Official Protocol Title:	A Phase 1/2 Open Label, Multi-Arm, Multicenter Study of MK-1308 in Combination with Pembrolizumab in Subjects with Advanced Solid Tumors
NCT number:	NCT03179436
Document Date:	02-Dec-2022

Title Page

THIS PROTOCOL AMENDMENT AND ALL OF THE INFORMATION RELATING TO IT ARE CONFIDENTIAL AND PROPRIETARY PROPERTY OF MERCK SHARP & DOHME LLC, RAHWAY, NJ, USA (MSD).

Protocol Title: A Phase 1 / 2 Open Label, Multi-Arm, Multicenter Study of MK-1308 in Combination with Pembrolizumab in Subjects with Advanced Solid Tumors

Protocol Number: 001-12

Compound Number: MK-1308

Sponsor Name and Legal Registered Address:

Merck Sharp & Dohme LLC
(hereafter referred to as the Sponsor or MSD)

126 East Lincoln Avenue
P.O. Box 2000
Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

IND NUMBER: 134,266

EudraCT NUMBER: 2019-003703-35

Approval Date: 02 December 2022

Sponsor Signatory

Typed Name: Date
Title:

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: Date
Title:

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 12	02-DEC-2022	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.
Amendment 11	18-OCT-2022	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.
Amendment 10	14-DEC-2021	The protocol was amended to remove Arm J from the study.
Amendment 09	12-JUL-2021	The protocol was amended to update the dose modification and toxicity management guidelines for irAEs, to remove Arm L (Japan) from the study, to clarify PK collection timings, to align with the biomarker plan, and to remove Translational Oncology Research from the study.
Amendment 08	16-NOV-2020	This amendment added additional cohorts to evaluate a coformulated product of MK-1308 + pembrolizumab (MK-1308A) in the global study as well as in China- and Japan-specific Arms: • Arm J - participants with PD-1/L1 refractory melanoma in specific countries. • Arm K - Chinese participants who reside in China with a diagnosis of any relapsed or refractory solid tumor. Arm K is open to sites in mainland China only. • Arm L - Japanese participants who reside in Japan with a diagnosis of Stage IV NSCLC. Arm L is open to sites in Japan only. Collection of pre- and on-treatment tumor biopsies from participants in Arms F, G, and J was added.

Document	Date of Issue	Overall Rationale
Amendment 07	13-MAR-2020	This amendment added a cohort (Arm I) to evaluate a coformulated product of MK-1308 + pembrolizumab (MK-1308A).
Amendment 06	11-NOV-2019	This amendment added Process 2 material and incorporated FDA feedback on Amendment 05.
Amendment 05	08-FEB-2019	The protocol was amended to add new interim analysis safety and efficacy data that supports the RP2D used in the melanoma expansion arm.
Amendment 04	02-NOV-2018	The protocol was amended to add an efficacy expansion phase in melanoma and to improve overall protocol clarity and consistency as well as to correct typographical errors identified post publishing.
Amendment 03	25-JAN-2018	The protocol was amended to explore an additional dose escalation cohort and dose confirmation arm, to modify the DLT reporting period for dose confirmation, to clarify pre-treatment requirements for brain metastases, and to modify the futility analysis.
Amendment 02	04-OCT-2018	The protocol was amended to add additional exploratory biomarker, safety assessments, and exclusion criteria.
Amendment 01	24-AUG-2017	Amendment developed due to requirement by regulatory authorities around safety monitoring of Japan-specific participants in the MK-1308-001 clinical trial.
Original Protocol	19-APR-2017	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment 12

Overall Rationale for the Amendment:

Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
Section 12.3, Appendix 3: Study Governance Considerations - Code of Conduct for Clinical Trials	Sponsor entity name and address change.	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1. Synopsis

Protocol Title:

A Phase 1 / 2 Open Label, Multi-Arm, Multicenter Study of MK-1308 in Combination with Pembrolizumab in Subjects with Advanced Solid Tumors

Short Title:

A Phase 1 / 2 Trial of MK-1308 in Combination with Pembrolizumab

Objectives/Hypotheses and Endpoints:

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

Objective	Endpoint
Primary	
• To determine the safety and tolerability of MK-1308 in combination with pembrolizumab and to establish a preliminary recommended Phase 2 dose when used in combination with pembrolizumab (Dose Escalation and Confirmation phases)	• Number of participants with ≥1 DLT • Number of participants with ≥1 AE • Number of participants discontinuing study treatment due to an AE
• To determine the safety and tolerability of MK-1308 as monotherapy (Efficacy Expansion phase)	• Number of participants with ≥1 AE • Number of participants discontinuing study treatment due to an AE
• To determine the safety and tolerability of MK-1308A (Coformulation phase)	• Number of participants with ≥1 AE • Number of participants discontinuing study treatment due to an AE • Number of participants with ≥1 DLT (Arm I only)
• To evaluate ORR as assessed by BICR per RECIST 1.1 in the efficacy expansion phase (Arms F and G). RECIST 1.1 is adjusted to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ (see Section 5.4.1.1)	• Objective Response: CR or PR

Secondary	
• To characterize the PK profiles and incidence of ADA, as appropriate, of pembrolizumab, of MK-1308 as monotherapy, and of MK-1308 when used in combination and in coformulation with pembrolizumab in the dose escalation phase as well as in Arms A, B, C, D, E, F, G, and I. • To characterize PK profiles and incidence of ADA of both MK-1308 and pembrolizumab in Chinese participants in Arm K when the study drugs are administered as a coformulated product (MK-1308A).	• Pharmacokinetic parameters including AUC, C_{min}, C_{max} • Anti-drug antibody levels
• To evaluate ORR as assessed by investigator per RECIST 1.1 in the dose escalation phase, the dose confirmation phase, and Arms I and K in the coformulation phase	• Objective response: CR or PR
• To evaluate DOR per RECIST 1.1 as assessed by BICR in the efficacy expansion phase (Arms F and G)	• DOR: The time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first (for responders only)

Overall Design:

Trial Phase	Phase I / II
Clinical Indication	The treatment of participants with advanced/metastatic solid tumors
Population	Participants[1] with advanced/metastatic solid tumors
Trial Type	Interventional
Type of design	Uncontrolled, combination, dose escalation, dose confirmation, efficacy expansion
Type of control	No treatment control
Trial Blinding	Unblinded Open-label

Estimated duration of trial	The Sponsor estimates that the trial will require approximately 6 years from the time the first participant signs the informed consent until the last participant's last study-related phone call or visit.
Duration of Participation	Each participant will participate in the study for approximately 3 years from the time the participant provides documented informed consent through the final contact. After a screening phase of 28 days, each participant will receive assigned intervention for approximately 24 months. After the end-of-treatment each participant will be followed for 1 year. After the end-of-treatment, each participant will be followed for the occurrence of AEs and spontaneously reported pregnancy. All participants will be followed for overall survival until death, withdrawal of consent, or end of the study.

Number of Participants:

Approximately 348 participants will be enrolled.

1. Sponsor has changed the terminology referring to individuals who take part in clinical trials as "Participant" from the previously used term "Subject." For the purpose of any trial-related documents using the previous terminology, the term "Participant" is equivalent to "Subject."

A list of abbreviations used in this document can be found in Appendix 1. Study governance considerations are outlined in Appendix 3.

