be reported by the investigator.
- All pregnancies and exposure during breastfeeding, from the time of treatment allocation/randomization through 120 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy must be reported by the investigator.
- Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately to the Sponsor if the event is considered to be drug-related.

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

All initial and follow-up AEs, SAEs and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 10.

Table 10 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event		Time Period				Time Frame to Report Event and Follow-up Information to SPONSOR:
		Consent to Randomization/ Allocation	Randomization/ Allocation through Protocol-Specified Follow-up Period	After the Protocol Specified Follow-up Period		
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 drug-induced liver injury (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

8.4.2 Method of Detecting AEs, SAEs, 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 nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.4.3 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, events of clinical interest (ECIs), 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 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 4.

8.4.4 Regulatory Reporting Requirements for SAE

- Prompt notification (within 24 hours) by the investigator to the Sponsor 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 has 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 AEs will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, ie, per ICH Topic E6 (R2) Guidelines for GCP.

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

8.4.5 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

Efficacy endpoints as outlined in this section will not be reported to the Sponsor as described in Section 8.4.1.

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

The Sponsor 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 Global Pharmacovigilance as an SAE within 24 hours of determination that the event is not progression of the cancer under study.

8.4.6 Pregnancy and Exposure During Breastfeeding

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

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.

8.4.7 Events of Clinical Interest (ECIs)

Selected nonserious and serious adverse events are also known as ECIs and must be reported to the Sponsor.

Events of clinical interest for this study include:

1. an overdose of Sponsor's product, as defined in Section 8.5, 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 study site guidance for assessment and follow-up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

8.5 Treatment of Overdose

For purposes of this study, an overdose will be defined as any dose exceeding the prescribed dose for MK-1697 by ≥20% of the indicated dose. No specific information is available on the treatment of overdose of MK-1697. In the event of overdose, MK-1697 therapy should be discontinued after discussion with the Sponsor and the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

8.6 Pharmacokinetics

To further evaluate MK-1697 immunogenicity and exposure in this indication, and also to evaluate exposure of the proposed dosing regimen, sample collections for analysis of antidrug antibodies (ADA) and PK are currently planned as shown in the SoA. Blood samples will be obtained to measure PK of serum MK-1697. The MK-1697 C_{max} and C_{min} at planned visits and times will be summarized. Sample collection, storage and shipment instructions will be provided in the Laboratory Manual.

8.6.1 Antidrug Antibodies

Sample collection, storage and shipment instructions for serum samples will be provided in the Laboratory Manual. Anti-MK-1697 antibody samples should be drawn according to the ADA collection schedule for all participants in the SoA. Every effort should be taken to collect samples at 30 days after end of study treatment for ADA. Simultaneous PK sampling is required for interpretation of ADA analysis. If additional samples are deemed necessary to evaluate the risk of immunogenicity (e.g. at early time points), the remaining content of a PK sample (after analysis for drug levels) may be used to perform the analysis for ADA.

8.7 Pharmacodynamics

Venous blood samples will be collected for measurement of sLAG-3 and PD-1 target engagement. Sample collection, storage and shipment instructions for blood samples will be provided in the Laboratory Manual.

Note: If ongoing PK, pharmacodynamic, and/or ADA sampling is deemed to be unnecessary by the Sponsor, it may be reduced or discontinued. This will be communicated to sites via an administrative letter.

8.8 Tumor Biopsies

Tumor biopsies will be collected pre-treatment and in Cycle 2 from the first 10 participants enrolled into the HNSCC or CRC expansion cohorts of Part B. An additional, optional biopsy will be performed within 4 weeks after disease progression for participants in the HNSCC or CRC cohorts of Part B who achieved either a CR, PR, or SD while participating in the study. Biopsies will be performed in keeping with local clinical practice. Additional details regarding the collection, storage, and shipment of tumor biopsies will be provided in the Laboratory Manual.

