Official Protocol Title:	Phase 1b Open-label Study of MK-7162 in Combination with Pembrolizumab (MK-3475) +/- other therapies in Participants with Advanced Solid Tumors
NCT number:	NCT03364049
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Title Page

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Protocol Title: Phase 1b Open-label Study of MK-7162 in Combination with Pembrolizumab (MK-3475) +/- other therapies in Participants with Advanced Solid Tumors

Protocol Number: 002-02

Compound Number: MK-7162

Sponsor Name and Legal Registered Address:

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

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Regulatory Agency Identifying Number(s):

IND NUMBER: 136641

EudraCT NUMBER: 2017-000418-49

Approval Date: 21 July 2020

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 trial 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
-02	21-JUL-2020	The overall rationale for the amendment is to allow participants who have completed the study to be discontinued and enrolled in a pembrolizumab extension study.
-01	09-NOV-2017	Revisions/updates incorporated based on feedback from regulatory agency and sites.
-00	02-OCT-2017	Original protocol

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment -02

Overall Rationale for the Amendment:

The overall rationale for the amendment is to allow participants who have completed the study to be discontinued and enrolled in a pembrolizumab extension study.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
1 Synopsis 5.1.2 Study Diagram 5.3 Beginning and End of Study Definition 9.1.7 Assignment of Treatment/Randomization Number	Language was added to allow participants who have completed the study to be discontinued and enrolled in a pembrolizumab extension study.	This change will allow this study to be closed.

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1. Synopsis

Protocol Title:

Phase 1b Open-label Study of MK-7162 in Combination with Pembrolizumab (MK-3475) +/- other therapies in Participants with Advanced Solid Tumors

Short Title:

Phase 1b MK-7162 in combinations with pembrolizumab (MK-3475) +/- other therapies in participants with advanced solid tumors

Objectives/Hypotheses and Endpoints:

Male/female participants of at least 18 years of age with advanced/metastatic solid tumors will be enrolled in this trial.

Objective	Endpoint
Primary	
1. To determine the safety and tolerability and to establish a preliminary recommended Phase 2 dose (RP2D) of MK-7162 administered in combination with pembrolizumab	• Dose-limiting toxicity (DLT) • Adverse events (AEs) • Discontinuation of study treatment due to an AE
Secondary	
1. To evaluate the pharmacokinetics (PK) of MK-7162 administered orally as monotherapy and in combination with pembrolizumab intravenous (IV) infusion	• PK parameters, including area under the curve (AUC), minimum observed combination (C_{min}), and maximum observed combination (C_{max})
2. To evaluate pharmacodynamics (PD) of MK-7162 alone and in combination with pembrolizumab through measurement of kynurenine (KYN) and tryptophan (TRP) levels	• KYN and TRP will be measured as PD biomarkers of Indoleamine-2,3-dioxygenase-1 (IDO1) inhibition
3. To evaluate the objective response rate (ORR) to MK-7162 in combination with pembrolizumab	• ORR based on Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST 1.1) and immune-based RECIST (iRECIST) as assessed by the investigator

Overall Design:

Trial Phase	Phase 1b
Clinical Indication	Treatment of participants with advanced solid tumors
Population	Participants with histologically or cytologically confirmed advanced solid tumors by pathology report who have received or been intolerant to all treatment known to confer clinical benefit will be enrolled.
Trial Type	Interventional
Type of Design	This is an open-label, multicenter, nonrandomized dose escalation and confirmation study of MK-7162 in combination with pembrolizumab.
Type of Control	No treatment control
Trial Blinding	Unblinded open-label
Estimated Duration of Trial	The Sponsor estimates that the trial will require approximately 2 years from the time the first participant signs the informed consent until the last participant's last study-related phone call or visit.

Number of Participants:

Approximately 40 participants will be enrolled in the dose escalation and confirmation phase of this trial. Enrollment of additional participants in expansion cohorts will be specified in a future protocol amendment.

Treatment Groups and Duration:

Treatment Groups	Participants will be allocated via Interactive voice response system/integrated web response system (IVRS/IWRS) to dose-level cohorts of MK-7162, administered orally (PO). MK-7162 will be administered as monotherapy once a day (QD) every day of each 21-day (3-week) cycle. Starting with treatment Cycle 2 until treatment Cycle 36, participants will receive MK-7162 daily QD in combination with pembrolizumab 200 mg IV every 3 weeks. Each treatment cycle is 3 weeks. The study will follow the modified toxicity probability interval (mTPI) method (Section 5.5.3.1) to identify a preliminary RP2D, maximum tolerated dose (MTD) and/or maximum administered dose (MAD) of MK-7162 in combination with pembrolizumab. The dose limiting toxicity (DLT) evaluation period will be 2 cycles (6 weeks/42 days). Upon identification of the preliminary RP2D of MK-7162 for use in combination with pembrolizumab, additional participants with solid tumors will be enrolled in the dose expansion phase of this trial. Participants in the expansion phase of this trial will receive MK-7162 in combination with pembrolizumab as dual therapy or in combination with additional chemotherapeutic or immune-modulatory agents. The dose expansion phase of this trial will be initiated through an amendment to this protocol.
Duration of Participation	The participant duration in the trial is approximately 2 years from the time the participant signs the Informed Consent Form (ICF) through the final contact. After a screening phase of up to 28 days, each participant will receive assigned treatment for up to 36 treatment cycles (approximately 2 years). Treatment may continue until 1 of the following occurs: disease progression, unacceptable AEs, intercurrent illness that prevents further administration of treatment, investigator decision to withdraw the participant, participant withdraws consent, pregnancy of the participant, noncompliance with trials treatment or procedure requirements, or administrative reasons requiring cessation of treatment. After the end of treatment, each participant will be followed for the occurrence of AEs and spontaneously reported pregnancy as described in Section 9.3. Once the participant has achieved the study objective or the study has ended, the participant will be discontinued from this study and may be enrolled in an extension study to continue protocol-defined assessments and treatment.

A list of abbreviations used in this document can be found in Appendix 1.

2. Schedule of Activities (SoA)

2.1 Dose Escalation and Confirmation

Trial Phase:	Screening	Treatment (Treatment Cycle = 21 days)								End of Treat-ment (EoT)	Post-treatment		
		MK-7162 Mono-therapy		MK-7162 and Pembrolizumab Combination Therapy						Last Dose / Discon-tinuation	Safety Follow-up	Survival Follow-up	
Visit or Cycle (C):		C1		C2		C3		C4	C5 thru C36		30 days after the last dose	Every 12 weeks after the last dose	
Scheduling Day (D):		D1	D15	D1	D15	D1	D15	D1	D1				
Schedule Window (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 5	± 3	± 3	± 7	± 7	± 14	**Notes**
Administrative Procedures													
Informed Consent Form (ICF)	X												• Written consent must be obtained prior to performing any protocol-specific procedures. • An ICF signed >28 days prior to C1D1 does not need to be replaced.
Informed Consent for Future Biomedical Research (FBR) (optional)	X												
Participant Identification Card	X												
Inclusion/Exclusion Criteria	X												
Demographics and Medical History	X												
Prior Medication and Concomitant Medication Review	X	X		X		X		X	X	X	X		

Trial Phase:	**Screening**	**Treatment (Treatment Cycle = 21 days)**								**End of Treat-ment (EoT)**	**Post-treatment**		
		MK-7162 Mono-therapy		MK-7162 and Pembrolizumab Combination Therapy						Last Dose / Discon-tinuation	Safety Follow-up	Survival Follow-up	
Visit or Cycle (C):		C1		C2		C3		C4	C5 thru C36		30 days after the last dose	Every 12 weeks after the last dose	
Scheduling Day (D):		D1	D15	D1	D15	D1	D15	D1	D1				
Schedule Window (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 5	± 3	± 3	± 7	± 7	± 14	**Notes**
Disease Details and Prior Oncology Treatment History	X												
MK-7162 Administration and Dispensing		X		X		X		X	X				• Participants are to be dosed within 3 days of allocation. • All treatment visits should follow an overnight fast. Some PK and PD samples must to be obtained in the morning prior to administration of a morning dose of MK-7162. **C1D1:** Minimum 8-hour observation period following initial MK-7162 monotherapy dose on C1D1 **C2D1-C36D1:** For pembrolizumab combination treatment day visits, MK-7162 should be administered in clinic a minimum of 1 h prior to initiation of pembrolizumab infusion.
Pembrolizumab Administration				X		X		X	X				**C2D1:** Minimum 8-hour observation period following completion of pembrolizumab infusion
New Anticancer Therapy Status											X	X	

Trial Phase:	**Screening**	**Treatment (Treatment Cycle = 21 days)**								**End of Treat-ment (EoT)**	**Post-treatment**		
		MK-7162 Mono-therapy		MK-7162 and Pembrolizumab Combination Therapy						Last Dose / Discon-tinuation	Safety Follow-up	Survival Follow-up	
Visit or Cycle (C):		C1		C2		C3		C4	C5 thru C36		30 days after the last dose	Every 12 weeks after the last dose	
Scheduling Day (D):		D1	D15	D1	D15	D1	D15	D1	D1				
Schedule Window (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 5	± 3	± 3	± 7	± 7	± 14	**Notes**
Survival Status		← - →										X	**Treatment and Safety Follow-up Phase**: Upon Sponsor request, participants may be contacted for survival status at any time during the course of the study **Survival Follow-up Phase**: After Investigator determined PD or start of new anticancer treatment.
Efficacy Procedures													
Tumor Imaging: RECIST 1.1 and iRECIST Response Assessment	X							X	X	X			• Imaging obtained via CT, PET/CT, or MRI. • Medical Photography for cutaneous lesions: Obtained on the same schedule as imaging • On-treatment visit window: ± 7 days **Screening Visit**: Baseline tumor imaging and/or medical photography for cutaneous lesions should be performed within 28 days prior to first dose of MK-7162. **Treatment Phase:** Obtain first on-treatment imaging at Week 9 (C4D1); Obtain subsequent imaging every 9 weeks thereafter.
Medical Photography (cutaneous lesions)	X							X	X	X			
Safety Assessments and Procedures													
AE/SAE Review	X	X ←							→ X	X	X		
Full Physical Examination	X									X	X		
Directed Physical Examination		X		X		X		X	X				

Trial Phase:	**Screening**	**Treatment (Treatment Cycle = 21 days)**								**End of Treat-ment (EoT)**	**Post-treatment**		
		MK-7162 Mono-therapy		MK-7162 and Pembrolizumab Combination Therapy						Last Dose / Discon-tinuation	Safety Follow-up	Survival Follow-up	
Visit or Cycle (C):		C1		C2		C3		C4	C5 thru C36		30 days after the last dose	Every 12 weeks after the last dose	
Scheduling Day (D):		D1	D15	D1	D15	D1	D15	D1	D1				
Schedule Window (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 5	± 3	± 3	± 7	± 7	± 14	**Notes**
Height	X												
Weight	X	X		X		X		X	X	X			
Vital Signs	X	X		X		X		X	X	X	X		Consists of temperature, pulse, respiratory rate, blood pressure, and oxygen (0_2) saturation. **C1D1:** Predose: Obtain within 1 h (± 30 min) prior to MK-7162 dose; Postdose**:** Obtain 2, 4, 6, and 8 h (± 30 min) after dosing **C2D1**: Predose: Obtain within 1 hour (± 30 min) prior to MK-7162 dose; Postdose**:** Obtain 2, 4, 6, and 8 h (± 30 min) after completion of MK-7162 and pembrolizumab dosing **C3D1 and beyond**: Predose: Obtain within 1 h (± 30 min) prior to MK-7162 dose.
12-lead ECG	X	X		X							X		**C1D1** Postdose: Obtain within 30 min after dosing **C2D1** Postdose: Obtain within 30 min after the end of the pembrolizumab infusion
Eastern Cooperative Oncology Group (ECOG) Status	X	X		X		X		X	X	X	X		Assessment to confirm eligibility must be performed within 7 days prior to C1D1 dosing

Trial Phase:	**Screening**	**Treatment (Treatment Cycle = 21 days)**								**End of Treat-ment (EoT)**	**Post-treatment**		
		MK-7162 Mono-therapy		MK-7162 and Pembrolizumab Combination Therapy						Last Dose / Discon-tinuation	Safety Follow-up	Survival Follow-up	
Visit or Cycle (C):		C1		C2		C3		C4	C5 thru C36		30 days after the last dose	Every 12 weeks after the last dose	
Scheduling Day (D):		D1	D15	D1	D15	D1	D15	D1	D1				
Schedule Window (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 5	± 3	± 3	± 7	± 7	± 14	**Notes**
Safety: Local Laboratory Evaluations		**Screening:** Obtain and evaluate clinical laboratory tests within 7 days prior to first dose of study medication (C1D1) unless otherwise specified. Tests performed prior to the participant signing IC as part of routine clinical management are acceptable in lieu of a screening test, if the test is performed within the specified time frame. **Day 1 for All Treatment Cycles:** Obtain samples prior to MK-7162 and pembrolizumab dosing, unless otherwise specified See Procedures Manual for details regarding collection and management of samples											
HIV, Hepatitis B and C screen	X												Historical results are acceptable unless testing is required by local regulation. Tests performed during the 28 day screening period are acceptable.
Hematology	X	X		X		X		X	X	X	X		
Urinalysis	X	X		X		X		X			X		
Comprehensive Chemistry Panel	X	X		X		X		X	X	X	X		
Lipase and Amylase	X										X		
LDH, GGT	X	X		X		X		X	X				
PT/INR and PTT/aPTT	X			X		X		X	X				Consider ongoing testing for participants on routine warfarin treatment.
Thyroid Function (T3, T4, TSH)	X	X				X			X		X		Tests performed during the 28-day screening period are acceptable for eligibility assessment. **Treatment Cycles**: Obtain every other treatment cycle, starting with C1: C1, C3, C5, etc.; Obtain at 30-day Safety Follow-up