2. Schedule of Activities (SoA)

2.1 Dose Escalation Phase

		Treatment Period Cycle = 21 days								Post-Treatment Period				Notes
Visit / Treatment Cycle	Screening	Cycle 1			Cycles 2-3			Cycles 4-5	Cycles ≥6	End of Treat-ment	Safety Follow-up	Disease Status Follow-up	Survival Follow-up	
Visit Timing / Cycle Day	Up to 28 days prior to first dose	1	8	15	1	8	15	1	1	Treat-ment discon-tinua-tion	30 days after the last dose	Every 9 weeks	Every 12 weeks	
Visit Window (Days)	-28 to -1	±3	±3	±3	±3	±3	±3	±3	±3		+14	+14	+14	
Administrative Procedures														
ICF and ICF for Future Biomedical Research	X													Any leftover biomarker samples will be stored for FBR if the participant signs the FBR consent.
Inclusion/Exclusion Criteria	X													
Participant Identification Card	X	X												Update at C1D1
Demographics and Medical History	X													
Medical, Oncology Disease Status and Prior Oncology Treatment History	X													
Concomitant Medication Review		X	X	X	X	X	X	X	X	X	X			

Visit / Treatment Cycle	Screening	Treatment Period Cycle = 21 days								Post-Treatment Period				Notes
		Cycle 1			Cycles 2-3			Cycles 4-5	Cycles ≥6	End of Treat-ment	Safety Follow-up	Disease Status Follow-up	Survival Follow-up	
Visit Timing / Cycle Day	Up to 28 days prior to first dose	1	8	15	1	8	15	1	1	Treat-ment discon-tinua-tion	30 days after the last dose	Every 9 weeks	Every 12 weeks	
Visit Window (Days)	-28 to -1	±3	±3	±3	±3	±3	±3	±3	±3		+14	+14	+14	
Clinical Procedures/ Assessments														
Full Physical Examination	X	X			X			X	X	X	X			
Height	X													
Weight	X	X			X			X	X	X	X			Required once per cycle
Vital Signs	X	X	X	X	X	X	X	X	X	X	X			To be collected at pre-dose and at the end of infusion. [Japan only: Vitals will also include pulse oximetry (SpO_2)]
ECOG Performance Status	X	X			X			X	X	X	X			ECOG Status must be performed **within 3 days** of beginning of Cycle 1 and prior to each treatment administration.
12-Lead ECG	X	X	X	X	X	X	X							Required up to C3D1 only. ECG may also be taken if clinically indicated.
MK-1308 Dosing[a]		X			X			X						
Pembrolizumab Dosing[a]					X			X	X					
AE/SAE Monitoring	X	X	X	X	X	X	X	X	X	X	X			Continuous Reporting
Tumor Imaging and RECIST Response Assessment	X	X								X		X		Every 9 weeks (±7 days) from first dose of study; after 54 weeks, every 12 weeks (±7 days)
New Anticancer Therapy Status											X	X		
Survival Status		◄								►			X	Refer to Sections 9.10.5 & 9.10.6.

Visit / Treatment Cycle	Screening	Treatment Period Cycle = 21 days								Post-Treatment Period				Notes
		Cycle 1			Cycles 2-3			Cycles 4-5	Cycles ≥6	End of Treat-ment	Safety Follow-up	Disease Status Follow-up	Survival Follow-up	
Visit Timing / Cycle Day	Up to 28 days prior to first dose	1	8	15	1	8	15	1	1	Treat-ment discon-tinua-tion	30 days after the last dose	Every 9 weeks	Every 12 weeks	
Visit Window (Days)	-28 to -1	±3	±3	±3	±3	±3	±3	±3	±3		+14	+14	+14	
Laboratory Procedures/ Assessments – LOCAL														
Hematology/ Chemistry (blood glucose)	X	X	X	X	X	X	X	X	X	X	X			Samples to be collected pre-dose. Screening samples should be collected within 14 days prior to dosing.
Urinalysis	X				X			X	X	X	X			
KL-6, SP-D	X	X			X			X	X	X	X			(Applies only to Japan)
PT/INR/aPTT	X													Participants on anticoagulant therapy should be monitored throughout the trial. Equivalent type testing is permissible.
LDH/GGT/CRP	X				X			X	X	X	X			
Thyroid Function Testing (T4, T3, TSH), ACTH and cortisol	X	X			X			X	X	X	X			After Cycle 6 samples are collected every other cycle; samples for cortisol and ACTH should be collected in the morning at the earliest feasible time. Investigator must review all of these results prior to C1D1 if participant has had prior anti-PD-1 or PD-L1 therapy.
Pregnancy Test for WOCBP	X	X			X			X	X	X	X			
Hepatitis Screen	X													
Laboratory Procedures/ Assessments – CENTRAL														
MK-1308 PK[b]		X	X	X	X	X	X	X	X	X	X			
Anti-MK-1308 Ab[b]		X			X			X	X	X	X			

Visit / Treatment Cycle	Screening	Treatment Period Cycle = 21 days								Post-Treatment Period				Notes
		Cycle 1			Cycles 2-3			Cycles 4-5	Cycles ≥6	End of Treat-ment	Safety Follow-up	Disease Status Follow-up	Survival Follow-up	
Visit Timing / Cycle Day	Up to 28 days prior to first dose	1	8	15	1	8	15	1	1	Treat-ment discon-tinua-tion	30 days after the last dose	Every 9 weeks	Every 12 weeks	
Visit Window (Days)	-28 to -1	±3	±3	±3	±3	±3	±3	±3	±3		+14	+14	+14	
Pembrolizumab PK[c]					X	X	X	X	X	X	X			
Anti-Pembrolizumab Ab[c]					X			X	X	X	X			
Serum Cytokine	X	X	X	X	X	X	X	X		X				Samples to be collected: C1D1(pre-dose, 30 min post-MK-1308 dose), C1D8, C1D15; C2D1(pre-dose, 30 min post-MK-1308 dose), C2D8, C2D15; C3D1(pre-dose, 30 min post-MK-1308 dose) C3D8, C3D15 C4D1 & C5D1(pre-dose)
Blood for T-Cell Receptor Repertoire		X			X			X		X				Samples to be collected Cycles 1-4: Day 1 (pre-dose)
Peripheral Blood for Immunophenotyping Biomarker Analyses		X	X	X	X	X	X	X		X				Sample to be collected: Cycles 1-3: Day 1(pre-dose), Days 8, and Day 15. Cycles 4-5: Day 1 (pre-dose)
Peripheral Blood for Mononuclear cells biomarker analysis		X			X			X	X	X				Samples to be collected Cycles 1-9: Day 1 (pre-dose)
Blood for RNA Analyses		X			X			X		X				Samples to be collected Cycles 1-4: Day 1 (pre-dose)
Blood for Genetic Analysis		X												Collect pre-dose. See Section 9.9.1.
Stool for Biomarker Analysis	X (2 samples)	X			X			X	X					Samples to be collected at home for all time points: First pre-dose sample (optional), collect any time in screening between 7 and 4 days before C1D1; second pre-dose sample (required) collect at least 2 days after first pre-dose sample; Post-dose samples (required) collect 2-5 days after dosing at C1, C2, C4 & C12, if clinically feasible
Blood for ctDNA		X						X	X					Samples to be collected Cycles 1, 4 and 12: Day 1 (pre-dose)