8.9 Biomarkers

To identify novel biomarkers, the following biospecimens to support exploratory analyses of cellular components (eg, protein, RNA, DNA, metabolites) and other circulating molecules will be collected from all participants in this study as specified in the SoA:

- Blood for Genetic Analysis
- Peripheral Blood for Immunophenotyping
- Blood for circulating tumor DNA

- Blood for RNA Analysis
- Blood for plasma biomarker analyses
- Blood for serum biomarker analyses
- Archival and/or recently obtained tumor tissue
- Tumor Biopsy

Note: Sampling for the above-mentioned biomarkers may be reduced or discontinued at any point during the trial based on collected data. This will be communicated to sites via an administrative letter.

Sample collection, storage and shipment instructions for the exploratory biomarker specimens will be provided in the laboratory manual.

The sample for genetic analysis will be drawn for HLA genotyping and for planned exploratory biomarker research. If the IRB/IEC does not approve of the exploratory genetic analysis, or if there is a local law or regulation prohibiting the same, data analysis will be limited to HLA. Leftover extracted DNA will be stored for future biomedical research if the participant signs the future biomedical research consent.

8.10 Future Biomedical Research Sample Collection

If the participant signs the future biomedical research consent, the following specimens will be obtained as part of future biomedical research:

- Leftover DNA
- Leftover RNA
- Leftover plasma from circulating tumor DNA
- Leftover plasma from biomarker analyses
- Leftover serum from biomarker analyses
- Leftover main study tumor

8.11 Visit Requirements

Visit requirements are outlined in Section 1.3. Specific procedure-related details are provided above in Section 8.

8.11.1 Screening Phase

Approximately 28 days prior to treatment allocation, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1 and Section 5.2. Screening procedures may be repeated after consultation with the Sponsor.

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

- Laboratory tests (urinalysis, hematology, chemistry, GGT, and PT/INR & aPTT) are to be performed within 7 days prior to the first dose of trial treatment. Exceptions are lipase & amylase, thyroid, HIV, and hepatitis serology testing, which may be done up to 28 days prior to the first dose of trial treatment.

- For women of reproductive potential, a urine or serum pregnancy test will be performed within 72 hours prior to the first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory).

- An archival or recently obtained tumor sample should be submitted during screening and may have been collected at any point prior to the first dose of treatment.

8.11.2 Treatment Phase

Visit requirements during the Treatment Phase of the study are outlined in Section 1.3 – Schedule of Activities (SoA). Specific procedure-related details are provided above in Section 8 – Study Assessments and Procedures.

8.11.3 Discontinued Participants Continuing to be Monitored in the Study

The End of Treatment/Discontinuation Visit should occur at the time study treatment is discontinued for any reason. If the End of Treatment/Discontinuation Visit occurs 30 days from the last dose of study treatment, at the time of the mandatory Safety Follow up Visit, the Discontinuation Visit procedures and any additional Safety Follow-up procedures should be performed. Visit requirements are outlined in Section 1.3. Additional details regarding participant withdrawal and discontinuation are presented in Section 7.

Participants who discontinue study treatment but remain in the study should continue to be followed as described in the SoA and below in Section 8.11.4.

8.11.4 Posttreatment Phase

8.11.4.1 Safety Follow-up Visit

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

All AEs that occur prior to the Safety Follow-Up Visit should be recorded (up to 30 days following end of treatment). Participants with an AE of Grade >1 will be followed until the resolution of the AE to Grade 0 to 1 or until the beginning of a new anticancer therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment, 30 days if the participant initiates new anticancer therapy less than 30 days after end of treatment, or the day new anticancer therapy is initiated if between 30 days and 90 days after end of treatment should also be followed and recorded.

8.11.4.2 Imaging Follow-up Visits

Participants who discontinue treatment for reasons other than verified PD should continue with imaging assessments per the protocol-defined schedule until: (1) PD is verified or further confirmed by the investigator, (2) initiation of a new anticancer treatment, (3) death, (4) withdrawal of consent, or (5) study conclusion or early termination, whichever occurs first.

8.11.4.3 Survival Follow-up Visits

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

8.11.5 Survival Status

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 Sponsor. 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 Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding participants that have a previously recorded death event in the collection tool).

9. Statistical Analysis Plan

This section outlines the statistical analysis strategies and procedures for the primary and secondary analyses of the study. Exploratory and other nonconfirmatory analyses will be outlined in a separate supplemental Statistical Analysis Plan (sSAP).