Trial Phase:	**Screening**	**Treatment (Treatment Cycle = 21 days)**								**End of Treat-ment (EoT)**	**Post-treatment**		
		MK-7162 Mono-therapy		MK-7162 and Pembrolizumab Combination Therapy						Last Dose / Discon-tinuation	Safety Follow-up	Survival Follow-up	
Visit or Cycle (C):		C1		C2		C3		C4	C5 thru C36		30 days after the last dose	Every 12 weeks after the last dose	
Scheduling Day (D):		D1	D15	D1	D15	D1	D15	D1	D1				
Schedule Window (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 5	± 3	± 3	± 7	± 7	± 14	**Notes**
Tumor Markers	X	X		X		X		X	X				Obtain as clinically appropriate (eg, CEA, CA-125, CA-19-9, alpha fetoprotein, etc.)
Pregnancy Test: Serum β-Human Chorionic Gonadotropin (β-hCG) or Urine Test	X									X	X		• For women of childbearing potential (WOCBP) only • Additional urine/serum testing may be performed if clinically warranted, and/or as defined by local regulations. • If a urine pregnancy test cannot be confirmed as negative, a serum pregnancy test is required. • Obtain urine pregnancy test within 72 hours prior to the first MK-7162 dose
Pharmacokinetics/Pharmacodynamics/Biomarkers		**C1D1:** Obtain samples predose MK-7162 **C2D1 thru C36D1:** Predose = prior to MK-7162 administration and prior to pembrolizumab infusion; Postdose = subsequent to MK-7162 administration and pembrolizumab infusion See Procedures Manual for collection and management of samples											
Blood (DNA) for Genetic Analysis		X											Obtain predose
Peripheral Blood Mononuclear Cell	X			X		X	X	X	X	X	X		**Screening**: Obtain predose on the same day as the Screening tumor biopsy **C2D1**: Obtain predose on the same day as the tumor biopsy **C3D15**: Obtain predose on the same day as the tumor biopsy **C3D1-C36D1:** Predose

Trial Phase:	**Screening**	**Treatment (Treatment Cycle = 21 days)**								**End of Treat-ment (EoT)**	**Post-treatment**		
		MK-7162 Mono-therapy		MK-7162 and Pembrolizumab Combination Therapy						Last Dose / Discon-tinuation	Safety Follow-up	Survival Follow-up	
Visit or Cycle (C):		C1		C2		C3		C4	C5 thru C36		30 days after the last dose	Every 12 weeks after the last dose	
Scheduling Day (D):		D1	D15	D1	D15	D1	D15	D1	D1				
Schedule Window (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 5	± 3	± 3	± 7	± 7	± 14	**Notes**
Plasma for MK-7162 Pharmacokinetics (PK)		X	X	X	X	X	X	X	X	X	X		**C1D1 & C1D15:** Predose: Obtain following an overnight fast. Postdose: 1, 2, 4, and 8 hrs. Participant to remain fasting for 1 hr subsequent to dosing. **C2D1:** Predose: Obtain following an overnight fast. Obtain same day as tumor biopsy. **C2D15:** Predose: Obtain following an overnight fast. **C3D1**: Predose: Obtain following an overnight fast. Postdose: 1, 2, 4, and 8 hrs. Participant to remain fasting for 1 hr subsequent to MK-7162 dosing. **C3D15**: Predose: Obtain following an overnight fast. Obtain on the same day as tumor biopsy. **C4D1-C36D1**: Predose every 4 cycles: C4, C8, C12, etc. Obtain following an overnight fast. **Collection time point windows:** 1 hr. (± 15 min), 2-8 hrs. (± 30 min)
Serum for Pembrolizumab Pharmacokinetics (PK)				X		X		X	X	X	X		**C2D1**: Predose; Postdose: 0.5 hrs. (± 5 min) following completion of pembrolizumab infusion **C3D1**: Predose **C4D1-C36D1:** Obtain predose every 4 cycles: C4, C8, C12, etc.

Trial Phase:	**Screening**	**Treatment (Treatment Cycle = 21 days)**								**End of Treat-ment (EoT)**	**Post-treatment**		
		MK-7162 Mono-therapy		MK-7162 and Pembrolizumab Combination Therapy						Last Dose / Discon-tinuation	Safety Follow-up	Survival Follow-up	
Visit or Cycle (C):		C1		C2		C3		C4	C5 thru C36		30 days after the last dose	Every 12 weeks after the last dose	
Scheduling Day (D):		D1	D15	D1	D15	D1	D15	D1	D1				
Schedule Window (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 5	± 3	± 3	± 7	± 7	± 14	**Notes**
Serum for Anti-pembrolizumab Antibodies				X		X		X	X	X	X		**C2D1 and C3D1:** Predose **C4D1-C36D1:** Obtain predose every 4 cycles: C4, C8, C12, etc.
Blood for Plasma Pharmacodynamic (PD) and Biomarker Analyses	X	X	X	X		X	X						**Screening**: Obtain on the same day as the Screening tumor biopsy. Obtain following an overnight fast. **C1D1 & C1D15:** Predose: Obtained following an overnight fast. Postdose: 1, 2, 4, and 8 hrs. **C2D1:** Predose: Obtain following an overnight fast. Obtain on the same day as tumor biopsy. **C3D1:** Predose: Obtained following an overnight fast. Postdose: 1, 2, 4, and 8 hrs. **C3D15:** Predose: Obtain following an overnight fast. Obtain the same day as tumor biopsy. **Collection timepoint windows:** 1 hr. (± 15 min), 2-8 hrs. (± 30 min)
Whole Blood for Immune profiling	X	X		X		X		X					Obtain during **Screening** **Treatment Cycles:** Obtain predose on **C1D1**, **C2D1**, **C3D1**, and **C4D1**
Blood for Serum Biomarker Analysis		X		X		X		X	X	X			**Treatment Cycles:** Obtain predose on D1 of every Cycle.
Blood for RNA Analysis		X		X		X			X	X			**Treatment Cycles:** Obtain predose **C1D1**, **C2D1, C3D1**, and **C6D1** only

Trial Phase:	**Screening**	**Treatment (Treatment Cycle = 21 days)**								**End of Treatment (EoT)**	**Post-treatment**		
		MK-7162 Monotherapy		MK-7162 and Pembrolizumab Combination Therapy						Last Dose / Discontinuation	Safety Follow-up	Survival Follow-up	
Visit or Cycle (C):		C1		C2		C3		C4	C5 thru C36		30 days after the last dose	Every 12 weeks after the last dose	
Scheduling Day (D):		D1	D15	D1	D15	D1	D15	D1	D1				
Schedule Window (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 5	± 3	± 3	± 7	± 7	± 14	**Notes**
Tumor Tissue Collection													
Archival Tumor Tissue	X												Archival tumor tissue is preferred. If archival tumor tissue is unavailable, freshly obtained biopsy tissue may be used (See Procedures Manual for details).
Tumor Biopsy	X												Collection of a newly biopsied tumor tissue specimen is required during screening prior to C1D1 dosing. Must be collected after overnight fast.
Tumor Biopsy				X			X						• Initial requirement: C2D1 = mandatory and C3D15 = optional • Upon site notification by Sponsor: C2D1 = optional and C3D15 = mandatory • All biopsies must be collected after an overnight fast and prior to administration of either MK-7162 or pembrolizumab on the day of the biopsy. **C2D1**: Obtain biopsy predose **C3D15**: Obtain biopsy predose (after 5 additional weeks of MK-7162 in combination with pembrolizumab following C2D1).

Abbreviations: AE = adverse event; CT = computed tomography; DNA = deoxynucleic acid; ECG = electrocardiogram; GGT = gamma glutamyl transferase; HIV = human immunodeficiency virus; LDH = Lactate dehydrogenase; MRI = magnetic resonance imaging; PET = ; positron emission tomography PT/INR = prothrombin time/international normalized ratio; PTT/aPTT = partial thromboplastin time/activated partial thromboplastin time; RECIST 1.1 = Response Evaluation Criteria In Solid Tumors version 1.1; iRECIST = immune-based RECIST; RNA = ribonucleic acid; SAE = serious adverse event; T3 = total triiodothyronine; T4 = total thyroxine; TSH = thyroid stimulating hormone.

3. Introduction

MK-7162 is a selective small-molecule inhibitor of Indoleamine-2,3-dioxygenase-1 (IDO1), administered orally, in development for use in combination therapy with pembrolizumab for the treatment of advanced solid tumors.

3.1 Study Rationale

The IDO1 protein contains a heme co-factor which is responsible for binding and activating oxygen to catalyze the ring opening of L-tryptophan (TRP) to generate N-formyl kynurenine (KYN). The presence of heme is indispensable for IDO1 catalytic activity. MK-7162 inhibits IDO1 by either displacing heme from intact protein and/or preventing binding of heme during protein synthesis and folding. In human cancers, the enzyme IDO1 is upregulated and facilitates evasion of the immune system by tumor cells. MK-7162 is a small molecule which inhibits activity of IDO1, thereby reducing conversion of TRP to KYN, and facilitating T-cell responses within the tumor microenvironment.

While there is no prior experience with dosing of MK-7162 in humans with cancer, clinical proof of concept for IDO1 inhibition in cancer is provided by epacadostat, an IDO1-selective heme-binding inhibitor, that has been used clinically in combination with both anti-programmed death 1 (PD-1) antibodies, including pembrolizumab [Gangadhar TC, Hamid O, Smith DC, Bauer, TM, Wasser, JS, Luke JJ 2015], and anti-CTLA4 antibody ipilimumab [Gibney GT, Hamid O, Lutzky, J, Olszanski, AJ, Gangadhar, TC 2015]. To date, epacadostat has demonstrated a favorable safety profile in humans.

Initiation of human studies of MK-7162 is supported by preclinical studies conducted in rats and dogs. Based on the dosing margins established in preclinical safety studies of MK-7162, there are no contraindications to conducting clinical trials in accordance with study protocols and applicable regulatory guidance. To date, the safety of single doses of MK-7162 up to 300 mg has been established in an ongoing normal human volunteer (NHV) single ascending dose (SAD) study.

IDO1 expression is highly correlated with programmed death ligand 1 (PD-L1) expression in human tumors. IDO1 expression is induced in preclinical models in response to anti- PD-1 treatment as well as treatment with other immunomodulatory agents. Therefore, MK-7162 will be developed for use in combination with pembrolizumab, an anti-PD-1 agent.

3.2 Background

Refer to the Investigator's Brochure (IB) for detailed background information on MK-7162, and the MK-3475 IB/approved labeling for detailed background information on pembrolizumab.

3.2.1 Pharmaceutical and Therapeutic Background

3.2.1.1 MK-7162 Pharmaceutical and Therapeutic Background

Malignant cells are known to evade the human immune system through a process known as immune tolerance. In recent years, immunotherapeutics have been developed that successfully counteract various cellular processes involved in cancer immune tolerance. Such therapies have expanded the range of options for treatment of various cancers. For example,

pembrolizumab is a monoclonal antibody that blocks the activity of PD-1, an immune checkpoint protein that promotes immune tolerance by suppressing T-cell activity against tumor cells. By blocking this pathway, pembrolizumab enables the antitumor immune response and has been shown to be efficacious in treatment of multiple malignancies including non-small cell lung cancer (NSCLC), malignant melanoma, head and neck squamous cell cancer (HNSCC), and Hodgkin lymphoma. However, despite the advances made in cancer immunotherapy, response to pembrolizumab treatment as well as to other immunotherapies is incomplete in many cases, and evidence suggests that malignant cells are able to utilize multiple other pathways to achieve immune escape.

IDO1 is an intracellular enzyme that catalyzes the first step of degradation of the essential amino acid TRP into KYN. Depletion of TRP and accumulation of KYN appear to interfere with multiple pathways required for T-cell activation and function. Studies demonstrate that expression of IDO1 by tumor cells in animal models leads to suppression of T-cell responses to tumor cells, contributing to immune tolerance.

MK-7162 is a selective small-molecule inhibitor of IDO1 that displaces the heme cofactor of IDO1, either by replacement of heme in the intact protein or by binding in place of heme during protein synthesis/folding. In vitro, MK-7162 shows potent inhibition of IDO1 in human cancer cells. Although MK-7162 is not directly cytotoxic to malignant cells, it is anticipated that inhibition of IDO1 activity will interfere with the immune tolerance phenomenon and enhance the antitumor effects of immunotherapeutic agents such as pembrolizumab.

ccl [redacted]

MK-7162 NHV single ascending-dose study yielded the following safety data. There were no serious adverse events (SAEs) reported. The reported AEs were low grade. Epacadostat is a small-molecule inhibitor of IDO1 which is currently being studied in clinical cancer trials in combination with PD-1 blockade. While the mechanism of IDO1 inhibition by this compound is distinct from that of MK-7162, the common molecular target supports the projected effects common to both.

Epacadostat Phase 1/2 data demonstrated the following: one DLT occurred at the dose of 300 mg BID (grade 3, radiation pneumonitis); another DLT occurred at 400 mg BID (grade 3, fatigue). The most common adverse events in >20% of patients overall were fatigue, nausea, decreased appetite, vomiting, constipation, abdominal pain, diarrhea, dyspnea, back pain, and cough. Treatment produced significant dose-dependent reductions in plasma KYN levels and in the plasma KYN:TRP ratio at all doses and in all patients. Epacadostat doses of 100 mg BID achieved >80% to 90% inhibition of IDO1 at peak and 50% inhibition at trough based on plasma KYN:TRP ratios. Although no objective responses were detected, stable disease lasting greater than or equal to 16 weeks was observed in 7 of 52 patients [Beatty, G. L., et al 2017]. Grade 3 AST/ALT elevation was observed in 1 patient but was attributed to biliary duct obstruction consistent with progressive disease. A second patient also experienced grade 3 AST/ALT elevations, but this was determined to be most likely related to acetaminophen ingestion over the maximum recommended daily dose for tumor fevers.