Visit / Treatment Cycle	Screening	Treatment Period Cycle = 21 days								Post-Treatment Period				Notes
		Cycle 1			Cycles 2-3			Cycles 4-5	Cycles ≥6	End of Treat-ment	Safety Follow-up	Disease Status Follow-up	Survival Follow-up	
Visit Timing / Cycle Day	Up to 28 days prior to first dose	1	8	15	1	8	15	1	1	Treat-ment discon-tinua-tion	30 days after the last dose	Every 9 weeks	Every 12 weeks	
Visit Window (Days)	-28 to -1	±3	±3	±3	±3	±3	±3	±3	±3		+14	+14	+14	
Tumor Tissue Collection	X													

a. In the dose escalation phase, MK-1308 will be administered on Cycle 1, Day 1 then every 21 days for a total of 5 doses (Day 1 of Cycle 1- 5). The first dose will be administered without pembrolizumab. Pembrolizumab will be administered every 21 days starting with Cycle 2 for a maximum of 35 cycles.

b. Pharmacokinetic/ Anti-drug antibody of MK-1308: For dose escalation phase: Pre-dose trough PK and ADA samples at Cycles 1, 2, 3, 5, 6, 7, 9 and every 4 cycles thereafter. All pre-dose trough samples should be drawn within 24 hours before infusion of drug from all participants. PK only of MK-1308: post-dose PK samples should be drawn within 30 minutes after end of infusion of MK-1308 at Cycles 1, 2, 3, 5, and 9. Additional post-dose PK samples in the dose escalation phase should be drawn on Day 8 and on Day 15 in Cycles 1, 2, and 3. After discontinuation of study drug, samples should be collected at the Safety Follow-Up (30-day) visit.

c. Pharmacokinetic/ Anti-drug antibody of pembrolizumab: For dose escalation phase**:** Pre-dose trough PK and ADA samples at Cycles 2, 3, 5, 6, 7, 9 and every 4 cycles thereafter. All pre-dose trough samples should be drawn within 24 hours before infusion of drug from all participants. PK only of pembrolizumab: post-dose PK samples should be drawn within 30 minutes after end of infusion of pembrolizumab in Cycles 2, 3, 5, and 9. Additional post-dose PK samples in the dose escalation phase should be drawn on Day 8 and on Day 15 in Cycles 2 and 3. After discontinuation of study drug, samples should be collected at the Safety Follow-Up (30-day) visit.

2.2 Dose Confirmation Phase

Visit / Treatment Cycle	Screening	Treatment Period Cycle = 21 days								Post-Treatment Period				Notes
		Cycle 1			Cycles 2-3			Cycles 4-5	Cycles ≥6	End of Treatment	Safety Follow-up	Disease Status Follow-up	Survival Follow-up	
Visit Timing / Cycle Day	Up to 28 days prior to first dose	1	8	15	1	8	15	1	1	Treatment discontinuation	30 days after the last dose	Every 9 weeks	Every 12 weeks	
Visit Window (Days)	-28 to -1	±3	±3	±3	±3	±3	±3	±3	±3		+14	+14	+14	
Administrative Procedures														
ICF and ICF for Future Biomedical Research	X													Any leftover biomarker samples will be stored for FBR if the participant signs the FBR consent
Inclusion/Exclusion Criteria	X													
Participant Identification Card	X	X												Update at C1D1
Demographics and Medical History	X													
Medical, Oncology Disease Status and Prior Oncology Treatment History	X													
Concomitant Medication Review		X	X	X	X	X	X	X	X	X	X			
Clinical Procedures/ Assessments														
Full Physical Examination	X	X			X			X	X	X	X			
Height	X													
Weight	X	X			X			X	X	X	X			Required once per cycle

Visit / Treatment Cycle	Screening	Treatment Period Cycle = 21 days								Post-Treatment Period				Notes
		Cycle 1			Cycles 2-3			Cycles 4-5	Cycles ≥6	End of Treatment	Safety Follow-up	Disease Status Follow-up	Survival Follow-up	
Visit Timing / Cycle Day	Up to 28 days prior to first dose	1	8	15	1	8	15	1	1	Treatment discontinuation	30 days after the last dose	Every 9 weeks	Every 12 weeks	
Visit Window (Days)	-28 to -1	±3	±3	±3	±3	±3	±3	±3	±3		+14	+14	+14	
Vital Signs	X	X	X	X	X	X	X	X	X	X	X			To be collected at pre-dose and at the end of infusion. ([Applies only to Japan: Vitals will include pulse oximetry (SpO_2)]
ECOG Performance Status	X	X			X			X	X	X	X			Must be performed **within 3 days** of beginning of Cycle 1 and prior to each treatment administration.
12-Lead ECG	X	X	X	X	X	X	X							Required up to C3D1 only. ECG may also be taken if clinically indicated
MK-1308 Dosing[a]		X			X			X	X					
Pembrolizumab Dosing[a]		X			X			X	X					
AE/SAE Monitoring	X	X	X	X	X	X	X	X	X	X	X			Continuous Reporting
Tumor Imaging and RECIST Response Assessment	X	X								X		X		Every 9 weeks (±7 days) from first dose of study. After 54 weeks, every 12 weeks (±7 days)
MRI brain	X	X								X		X		Required for all thyroid cancer, melanoma, and SCLC participants at screening and at other time points as needed. Also required for other participants with new neurologic symptoms or prior history of brain metastasis.
New Anticancer Therapy Status											X	X		
Survival Status		←								→			X	Refer to Sections 9.10.5 & 9.10.6.

Visit / Treatment Cycle	Screening	Treatment Period Cycle = 21 days								Post-Treatment Period				Notes
		Cycle 1			Cycles 2-3			Cycles 4-5	Cycles ≥6	End of Treatment	Safety Follow-up	Disease Status Follow-up	Survival Follow-up	
Visit Timing / Cycle Day	Up to 28 days prior to first dose	1	8	15	1	8	15	1	1	Treatment discontinua-tion	30 days after the last dose	Every 9 weeks	Every 12 weeks	
Visit Window (Days)	-28 to -1	±3	±3	±3	±3	±3	±3	±3	±3		+14	+14	+14	
Laboratory Procedures/ Assessments – LOCAL														
Hematology/Chemistry (blood glucose)	X	X	X	X	X	X	X	X	X	X	X			Samples to be collected pre-dose. Screening samples should be collected within 14 days prior to dosing.
Urinalysis	X				X			X	X	X	X			
KL-6, SP-D	X	X			X			X	X	X	X			(Applies only to Japan)
PT/INR/aPTT	X													Participants on anticoagulant therapy should be monitored throughout the trial. Equivalent type testing is permissible.
LDH/GGT/CRP	X				X			X	X	X	X			
Thyroid Function Testing (T4, T3, TSH), ACTH and cortisol	X	X			X			X	X	X	X			After Cycle 6 samples are collected every other cycle, samples for cortisol and ACTH should be collected in the morning at the earliest feasible time.
Pregnancy Test for WOCBP	X	X			X			X	X	X	X			
Hepatitis Screen	X													