If, after the study has begun, changes are made to primary and/or secondary objectives, or the statistical methods related to those objectives, then the protocol will be amended (consistent with ICH Guideline E9). Changes to exploratory or other nonconfirmatory analyses made

after the protocol has been finalized, but prior to final database lock, will be documented in the sSAP as needed and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

9.1 Statistical Analysis Plan Summary

This section contains a brief summary of the statistical analyses for this trial. Full details are in the Statistical Analysis Plan (SAP), Section 9.2 through 9.12.

Study Design Overview	Phase 1 trial of MK-1697 in participants with advanced solid tumors. The study applies a modified TPI design for dose finding.
Treatment Assignment	Participants will be allocated centrally through IVRS/IWRS to MK-1697 dose levels.
Analysis Populations	Safety (Primary): All-Subjects-as-Treated (ASaT) and DLT evaluable population PK (Secondary): Per-Protocol (PP) Efficacy: (Secondary and Exploratory): Full Analysis Set (FAS)
Primary Endpoint(s)	• Dose-limiting toxicity (DLT) • Adverse event (AE) • Discontinuing study intervention due to an AE
Secondary Endpoints	• Objective response • PK parameters of MK-1697 including AUC, C_{max}, and C_{min}
Statistical Methods for Efficacy/ Immunogenicity/ Pharmacokinetic Analyses	ORR will be estimated using an exact method based on the binomial distribution (Clopper-Pearson interval) together with its 95% confidence interval. Methods for the rest of efficacy analyses are documented in the sSAP. PK parameters of study medicines will be summarized by planned visit and time for each dose separately. Target engagement parameters will be summarized by planned visit and time for each dose separately.
Statistical Methods for Safety Analyses	Summary statistics will be provided for the safety endpoints as appropriate (e.g. counts, percentages). The pool-adjacent-violators-algorithm [Ji Y, Li Y, Bekele BN 2007] will be used to estimate the DLT rates across doses. The estimate of the DLT rate among participants treated at RP2D of MK-1697 and the 80% Bayesian credible intervals for the estimate will be provided for each treatment arm.

Interim Analyses	An interim analysis may be conducted to enable future trial planning at the Sponsor's discretion and data will be examined on a continuous basis to allow for dose-finding decisions. For the CRC expansion cohort in Part B, if there are no responders among approximately the first 15 evaluable participants, the cohort may be stopped early. For the HNSCC expansion cohort in Part B, if there are 1 or fewer responders among approximately the first 15 evaluable participants, the cohort may be stopped early.
Multiplicity	No multiplicity adjustment is planned in this Phase 1 trial.
Sample Size and Power	The overall sample size for this study depends on the observed DLT profiles of MK-1697. A maximum target sample size of 122 participants will be used for study planning purposes.

9.2 Responsibility for Analyses/In-house Blinding

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

The trial is open-label, ie, participants, investigators, and Sponsor personnel will be aware of participant treatment assignment after each participant is enrolled and treatment is assigned. Allocation to treatment will not be randomized.

9.3 Hypotheses/Estimation

Objectives and hypotheses of the study are outlined in Section 3 – Objectives/Hypotheses and Endpoints.

9.4 Analysis Endpoints

9.4.1 Efficacy/Immunogenicity/Pharmacokinetics Endpoints

Objective response rate is the secondary endpoint in this study. Objective response rate is defined as the proportion of participants in the analysis population who experience complete response (CR) or partial response (PR) using RECIST 1.1 and iRECIST criteria as assessed by investigator review.

Other efficacy endpoints (e.g., PFS, OS) are exploratory endpoints in this trial and details of the analysis plan will be documented in the sSAP. Progression-free survival (PFS) is defined as the time from the first dose of study medication to the first documented PD, using RECIST 1.1 criteria as assessed by investigator review, or death due to any cause, whichever occurs first. Overall survival (OS) is defined as the time from the first dose of study medication to death due to any cause. Participants who did not die will be censored on the date of last study assessment or contact.

Pharmacokinetic endpoints include serum concentrations of MK-1697, as well as derived PK parameters (AUC, C_{max}, C_{min}).

Target engagement of MK-1697 will be measured by total sLAG-3 and PD-1 receptor occupancy.