BMS-986205, an IDO1 inhibitor with similar mechanism of action to that of MK-7162, is being evaluated in an ongoing clinical study in combination with the anti-PD-1 mAb nivolumab. Forty-two treated patients were reported. All treatment-related adverse events were grade 1 or 2 except three grade 3 toxicities (autoimmune hepatitis [dose limiting; BMS-986205 100 mg/nivolumab 240 mg], rash, and asymptomatic hypophosphatemia). Day 14 individual trough concentrations began exceeding the human whole blood 50% maximal inhibitor concentration (IC_{50}) starting with 25 mg QD, and the 90% maximal inhibitor concentration (IC_{90}) starting with 50 mg QD. All patients treated at 200 mg QD exceeded the IC_{90}. Serum KYN was substantially reduced at all doses (>45% mean reduction at each dose), with >60% mean reduction at the 100 and 200 mg QD doses. Intratumoral KYN was reduced from between 23% and 90% in evaluable paired pre- and monotherapy on-treatment samples [Siu, L. L., et al 2017] [Hunt, J. T., et al 2017].

3.2.1.2 Pembrolizumab (MK-3475) Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [Disis, M. L. 2010]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [Dudley, M. E., et al 2005] [Hunder, N. N., et al 2008].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene *Pdcd1*) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD L1 and/or PD-L2) [Greenwald, R. J., et al 2005] [Okazaki, T., et al 2001].

The structure of murine PD-1 has been resolved [Zhang, X., et al 2004]. PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type (IgV type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade [Okazaki, T., et al 2001] [Chemnitz, J. M., et al 2004] [Sheppard, K-A, et al 2004] [Riley, J. L. 2009]. The mechanism by which PD-1 down-modulates T cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [Parry, R. V., et al 2005]

[Francisco, L. M., et al 2010]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in solid tumors.

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

3.2.2 Preclinical Trials

3.2.2.1 MK-7162 Preclinical Trials

Refer to the MK-7162 IB for detailed preclinical information.

3.2.3 Ongoing Clinical Trials

3.2.3.1 MK-7162 Ongoing Clinical Trials

A NHV trial for MK-7162 is ongoing. Refer to the MK-7162 IB for clinical trial details.

3.2.3.2 Pembrolizumab (MK-3475) Ongoing Clinical Trials

Ongoing clinical trials with pembrolizumab are being conducted in multiple solid tumors. In addition, multiple other agents in combination with pembrolizumab are also being investigated. Refer to the pembrolizumab IB for clinical trial details.

3.3 Benefit/Risk Assessment

Participants in clinical trials generally cannot expect to receive direct benefit from treatment during participation, as clinical trials 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 trial may be found in the accompanying IB and Informed Consent documents.

4. Objectives/Hypotheses and Endpoints

In male and female participants at least 18 years of age with advanced solid tumors:

Objective	Endpoint
Primary	
1. To determine the safety and tolerability and to establish a preliminary RP2D of MK-7162 administered in combination with pembrolizumab	• Dose-limiting toxicity (DLT) • Adverse events (AEs) • Discontinuation of study treatment due to an AE
Secondary	
1. To evaluate the pharmacokinetics (PK) of MK-7162 administered orally as monotherapy and in combination with pembrolizumab intravenous (IV) infusion	• PK parameters of MK-7162, including area under the cure (AUC), C_{min}, and C_{max}
2. To evaluate pharmacodynamics (PD) of MK-7162 through measurement of KYN and TRP levels	• KYN and TRP will be measured as PD markers of IDO1 inhibition.
3. To evaluate the objective response rate (ORR) of MK-7162 in combination with pembrolizumab	• ORR based on Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST 1.1) and immune-based RECIST (iRECIST) as assessed by the Investigator
Tertiary/Exploratory	
1. To evaluate overall survival (OS) and Progression Free Survival (PFS) of participants treated with MK-7162 in combination with pembrolizumab	• OS • PFS based on Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) and immune-based RECIST (iRECIST) as assessed by the Investigator
2. To evaluate the PK of pembrolizumab when administered in combination with orally administered MK-7162	• PK parameters of pembrolizumab, including area under the cure (AUC), C_{min}, and C_{max}
3. To identify molecular (genomic, metabolic and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, PD activity, and/or the mechanism of action of MK-7162 as monotherapy and in combination with pembrolizumab	• Molecular (genomic, metabolic, and/or proteomic) determinants of response or resistance to treatments, using blood and/or tumor tissue; pembrolizumab anti-drug antibodies (ADA).

5. Study Design

5.1 Overall Design

This is a nonrandomized, multicenter open-label trial of MK-7162 in combination with pembrolizumab in participants with a histologically or cytologically confirmed diagnosis of advanced solid tumor.

Part A, the Dose Escalation and Confirmation Phase as outlined in this protocol, will follow the mTPI method (see Section 5.5.3.1) to identify a RP2D, MTD and/or MAD of MK-7162 for use in combination with pembrolizumab.

Upon identification of the preliminary RP2D of MK-7162 for use in combination with pembrolizumab, an amendment will be issued to this protocol. That amendment will contain the study details of Part B, the Dose Expansion Phase for participants with specified solid tumor types to receive MK-7162 in combination with pembrolizumab either as dual therapy or plus an additional chemotherapeutic or immune-modulatory agents.

5.1.1 Dose Escalation and Confirmation

This study will evaluate the safety and tolerability of MK-7162 alone and the safety, tolerability, and preliminary efficacy of MK-7162 in combination therapy with pembrolizumab.

All participants will be required to undergo a newly performed tumor biopsy during Screening, unless deemed medically unsafe by the Investigator. An additional on-study biopsy at one of two timepoints will also be required, unless deemed medically unsafe by the Investigator, with the biopsy at the other time point being optional. Initially, this biopsy will be required to occur on Cycle 2 Day 1 predose (prior to administration of MK-7162 study medication and prior to administration of IV pembrolizumab on that day), with a Cycle 3 Day 15 biopsy being optional. This will allow full characterization of the MK-7162 dose and intratumoral PD response relationship after three weeks of MK-7162 monotherapy. In addition, this tissue biopsy will facilitate characterization of the MK-7162 dose that maximally inhibits intratumoral IDO1. After a sufficient number of biopsy specimens at the Cycle 2 Day 1 timepoint have been collected, the Sponsor may notify the sites that the Cycle 2 Day 1 biopsy will become optional and the Cycle 3 Day 15 biopsy will be required. Characterization of the MK-7162 dose and intratumoral PD response relationship at this time point will confirm whether the intratumoral PD effect of a given MK-7162 dose is maintained during concurrent PD-1 blockade with pembrolizumab, since IDO1 upregulation occurs during immune responses.

Treatment allocation will be accomplished by nonrandom assignment through the interactive voice response system/integrated web response system IVRS/IWRS. Participants will receive MK-7162 monotherapy during the first treatment cycle followed by MK-7162 in combination with pembrolizumab for subsequent cycles.

MK-7162 will be administered PO QD, every day of each 21-day (3-week) cycle. Starting on Cycle 2, Day 1, MK-7162 will be administered in combination with pembrolizumab 200 mg IV, which will be administered on Day 1 of every cycle (every 3 weeks). The DLT evaluation period will be 2 cycles (6 weeks). Treatment of the first and second participants

enrolled in each cohort will occur at least 7 days apart. Treatment of the second and third participants enrolled in each cohort will occur at least 3 days apart.

An mTPI design [Ji, Y. and Wang, S.-J. 2013] will be used to identify and confirm the RP2D of MK-7162 in combination with pembrolizumab. Participants will initially be enrolled in the first dose-level cohort, receiving MK-7162 monotherapy for Cycle 1, and then receiving MK-7162 in combination with pembrolizumab for subsequent cycles (Cycles 2 to Cycle 36). Lower and/or higher doses of MK-7162 may then be explored depending on the combined safety, PK, PD, and preliminary efficacy data available at each dose level. The dose of pembrolizumab will remain constant at 200 mg IV Q3W.

The final number of participants enrolled will depend on the DLT observations and what dose is ultimately identified as the RP2D using the mTPI design. For the purposes of dose escalation decisions from a safety perspective, participants will be considered evaluable for DLT if they have completed the 6-week DLT evaluation period (completed the first and second cycles or discontinued treatment due to a DLT).

Dose finding and confirmation in Part A of the trial will end after 14 participants have been treated at any of the selected doses (which may include optional doses). In the event the dose-finding decision is not to stay at the current dose based on the 14 participants, the dose may be escalated or de-escalated and additional participants may be treated. The pool-adjacent-violators algorithm [Ji, Y. and Wang, S.-J. 2013] will be used to estimate the DLT rates under the assumption of monotonicity between DLT rates and dose levels. The dose with an estimated DLT rate closest to 30% may be treated as a preliminary RP2D. The totality of the data will be considered before deciding on the dose(s) to carry forward to Part B (dose expansion).

The primary objective is to identify the RP2D of MK-7162 for use in combination with pembrolizumab. The preliminary RP2D may be the same as the MTD/MAD, or the preliminary RP2D may be selected based on overall exposure, emerging safety and tolerability data, PK data, PD data, and preliminary clinical benefit data from this study.

Upon identification of the preliminary RP2D of MK-7162 for use in combination with pembrolizumab, additional participants with solid tumors will be enrolled in the dose expansion phase (Part B) of this trial to receive MK-7162 in combination with pembrolizumab as dual therapy, or in combination with additional chemotherapeutic or immune-modulatory agents. This dose expansion phase (Part B) of this trial will be initiated through a future protocol amendment.

Preliminary efficacy will be evaluated using objective response rate (ORR) and Progression Free Survival (PFS) assessed by the investigator based on the RECIST 1.1. ORR and PFS will also be assessed by iRECIST. ORR will be evaluated as a secondary objective. PFS and overall survival (OS) will be evaluated as exploratory objectives.

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 may be used by the investigator for treatment decision. In participants who have initial evidence of radiological progressive disease 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 and confirms 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-7162 when administered as monotherapy and in combination with pembrolizumab, as per the primary objective of this study.

There will be no intra-participant dose escalation for participants enrolled in this study. The definition of DLTs and criteria for dose modification of MK-7162 are outlined in Sections 7.2.2 and 7.2.4. Pembrolizumab will be administered at a fixed dose of 200 mg IV every 3 weeks, which will not be modified.

Participants may receive study medication for up to 36 cycles. Participants will be treated until progressive disease, 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 study medication or procedure requirements, participant completes treatment, or administrative reasons requiring cessation of treatment, at which point they will be discontinued from the study.

All participants will be followed for at least 30 days after their last dose of MK-7162 for AE monitoring. Serious adverse events will be collected for 90 days after discontinuation, 30 days if the participant initiates new anticancer therapy less than 30 days after study treatment discontinuation, or the day new anticancer therapy is initiated if between 30 days and 90 days after study treatment discontinuation. 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 progressive disease will have post-treatment follow-up for disease status (including imaging) until disease progression, initiating a new anticancer therapy, withdrawing consent for study participation, or becoming lost to follow-up.

After confirmed disease progression, each participant who discontinues treatment will be contacted by telephone every 12 weeks (±14 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 trial, as well as their prescribed times and associated visit windows, are outlined in the Trial SoA - Section 2. Details of each procedure are provided in Section 9 – Study Assessments and Procedures.

This trial will use an adaptive design based on prespecified criteria. Interim analyses will be conducted to examine clinical trial data on a continuous basis to allow for dose-finding decisions, safety, tolerability, and efficacy analysis.

5.1.2 Study Diagram

The trial design is depicted in Figure 1.

Figure 1 Study Diagram

MK-7162 in Combination with Pembrolizumab				
MK-7162 @ 25 mg QD	MK-7162 @ 50 mg QD	MK-7162 @ 100 mg QD	MK-7162 @ 200 mg QD	MK-7162 @ 400 mg QD
Pembrolizumab @ 200 mg IV Q3W	Pembrolizumab @ 200 mg IV Q3W	Pembrolizumab @ 200 mg IV Q3W	Pembrolizumab @ 200 mg IV Q3W	Pembrolizumab @ 200 mg IV Q3W

- Dose escalation and confirmation using an mTPI design based on a 6 week DLT observation period to identify a preliminary RP2D
- One 3-week treatment cycle of MK-7162 monotherapy is followed by MK-7162 combination with pembrolizumab for 35 treatment cycles (total of 36 cycles on treatment)
- MK-7162 is administered orally QD. Pembrolizumab is administered by IV infusion, and is administered on Day 1 of each 3 week treatment cycle
- Treatment of the first and second participants enrolled in each cohort will occur at least 7 days apart. Treatment of the second and third participants enrolled in each cohort will occur at least 3 days apart
- Once participants have achieved the study objectives or the study has ended, they will be discontinued from this study and may be enrolled into an extension study to continue protocol-defined assessments and treatment.

IV=intravenous; mTPI=modified toxicity probability interval; QD=once daily; Q3W=every 3 weeks; RP2D=recommended Phase 2 dose

5.2 Number of Participants

Approximately 40 participants will be allocated to the dose escalation and confirmation phase (Part A) of this trial. An estimated additional 150 participants will be enrolled into the dose expansion phase (Part B) of this trial.

5.3 Beginning and End of Study Definition

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

Upon study completion, participants are discontinued and may be enrolled in a pembrolizumab extension study.

5.3.1 Clinical Criteria for Early Trial Termination

Early trial 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-7162 and/or pembrolizumab.

5.4 Scientific Rationale for Study Design

This Phase 1b study is being conducted to evaluate the safety, tolerability, and efficacy of MK-7162 in individuals with solid tumors when administered in combination with pembrolizumab. In the dose expansion phase of this trial, which will be detailed in a future protocol amendment, MK-7162 will be administered with pembrolizumab as dual therapy or in combination with additional chemotherapeutic or immune-modulatory agents.