Visit / Treatment Cycle	Screening	Treatment Period Cycle = 21 days								Post-Treatment Period				Notes
		Cycle 1			Cycles 2-3			Cycles 4-5	Cycles ≥6	End of Treatment	Safety Follow-up	Disease Status Follow-up	Survival Follow-up	
Visit Timing / Cycle Day	Up to 28 days prior to first dose	1	8	15	1	8	15	1	1	Treatment discontinuation	30 days after the last dose	Every 9 weeks	Every 12 weeks	
Visit Window (Days)	-28 to -1	±3	±3	±3	±3	±3	±3	±3	±3		+14	+14	+14	
Clinical Procedures/Assessments														
Laboratory Procedures/ Assessments – CENTRAL														
MK-1308 PK[b]		X	X	X	X	X	X	X	X	X	X			
Anti-MK-1308 Ab[b]		X			X			X	X	X	X			
Pembrolizumab PK[c]		X	X	X	X	X	X	X	X	X	X			
Anti-Pembrolizumab Ab[c]		X			X			X	X	X	X			
Serum Cytokine[d]	X	X	X	X	X	X	X	X		X				Samples to be collected: C1D1(pre-dose, 30 min post-MK-1308 dose), C1D8, C1D15; C2D1 (pre-dose, 30 min post-MK-1308 dose), C2D8, C2D15; C3D1 (pre-dose, 30 min post-MK-1308 dose) C3D8, C3D15; C4D1 & C5D1(pre-dose)
Blood for T-Cell Receptor (TCR) Repertoire		X			X			X	X	X				Samples to be collected Cycles 1-6: Day 1 (pre-dose)
Peripheral Blood for Immunophenotyping Biomarker Analyses[*]		X	X	X	X	X	X	X	X	X				Sample to be collected Cycles 1-3: Day 1 (pre-dose, Days 8, Day 15). Cycles 4-9: Day 1 (pre-dose)
Peripheral Blood for Mononuclear cells biomarker analysis		X			X			X	X	X				Samples to be collected All Cycles: Day 1 (pre-dose)

Visit / Treatment Cycle	Screening	Treatment Period Cycle = 21 days								Post-Treatment Period				Notes
		Cycle 1			Cycles 2-3			Cycles 4-5	Cycles ≥6	End of Treatment	Safety Follow-up	Disease Status Follow-up	Survival Follow-up	
Visit Timing / Cycle Day	Up to 28 days prior to first dose	1	8	15	1	8	15	1	1	Treatment discontinuation	30 days after the last dose	Every 9 weeks	Every 12 weeks	
Visit Window (Days)	-28 to -1	±3	±3	±3	±3	±3	±3	±3	±3		+14	+14	+14	
Blood for RNA analyses*		X			X			X		X				Samples to be collected Cycles 1 to 4: Day 1 (pre-dose)
Blood for genetic analysis		X												Collect pre-dose. See Section 9.9.1.
Tumor Tissue Collection	X													Known PD-L1 status should be reported. EGFR mutation and ALK trans. docs must be provided.
On-Treatment Tumor Biopsy						X								A single biopsy can be collected at any date after C3D1.
Stool for Biomarker Analysis	X (2 samples)	X			X			X	X					Samples to be collected at home for all time points: First pre-dose sample (optional), collect any time in screening between 7 and 4 days before C1D1; second pre-dose sample (required) collect at least 2 days after first pre-dose sample. Post-dose samples (required) collect 2-5 days after dosing at C1, C2, C4 & C12, if clinically feasible
Blood for ctDNA		X						X	X					Samples to be collected Cycles 1, 4 and 12: Day 1 (pre-dose)

a. In the dose confirmation phase: For Arm A & E, MK-1308 will be administered every 21 days (Q3W). For Arms B, C, and D MK-1308 will be administered every 42 days (Q6W). Pembrolizumab will be administered every 21 days starting with Cycle 1 for a maximum of 35 cycles.
b. Pharmacokinetic/Anti-drug antibody of MK-1308: For dose confirmation phase: Pre-dose trough PK and ADA samples at Cycles 1, 2, 3, 4, 5, 6, 8, and every 4 cycles thereafter. All pre-dose samples should be drawn within 24 hours of the infusion of drug from all participants. PK only of MK-1308: post-dose PK samples should be drawn within 30 minutes after end of infusion of MK-1308 at Cycles 1, 2, 3, 4, and 8. Additional post-dose samples in the dose confirmation phase should be drawn at 168 hours (Day 8), and 336 hours (Day 15) in Cycle 1, 2, and 3. After discontinuation of study drug, samples should be collected at the Safety Follow-Up (30-day) visit. **In Arms B, C, and D, where MK-1308 is given every 6 weeks, PK samples 30 minutes post-MK-1308 infusion should not be collected at C2, C4 and C8. However, PK samples for MK-1308 should be collected in Arm B, C, and D at C3D8 and C3D15.**
c. Pharmacokinetic/ADA of pembrolizumab: For dose confirmation phase**:** Pre-dose trough PK and ADA samples at Cycles 1, 2, 3, 4, 5, 6, 8 and every 4 cycles thereafter. All pre-dose trough samples should be drawn within 24 hours before infusion of drug from all participants. PK only of pembrolizumab: Post-dose PK samples should be drawn within 30 minutes after end of infusion of pembrolizumab at Cycles 1, 2, 3, 4, and 8. Additional post-dose samples in the dose confirmation phase should be drawn at 168 hours (Day 8), and 336 hours (Day 15) at Cycles 1, 2, and 3. After discontinuation of study drug, samples should be collected at the Safety Follow-Up (30-day) visit.
d. In Arms B, C, and D, where MK-1308 is given every 6 weeks, the C2D1 30-minute post-MK-1308 sample is not collected. However, cytokine samples should still be collected at C2D8 and C2D15.

2.3 Efficacy Expansion and Crossover Phases - Pembrolizumab Q6W + MK-1308 Q6W (Arm F) or MK-1308 Q6W Monotherapy (Arm G)

Efficacy Expansion Arms F and G			**Treatment Period Cycle = 42 days**										Post-Treatment Period					Notes
Visit / Treatment Cycle	Screening	Crossover Screening*	Cycle 1			Cycle 2		Cycle 3		Cycle 4		Cycle 5	Cycles ≥6	End of Treatment	Safety Follow-up		Disease Status Follow-up	Survival Follow-up	*For crossover: screening participants assessments do not need to be repeated if they have been performed within the last 4 weeks.
Visit Timing / Cycle Day	Up to 28 days prior to first dose	Up to 28 days prior to first dose	1	8	21	1	21	1	21	1	21	1	1	Treatment discon-tinuation	30 days after the last dose	90 days after the last dose	Every 9 weeks	Every 12 weeks	
Visit Window (Days)	-28 to -1	-28 to -1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		+14	+14	+14	+14	
ICF and ICF for Future Biomedical Research	X																		Any leftover biomarker samples will be stored for FBR if the participant signs the FBR consent.
Inclusion/Exclusion Criteria	X																		
Participant Identification Card	X		X																Update at C1D1
Demographics and Medical History	X																		
Medical, Oncology Disease Status and Prior Oncology Treatment History	X																		
Concomitant Medication Review		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			

Efficacy Expansion Arms F and G			**Treatment Period Cycle = 42 days**											Post-Treatment Period					Notes
Visit / Treatment Cycle	Screening	Crossover Screening*	Cycle 1			Cycle 2		Cycle 3		Cycle 4		Cycle 5	Cycles ≥6	End of Treatment	Safety Follow-up		Disease Status Follow-up	Survival Follow-up	*For crossover: screening participants assessments do not need to be repeated if they have been performed within the last 4 weeks.
Visit Timing / Cycle Day	Up to 28 days prior to first dose	Up to 28 days prior to first dose	1	8	21	1	21	1	21	1	21	1	1	Treatment discon-tinuation	30 days after the last dose	90 days after the last dose	Every 9 weeks	Every 12 weeks	
Visit Window (Days)	-28 to -1	-28 to -1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		+14	+14	+14	+14	
Full Physical Examination	X	X	X			X		X		X		X	X	X	X	X			
Directed Physical Examination				X	X		X		X		X								
Height	X																		
Weight	X		X			X		X		X		X	X	X	X	X			Required once per cycle
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			Collected at pre-dose and at the end of infusion.
ECOG Performance Status	X	X	X			X		X		X		X	X	X	X	X			Must be performed **within 3 days** of beginning of Cycle 1 and prior to each treatment administration.
12-Lead ECG	X																		Repeat if clinically indicated
MK-1308 Q6W Dosing[a]			X			X		X		X		X	X						