9.4.2 Safety Endpoints

The primary safety endpoint is the number/proportion of participants with DLT(s), AE(s), and who discontinue study treatment due to AE(s). In addition, safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests, and vital signs.

A description of safety measures is provided in Section 8.3 – Safety Assessments.

9.5 Analysis Populations

9.5.1 Safety Analysis Populations

The All-Subjects-as-Treated (ASaT) population will be used for the analysis of safety data in this study. The ASaT population consists of all participants who received at least 1 dose of study treatment.

The DLT evaluable population includes ASaT participants that meet the criteria for DLT evaluability (eg, finished Cycle 1 without a DLT or experienced a DLT in Cycle 1).

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

9.5.2 Pharmacokinetic Analysis Populations

The Per-Protocol (PP) population will be used for the analysis of PK and target engagement data in this study. The PP population consists of the subset of participants who complied with the protocol sufficiently to ensure that their data will be likely to exhibit the effects of treatment, according to the underlying scientific model. Compliance includes such considerations as exposure to treatment, availability of measurements, and the absence of major protocol violations. Any participants or data values excluded from the analyses will be identified, along with the reasons for exclusion, in the CSR. At the end of the study, all participants who were compliant with the study procedures and have available data from at least 1 treatment may be included in the PP analysis dataset.

9.5.3 Efficacy Analysis Populations

For the expansion cohorts in Part B, the Full Analysis Set (FAS) population will be used for the analyses for both secondary (ORR) and exploratory efficacy data (PFS, OS) in this study. It consists of all participants with a baseline scan that demonstrated measurable disease by the investigator's assessment, and who were administered at least 1 dose of study medicine. There will be no formal efficacy analysis during dose escalation in Part A, though participants in Part A that meet the inclusion criteria for the respective Part B tumor type and received the same dose level may be pooled as part of the FAS population.

9.6 Statistical Methods

This section describes the statistical methods that address the primary and secondary objectives. Methods related to exploratory endpoints will be described in the sSAP. Analyses for each Part B expansion cohort will pool Part A participants who meet the inclusion criteria for the respective Part B tumor type and received the same dose level.

9.6.1 Statistical Methods for Efficacy Analysis

The statistical methods for efficacy analyses of exploratory nature (PFS, OS) will be documented in the sSAP. ORR, along with the confidence interval, will be estimated using an exact method based on the binomial distribution [Clopper-Pearson].

9.6.2 Statistical Methods for Safety Analysis

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

Adverse events will be summarized by counts and frequencies for each dose level. Laboratory tests, vital signs, and other safety endpoints will be summarized as appropriate (eg, counts, percentages).

DLTs will be listed and summarized by dose level. The pool-adjacent-violators algorithm (PAVA) [Ji Y, Li Y, Bekele BN 2007], which forces the DLT rate estimates to be nondecreasing with increasing dose levels and pools adjacent violators for weighted estimates by sample size, will be used to estimate the DLT rates across doses in each treatment arm. The estimate of the DLT rate among participants treated at the RP2D and the 80% Bayesian credible interval based on a prior distribution of Beta (1,1) will be provided.

9.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

9.6.3.1 Demographic and Baseline Characteristics

Demographic variables and baseline characteristics will be summarized.

9.6.3.2 Pharmacokinetic and Pharmacodynamic Modeling Analysis

PD-1 receptor availability and total s-LAG3 will be summarized by planned visit and time for each dose separately.

Pharmacokinetic parameters of study medicines will be summarized by planned visit and time for each dose separately.

Pharmacokinetics and pharmacodynamics modeling analyses will be documented in the sSAP.

9.7 Interim Analyses

An interim analysis (eg for efficacy) may be conducted to enable future trial planning at the Sponsor’s discretion. Data will be examined on a continuous basis to allow for dose-escalation decisions and at the end of Part A to make dose-finding decisions.