This study is being conducted in male and female participants at least 18 years of age with advanced solid tumors.

The precise timing of clinical/laboratory safety evaluations and/or efficacy evaluations currently outlined in the protocol may be modified during the study based on newly available MK-7162 clinical and/or preclinical safety, tolerability, or efficacy data. Additional visits may be required if changes are made to the PK/PD sampling scheme. Other modifications to the dosing and/or clinical procedures currently outlined in the protocol may be required to achieve the scientific goals of the study objectives and/or to ensure appropriate safety monitoring of the study participants.

5.4.1 Rationale for Endpoints

5.4.1.1 Efficacy Endpoints

A secondary objective for this trial is to evaluate the antitumor activity of MK-7162 in combination with pembrolizumab in participants with advanced or metastatic solid tumors. Tumor response in participants with solid tumors will be assessed by investigator using RECIST 1.1 and iRECIST. A central imaging vendor will also be used to collect, clean, and hold tumor imaging and medical photography for possible analysis by blinded, independent central review.

Sites are encouraged to have a multidisciplinary assessment plan to determine in advance which lesions will be biopsied and/or targeted for tumor assessment. If feasible, biopsied tumors should not be used for assessment by RECIST 1.1/iRECIST.

5.4.1.1.1 Response Rate Assessed by RECIST version 1.1

RECIST 1.1 will be used to determine the objective response.

5.4.1.1.2 Response Rate Assessed by Immune-based RECIST (iRECIST)

RECIST 1.1 has been adapted to account for the unique tumor response characteristics seen following treatment with immunotherapeutic agents (Section 9.2.5). Immunotherapeutic agents 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 may manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Thus, standard RECIST 1.1 may not provide an accurate response assessment to immunotherapeutic agents. Based on an analysis of participants with melanoma enrolled in KEYNOTE-001 (KN001), 7% of evaluable participants experienced tumor pseudo-progression. Of note, participants who had progressive disease (PD) by RECIST 1.1 but not by the immune-related response criteria [Wolchok, J. D., et al 2009] had longer overall survival than participants with PD by both criteria [Hodi, F. S., et al 2014]. Additionally, the data suggest that RECIST 1.1 may underestimate the benefit of pembrolizumab in approximately 10% of participants. These findings support the need to apply a modification to RECIST 1.1 that takes into account the unique patterns of atypical responses in immunotherapy and enables treatment beyond initial radiographic progression, if the participant is clinically stable.

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

For further information on iRECIST, see Section 9.2.5.

5.4.1.2 Safety Endpoints

The primary objective of this trial is to characterize the safety and tolerability of MK-7162 in participants with advanced/ metastatic solid tumors when administered in combination with pembrolizumab. The primary safety analysis will be based on participants who experience toxicities as defined by CTCAE Version 4.0 criteria. Safety will be assessed by quantifying the toxicities and grades of toxicities experienced by participants who have received MK-7162 as monotherapy and in combination with pembrolizumab.

Safety parameters commonly used for evaluating investigational systemic anti-cancer treatments are included as safety endpoints for the study including, but not limited to, the incidence of, causality to, and outcome of AEs/SAEs; changes in vital signs and laboratory values.

5.4.1.3 Pharmacokinetic Endpoints

A secondary objective of this study is to characterize the PK profile of MK-7162 following administration as a single agent and to characterize the PK profiles of MK-7162 and pembrolizumab following administration as combination therapy. The concentrations of these agents will serve as the primary readout for the PK, and these data will be used to derive PK parameters of the agents when administered alone and in combination. Furthermore, the results of these analyses will be used in conjunction with the PD, safety, and exploratory endpoint data to help assess future dosing strategies for MK-7162.

5.4.1.4 Pharmacodynamic Endpoints

5.4.1.4.1 Kynurenine (KYN):Tryptophan (TRP)

The ratio of KYN to TRP will be measured in both plasma and in tumor biopsy specimens as a downstream PD marker of target engagement.

5.4.1.4.1.1 Target Engagement

An assay directly assessing target engagement will not be utilized and has therefore not been developed. Target engagement with be indirectly inferred by the KYN:TRP PD biomarker assay results.

5.4.1.5 Anti-Drug Antibodies (ADA)

Anti-pembrolizumab ADA response will be determined to understand drug metabolism, exposure, and safety. 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 specified treatment 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 antidrug antibodies and PK and PD markers, activity, and safety will be explored.

5.4.1.6 Planned Exploratory Biomarker Research

In addition to the specified analyses, exploratory analyses of metabolite profiles may be conducted in plasma and/or serum.

5.4.1.6.1 Germline Genetic Analyses

Germline (blood) genetic analyses (eg, single nucleotide polymorphism analyses, whole exome sequencing, whole genome sequencing): This research may evaluate whether genetic variation within a clinical trial population correlates with response to the treatment(s) under evaluation. If genetic variation is found to predict efficacy or AEs, the data might inform optimal use of therapies in the patient population. Furthermore, it is important to evaluate germline deoxynucleic acid (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 biomarker of response to immunotherapy with pembrolizumab.

5.4.1.6.2 Tumor Genetic Analyses

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 immune-oncology drug development include (for example) 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. MSI may also be evaluated as this is an important biomarker of response to immunotherapy with pembrolizumab.

5.4.1.6.3 Tumor and Blood Ribonucleic Acid Analyses

Tumor and blood ribonucleic acid (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 pembrolizumab or other immunotherapies. Pembrolizumab induces 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.

5.4.1.6.4 Proteomic Biomarkers and Immunohistochemistry (IHC)

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 pembrolizumab in patients with NSCLC, and an in vitro diagnostic (IVD) has been developed for use with pembrolizumab in NSCLC. Preliminary data indicates that this association may also be true in additional cancer types (eg, triple-negative breast cancer [TNBC], head and neck squamous cell carcinoma [HNSCC], and gastric cancer). Additional tumor or blood-derived proteins may also correlate with response to pembrolizumab. 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 may identify novel protein biomarkers that could aid in patient selection for MK-7162 and pembrolizumab (MK-3475) therapy.

5.4.1.6.5 Peripheral Blood Mononuclear Cell (PBMC) Phenotypic Analysis

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

5.4.1.6.6 Other Blood-derived Biomarkers

Other blood derived 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 can measure such proteins in serum. Correlation of expression with response to pembrolizumab therapy may identify new approaches for predictive biomarkers in blood, representing a major advance from today's reliance on assessing tumor-based biomarkers. This research would serve to develop such assays for future clinical use.

5.4.1.7 Future Biomedical Research

The Sponsor will conduct Future Biomedical Research on specimens consented for future biomedical research during this clinical trial. This research may include genetic analyses (DNA), gene expression profiling (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 trial) 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 sub-trial are presented in Appendix 6 – Collection and Management of Specimens for Future Biomedical Research.

5.5 Justification for Dose

5.5.1 Rationale for Starting and Maximum Dose of MK-7162

[redacted]

While the mechanism of IDO1 inhibition by MK-7162 is distinct from that of epacadostat, due to the common molecular target, there may be effects common to both. In published results of early clinical trials, epacadostat has been associated with common adverse effects (>20%) of fatigue, nausea, decreased appetite, and vomiting, constipation, abdominal pain, diarrhea, dyspnea, back pain, and cough. Two dose-limiting toxicities were observed, radiation pneumonitis and fatigue, both of which were grade 3 and were determined to be possibly related to therapy. This includes the following: one DLT occurred at the dose of 300 mg BID (grade 3, radiation pneumonitis); another DLT occurred at 400 mg BID (grade 3, fatigue).

Treatment with epacadostat produced significant dose-dependent reductions in plasma KYN levels and in the plasma KYN:TRP ratio at all doses and in all patients. Epacadostat doses of 100 mg BID achieved >80% to 90% inhibition of IDO1 at peak and 50% inhibition at trough. Although no objective responses were detected, stable disease lasting greater than or equal to 16 weeks was observed in 7 of 52 patients [Beatty, G. L., et al 2017]. Grade 3 AST/ALT elevation was observed in 1 patient but was attributed to biliary duct obstruction consistent with progressive disease. A second patient also experienced grade 3 AST/ALT elevations, but this was determined to be most likely related to acetaminophen ingestion over the maximum recommended daily dose for tumor-related fevers.

[redacted] The NHV study assessed a starting MK-7162 dose of 3 mg, which was based on the no-observed adverse effect level (NOAEL) determined in nonclinical safety studies performed in the most sensitive and relevant animal species, adjusted with allometric factors to calculate the Human Equivalent Dose (HED), reduced by appropriate safety factors according to the particular aspects of the molecule and the design of the clinical trials. The maximum dose selected for the NHV study is currently 300 mg, based on the exposures at the NOAEL dose level in the preclinical species of rat and dog, and was projected to have an exposure lower than the NOAEL exposure of either preclinical species. The analysis of clinical PK data from the NHV SAD study has been reviewed alongside safety and tolerability data. The PK data in normal healthy participants over the dose range of 3 to 300 mg will continue to inform the dosing range for this study.

Based on data from in vitro experimentation, animal models, and human experience with other inhibitors of IDO1, MK-7162 is expected to have broad clinical efficacy against a variety of tumor types when used in conjunction with pembrolizumab. [redacted] Prior studies of IDO1 inhibition in cancer patients have shown that this level of IDO1 inhibition is well tolerated, and preliminary studies suggest that there may be enhancement of the anti-tumor response with PD-1/PD-L1 blockade at this level of IDO1 inhibition.

[redacted] This dose was found to be both safe and well tolerated when administered as a single dose to normal healthy participants. Therefore, an MK-7162 dose of 25 mg PO QD will be the starting dose for the dose escalation and confirmation phase (Part A) of this Phase 1b trial.

5.5.2 Maximum Dose of MK-7162

The determination of a preliminary RP2D for MK-7162 is a primary objective for this study. This study will evaluate the following dose levels: 25 mg PO QD, 50 mg PO QD, 100 mg PO QD, 200 mg, and 400 mg PO QD. [redacted] Corresponding IDO1 inhibition

in tumor cells at the tested dose levels will be evaluated using the KYN:TRP PD biomarker and fresh tumor biopsy specimens.

cci [redacted].

5.5.3 Rationale for Dose Interval and Escalation Increments

The starting dose and dosing interval in participants of the MK-7162 Phase 1b study are based on an integration of clinical, nonclinical, toxicological, PK, and PD data. Dose finding will proceed with a model-based dose mTPI approach with a minimum of 3 participants treated per dose level: 25 mg QD, 50 mg QD, 100 mg QD, 200 mg, and 400 mg QD.

5.5.3.1 Dose Finding Using a Modified Toxicity Probability Interval Design

The mTPI design [Ji Y, Li Y, Bekele BN 2007] of this study will target a DLT rate of 30%. The starting dose for the mTPI will be MK-7162 25 mg QD. Dose escalation and de-escalation decisions are based on the mTPI design and depend on the number of participants enrolled and number of DLTs observed at the current dose level.

A minimum of 3 participants are required at each dose. However, depending on the accrual rate and the occurrence of DLTs, 3, 4, 5, or 6 participants may be enrolled at each new dose level. In [Table 1], the columns indicate the numbers of participants treated at the current dose level, and the rows indicate the numbers of participants experiencing DLT. The entries of the table are the dose-finding decisions: E, S, D, and DU represent escalating the dose, staying at the same dose, de-escalating the dose, and excluding the dose from the trial due to unacceptable toxicity, respectively. For example, if 0 out of 3 participants at a given dose level develop a DLT, then the dose can escalate to the next level. If 2 participants out of 3 develop a DLT, the dose will be de-escalated to the next lower dose level. If 3 out of 3 participants develop a DLT, this indicates an unacceptable toxicity at this dose. The dose should be de-escalated and the current dose will not be explored further. If 1 out of 3 participants at a given dose level develops a DLT, then additional participants should be enrolled at that dose level following the rules below.

When adding participants to a dose level in response to a “stay” decision, the same principles will be applied whether 3, 4, 5, or 6 participants are initially enrolled at that dose level. First, the number of additional participants to be enrolled is capped to minimize the exposure to a dose that may be unacceptably toxic (denoted as DU in [Table 1]). Secondly, to determine how many more participants can be enrolled at the dose level, one can count steps in diagonal direction (down and to the right) from the current cell to the first cell marked DU. For example, if 1 of 3 participants have experienced a DLT at a given dose level, no more than an additional 3 participants should be enrolled at this dose level until additional DLT data are available. This is because this dose level would be considered unacceptably toxic if all 3 of the additional participants experience a DLT (ie, 4/6 participants with DLT in [Table 1]).

A D or DU decision at the lowest dose level will stop the trial. An E decision at the highest dose level will result in staying at that level. During dose finding, it may be acceptable to de-escalate to an intermediate dose that was not predefined and not previously studied if evaluation of toxicity at such a dose is desired. If this approach is taken, 3 to 6 new participants may be enrolled at the new intermediate dose, and the aforementioned rules should be used to determine further enrollment at this dose level.

Dose finding will end after 14 participants have been enrolled at any of the tested doses (including intermediate doses). In the event the dose-finding decision is not to stay at the current dose based on the 14 participants, the dose may be escalated or de-escalated and additional participants may be treated.

The pool-adjacent-violators-algorithm [Ji, Y. and Wang, S.-J. 2013] will be used to estimate the DLT rates across doses. The dose with an estimated DLT rate closest to 30% will be treated as a preliminary MTD. The final RP2D for future studies will be based on all available safety and tolerability assessments from the Dose Escalation and Confirmation Phase, Dose Expansion Phase, as well as PK and PD data, and preliminary efficacy assessments from this trial.

Note that although 30% was the target toxicity rate used to generate the guidelines in [Table 1], the observed rates of participants with DLTs at the MTD may be slightly above or below 30%.