Efficacy Expansion Arms F and G			**Treatment Period Cycle = 42 days**										Post-Treatment Period					Notes
Visit / Treatment Cycle	Screening	Crossover Screening*	Cycle 1			Cycle 2		Cycle 3		Cycle 4		Cycle 5	Cycles ≥6	End of Treatment	Safety Follow-up		Disease Status Follow-up	Survival Follow-up	*For crossover: screening participants assessments do not need to be repeated if they have been performed within the last 4 weeks.
Visit Timing / Cycle Day	Up to 28 days prior to first dose	Up to 28 days prior to first dose	1	8	21	1	21	1	21	1	21	1	1	Treatment discon-tinuation	30 days after the last dose	90 days after the last dose	Every 9 weeks	Every 12 weeks	
Visit Window (Days)	-28 to -1	-28 to -1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		+14	+14	+14	+14	
Pembrolizumab Q6W Dosing[a]			X			X		X		X		X	X						Does not apply to monotherapy MK-1308 Arm G
AE/SAE Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			Continuous Reporting
Tumor Imaging and RECIST Response Assessment	X	X	X														X		Every 9 weeks (±7 days) from first dose of study. After 54 weeks, every 12 weeks (±7 days)
Submission of Pre-trial Imaging	X																		The site must have reviewed and submitted pre-trial images that are of diagnostic quality from at least 3 dates to determine that radiographic progression has occurred.

Efficacy Expansion Arms F and G			**Treatment Period Cycle = 42 days**										Post-Treatment Period					Notes
Visit / Treatment Cycle	Screening	Crossover Screening*	Cycle 1			Cycle 2		Cycle 3		Cycle 4		Cycle 5	Cycles ≥6	End of Treatment	Safety Follow-up		Disease Status Follow-up	Survival Follow-up	*For crossover: screening participants assessments do not need to be repeated if they have been performed within the last 4 weeks.
Visit Timing / Cycle Day	Up to 28 days prior to first dose	Up to 28 days prior to first dose	1	8	21	1	21	1	21	1	21	1	1	Treatment discon-tinuation	30 days after the last dose	90 days after the last dose	Every 9 weeks	Every 12 weeks	
Visit Window (Days)	-28 to -1	-28 to -1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		+14	+14	+14	+14	
MRI brain	X		X														X		Required at screening for all melanoma participants. For subsequent tumor assessment time points, brain MRI is required only if brain disease was observed at screening or if clinically indicated.

Efficacy Expansion Arms F and G			**Treatment Period Cycle = 42 days**										Post-Treatment Period					Notes
Visit / Treatment Cycle	Screening	Crossover Screening*	Cycle 1			Cycle 2		Cycle 3		Cycle 4		Cycle 5	Cycles ≥6	End of Treatment	Safety Follow-up		Disease Status Follow-up	Survival Follow-up	*For crossover: screening participants assessments do not need to be repeated if they have been performed within the last 4 weeks.
Visit Timing / Cycle Day	Up to 28 days prior to first dose	Up to 28 days prior to first dose	1	8	21	1	21	1	21	1	21	1	1	Treatment discon-tinuation	30 days after the last dose	90 days after the last dose	Every 9 weeks	Every 12 weeks	
Visit Window (Days)	-28 to -1	-28 to -1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		+14	+14	+14	+14	
BRAF Testing	X																		BRAF V600 mutation analysis should be performed locally by the sites during screening in participants without documented BRAF status. If the local laboratory is unable to perform BRAF testing, the site should submit the sample to the central laboratory for testing.
Survival Status			←										→					X	Refer to Sections 9.10.5 & 9.10.6.

Efficacy Expansion Arms F and G			**Treatment Period Cycle = 42 days**											Post-Treatment Period				Notes
Visit / Treatment Cycle	Screening	Crossover Screening*	Cycle 1			Cycle 2		Cycle 3		Cycle 4		Cycle 5	Cycles ≥6	End of Treatment	Safety Follow-up		Disease Status Follow-up	Survival Follow-up	*For crossover: screening participants assessments do not need to be repeated if they have been performed within the last 4 weeks.
Visit Timing / Cycle Day	Up to 28 days prior to first dose	Up to 28 days prior to first dose	1	8	21	1	21	1	21	1	21	1	1	Treatment discon-tinuation	30 days after the last dose	90 days after the last dose	Every 9 weeks	Every 12 weeks	
Visit Window (Days)	-28 to -1	-28 to -1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		+14	+14	+14	+14	
Hematology/ Chemistry (blood glucose)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			Samples to be collected pre-dose. For C1D1 samples need to be collected within 72 hours prior to the first dose.
Urinalysis	X	X				X		X		X		X	X	X	X	X			
PT/INR/aPTT	X	X																	Equivalent type testing is permissible.
LDH	X	X																	
Thyroid Function Testing (T4, T3, TSH), ACTH and cortisol	X	X	X			X		X		X		X	X	X	X	X			After Cycle 6 samples are collected every other cycle; samples for cortisol and ACTH should be collected in the morning at the earliest feasible time.

Efficacy Expansion Arms F and G			**Treatment Period Cycle = 42 days**										Post-Treatment Period					Notes
Visit / Treatment Cycle	Screening	Crossover Screening*	Cycle 1			Cycle 2		Cycle 3		Cycle 4		Cycle 5	Cycles ≥6	End of Treatment	Safety Follow-up		Disease Status Follow-up	Survival Follow-up	*For crossover: screening participants assessments do not need to be repeated if they have been performed within the last 4 weeks.
Visit Timing / Cycle Day	Up to 28 days prior to first dose	Up to 28 days prior to first dose	1	8	21	1	21	1	21	1	21	1	1	Treatment discon-tinuation	30 days after the last dose	90 days after the last dose	Every 9 weeks	Every 12 weeks	
Visit Window (Days)	-28 to -1	-28 to -1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		+14	+14	+14	+14	
Pregnancy Test for WOCBP	X		X			X		X		X		X	X	X	X				
Hepatitis Screen	X																		HBsAg and HBV-DNA. Hep C Ab, quantitative HCV RNA
MK-1308 PK			X		X	X	X	X	X	X	X			X	X				PK should be taken within 24 h pre-dose and within 30 minutes post end of infusion on C1D1, C2D1, C3D1, and C4D1. Additional PK should be taken on C1D21, C2D21, C3D21 and C4D21.
Anti-MK-1308 Ab (ADA)			X			X		X		X				X	X				Serum antibody samples should be taken within 24 h pre-dose on C1D1, C2D1, C3D1, and C4D1.