For the CRC expansion cohort in Part B, if there are no responders among approximately the first 15 evaluable participants, the cohort may be stopped early. For the HNSCC expansion cohort in Part B, if there are 1 or less responders among approximately the first 15 evaluable participants, the cohort may be stopped early. An evaluable participant has at least one posttreatment tumor assessment that is evaluable. The estimated response rate for the CRC expansion cohort in Part B is approximately 1% to 2%, and for the HNSCC expansion cohort, the estimated response rate is 18% (based on data from KEYNOTE-055). For the CRC expansion cohort, if the true response rate is 10%, then there is a ~21% chance of declaring futility; if the true response rate is 15%, then there is a ~9% chance of declaring futility. For the HSNCC expansion cohort, if the true response rate is 18%, then there is a ~19% chance of declaring futility. These bars are not binding, and the totality of the data will be evaluated before making a decision to discontinue enrollment. The data will be analyzed on a continuous basis and enrollment will not be paused in the time between when the 15th participant in a particular cohort is enrolled and when the interim analysis is performed.

9.8 Multiplicity

There will be no multiplicity control in this study.

9.9 Sample Size and Power Calculations

For study planning purposes and under the assumption that 3 doses will be tested during dose escalation, with up to 14 participants in each of the 3 dose levels, we assume an approximate maximum sample size for Part A of 42 participants. In Part B, 2 expansion cohorts will enroll up to 40 participants each so we assume an approximate maximum sample size of 80 participants. The total maximum enrollment for the study across Part A and Part B is approximately 122 participants.

The actual sample size will depend on the safety profiles and the number of doses studied as well as which expansion cohorts (if any) are discontinued early.

In Part B, approximately 80 participants (40 in each expansion cohort) are expected to be enrolled. The key efficacy endpoint will be the objective response rate based on the investigator assessment per RECIST 1.1. Table 11 shows the ORR estimate and its associated 80% and 95% CIs (Clopper-Pearson intervals).

Table 11 Estimate and 80%, 95% CI of ORR

Sample Size	Number of Responses (PR/CR)	ORR	95% CI	80% CI
40	8	20%	(9.1%, 35.6%)	(12.0%, 30.4%)
	9	22%	(10.8%, 38.5%)	(14.1%, 33.2%)
	10	25%	(12.7%, 41.2%)	(16.2%, 35.9%)
	11	28%	(14.6%, 43.9%)	(18.3%, 38.5%)
	12	30%	(16.6%, 46.5%)	(20.5%, 41.2%)
	20	50%	(33.8%, 66.2%)	(38.8%, 61.2%)
	25	62%	(45.8%, 77.3%)	(51.1%, 72.9%)

9.10 Subgroup Analyses

Subgroup analyses of efficacy endpoints will be documented in the sSAP. Subgroups of interest for this study may include:

1. Participants with PD-L1 positive tumors
2. Participants with LAG-3 expression in tumors
3. Participants by HPV status in the HNSCC expansion cohort

9.11 Compliance (Medication Adherence)

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

9.12 Extent of Exposure

The extent of exposure will be summarized as duration of treatment in cycles.

10. Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical and Study Oversight Considerations

Code of Conduct for Clinical Trials

Merck Sharp and Dohme Corp., a subsidiary of Merck & Co., Inc. (MSD)
Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, 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 participants in clinical trials is the overriding concern in the design of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (e.g., International Council for Harmonisation Good Clinical Practice [ICH-GCP]) and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

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

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

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

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish the primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the pre-specified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. 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 such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). 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. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

A. Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

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

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Participants may withdraw from an MSD 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

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

D. Genomic Research

Genomic research will only be conducted in accordance with a protocol and informed consent authorized by an ethics committee.

IV. Financial Considerations

A. Payments to Investigators

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

MSD does not pay for participant referrals. However, MSD 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 MSD, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local ethics committee may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, all publications resulting from MSD trials will indicate MSD as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices.

V. Investigator Commitment

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

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 the Sponsor'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 the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor 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 the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor 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 the Sponsor. Any participant records or datasets that are transferred to the Sponsor 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 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 the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the 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 study 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 (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents in order to verify worksheet/CRF data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying

worksheet/CRF information, the participant will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

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

Confidentiality of IRB/IEC Information

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

Publication Policy

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor 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, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor 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 Study 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 study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and 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 study or its results to those registries.

Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP (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 GCP); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical study.

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

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this study.

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

Persons debarred from conducting or working on clinical studies by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study 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 the Sponsor 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.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the study site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are

requested by the Sponsor or any regulatory authorities as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/CRFs.