Table 1 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

DLT = Dose limiting toxicity; D = De-escalate to the next lower dose; DU = The current dose is unacceptably toxic; E = Escalate to the next higher dose; S = Stay at the current dose.
Target toxicity rate = 30%
Flat noninformative prior Beta (1,1) is used as a prior and ε1=ε2=0.03 [Ji Y, Li Y, Bekele BN 2007], [Ji, Y., et al 2007], [Ji, Y. and Wang, S.-J. 2013]

6. Study Population

Male and female participants at least 18 years of age with advanced solid tumors (of any type) will be enrolled in this trial.

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

6.1 Inclusion Criteria

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

1. 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 treatment known to confer clinical benefit. Participants with solid tumors of any type are eligible for enrollment.
2. Have stage III or stage IV disease that is not surgically resectable.
3. Have measureable disease by RECIST 1.1 criteria as assessed by the local site investigator/radiology. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
4. Be ≥18 years of age on the day of signing informed consent.
5. Have one or more discrete malignant lesions that are amenable to a minimum of two separate biopsies guided by one of the following modalities: visual inspection, ultrasound guidance, or cross-sectional image guidance (computed tomography/magnetic resonance imaging [CT/MRI]).

   Note: Participants should only be enrolled if during the screening assessment the investigator deems the biopsy of such lesions to be medically safe.
6. Have an evaluable baseline tumor sample to submit for analysis. Archival samples are preferred, if available. Details pertaining to tumor tissue submission can be found in the Procedures Manual.
7. Have a performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) Performance Scale.
8. Demonstrate adequate organ function as defined by the following table ([Table 2])

   All screening evaluations should be performed within the Screening period, and labs are to be obtained within 7 days of initiation of treatment.

Table 2 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count	≥1,500/mcL
Platelets	≥100,000/mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L [a]
Renal	
Serum creatinine **or** creatinine clearance (CrCl) (measured **or** calculated) [b] **or** Glomerular Filtration Rate (GFR) in place of CrCl	≤1.5 X upper limit of normal (ULN) **or** ≥60 mL/min for participant with creatinine levels ≥1.5 X ULN
Hepatic	
Total bilirubin (serum)	≤1.5 X ULN **or** Direct bilirubin <ULN for participants with total bilirubin levels ≥1.5 X ULN
Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT)	<2.5 X ULN **or** ≤5 X ULN for participants with liver metastases
Coagulation	
International Normalized Ratio (INR) **or** Prothrombin Time (PT)	< 1.5 X ULN unless participant is receiving anticoagulant therapy
Activated Partial Thromboplastin Time (aPTT) or Partial Thromboplastin Time (PTT)	< 1.5 X ULN unless participant is receiving anticoagulant therapy

[a] Criteria must be met without packed red blood cell (pRBC) transfusion within the prior 2 weeks. Participants may be on stable doses of erythropoietin (≥ approximately 3 months).

[b] 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 and guidelines for the administration of specific chemotherapies.

Demographics

Male participants:

9. A male participant must agree to use a contraception, and refrain from donating sperm, as detailed in Appendix 5 of this protocol during the treatment period and for at least 120 days, corresponding to time needed to eliminate any study treatments (MK-7162 and pembrolizumab), after the last dose of study treatment.

Female participants:

10. A female participant is eligible to participate if she is not pregnant (Appendix 5), not breastfeeding, and at least one of the following conditions applies: A woman of childbearing potential (WOCBP) who agrees to follow the contraception guidance in Appendix 5 during the treatment period for at least 120 days (corresponding to time needed to eliminate any study treatment(s) (MK-7162 and pembrolizumab).

Informed Consent

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

6.2 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 2 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, *in situ* cervical cancer, or other *in-situ* cancers.

2. Has a known active central nervous system (CNS) metastasis and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable, ie, without evidence of progression for at least 4 weeks by repeat imaging (note that this repeat imaging should be performed during study screening), clinically stable and without requirement for steroid treatment for at least 14 days prior to first dose of study treatment.
3. Has had a severe hypersensitivity reaction to treatment with a monoclonal antibody/components of the study drug(s).
4. 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 non-systemic steroids is permitted.
5. Has a history of vasculitis.
6. Has an active infection requiring systemic therapy.
7. Has symptomatic ascites or pleural effusion. A participant who is clinically stable following treatment for these conditions (including therapeutic thoracentesis or paracentesis) is eligible.

8. Has interstitial lung disease that has required oral or intravenous glucocorticoids to assist with management.
9. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.
10. Has undergone prior allogeneic hematopoietic stem cell transplantation within the last 5 years.

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

11. Has a known history of human immunodeficiency virus (HIV) infection. No HIV testing is required unless mandated by local health authority.
12. Has known active Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection.

    Note: No testing for Hepatitis B and Hepatitis C is required unless mandated by local health authority.

13. 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 drugs 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.
14. Has known psychiatric or substance abuse disorders that would interfere with the participant's ability to cooperate with the requirements of the study.
15. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the study.
16. Has not fully recovered from any effects of major surgery without significant detectable infection. Surgeries that required general anesthesia must have been completed at least 2 weeks before first study drug administration. Surgery that required regional/epidural anesthesia must have been completed at least 72 hours before first study drug administration and participants should have recovered.
17. A WOCBP who has a positive urine pregnancy test within 72 hours prior to treatment allocation (see Appendix 5). 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 has elapsed between the screening pregnancy test (urine or serum) and the first dose of study treatment, repeat pregnancy testing must be performed and must be negative in order for participant to start receiving study medication.

Prior/Concomitant Therapy

18. Has received prior systemic anti-cancer therapy including investigational agents or has used an investigational device within 28 days prior to the first dose of study treatment.

    Note: Participants must have recovered from all AEs due to previous therapies to ≤ Grade 1 or baseline. Participants with ≤ Grade 2 neuropathy or alopecia may be eligible. Participants receiving ongoing replacement hormone therapy for endocrine immune-related adverse events will not be excluded from participation in this study.

    Note: Prior exposure to immunotherapeutics is allowed, including PD-1 and PD-L1 inhibitors, provided the participant did not experience ≥ Grade 3 drug-related toxicity on monotherapy with a PD-1 or PD-L1 inhibitor.

19. Has been previously treated with an IDO1 inhibitor (eg, epacadostat, BMS-986205)
20. Has received prior radiotherapy within 2 weeks of start of study treatment. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤ 2 weeks of radiotherapy) to non-CNS disease.
21. Is receiving an MAO-inhibitors (MAOI) or any drug which has significant MAOI activity (eg, meperidine, linezolid, methylene blue) within the 21 days before screening, or has a history of Serotonin Syndrome after receiving serotonergic drugs.
22. Is expected to require any non-protocol antineoplastic therapy while on study.
23. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy in excess of replacement doses (the equivalent of prednisone ≤10 mg/day is acceptable), or on any other form of immunosuppressive medication.

    Note: The use of physiologic replacement doses of corticosteroids may be approved after consultation with the Sponsor Medical Monitor or designee.

24. Has received a live-virus vaccine within 30 days prior to first dose of study medication. Vaccines that do not contain live virus are permitted.

6.3 Lifestyle Restrictions

6.3.1 Dietary Restrictions

For C1D1, C1D15 and C3D1 participants are to remain fasted overnight. The participant must remain fasting up to 1 hour following treatment with MK-7162 on C1D1, C1D15, and C3D1; clear fluids are permitted.

There are no other diet restrictions.

6.3.2 Contraception

MK-7162 and pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if MK-7162 or pembrolizumab have transient adverse effects on the composition of sperm.

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

6.3.3 Pregnancy

If a participant inadvertently becomes pregnant while on treatment with MK-7162 and/or pembrolizumab, 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 9.3.6.

6.3.4 Use in Nursing Women

It is unknown whether MK-7162 or pembrolizumab is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, participants who are breastfeeding are not eligible for enrollment.

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled 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 or serious adverse events (SAE) meeting reporting requirements as outlined in the entry guidelines.

6.5 Participant Replacement Strategy

In order to adequately evaluate the safety of the doses administered in Part A (Dose Escalation and Confirmation Phase), all participants enrolled must meet the criteria for evaluability for the first 2 cycles (42 days from the first dose of study medication). Criteria for evaluability of participants in Part B (Dose Expansion Phase) will be clarified in a future protocol amendment.

Participants are considered non-evaluable 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 AEs
- They receive less than 90% of the total oral MK-7162 or pembrolizumab infusion in Cycle 1 and Cycle 2 and did not experience a DLT.

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

7. Treatments

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

Clinical supplies [study treatment(s) provided by the Sponsor] will be packaged to support enrollment and replacement participants as required. When a replacement participant is required, the Sponsor or designee needs to be contacted prior to dosing the replacement supplies. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

7.1 Treatments Administered

The study treatment(s) to be used in this trial are outlined below in Table 3.

Table 3 Study Treatment

Study Treatment Name	Dosage Formulation	Unit Dose Strength(s)	Dose Frequency	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period	Sourcing
MK-7162	Oral Compressed Tablet (OCT)	1, 10, and 100 mg potency tablets	QD	25 mg up to 400 mg	Oral	Cycles 1-36; 21-day treatment cycle	Provided centrally by the Sponsor.
Pembrolizumab (MK-3475)	Solution for Infusion	100 mg/4 mL	Q3W	200 mg	IV infusion	Cycles 2-36: Day 1 of each 21-day treatment cycle	Provided centrally by the Sponsor.
For pembrolizumab combination treatment-day visits, MK-7162 should be administered in clinic a minimum of 1 h prior to initiation of pembrolizumab infusion.							

All supplies indicated in Table 3 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. The trial site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

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

7.2 Dose Modification (Escalation/Titration/Other)

7.2.1 Dose Administration/Escalation/Cohort Expansion

7.2.1.1 Dose Administration (Preparation)

Details on preparation and administration of MK-7162 and pembrolizumab are provided in the appropriate Pharmacy/Procedures Manual.

7.2.2 Definition of Dose Limiting Toxicity

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

In this study, the DLT window of observation will be during the first 6 weeks of treatment (Cycles 1 and 2). The occurrence of any of the following toxicities will be considered a DLT, if assessed by the investigator to be possibly, probably, or definitely related to study drug administration, excluding toxicities clearly not related to the drug, such as disease progression, environmental factors, unrelated trauma, etc.:

1. Grade 4 nonhematologic toxicity (not laboratory)
2. Grade 4 hematologic toxicity lasting ≥7 days, except thrombocytopenia:
   - Grade 4 thrombocytopenia of any duration
   - Grade 3 thrombocytopenia associated with bleeding.
3. Any nonhematologic AE ≥Grade 3 in severity should be considered a DLT, with the following exceptions: Grade 3 fatigue lasting ≤3 days; Grade 3 diarrhea, nausea, or vomiting without use of anti-emetics or anti-diarrheals per standard of care; Grade 3 fever and Grade 3 flu-like symptoms lasting ≤24 hours with negative infectious disease workup (including negative blood and urine cultures)
4. 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 >1 week
   - The abnormality results in a Drug-induced Liver Injury (DILI) (see Sections 9.3.1 and 9.3.7 for criteria)

     Exceptions: Clinically nonsignificant, treatable, or reversible laboratory abnormalities including liver function tests, uric acid, etc.

5. Febrile neutropenia Grade 3 or Grade 4
    - Grade 3 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
    - 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.
6. Any treatment-related toxicity that causes the participant to discontinue treatment during Cycle 1 or Cycle 2
7. Prolonged delay (>2 weeks) in initiating Cycle 2 or Cycle 3 due to treatment-related toxicity
8. Missing >25% of MK-7162 doses as a result of drug-related AE(s) during the first 2 cycles of treatment
9. Grade 5 toxicity

7.2.3 Timing of Dose Administration

7.2.3.1 Timing of Administration for MK-7162

MK-7162 will be administered once a day. The reason for any variability in administration of MK-7162 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, trial therapy should be initiated no later than 3 days from the date the study treatment cohort is allocated. All study treatments will begin on Day 1 of each cycle after all predose study procedures and assessments have been completed as detailed in Section 2 - Summary of Activities. On Day 1 of each cycle (Cycles 2-36), MK-7162 should be administered in the clinic a minimum of 1 hour prior to initiation of pembrolizumab infusion.

The Pharmacy Manual contains specific instructions for MK-7162 administration.

All study medications will be administered on an outpatient basis.

7.2.3.2 Timing of Administration for Pembrolizumab

Trial treatment of pembrolizumab should be administered on Day 1 of each 3 week cycle, beginning at Cycle 2, after all procedures/assessments have been completed as detailed in the Trial Flow Chart (Section 2).

Trial treatment of pembrolizumab may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

The Pharmacy Manual contains specific instructions for pembrolizumab administration.

All study medications will be administered on an outpatient basis.

7.2.4 Guidelines for Dose Modification due to Adverse Events

Adverse events (both nonserious and serious) associated with MK-7162 and pembrolizumab exposure may represent an immunologic etiology. These AEs may occur shortly after the first dose or several months after the last dose of treatment.

CTCAE 4.0 must be used to grade the severity of adverse events. The investigator may attribute each toxicity event to MK-7162 alone, to pembrolizumab alone, or to the combination, and modify the dose according to Table 4 and Table 5. If a dose modification for toxicity occurs with MK-7162, the dose may not be re-escalated to the dose that preceded the dose modification. Dose modifications are always based on the previous cycle.

Reduction or holding of 1 agent and not the other agent is appropriate if, in the opinion of the investigator, the toxicity is clearly related to 1 of the study medications and Sponsor consultation and approval is obtained. For example, if MK-7162 is held due to an adverse event attributed to that drug, then pembrolizumab may continue to be administered in consultation with the Sponsor. Appropriate documentation is required regarding the drug to which the investigator is attributing the adverse event. If, in the opinion of the investigator, the toxicity is related to the combination of 2 or more agents, then the corresponding drugs should be held according to recommended dose modifications.