Efficacy Expansion Arms F and G			**Treatment Period Cycle = 42 days**										Post-Treatment Period					Notes
Visit / Treatment Cycle	Screening	Crossover Screening*	Cycle 1			Cycle 2		Cycle 3		Cycle 4		Cycle 5	Cycles ≥6	End of Treatment	Safety Follow-up		Disease Status Follow-up	Survival Follow-up	*For crossover: screening participants assessments do not need to be repeated if they have been performed within the last 4 weeks.
Visit Timing / Cycle Day	Up to 28 days prior to first dose	Up to 28 days prior to first dose	1	8	21	1	21	1	21	1	21	1	1	Treatment discon-tinuation	30 days after the last dose	90 days after the last dose	Every 9 weeks	Every 12 weeks	
Visit Window (Days)	-28 to -1	-28 to -1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		+14	+14	+14	+14	
Exploratory Sample for T-cell Response			X		X	X								X					Whole blood sample at pre-dose C1D1, C1D21, C2D1, and at EoT.
Pembrolizumab PK (For Arm F only)			X		X	X	X	X	X	X	X			X	X				PK should be taken within 24 h pre-dose and within 30 minutes post-dose on C1D1, C2D1, C3D1, and C4D1. Additional PK should be taken C1D21, C2D21, C3D21 and C4D21.
Anti-Pembrolizumab Ab (ADA for Arm F only)			X			X		X		X				X	X				Serum antibody samples should be taken within 24 h pre-dose on Day 1 of C1, C2, C3 and C4. Does not apply to Arm G.

Efficacy Expansion Arms F and G			**Treatment Period Cycle = 42 days**										Post-Treatment Period					Notes
Visit / Treatment Cycle	Screening	Crossover Screening*	Cycle 1			Cycle 2		Cycle 3		Cycle 4		Cycle 5	Cycles ≥6	End of Treatment	Safety Follow-up		Disease Status Follow-up	Survival Follow-up	*For crossover: screening participants assessments do not need to be repeated if they have been performed within the last 4 weeks.
Visit Timing / Cycle Day	Up to 28 days prior to first dose	Up to 28 days prior to first dose	1	8	21	1	21	1	21	1	21	1	1	Treatment discon-tinuation	30 days after the last dose	90 days after the last dose	Every 9 weeks	Every 12 weeks	
Visit Window (Days)	-28 to -1	-28 to -1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		+14	+14	+14	+14	
Peripheral Blood for Immunophenotyping Biomarker Analyses			X	X															Sample to be collected pre-dose C1D1 and C1D8.
Blood for RNA analyses			X			X		X		X				X					Samples to be collected Cycles 1 to 4: Day 1 (pre-dose)
Blood for genetic analysis			X																Collect pre-dose. See Section 9.9.1.

Efficacy Expansion Arms F and G			**Treatment Period Cycle = 42 days**										Post-Treatment Period					Notes
Visit / Treatment Cycle	Screening	Crossover Screening*	Cycle 1			Cycle 2		Cycle 3		Cycle 4		Cycle 5	Cycles ≥6	End of Treatment	Safety Follow-up		Disease Status Follow-up	Survival Follow-up	*For crossover: screening participants assessments do not need to be repeated if they have been performed within the last 4 weeks.
Visit Timing / Cycle Day	Up to 28 days prior to first dose	Up to 28 days prior to first dose	1	8	21	1	21	1	21	1	21	1	1	Treatment discon-tinuation	30 days after the last dose	90 days after the last dose	Every 9 weeks	Every 12 weeks	
Visit Window (Days)	-28 to -1	-28 to -1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		+14	+14	+14	+14	
Stool for Biomarker Analysis	X (2 samples)		X			X				X			X						Samples to be collected at home for all time points: First pre-dose sample, collect any time in screening between 7 and 4 days before C1D1; second pre-dose sample collect at least 2 days after first pre-dose sample; Post-dose samples collected 2-5 days after dosing at C1, C2, C4 & C12, if clinically feasible
Tumor Tissue	X																		Known PD-L1 status should be reported. If archival tissue is not available, newly obtained tumor tissue is required.

Efficacy Expansion Arms F and G			**Treatment Period Cycle = 42 days**										Post-Treatment Period					Notes
Visit / Treatment Cycle	Screening	Crossover Screening*	Cycle 1			Cycle 2		Cycle 3		Cycle 4		Cycle 5	Cycles ≥6	End of Treatment	Safety Follow-up		Disease Status Follow-up	Survival Follow-up	*For crossover: screening participants assessments do not need to be repeated if they have been performed within the last 4 weeks.
Visit Timing / Cycle Day	Up to 28 days prior to first dose	Up to 28 days prior to first dose	1	8	21	1	21	1	21	1	21	1	1	Treatment discon-tinuation	30 days after the last dose	90 days after the last dose	Every 9 weeks	Every 12 weeks	
Visit Window (Days)	-28 to -1	-28 to -1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		+14	+14	+14	+14	
Blood for TCR			X		X	X													Collected pre-dose on dosing days.
Blood for ctDNA			X			X		X						X					Collected pre-dose (C1D1, C2D1, C3D1 and EOT)

a) Efficacy expansion phase: In Arm F, MK-1308 will be co-administered as an admixture with pembrolizumab every 6 weeks for a total of up to 24 months (ie, 18 cycles). In Arm G, MK-1308 will be given as monotherapy every 6 weeks for a total of up to 24 months (ie, 18 cycles). Participants in Arm G with radiographically confirmed progressive disease will be allowed to crossover to Arm F (Section 5).

2.4 Coformulation Phase: Arm I (MK-1308A Q6W)

Arm I (MK-1308A Q6W)		**Treatment Period Cycle = 42 days**											Post-Treatment Period					Notes
Visit / Treatment Cycle	Screening	Cycle 1			Cycle 2		Cycle 3		Cycle 4		Cycle 5	Cycles ≥6	End of Treatment	Safety Follow-up		Disease Status Follow-up	Survival Follow-up	
Visit Timing / Cycle Day	Up to 28 days prior to first dose	1	8	21	1	21	1	21	1	21	1	1	Treatment discon-tinuation	30 days after the last dose	90 days after the last dose	Every 9 weeks	Every 12 weeks	
Visit Window (Days)	-28 to -1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		+14	+14	+14	+14	
ICF and ICF for Future Biomedical Research	X																	
Inclusion/Exclusion Criteria	X																	
Participant Identification Card	X	X																Update at C1D1
Demographics and Medical History	X																	
Medical, Oncology Disease Status and Prior Oncology Treatment History	X																	
Concomitant Medication Review		X			X		X		X		X	X	X	X	X			
Full Physical Examination	X	X			X		X		X		X	X	X	X	X			
Directed Physical Examination				X		X		X		X								
Height	X																	
Weight	X	X			X		X		X		X	X	X	X	X			Required once per cycle
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			Collected at pre-dose and at the end of infusion.

Arm I (MK-1308A Q6W)		**Treatment Period Cycle = 42 days**											Post-Treatment Period					Notes
Visit / Treatment Cycle	Screening	Cycle 1			Cycle 2		Cycle 3		Cycle 4		Cycle 5	Cycles ≥6	End of Treatment	Safety Follow-up		Disease Status Follow-up	Survival Follow-up	
Visit Timing / Cycle Day	Up to 28 days prior to first dose	1	8	21	1	21	1	21	1	21	1	1	Treatment discon-tinuation	30 days after the last dose	90 days after the last dose	Every 9 weeks	Every 12 weeks	
Visit Window (Days)	-28 to -1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		+14	+14	+14	+14	
ECOG Performance Status	X	X			X		X		X		X	X	X	X	X			Must be performed **within 3 days** of beginning C1, and prior to each treatment.
12-Lead ECG	X																	Repeat if clinically indicated
MK-1308A Q6W Dosing		X			X		X		X		X	X						
AE/SAE Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			Continuous Reporting
Tumor Imaging and RECIST Response Assessment	X	X														X		Every 9 weeks (±7 days) from first dose of study. After 54 weeks, every 12 weeks (±7 days)
MRI brain	X	X														X		See Section 9.2.1.1.
Survival Status		←													→		X	Refer to Sections 9.10.5 & 9.10.6.
Hematology/Chemistry (blood glucose)	X	X		X	X	X	X	X	X	X	X	X	X	X	X			Collected pre-dose. For C1D1, collect within 72 hours prior to the first dose.
Urinalysis	X				X		X		X		X	X	X	X	X			