The Sponsor 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 the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

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

The Sponsor or its designee 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 the Sponsor prematurely terminates a particular study site, the Sponsor will promptly notify that study site's IRB/IEC.

10.2 Appendix 2: Collection and Management of Specimens for Future Biomedical Research

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens consented and/or collected in this study as outlined in Section 8.10 will be used in various experiments to understand:

- The biology of how drugs/vaccines work
- Biomarkers responsible for how a drug/vaccine enters and is removed by the body
- Other pathways drugs/vaccines may interact with
- The biology of disease

The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

3. Summary of Procedures for Future Biomedical Research

a. Participants for Enrollment

All participants enrolled in the clinical study will be considered for enrollment in the future biomedical research substudy.

b. Informed Consent

Informed consent for specimens (ie, DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all participants or legal guardians, at a study visit by the investigator or his or her designate. Informed consent for future biomedical research should be presented to the participants on the visit designated in the SoA. If delayed, present consent at next possible Participant Visit. Consent forms

signed by the participant will be kept at the clinical study site under secure storage for regulatory reasons.

A template of each study site's approved informed consent will be stored in the Sponsor's clinical document repository.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of participant consent for future biomedical research will be captured in the eCRFs. Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)

Collection of specimens for future biomedical research will be performed as outlined in the SoA. In general, if additional blood specimens are being collected for future biomedical research, these will usually be obtained at a time when the participant is having blood drawn for other study purposes.

4. Confidential Participant Information for Future Biomedical Research

In order to optimize the research that can be conducted with future biomedical research specimens, it is critical to link participant' clinical information with future test results. In fact little or no research can be conducted without connecting the clinical study data to the specimen. The clinical data allow specific analyses to be conducted. Knowing participant characteristics like gender, age, medical history and treatment outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for future biomedical research, the Sponsor has developed secure policies and procedures. All specimens will be single-coded per ICH E15 guidelines as described below.

At the clinical study site, unique codes will be placed on the future biomedical research specimens. This code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between participant identifiers and this unique code will be held at the study site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses utilizing the future biomedical research specimens may be performed by the Sponsor, or an additional third party (eg, a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third party analyses will conform to the specific scope of analysis outlined in this substudy. Future biomedical research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research

Participants may withdraw their consent for future biomedical research and ask that their biospecimens not be used for future biomedical research. Participants may withdraw consent at any time by contacting the principal investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to main study use only. If specimens were collected from study participants specifically for future biomedical research, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main study records) or the specimens have been completely anonymized, there will no longer be a link between the participant’s personal information and their specimens. In this situation, the request for withdrawal of consent and/or destruction cannot be processed.

7. Retention of Specimens

Future biomedical research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the main study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the study site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not utilized in a particular study, the study site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated study administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Participants

No information obtained from exploratory laboratory studies will be reported to the participant, family, or physicians. Principle reasons not to inform or return results to the participant include: Lack of relevance to participant health, limitations of predictive capability, and concerns regarding misinterpretation.

If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and participants. Participants will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population

Every effort will be made to recruit all participants diagnosed and treated on Sponsor clinical studies for future biomedical research.

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the participant have been minimized and are described in the future biomedical research informed consent.

The Sponsor has developed strict security, policies and procedures to address participant data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation there is risk that the information, like all medical information, may be misused.

12. Questions

Any questions related to the future biomedical research should be e-mailed directly to clinical.specimen.management@merck.com.

13. References

1. National Cancer Institute [Internet]: Available from https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45618
2. International Conference on Harmonization [Internet]: E15: Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. Available from http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html
3. Industry Pharmacogenomics Working Group [Internet]: Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/
4. Industry Pharmacogenomics Working Group [Internet]: Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

10.3 Appendix 3: Contraceptive Guidance and Pregnancy Testing

Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal 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 hormone 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 nonhormonal 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.

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 5.1:

- 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, postovulation 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 12 during the protocol-defined time frame in Section 5.1.

Table 12 Highly Effective Contraception Methods

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

Pregnancy testing will be performed at the timepoints indicated in the SoA and as required locally.

Pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.