7.2.4.1 Dose Modification for MK-7162

Participants may have up to 2 dose modifications of MK-7162 throughout the course of the study, as described in Table 4. If further toxicity occurs or the criteria for resuming treatment are not met, the participant must be discontinued from the attributed study treatment. If a participant experiences several toxicities and there are conflicting recommendations, the most conservative dose adjustment recommendations (dose reduction appropriate to the most severe toxicity) should be followed.

Exceptional circumstances to the following dose modification tables below may be considered after consultation with and approval by the Sponsor.

Table 4 MK-7162 Dose Modification and Treatment Discontinuation Guidelines for Drug-Related Adverse Events

Toxicity	Hold Treatment	Criteria for Restarting Treatment	Dose/Schedule for Restarting Treatment	Criteria for Discontinuation after Consultation with Sponsor
Hematological toxicities:				
• Any Grade 1 hematological toxicity	No	N/A	N/A	N/A
• Any Grade 2 hematological toxicity, or Grade 3 toxicity that persists for ≤5 days	Per medical assessment of the investigator	If treatment held, may be restarted when AE resolves back to baseline or to Grade 1	Per medical assessment of the Investigator: may decrease dose by 1 dose level	If AE persists for 12 weeks without resolution following reduction in dose
• Any Grade 3 hematologic toxicity that persists for >5 days, or Grade 4 hematological toxicity • Febrile neutropenia • Grade 3 thrombocytopenia of any duration if associated with bleeding	Yes	Treatment may be restarted when AE resolves back to baseline or to Grade 1	Decrease dose by 1 dose level	If AE persists for 12 weeks without resolution following reduction in dosing schedule Permanent discontinuation should be considered for any severe or life-threatening event
Nonhematological toxicities:				
Toxicity	**Hold Treatment**	**Criteria for Restarting Treatment**	**Dose/Schedule for Restarting Treatment**	**Criteria for Discontinuation after Consultation with Sponsor**
• Any Grade 1 nonhematological toxicity • Grade 2 alopecia • Grade 2 fatigue	No	N/A	N/A	N/A
• Any Grade 2 nonhematological toxicity except Grade 2 alopecia and Grade 2 fatigue	Per medical assessment of the investigator	If treatment held, may be restarted when AE resolves back to baseline or to Grade 1	Per medical assessment of the Investigator: may decrease dose by 1 dose level	If AE persists for 12 weeks without resolution following reduction in dose

Toxicity	Hold Treatment	Criteria for Restarting Treatment	Dose/Schedule for Restarting Treatment	Criteria for Discontinuation after Consultation with Sponsor
• Any Grade 3 or 4 nonhematological toxicity (not including laboratory, unless clinically significant medical intervention is required to treat the participant, or the abnormality leads to hospitalization, or the abnormality persists for >1 week)	Yes	Treatment may be restarted when AE resolves back to baseline or to Grade 1	Decrease dose by 1 dose level	If AE persists for 12 weeks without resolution following reduction in dose Permanent discontinuation from study treatment should be considered for any severe or life-threatening event

If toxicity is attributed to MK-7162, and requires a treatment hold and does not resolve to Grade 0-1 within 12 weeks after the last treatment, then MK-7162 should be discontinued.

With Investigator and Sponsor agreement, participants with a laboratory adverse event still at Grade 2 after 12 weeks may continue treatment in the trial only if asymptomatic and controlled.

After any Grade 4, drug-related adverse event, participants should not restart study treatment without consultation with the Sponsor (Toxicity must have resolved to Grade 0-1 or baseline prior to restarting).

Pembrolizumab treatment will be modified for the adverse events described Section 7.2.4.2.

7.2.4.2 Dose Modification for Pembrolizumab

7.2.4.2.1 Dose Modification and Toxicity Management for Immune-related AEs Associated with Pembrolizumab

AEs associated with pembrolizumab exposure 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 pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical trial data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids, and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, or skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 5.

Table 5 Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab 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 pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue		

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	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 pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.

NOTE:

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

7.2.4.2.2 Dose Modification and Toxicity Management of Infusion Reactions Related to Pembrolizumab

Pembrolizumab may cause severe or life-threatening infusion reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab-associated infusion reaction are provided in Table 6.

Table 6 Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 h	**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/h to 50 mL/h). 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 min) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg PO (or equivalent dose of antihistamine) and/or 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		

7.2.4.2.3 Other allowed dose interruption(s) for pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to study treatment. Participants should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

7.3 Method of Treatment Assignment

Study treatment will be allocated via IVRS. Each new dose level will open for enrollment without delay once the 42-day DLT observation period of the previous dose cohort is completed, and a dose escalation decision is made.

7.3.1 Stratification

No stratification based on age, sex or other characteristics will be used in this trial.

7.4 Blinding

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

7.5 Preparation/Handling/Storage/Accountability

7.5.1 Dose Preparation

The rationale for selection of doses to be used in this trial is provided in Section 5.5.1. There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each participant.

7.5.2 Handling, Storage and Accountability

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

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

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

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

7.6 Treatment Compliance

Compliance will be assessed at each clinic visit.

All doses of pembrolizumab will be administered under the supervision of a qualified physician and/or qualified designee experienced in the use of anticancer agents.

Interruptions from the protocol specified treatment plan for >12 weeks between MK-7162 or pembrolizumab doses for non-drug related or administrative reasons require consultation

between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

7.7 Concomitant Therapy

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

7.7.1 Acceptable Concomitant Medication

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 except for those that are prohibited as described in Section 7.7.2. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date should also be included on the CRF.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered more than 30 days after the last dose of trial treatment should be recorded for SAEs and events of clinical interest (ECIs) as defined in Section 9.3. The investigator or qualified designee will record medication, if any taken by the participant during the trial.

7.7.2 Prohibited Concomitant Medications

Participants are prohibited from receiving the following therapies during the Screening and Treatment Phases (including retreatment for post-complete response relapse) of this trial:

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

  Note: Palliative radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion, but only after the DLT observation period in order for the participant to be considered evaluable for DLT.

- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, 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.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an AE of suspected immunologic etiology. Physiologic doses of corticosteroids may be administered, but only after consultation with and approval by the Sponsor.
- MAO-inhibitors (MAOI) or any drug which has significant MAOI activity (eg, meperidine, linezolid, methylene blue)

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

Treatment by local surgery (and/or radiation therapy) of isolated or symptomatic progressing lesions in the setting of improving baseline disease may be permitted for palliative or potentially curative management following completion of Cycle 2. All such interventions, including continuation of study treatment, should be discussed with the Sponsor.

7.7.3 Supportive Care

Supportive care for participants should follow the pembrolizumab supportive care guidelines located in Section 7.2.4.2.

7.8 Treatment After the End of the Study

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

7.9 Clinical Supplies Disclosure

This trial is open-label; therefore, the participant, the trial 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.

8. Discontinuation/Withdrawal Criteria

8.1 Discontinuation of Study Treatment

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

As certain data on clinical events beyond study treatment discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study treatment. Therefore, all participants who discontinue study treatment prior to completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 2 - SoA and Section 9.11.3 – Discontinued Participants Continuing to be Monitored in the Study.

Participants may discontinue study treatment at any time for any reason or be dropped from the study treatment at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study treatment by the investigator or the Sponsor if study treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study treatment discontinuation are provided in Section 9.1.9 – Withdrawal/Discontinuation.

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

- The participant or participant's legally acceptable representative requests to discontinue study treatment.
- The participant interrupts study medication administration for more than 12 consecutive weeks.
- The participant interrupts MK-7162 for more than 84 (QD) cumulative missed doses.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or sponsor, places the participant at unnecessary risk from continued administration of study treatment.
- The participant has a confirmed positive serum or urine pregnancy test.
- Non-compliance with trial treatment or procedure requirements.
- Confirmed radiographic disease progression outlined in Section 9.11 – Visit Requirements (Exception is if Sponsor approves treatment continuation).
- Unacceptable adverse experiences as described in Section 9.3 – Adverse Events, Serious Adverse Events and Other Reportable Safety Events.
- Intercurrent illness other than another malignancy as noted above (Section 5.1.1 – Dose Escalation and Confirmation) that prevents further treatment administration.
- Investigator's decision to discontinue treatment.
- Recurrent Grade 2 pneumonitis.
- Progression or recurrence of any malignancy, or occurrence of another malignancy that requires active treatment.

Completion of 36 treatment cycles.

For participants who are discontinued from study treatment but continue to be monitored in the trial, see Section 2 –SoA, and Section 9.11.3 – "Discontinued Participants Continuing to be Monitored in the Study" for those procedures to be completed at each specified visit.

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

8.2 Withdrawal from the Study

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

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

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from Future Biomedical Research , are outlined in Section 9.1.9 – Withdrawal/Discontinuation. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 8.3.

8.3 Lost to Follow Up

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

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

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

9. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.

The approximate amount of blood collected from each participant for laboratory evaluations is provided in the Procedures Manual.

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.

Efficacy and safety evaluations must be obtained prior to study treatment administration on treatment cycle visit days, unless otherwise specified in the SoA.

9.1 Administrative and General Procedures

9.1.1 Informed Consent

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

9.1.1.1 General Informed Consent

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

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

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

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

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

9.1.1.2 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 sub-trial. A copy of the informed consent will be given to the participant.

9.1.2 Inclusion/Exclusion Criteria

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

9.1.3 Participant Identification Card

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

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

9.1.4 Medical History

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

9.1.5 Prior and Concomitant Medications Review

9.1.5.1 Prior Medications

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

9.1.5.2 Concomitant Medications

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

All medications related to reportable SAEs and ECIs should be recorded as defined in Section 9.3 (Adverse Events, Serious Adverse Events and Other Reportable Safety Events).

All new anticancer therapy initiated after the study start must be recorded in the eCRF. If a participant initiates another anticancer therapy other than the assigned study treatment(s), the study treatment(s) should be discontinued and the participant will move into the survival follow-up phase; if a participant initiates a new anticancer therapy within 30 days after the last dose of the trial treatment, the 30-day Safety Follow-up visit should occur before the first dose of the new therapy.

9.1.6 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.

Specific details on the screening visit requirements (screening/rescreening) are provided in Section 9.11.1.

9.1.7 Assignment of Treatment/Randomization Number

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

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

9.1.8 Treatment Administration

All study treatments will be administered on an out-patient basis. Study treatment should begin within 3 days of allocation or as close as possible to the allocation date.

9.1.8.1 Timing of Dose Administration

9.1.8.1.1 Timing of Dose Administration for MK-7162

During on-site visits, administration of study medication will occur at the study site under the direction of the investigator and/or trial staff. The administration, the dose, the time of administration, as well as any immediate reactions at the time of intake will be documented in the eCRF.

For non-visit days, MK-7162 will be taken at home. When a participant attends a study visit, he/she will bring any unused tablets.

Refer to Section 7.2.4 (Timing of Dose Administration) for dose and treatment details.

9.1.8.1.2 Timing of Dose Administration for Pembrolizumab

The first dose of pembrolizumab is administered on C2D1. Pembrolizumab is administered once every 21 days during a morning visit in the clinic. Details on administration of pembrolizumab are provided in the appropriate Pharmacy/Procedures Manual. Refer to Section 7.2.4 (Timing of Dose Administration) for dose and treatment details.

9.1.9 Withdrawal/Discontinuation

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

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

9.1.9.1 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 trial. If medical records for the main trial 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 trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main trial 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.

9.1.10 Participant Blinding/Unblinding

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

9.1.11 Calibration of Critical Equipment

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

Critical Equipment for this trial includes:

- Laboratory equipment as required for inclusion laboratory assessments and for safety laboratory assessments
- Imaging equipment as required for disease assessments relevant to trial objectives
- Infusion equipment as required for administering study treatment

Additional guidance regarding critical equipment (if applicable) is provided in the Procedures Manual, Pharmacy Manual, and Site Imaging Manual.

9.2 Efficacy Assessments

9.2.1 Tumor Imaging and Assessment of Disease

The process for image collection and transmission to the central imaging vendor can be found in the Site Imaging Manual (SIM). Tumor imaging of the chest, abdomen, and pelvis is strongly preferred to be acquired by computed tomography (CT) with IV contrast. Contrast-enhanced magnetic resonance imaging (MRI) may be used when CT with iodinated contrast

is contraindicated. MRI is the strongly preferred modality for imaging the brain. The same imaging technique regarding modality, ideally the same scanner, and the use of contrast should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the assessment of response or progression based on imaging. Note: for the purposes of assessing tumor imaging, the term "Investigator" refers to the local investigator at the site and/or the radiological reviewer located at the site or at an offsite facility.

9.2.2 Initial Tumor Imaging

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

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

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

9.2.3 Tumor Imaging During the Study

The first on-study imaging assessment should be performed at 9 weeks (±7 days) from the date of first dose of study treatment (C1D1). Subsequent tumor imaging should be performed every 9 weeks (±7 days) or more frequently if clinically indicated. 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 is identified by the Investigator, the start of new anticancer treatment, withdrawal of consent, or death, whichever occurs first. All supplemental imaging for study participants and related to disease progression/response must be submitted to the central imaging vendor.

Objective response should be confirmed by a repeat imaging assessment. Tumor imaging to confirm PR or CR should be performed at least 4 weeks after the first indication of a response is observed. Participants will then return to regular scheduled imaging, starting with the next scheduled imaging time point. Participants who receive additional imaging for confirmation do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point.

Per iRECIST (Section 5.4.1.1.2), disease progression should be confirmed by the site 4 to 8 weeks after site-assessed 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 by the site, provided they have

met the conditions detailed in Section 5.4.1.1.2. Participants who receive confirmatory imaging do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point, if clinically stable. Participants who have confirmed disease progression by iRECIST, as assessed by the site, will discontinue study treatment. Exceptions are detailed in Section 5.4.1.1.2.