Arm I (MK-1308A Q6W)		**Treatment Period Cycle = 42 days**										Post-Treatment Period					Notes
Visit / Treatment Cycle	Screening	Cycle 1			Cycle 2		Cycle 3		Cycle 4		Cycle 5	Cycles ≥6	End of Treatment	Safety Follow-up		Disease Status Follow-up	Survival Follow-up	
Visit Timing / Cycle Day	Up to 28 days prior to first dose	1	8	21	1	21	1	21	1	21	1	1	Treatment discon-tinuation	30 days after the last dose	90 days after the last dose	Every 9 weeks	Every 12 weeks	
Visit Window (Days)	-28 to -1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		+14	+14	+14	+14	
PT/INR/aPTT	X																	Equivalent type testing is permissible.
LDH	X																	
Thyroid Function Testing (T4, T3, TSH), ACTH and cortisol	X	X			X		X		X		X	X*	X	X	X			* After C6, samples collected every other cycle. Samples for cortisol and ACTH should be collected in the morning at the earliest feasible time.
Pregnancy Test for WOCBP	X	X			X		X		X		X	X	X	X				
Hepatitis Screen	X																	

Arm I (MK-1308A Q6W)		**Treatment Period Cycle = 42 days**										Post-Treatment Period					Notes
Visit / Treatment Cycle	Screening	Cycle 1			Cycle 2		Cycle 3		Cycle 4		Cycle 5	Cycles ≥6	End of Treatment	Safety Follow-up		Disease Status Follow-up	Survival Follow-up	
Visit Timing / Cycle Day	Up to 28 days prior to first dose	1	8	21	1	21	1	21	1	21	1	1	Treatment discon-tinuation	30 days after the last dose	90 days after the last dose	Every 9 weeks	Every 12 weeks	
Visit Window (Days)	-28 to -1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		+14	+14	+14	+14	
MK-1308 PK		X	X*	X	X	X	X	X	X	X			X	X				Collect within 24 h pre-dose and within 30 minutes after end of infusion on C1D1, C2D1, C3D1, and C4D1. Additional PK on C1D8*, C1D21, C2D21, C3D21 and C4D21. *Optional
Anti-MK-1308 Ab (ADA)		X			X		X		X				X	X				Collect within 24 h pre-dose on C1D1, C2D1, C3D1, and C4D1.
Exploratory Sample for T-cell Response													X					Whole blood collected at EoT.

Arm I (MK-1308A Q6W)		**Treatment Period Cycle = 42 days**										Post-Treatment Period					Notes
Visit / Treatment Cycle	Screening	Cycle 1			Cycle 2		Cycle 3		Cycle 4		Cycle 5	Cycles ≥6	End of Treatment	Safety Follow-up		Disease Status Follow-up	Survival Follow-up	
Visit Timing / Cycle Day	Up to 28 days prior to first dose	1	8	21	1	21	1	21	1	21	1	1	Treatment discon-tinuation	30 days after the last dose	90 days after the last dose	Every 9 weeks	Every 12 weeks	
Visit Window (Days)	-28 to -1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		+14	+14	+14	+14	
MK-3475 PK		X	X*	X	X	X	X	X	X	X			X	X				Collected within 24 h pre-dose and within 30 minutes after end of infusion on C1D1, C2D1, C3D1, C4D1. Additional PK on C1D8*, C1D21, C2D21, C3D21 and C4D21. *Optional
Anti-MK-3475 Ab (ADA)		X			X		X		X				X	X				Collect within 24 h pre-dose on C1D1, C2D1, C3D1, and C4D1.
Blood for genetic analysis		X																Collect pre-dose. See Section 9.9.1.
Tumor Tissue	X																	If archival tissue is not available, newly obtained tumor tissue is required. For participants providing additional biopsies, archival tissue is also requested.

Arm I (MK-1308A Q6W)		**Treatment Period Cycle = 42 days**										Post-Treatment Period					Notes
Visit / Treatment Cycle	Screening	Cycle 1			Cycle 2		Cycle 3		Cycle 4		Cycle 5	Cycles ≥6	End of Treatment	Safety Follow-up		Disease Status Follow-up	Survival Follow-up	
Visit Timing / Cycle Day	Up to 28 days prior to first dose	1	8	21	1	21	1	21	1	21	1	1	Treatment discon-tinuation	30 days after the last dose	90 days after the last dose	Every 9 weeks	Every 12 weeks	
Visit Window (Days)	-28 to -1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		+14	+14	+14	+14	
Blood for TCR		X		X	X													Collect predose
Peripheral Blood for Immunophenotyping Biomarker Analyses		X	X															Collect pre-dose
Blood for ctDNA		X			X		X						X					Collect pre-dose, except EOT

2.5 Coformulation Phase in China: Arm K (MK-1308A Q6W)

Arm K (MK-1308A Q6W)		**Treatment Period Cycle = 42 days**																		Post-Treatment Period					Notes
Visit / Treatment Cycle	Screen-ing	Cycle 1					Cycle 2					Cycle 3		Cycle 4					Cycle 5	Cycles ≥6	End of Treatment	Safety Follow-up		Disease Status Follow -up	Survival Follow-up	
Visit Timing / Cycle Day	Up to 28 days prior to first dose	1	2	8	15	21	1	2	8	15	21	1	21	1	2	8	15	21	1	1	Treatment discon-tinuation	30 days after the last dose	90 days after the last dose	Every 9 weeks	Every 12 weeks	
Visit Window (Days)	-28 to -1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		+14	+14	+14	+14	
ICF	X																									
Inclusion/ Exclusion Criteria	X																									
Participant Identification Card	X	X																								Update at C1D1
Demographics and Medical History	X																									
Medical, Oncology Disease Status and Prior Oncology Treatment History	X																									
Concomitant Medication Review		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Full Physical Examination	X	X					X					X		X					X	X	X	X	X			
Directed Physical Examination						X					X		X					X								
Height	X																									

Arm K (MK-1308A Q6W)	**Treatment Period Cycle = 42 days**																			Post-Treatment Period					Notes
Visit / Treatment Cycle	Screen-ing	Cycle 1					Cycle 2					Cycle 3		Cycle 4					Cycle 5	Cycles ≥6	End of Treatment	Safety Follow-up		Disease Status Follow-up	Survival Follow-up	
Visit Timing / Cycle Day	Up to 28 days prior to first dose	1	2	8	15	21	1	2	8	15	21	1	21	1	2	8	15	21	1	1	Treatment discon-tinuation	30 days after the last dose	90 days after the last dose	Every 9 weeks	Every 12 weeks	
Visit Window (Days)	-28 to -1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		+14	+14	+14	+14	
Weight	X	X					X					X		X					X	X	X	X	X			Required once per cycle
Vital Signs	X	X					X					X		X					X	X	X	X	X			Pre-dose and end of infusion and if clinically indicated
ECOG Performance Status	X	X					X					X		X					X	X	X	X	X			Must be performed **within 3 days** of beginning C1, and prior to each treatment.
12-Lead ECG	X																									Repeat if clinically indicated
MK-1308A Q6W Dosing		X					X					X		X					X	X						
AE/SAE Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			Continuous Reporting