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

Definition of AE

AE definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment. • NOTE: for purposes of AE definition, study treatment (also referred to as Sponsor's product) 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 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 AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose of study treatment 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 8.4.5 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 8.4.5 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

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

e. Is a congenital anomaly/birth defect

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

f. Other important medical events:

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

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

Additional Events Reported in the Same Manner as SAE

Additional events which require reporting in the same manner as SAE

- In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same time frame as SAEs to meet certain local requirements. Therefore, these events are considered serious by the Sponsor 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 AE CRFs/worksheets at each examination.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. 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 the Sponsor.
- 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 Criteria for Adverse Events (CTCAE), version 4.0. Any AE which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.
  - Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
  - Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).
  - Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
  - Grade 4: Life threatening consequences; urgent intervention indicated.
  - Grade 5: Death related to AE.

Assessment of causality

- Did the Sponsor's product cause the AE?
  - The determination of the likelihood that the Sponsor's product caused the AE 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 AE based upon the available information
  - **The following components are to be used to assess the relationship between the Sponsor's product and the AE;** the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the AE:
    - **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
    - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies 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 Sponsor's product discontinued or dose/exposure/frequency reduced?
  - If yes, did the AE resolve or improve?
    - If yes, this is a positive dechallenge.
  - If no, this is a negative dechallenge.

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

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

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL, AND IF REQUIRED, THE INIRB/IEC.

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

- The assessment of relationship will be reported on the CRFs/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 Sponsor's product relationship).
  - Yes, there is a reasonable possibility of Sponsor's product relationship:
    There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.

- No, there is not a reasonable possibility of Sponsor's product relationship: Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (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 the Sponsor. 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 the Sponsor.

- 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

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 Sponsor 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 the Sponsor within 24 hours of receipt of the information.

Reporting of AEs, SAEs, and Other Reportable Safety Events to the Sponsor

AE, SAE, and other reportable safety event reporting to Sponsor via electronic data collection tool

- The primary mechanism for reporting to the Sponsor 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 8.4.1 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 EDC 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 EDC 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 the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure e-mail of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.
- 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).

10.5 Appendix 5: Clinical Laboratory Tests

- The tests detailed in Table 13 will be performed by the local laboratory at the frequencies specified in Section 1.3 - Schedule of Activities.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 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 13 Protocol-Required Safety Laboratory Assessments

Hematology	Comprehensive Chemistry Panel	Urinalysis	Other
Hematocrit	Albumin	Blood	Pregnancy test (urine or serum)[a]
Hemoglobin	Alkaline phosphatase	Glucose	PT/INR
Platelet count	Alanine aminotransferase	Protein	aPTT or PTT
WBC (total and differential)[d]	Aspartate aminotransferase	Specific gravity	Total T3 (or FT3), Total T4 (or FT4), and TSH[b,c]
RBC	Bicarbonate	Microscopic exam, if abnormal results are noted	Anti-HCV
Absolute lymphocyte count[d]	Calcium		HCV viral load[c]
Absolute neutrophil count[d]	Chloride		HCV genotype[c]
	Creatinine (or measured/calculated Creatinine Clearance)		anti-HBs[c]
	Glucose		HBsAg
	Phosphorus		Anti-HBc (total and IgM)[c]
	Potassium		HBeAg[c]
	Sodium		anti-HBe[c]
	Total bilirubin		HBV viral load[c]
	Direct bilirubin		Anti-HDV [c]
	Total protein		GGT
	Blood urea nitrogen		Tumor markers (eg, CEA, CA-125, CA-19-9)
			Cytokine panel
			Lipase and Amylase

a. Perform on women of childbearing potential only. Perform urine pregnancy test first; if it cannot be confirmed as negative, a serum pregnancy test is required.
b. T3 is preferred; if not available, Free T3 may be tested.
c. If the local laboratory is unable to perform these tests, the site should submit the sample to the central laboratory for testing. Details are provided in the Laboratory Manual.
d. Report % or absolute results per standard of practice. Report the results in the same manner throughout the study.

Investigators must document their review of each laboratory safety report.