9.2.4 End of Treatment and Follow-up Tumor Imaging

For participants who discontinue study treatment, tumor imaging should be performed at the time of treatment discontinuation (±4 week window). If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory. For participants who discontinue study treatment due to documented disease progression, this is the final required tumor imaging if the Investigator elects not to implement iRECIST.

For participants who discontinue study treatment without documented disease progression, every effort should be made to continue monitoring disease status by tumor imaging using the same imaging schedule used while on treatment (every 9 weeks) until the start of a new anticancer treatment, disease progression, death, withdrawal of consent, or the end of the study, whichever occurs first. Such imaging should be submitted to the central imaging vendor.

9.2.5 RECIST 1.1 Assessment of Disease

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

9.2.6 iRECIST 1.1 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 the Investigator to assess tumor response and progression and to make treatment decisions. When clinically stable, participants should not be discontinued until progression is confirmed by the Investigator, working with local radiology, according to the rules outlined in Appendix 7. This allowance to continue treatment despite initial radiologic 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. This data will be captured in the clinical database.

Clinical stability is defined as the following:

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

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

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

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

If a participant has confirmed radiographic progression (iCPD) as defined in Appendix 8, study treatment should be discontinued; however, if the participant is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered following consultation with the Sponsor. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 2 and submitted to the central imaging vendor.

A description of the adaptations and iRECIST process is provided in Appendix 8, with additional details in the iRECIST publication [Seymour, L., et al 2017]. A summary of imaging and treatment requirements after first radiologic evidence of progression is provided in Table 7.

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

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

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

iCPD=iRECIST confirmed progressive disease; iCR=iRECIST complete response; iRECIST=modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; iSD=iRECIST stable disease; iUPD=iRECIST unconfirmed progressive disease; PD=progressive disease; RECIST 1.1=Response Evaluation Criteria in Solid Tumors 1.1; VOP=verification of progression

9.2.7 Medical Photography (cutaneous lesions)

If applicable, medical photography should be obtained. The collection time points follow the same schedule as imaging and may be performed more often if clinically indicated. Collection timepoints specified in the SoA are based on calendar days and are not adjusted for delays in treatment cycle start dates. Imaging and/or medical photography continues to be captured until disease progression or discontinuation (end of treatment [EoT]). The Site Imaging Manual (SIM) provides guidance in obtaining and submitting medical photography to the central imaging vendor.

9.2.8 Eastern Cooperative Oncology Group (ECOG) Performance Scale

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 Section 2 - SoA. Additional ECOG assessments may be performed as clinically indicated.

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

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

Progression of the cancer under study is not considered an adverse event as described in Section 9.3.5 – Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs, and Appendix 4.

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

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

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

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

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

From the time of treatment allocation/randomization through 14 days following cessation of treatment, all AEs, SAEs and other reportable safety events 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 in the previous paragraph 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 timeframes as indicated in Table 8.

Table 8 Reporting Time Periods and Timeframes for Adverse Events and Other Reportable Safety Events

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

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

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

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AE, SAE and other reportable safety events including pregnancy and exposure during breastfeeding, ECI, Cancer and Overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). In addition, the investigator will make every attempt to follow all non-serious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 4.

9.3.4 Regulatory Reporting Requirements for SAE

1. 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.
2. 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 Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, i.e., per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.
3. Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
4. An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAE) from the sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

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

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

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

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

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

9.3.6 Pregnancy and Exposure During Breastfeeding

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

9.3.7 Events of Clinical Interest (ECI)

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

Events of clinical interest for this trial include:

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

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

9.4 Treatment of Overdose

For this study, an overdose of pembrolizumab will be defined as any dose of 1000 mg or greater (≥5 times the indicated dose).

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

For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for MK-7162 by ≥20% of the indicated dose. No specific information is available on the treatment of overdose of MK-7162. In the event of overdose, MK-7162 should be discontinued and the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

9.5 Safety

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

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

9.5.1 Physical Examinations

9.5.1.1 Full Physical Exam

The investigator or qualified designee will perform a 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 Section 2 (SoA). Height is recorded only at Screening; weight is recorded at Screening and at the visits indicated in the SoA. After the first dose of trial treatment, new clinically significant abnormal findings should be recorded as AEs.

9.5.1.2 Directed Physical Exam

The time points for a directed physical exam are outlined in Section 2 (SoA). The investigator or qualified designee will perform a directed physical exam as clinically indicated prior to study treatment administration. Weight is recorded at Screening and at the visits indicated in the SoA. New clinically significant abnormal findings should be recorded as AEs.

9.5.2 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment on Day 1 of each Cycle and during the follow-up period as specified in Section 2, SoA. Vital signs (VS) include temperature, pulse rate, respiratory rate, oxygen (0_2) saturation and blood pressure.

On Cycle 1 Day 1, collect VS within 1 hour (± 30 minutes) prior to MK-7162 administration and postdose MK-7162 at 2 hours, 4 hours, 6 hours, and 8 hours (± 30 minutes for each time point). On Cycle 2 Day 1, VS will be monitored within 1 hour (± 30 minutes) prior to MK-7162 and pembrolizumab administration, and after completion of dosing of both MK-7162 and infusion of pembrolizumab at 2 hours, 4 hours, 6 hours, and 8 hours (± 30 minutes for each time point). For Day 1 of each subsequent Cycle, VS will be monitored within 1 hour (± 30 minutes) prior to MK-7162 and pembrolizumab administration. Additional VS monitoring may be obtained as clinically indicated.

9.5.3 Electrocardiograms

A standard 12-lead electrocardiogram (ECG) will be performed using local standard procedures. The ECG collection time points are outlined in the SoA. Clinically significant abnormal findings should be recorded as medical history. Additional ECGs may be performed as clinically necessary. Clinically significant abnormal findings seen on any ECGs performed after Screening should be recorded as AEs.

The Screening ECG will be obtained within 7 days prior to MK-7162 administration on C1D1.

9.5.4 Clinical Safety Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from non-protocol specified laboratory assessments performed at the institution’s local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).
- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study treatment, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided in Appendix 2. 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 Procedures Manual. Refer to Section 2 (SoA), for the schedule of laboratory assessments.

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

Laboratory tests for hematology, chemistry, and urinalysis are specified in Appendix 2.

Laboratory tests for screening should be performed within 7 days prior to the first dose of study treatment. An exception is hepatitis and thyroid serologies, which may be performed within 28 days prior to first dose. After Cycle 1, predose laboratory safety tests can be

conducted up to 72 hours prior to that Cycle Day 1 dosing, unless otherwise noted on the SoA.

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.

9.5.4.2 Pregnancy Test

All women who are being considered for participation in the trial, and who are not surgically sterilized or postmenopausal, must be tested for pregnancy within 72 hours prior to first dose of study treatment. 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 test result. Pregnancy test (such as monthly testing) may be conducted if required by local regulations.

9.6 Pharmacokinetics

To further evaluate the PK profile of MK-7162, sample collection is currently planned as shown in Section 2 (SoA). Maximum concentration (C_{max}) and minimum concentration (C_{trough}) at planned visits and times will be summarized.

9.6.1 Blood Collection for Plasma for MK-7162 Pharmacokinetics

Sample collection, storage and shipment instructions for plasma samples will be provided in the Procedures Manual.

9.6.2 Blood Collection for MK-7162 Metabolites

Exploratory analysis of metabolites may also be conducted.

9.7 Pharmacodynamics

Venous blood samples will be collected after an overnight fast for measurement of plasma levels of KYN and TRP in participants treated with MK-7162. Sample collection, storage and shipment instructions for blood samples will be provided in the Procedures Manual.

Urine samples will be collected for measurement of MK-7162. Sample collection, storage and shipment instructions for urine samples will be provided in the Procedures Manual.

Intratumoral KYN and TRP will be measured using required as well as optional on-study tumor biopsy specimens. Unless deemed medically unsafe by the Investigator, all participants will be required to undergo a baseline biopsy during Screening, following an overnight fast. Unless deemed medically unsafe by the Investigator, participants will be required to undergo one of two additional biopsies. Initially this second biopsy will occur on Cycle 2 Day 1, after an overnight fast and prior to the initial dose of pembrolizumab. The additional optional biopsy on Cycle 3 Day 15, will also occur following an overnight fast. As the trial progresses, the Sponsor may designate the Cycle 3 Day 15 biopsy as required, with the Cycle 2 Day 1 biopsy designated as optional.

9.8 Future Biomedical Research Sample Collection

The following specimens are to be obtained as part of Future Biomedical Research:

- Leftover samples listed in Section 9.7 (Pharmacodynamics) and 9.9 (Biomarkers)

9.9 Biomarkers

Collection of samples for other biomarker research is also part of this study. The following samples for biomarker research will be collected from all participants in this study as specified in the SoA:

1. Blood (DNA) for genetic analysis
2. Peripheral Blood Mononuclear Cells (PBMC)
3. Blood for plasma biomarker analyses
4. Whole blood for immune profiling
5. Blood for serum biomarker analyses
6. Blood for RNA analyses
7. Archival tumor specimen
8. Tumor tissue biopsies

9.9.1 Planned Genetic Analysis Sample Collection

Sample collection, storage and shipment instructions for Planned Genetic Analysis samples will be provided in the Procedures Manual. Samples should be collected for planned analysis of associations between genetic variants in germline/tumor DNA and drug response. If a documented law or regulation prohibits (or local Institutional Review Board/Independent Ethics Committee [IRB/IEC] does not approve) sample collection for these purposes, then such samples should not be collected at the corresponding sites. Leftover DNA extracted from planned genetic analysis samples will be stored for future biomedical research only if participant signs the Future Biomedical Research consent.

9.9.2 Blood Collection for Anti-Drug Antibodies

Sample collection, storage and shipment instructions for serum samples will be provided in the procedure manual. ADA samples should be drawn according to the ADA collection schedule for all participants (Section 6.0). Simultaneous PK sampling is required for interpretation of ADA analysis.

9.10 Visit Requirements

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

9.10.1 Screening

Approximately 28 days prior to treatment allocation/randomization, potential participants will begin evaluation to determine that they fulfill the entry requirements as set forth in

Sections 6.1 (Inclusion Criteria) and 6.2 (Exclusion Criteria). 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 are to be performed within 7 days prior to the first dose of study medication. Exceptions are hepatitis and thyroid testing, which may be done up to 28 days prior to the first dose of trial treatment.
    - Tests performed prior to the participant signing the informed consent (IC) as part of routine clinical management are acceptable in lieu of a screening text, if the test is performed within the specified time frame.
- Evaluation of ECOG (for eligibility confirmation) is to be performed within 7 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 study medication. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory).
- Archival tumor sample submission is not required within 28 days prior to the first dose of trial treatment. This tissue may be confirmed as available and submitted up to 90 days after treatment initiation.
- Screening evaluations/procedures and Cycle 1 Day 1 (C1D1) cannot be on the same day.

9.10.2 Treatment Period

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

Participants with a clinical benefit (ie, stable disease, partial response, or complete response) as determined by the Investigator may receive up to 36 cycles (approximately 2 years) of treatment: 1 cycle of MK-7162 monotherapy followed by 35 cycles of MK-7162 combination therapy with pembrolizumab.

9.10.3 Discontinued Participants Continuing to be Monitored in the Study

The Discontinuation Visit should occur at the time study treatment is discontinued for any reason. If the 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 2 (SoA). Additional details regarding participant withdrawal and discontinuation are presented in Section 8 (Discontinuation/Withdrawal Criteria).

9.10.3.1 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 30 days (90 days following administration of pembrolizumab) of the end of treatment or before initiation of a new anticancer treatment should also be followed and recorded.

9.10.3.2 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.

9.10.4 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 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).

10. Statistical Analysis Plan

This section outlines the statistical analysis strategies and procedures for the primary and secondary analyses of the study. Exploratory and other non-confirmatory 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 non-confirmatory analyses made after the protocol has been finalized, but prior to the conduct of any analyses, 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.

10.1 Statistical Analysis Plan Summary

This section contains a brief summary of the statistical analyses for this trial. Additional details follow in Sections 10.2 through 10.9.

Study Design Overview	Phase 1b trial of MK-7162 in combination with pembrolizumab in participants with advanced/metastatic solid tumors. Dose Escalation and Confirmation (Part A) applies a modified TPI design to determine a preliminary RP2D. Dose Expansion cohorts (Part B) will be the subject of a future amendment.
Analysis Populations	Safety (Primary): All-Subjects-as-Treated (ASaT) PK (Secondary): Per-Protocol (PP) Efficacy (Secondary/ Exploratory): Full Analysis Set (FAS)
Primary Endpoint(s)	Safety: • DLT • AE • Discontinuation of study treatment due to an AE
Secondary Endpoints	PK parameters of MK-7162 monotherapy and MK-7162 in combination with pembrolizumab; PK parameters of pembrolizumab in combination with MK-7162 ORR based on RECIST 1.1 and iRECIST as assessed by investigator KYN and TRP will be measured as PD markers of IDO1 inhibition
Statistical Methods for Efficacy/Immunogenicity/ Pharmacokinetic Analyses	ORR will be estimated using an exact method based on the binomial distribution (Clopper-Pearson interval). Exploratory efficacy analyses are documented in the sSAP. PK parameters of study medicines will be summarized by planned visit and time for each dose separately.
Treatment Assignment	Participants will be allocated centrally through IVRS/IWRS to single agent MK-7162 followed by MK-7162 in combination with pembrolizumab. Participants will be allocated by nonrandom assignment. The trial is open-label.