10.6 Appendix 6: Abbreviations

Abbreviation	Definition
ADA	Antidrug antibody
AE	Adverse event
AFP	Alpha-ferroprotein
ALT (SGPT)	Alanine aminotransferase (serum glutamic pyruvic transaminase)
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST (SGOT)	Aspartate aminotransferase (serum glutamic oxaloacetic transaminase)
AUC	Area under the curve
β-HCG	β-Human Chorionic Gonadotropin
C_{max}	Maximum concentration
C_{min}	Minimum concentration
CNS	Central nervous system
CR	Complete response
CRC	Colorectal cancer
CrCl	Creatinine clearance
CRP	C-reactive protein
CT	Computed tomography
CTFG	Clinical Trial Facilitation Group
DILI	Drug-induced liver injury
DL	Dose level
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
ECG	Electrocardiograph
ECI	Event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
FT3	Free triiodothyronine
FT4	Free thyroxine
GFR	Glomerular filtration rate
GGT	Gamma-Glutamyl transferase
GVHD	Graft-versus-host disease
HBsAG	Hepatitis B antigen
HBV	Hepatitis B virus
HER-2	Human epidermal growth factor receptor 2
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HNSCC	Head and neck squamous cell cancer
IB	Investigator's Brochure
ICF	Informed consent form
iCPD	Confirmed progressive disease (by iRECIST)

Abbreviation	Definition
IHC	Immunohistochemistry
IMR	Immuno-modulatory receptor
INR	International normalized ratio
irAE	Immune-related AE
iRECIST	modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics (iRECIST)
iSD/iPR/iCR	Stable disease/partial response/complete response (by iRECIST)
IUD	Intrauterine device
iUPD	Unconfirmed progressive disease (by iRECIST)
IUS	Intrauterine hormone-releasing system
IV	Intravenous
IVRS/IWRS	Interactive voice response system / interactive web response system
LAG-3	Lymphocyte activation gene 3
LAM	Lactational amenorrhea method
mAb	Monoclonal antibody
MMR	(DNA) mismatch repair genes
MRI	Magnetic resonance imaging
mRNA	Messenger RNA
MSI	microsatellite instability
MSS	Microsatellite stable
mTPI	Modified toxicity probability interval
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHP	Nonhuman primate
NOAEL	No-observed-adverse-effect-level
NSAID	Non-steroidal anti-inflammatory drugs
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
OTC	Over the counter
PD	Progressive disease
PD-1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PICC	Peripherally inserted central catheter
PK	Pharmacokinetics
PR	Partial response
pRBC	Packed red blood cell
PT	Prothrombin
Q3W	Every 3 weeks
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
RNA	Ribonucleic acid

Abbreviation	Definition
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
sLAG-3	Soluble LAG-3
SIM	Site Imaging Manual
SoA	Schedule of Activities
sSAP	Supplemental Statistical Analysis Plan
T1DM	Type 1 diabetes mellitus
T3	Triiodothyronine
T_{reg}	Regulatory T cell
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
WOCBP	Woman of child bearing potential

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

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). This decision by the investigator should be based on the participant's overall clinical condition.

Clinical stability is defined as the following:

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

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

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

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

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

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

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

New lesions will be classified as measurable or non-measurable, using the same size thresholds and rules as for baseline lesion assessment in RECIST 1.1. 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 iUPD at the previous visit show worsening
    - For target lesions, worsening is a further increase in the sum of diameters of ≥5 mm, compared to any prior iUPD time point
    - For non-target lesions, worsening is any significant growth in lesions overall, compared to a prior iUPD time point; this does not have to meet the "unequivocal" standard of RECIST 1.1
    - For new lesions, worsening is any of these:
        - An increase in the new lesion sum of diameters by ≥5 mm from a prior iUPD time point
        - Visible growth of new non-target lesions
        - The appearance of additional new lesions
- Any new factor appears that would have triggered PD by RECIST 1.1

Persistent iUPD

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

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

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

Resolution of iUPD

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

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

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

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

Management Following the Confirmatory Imaging

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

NOTE: If a participant has confirmed radiographic progression (iCPD) as defined above, but the participant is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered following consultation with the Sponsor. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 1.3 – Schedule of Activities and submitted to the central imaging vendor.

Detection of Progression at Visits After Pseudo-progression Resolves

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

- Target lesions
    - Sum of diameters reaches the PD threshold (≥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 trial, 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].

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