Statistical Methods for Safety Analyses	Summary statistics (counts, percentages, means, standard deviations, etc.) will be provided for the safety endpoints as appropriate. 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 MTD (or MAD) of MK-7162 in combination with pembrolizumab and the 80% Bayesian credible intervals for the estimate will be provided.
Interim Analyses	Interim analyses will be conducted to examine clinical trial data on a continuous basis to allow for dose-finding decisions, safety, tolerability, and efficacy analysis.
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-7162 in combination with pembrolizumab. A target sample size of approximately 40 participants will be used for study planning purposes for the Dose Escalation and Confirmation.

10.2 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.

10.3 Hypotheses/Estimation

Objectives and hypotheses of the study are outlined in Section 4.

10.4 Analysis Endpoints

10.4.1 Efficacy/Immunogenicity/Pharmacokinetics Endpoints

ORR, based on RECIST 1.1 and iRECIST as assessed by the investigator, is a secondary endpoint, and PFS and OS are exploratory endpoints in this study. A description of efficacy measures is provided in Section 9.2.

PK endpoints include concentrations of MK-7162 and pembrolizumab, as well as derived PK parameters, and are described in Section 9.6.

The exploratory evaluation of biomarkers to be measured in the trial is described in Section 9.9.

10.4.2 Safety Endpoints

The primary safety endpoint is the incidence of DLTs. In addition, safety and tolerability will be assessed by clinical review of all relevant parameters including adverse events (AEs), laboratory tests, and vital signs.

A description of safety measures is provided in Section 9.3 and 9.5.

10.5 Analysis Populations

10.5.1 Safety Analysis Populations

The 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 one dose of study treatment. In case of treatment administration errors, participants will be analyzed according to the treatment they actually received. The DLT evaluable population includes ASaT participants that were observed for safety for 42 days after the first dose of assigned treatment or experienced a DLT prior to 42 days after the first dose of assigned treatment. The replacement participants will also be considered evaluable if the above specified criteria are met. See Section 6.5 for details.

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

10.5.2 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 the data generated will likely 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 participant 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 one treatment will be included in the PP analysis dataset.

10.5.3 Efficacy Populations

The FAS population will be used for the analyses of exploratory efficacy data 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 one dose of study treatment.

10.6 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.

10.6.1 Statistical Methods for Efficacy Analysis

ORR will be estimated using an exact method based on the binomial distribution (Clopper-Pearson interval). The statistical methods for analyses of PFS and OS will be documented in the sSAP.

10.6.2 Statistical Methods for Safety Analysis

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

Adverse events will be summarized by counts and frequencies for each dose level. Laboratory tests, VS, and other safety endpoints will be summarized as appropriate.

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

10.6.3 Summaries of Baseline Characteristics, Demographics and Other Analyses

10.6.3.1 Demographic and Baseline Characteristics

Demographic variables, baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized.

10.6.3.2 Pharmacokinetic and Pharmacodynamic Modeling Analysis

Serum concentrations of study treatment will be summarized by planned visit and time for each dose separately; PK parameters will be summarized by dose.

Details of statistical analysis on peripheral blood receptor and other PK and pharmacodynamics modeling analyses will be documented in the sSAP.

10.7 Interim Analyses

Interim analyses will be conducted to examine clinical trial data on a continuous basis to allow for dose-finding decisions, safety, tolerability, and efficacy analysis.

10.8 Multiplicity

There will be no multiplicity control in this study.

10.9 Sample Size and Power Calculations

The sample size for the Dose Escalation and Confirmation is expected to be approximately 40 participants for study planning purposes. Based on the occurrence of DLTs, up to 14 participants may enroll per dose level in the mTPI phase. The final sample size is dependent on the number of dose levels tested and emerging safety data. For example, in the absence of DLTs, 3 participants per dose level would be treated at 25 mg QD, 50 mg QD, 100 mg QD,

and 200 mg QD and 14 participants would be treated at a dose level of 400 mg QD in the mTPI phase. In this scenario, the total sample size for Part A would be 26 participants.

10.10 Subgroup Analyses

Subgroup analyses of efficacy endpoints will be documented in the sSAP.

10.11 Compliance (Medication Adherence)

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

10.12 Extent of Exposure

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

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12. Appendices

12.1 Appendix 1: Abbreviations and Trademarks

Abbreviation	Definition
ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine aminotransferase
AMP	Adenosine monophosphate
aPTT	Activated partial thromboplastin time
ASaT	All-Subjects-as-Treated
AST	Aspartate aminotransferase
AUC	Area under the curve
βhCG	Beta-human chorionic gonadotropin
BID	Twice per day
C	Cycle
CBC	Complete blood count
CD	Cluster of differentiation (eg, CD8, CD28)
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case report form
CrCl	Creatinine clearance
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
D	Day
DLT	Dose-limiting toxicity
DNA	Deoxynucleic acid
ECG	Electrocardiogram
ECI	Event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EMA	European Medicines Agency
EoT	End of treatment

Abbreviation	Definition
FBR	Future biomedical research
FDA	Food and Drug Administration
FDAA	Food and Drug Administration Amendments Act
GCP	Good clinical practice
GFR	Glomerular filtration rate
GGT	Gamma glutamyl transferase
GVHD	Graft-versus-host disease
HBsAg/HBV	Hepatitis B surface antigen/Hepatitis B virus
HIV	Human immunodeficiency virus
HNSCC	Head and neck squamous cell cancer
IB	Investigator's Brochure
IC_{50}	50% maximal inhibitor concentration
IC_{90}	90% maximal inhibitor concentration
ICF	Informed consent form
ICH	International Conference on Harmonisation
IHC	Immunohistochemistry
INR	International normalized ratio
IRB/IEC	Institutional Review Board/Independent Ethics Committee
iRECIST	Immune Response Evaluation Criteria In Solid Tumors
IT	Intratumoral
IV	Intravenous
IVD	In vitro diagnostic
IVRS/IWRS	Interactive voice response system/integrated web response system
KYN	Kynurenin
LDH	Lactate dehydrogenase
MAD	Maximum administered dose
MRI	Magnetic Resonance Imaging
mRNA	Messenger ribonucleic acid
MTD	Maximum tolerated dose
mTPI	Modified toxicity probability interval

Abbreviation	Definition
MSI	Microsatellite instability
NCI	National Cancer Institute
NHV	Normal healthy volunteer
NSCLC	Non-small-cell lung cancer
ORR	Overall response rate
OS	Overall survival
OTC	Over-the-counter
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PD-1	Programmed cell death-1
PD-L1	Programmed cell death-1 ligand 1
PD-L2	Programmed cell death-1 ligand 2
PET	Positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetic
PO	Per os; by mouth
PP	Per-Protocol
pRBC	Packed red blood cells
PT	Prothrombin time
PTT	Partial thrombin time
QD	Once per day
Q3W	Every 3 weeks
RCC	Renal cell cancer
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	ribonucleic acid
RP2D	Recommended Phase 2 Dose
SAD	Single ascending dose
SAE	Serious adverse events
SIM	Site Imaging Manual
SoA	Schedule of Activities

Abbreviation	Definition
sSAP	Supplemental Statistical Analysis Plan
TRP	Tryptophan
ULN	Upper limit of normal
US	United States
WOCBP	Woman of Childbearing Potential

12.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 9 will be performed by the local laboratory.
- Laboratory safety tests for screening should be performed within 28 days prior to first dose of study medication. After Cycle 1, predose laboratory tests can be performed up to 72 hours prior to dosing. Results must be reviewed by the Investigator or qualified designee and found to be acceptable prior to dosing.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 9 Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Follicle Stimulating Hormone (FSH)
Hemoglobin	Alkaline phosphatase	Glucose	Serum β-human chorionic gonadotropin (β-hCG) [a]
Platelet count	Alanine aminotransferase (ALT)	Protein	Hepatitis
WBC (total and differential) [b]	Aspartate aminotransferase (AST)	Specific gravity	Total triiodothyronine (T3) (or Free T3 [FT3]) [b]
RBC	Carbon Dioxide or Bicarbonate	Microscopic exam, if abnormal results are noted	Total thyroxine (T4) (or Free T4 [FT4])
PT or INR	Calcium	Urine pregnancy test [a]	Thyroid Stimulating Hormone (TSH)
aPTT or PTT	Chloride		Cytokines
	Creatinine [c]		
	Gamma glutamyl transpeptidase (GGT)		
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Total Bilirubin		
	Direct Bilirubin, if total bilirubin is elevated above the upper limit of normal		
	Total protein		
	Blood Urea Nitrogen [d]		
	Lactic dehydrogenase		
	Uric acid		

[a] Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.

[b] Absolute or % acceptable per institutional standard

[c] For participants with a baseline calculated creatinine clearance that is below the normal institutional laboratory range, a baseline measured creatinine clearance should be performed.

[d] Blood Urea Nitrogen is preferred; if not available urea may be tested

Investigators must document their review of each laboratory safety report.

12.3 Appendix 3: Study Governance Considerations

Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

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

III. Participant Protection

A. IRB/IEC review

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

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

Financial Disclosure

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is 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 institutional review board, ethics review committee (IRB/IEC) or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this trial will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

Confidentiality of Participant Records

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

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

Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this trial. 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 Trial Registration and Results Posting Requirements

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

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

Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (eg, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated

Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

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

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

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

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

Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to 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.

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

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 trial site, the Sponsor will promptly notify that trial site's IRB/IEC.

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

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment. • NOTE: for purposes of AE definition, study treatment (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 adverse event, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect." • Any new cancer (that is not a condition of the study). Note: Progression of the cancer under study is not a reportable event. Refer to Section 9.3.5 for additional details.

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

Definition of SAE

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

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

e. Is a congenital anomaly/birth defect

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

f. Other important medical events:

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

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

Additional Events reported in the same manner as SAE

Additional Events which require reporting in the same manner as SAE

- In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same timeframe 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 Adverse Event case report forms/worksheets at each examination.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to 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 for Adverse Events (CTCAE), version 4.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.
  - Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
  - Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
  - Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
  - Grade 4: Life threatening consequences; urgent intervention indicated.
  - Grade 5: Death related to AE.

Assessment of Causality

- Did the Sponsor's product cause the adverse event?
  - The determination of the likelihood that the Sponsor's product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the adverse event 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 adverse event:
    - **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 trials with investigational medicinal product)?

- **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors
- **Dechallenge:** Was the 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 trial is a single-dose drug trial); 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 trial?
  - If yes, did the AE recur or worsen?
    - If yes, this is a positive rechallenge.
  - If no, this is a negative rechallenge.

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

NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY 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 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.

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

- The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.
- 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

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

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by 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 AE, SAE, 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 9.3.1 – Time Period and Frequency for Collecting AE and SAE and Other Reportable Safety Event Information for reporting time requirements
• The site will enter the SAE data into the electronic system as soon as it becomes available.
• After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
• If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
• Contacts for SAE reporting can be found in the Investigator Trial File Binder (or equivalent).

SAE Reporting to the Sponsor via Paper CRF
• If the electronic data collection tool is not operational, facsimile transmission or secure e-mail of the SAE paper CRF is the preferred method to transmit this information to 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).

12.5 Appendix 5: Contraceptive Guidance and Pregnancy Testing

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

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

Contraception Requirements

Male Participants:

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

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
- Use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in Table 10 when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.
  - Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

Female Participants:

Female participants of childbearing potential are eligible to participate if they agree to use one of the contraception methods described in Table 10 consistently and correctly during the protocol-defined time frame in Section 6.1.

Table 10 Contraceptive Methods

Acceptable Contraceptive Methods *Failure rate of >1% per year when used consistently and correctly.*
• Male or female condom with or without spermicide • Cervical cap, diaphragm or sponge with spermicide
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]
  ○ Oral
  ○ Intravaginal
  ○ Transdermal
  ○ Injectable

• Progestogen-only hormonal contraception [b]
  ○ Oral
  ○ Injectable

Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen- only contraceptive implant [b, c] • Intrauterine hormone-releasing system (IUS) [b] • Intrauterine device (IUD) • Bilateral tubal occlusion
• **Vasectomized partner** A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
• **Sexual abstinence** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)

Notes:

Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies.

a) Typical use failure rates are higher than perfect-use failure rates (i.e. when used consistently and correctly).
b) If hormonal contraception efficacy is potentially decreased due to interaction with study treatment, condoms must be used in addition to the hormonal contraception during the treatment period and for at least 120 days, corresponding to time needed to eliminate study treatment plus 30 days for study treatments with genotoxic potential, after the last dose of study treatment.
c) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation.

Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test.

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

12.6 Appendix 6: 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 trial as outlined in Section 9.8 – Future Biomedical Research Samples 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 trial will be considered for enrollment in the Future Biomedical Research sub-trial.

b. Informed Consent

Informed consent for specimens (i.e., DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all participants or legal guardians, at a trial 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 trial flow chart. If delayed, present consent at next possible Participant Visit.

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

A template of each trial 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 electronic Case Report Forms (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 trial flow chart. 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 trial 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 trial 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 trial 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 trial 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 sub-trial. 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 trial. If medical records for the main trial 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 trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main trial 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 trial 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 trial, the trial 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 trial 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 trials for Future Biomedical Research.

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the participant have been minimized. No additional risks to the participant have been identified as no additional specimens are being collected for Future Biomedical Research (i.e., only leftover samples are being retained).'

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: http://www.cancer.gov/dictionary/?searchTxt=biomarker
2. International Conference on Harmonization: DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES - E15; http://www.ich.org/LOB/media/MEDIA3383.pdf
3. Industry Pharmacogenomics Working Group. 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. Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

12.7 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 (see Table [X]). 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 iUPD (unconfirmed progressive disease) and iCPD (confirmed progressive disease). For purposes of iRECIST assessment, the first visit showing progression according to RECIST 1.1 will be assigned a visit (overall) response of iUPD, regardless of which factors caused the progression.

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

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

Assessment at the Confirmatory Imaging

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

Confirmation of Progression

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

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

Persistent iUPD

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

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

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

Resolution of iUPD

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

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

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

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

Management Following the Confirmatory Imaging

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

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

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].