Arm K (MK-1308A Q6W)	**Treatment Period Cycle = 42 days**																			Post-Treatment Period					Notes
Visit / Treatment Cycle	Screen-ing	Cycle 1					Cycle 2					Cycle 3		Cycle 4					Cycle 5	Cycles ≥6	End of Treatment	Safety Follow-up		Disease Status Follow-up	Survival Follow-up	
Visit Timing / Cycle Day	Up to 28 days prior to first dose	1	2	8	15	21	1	2	8	15	21	1	21	1	2	8	15	21	1	1	Treatment discon-tinuation	30 days after the last dose	90 days after the last dose	Every 9 weeks	Every 12 weeks	
Visit Window (Days)	-28 to -1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		+14	+14	+14	+14	
Tumor Imaging and RECIST Response Assessment	X	X																						X		Every 9 weeks (±7 days) from first dose of study. After 54 weeks, every 12 weeks (±7 days)
MRI brain	X	X																						X		See Section 9.2.1.1.
Survival Status		←																		→					X	Refer to Sections 9.10.5 & 9.10.6.
Hematology/Chemistry (blood glucose)	X	X				X	X				X	X	X	X				X	X	X	X	X	X			Collected pre-dose. For C1D1, collect within 72 hours prior to the first dose.
Urinalysis	X						X					X		X					X	X	X	X	X			

Arm K (MK-1308A Q6W)	**Treatment Period Cycle = 42 days**																			Post-Treatment Period					Notes
Visit / Treatment Cycle	Screen-ing	Cycle 1					Cycle 2					Cycle 3		Cycle 4					Cycle 5	Cycles ≥6	End of Treatment	Safety Follow-up		Disease Status Follow-up	Survival Follow-up	
Visit Timing / Cycle Day	Up to 28 days prior to first dose	1	2	8	15	21	1	2	8	15	21	1	21	1	2	8	15	21	1	1	Treatment discon-tinuation	30 days after the last dose	90 days after the last dose	Every 9 weeks	Every 12 weeks	
Visit Window (Days)	-28 to -1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		+14	+14	+14	+14	
PT/INR/aPTT	X																									Equivalent type testing is permissible.
LDH	X																									
Thyroid Function Testing (T4, T3, TSH), ACTH and cortisol	X	X					X					X		X					X	X*	X	X	X			* After C6, samples collected every other cycle. Samples for cortisol and ACTH should be collected in the morning at the earliest feasible time
Pregnancy Test for WOCBP	X	X					X					X		X					X	X	X	X				

Arm K (MK-1308A Q6W)		**Treatment Period Cycle = 42 days**																		Post-Treatment Period					Notes
Visit / Treatment Cycle	Screen-ing	Cycle 1					Cycle 2					Cycle 3		Cycle 4					Cycle 5	Cycles ≥6	End of Treatment	Safety Follow-up		Disease Status Follow-up	Survival Follow-up	
Visit Timing / Cycle Day	Up to 28 days prior to first dose	1	2	8	15	21	1	2	8	15	21	1	21	1	2	8	15	21	1	1	Treatment discon-tinuation	30 days after the last dose	90 days after the last dose	Every 9 weeks	Every 12 weeks	
Visit Window (Days)	-28 to -1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		+14	+14	+14	+14	
Hepatitis Screen	X																									HBsAg and HBV-DNA. Hep C Ab, quantitative HCV RNA

Arm K (MK-1308A Q6W)		**Treatment Period Cycle = 42 days**																		Post-Treatment Period					Notes
Visit / Treatment Cycle	Screen-ing	Cycle 1					Cycle 2					Cycle 3		Cycle 4					Cycle 5	Cycles ≥6	End of Treatment	Safety Follow-up		Disease Status Follow-up	Survival Follow-up	
Visit Timing / Cycle Day	Up to 28 days prior to first dose	1	2	8	15	21	1	2	8	15	21	1	21	1	2	8	15	21	1	1	Treatment discon-tinuation	30 days after the last dose	90 days after the last dose	Every 9 weeks	Every 12 weeks	
Visit Window (Days)	-28 to -1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		+14	+14	+14	+14	
MK-1308 PK		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X				For C1, C2, and C4, collect within 24 h pre-dose, within 30 min, and at 6 h after end of infusion as well as anytime on Days 2, 8, 15, and 21. For C3D1, collect within 24 h pre-dose and within 30 min after end of infusion. On C3D21, collect one PK sample anytime. After C4, collect PK within 24 h pre-dose every 2 cycles.

Arm K (MK-1308A Q6W)		**Treatment Period Cycle = 42 days**																		Post-Treatment Period					Notes
Visit / Treatment Cycle	Screen-ing	Cycle 1					Cycle 2					Cycle 3		Cycle 4					Cycle 5	Cycles ≥6	End of Treatment	Safety Follow-up		Disease Status Follow-up	Survival Follow-up	
Visit Timing / Cycle Day	Up to 28 days prior to first dose	1	2	8	15	21	1	2	8	15	21	1	21	1	2	8	15	21	1	1	Treatment discon-tinuation	30 days after the last dose	90 days after the last dose	Every 9 weeks	Every 12 weeks	
Visit Window (Days)	-28 to -1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		+14	+14	+14	+14	
Anti-MK-1308 Ab (ADA)		X					X					X		X						X	X	X				Collect within 24 h pre-dose on D1 for C1, C2, C3, and C4. After C4, collect ADA within 24 h pre-dose every 2 cycles.

Arm K (MK-1308A Q6W)		**Treatment Period Cycle = 42 days**																		Post-Treatment Period					Notes
Visit / Treatment Cycle	Screen-ing	Cycle 1					Cycle 2					Cycle 3		Cycle 4					Cycle 5	Cycles ≥6	End of Treatment	Safety Follow-up		Disease Status Follow-up	Survival Follow-up	
Visit Timing / Cycle Day	Up to 28 days prior to first dose	1	2	8	15	21	1	2	8	15	21	1	21	1	2	8	15	21	1	1	Treatment discon-tinuation	30 days after the last dose	90 days after the last dose	Every 9 weeks	Every 12 weeks	
Visit Window (Days)	-28 to -1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		+14	+14	+14	+14	
MK-3475 PK		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X				For C1, C2, and C4, collect within 24 h pre-dose, within 30 min, and at 6 h after end of infusion as well as anytime on Days 2, 8, 15 and 21. For C3D1, collect within 24 h pre-dose and within 30 min after end of infusion. On C3D21, collect one PK sample anytime. After C4, collect PK within 24 h pre-dose every 2 cycles.

Arm K (MK-1308A Q6W)		**Treatment Period Cycle = 42 days**																		Post-Treatment Period					Notes
Visit / Treatment Cycle	Screen-ing	Cycle 1					Cycle 2					Cycle 3		Cycle 4					Cycle 5	Cycles ≥6	End of Treatment	Safety Follow-up		Disease Status Follow-up	Survival Follow-up	
Visit Timing / Cycle Day	Up to 28 days prior to first dose	1	2	8	15	21	1	2	8	15	21	1	21	1	2	8	15	21	1	1	Treatment discon-tinuation	30 days after the last dose	90 days after the last dose	Every 9 weeks	Every 12 weeks	
Visit Window (Days)	-28 to -1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		+14	+14	+14	+14	
Anti-MK-3475 Ab (ADA)		X					X					X		X						X	X	X				Collect within 24 h pre-dose on D1 for C1, C2, C3, and C4. After C4, collect ADA within 24 h pre-dose every 2 cycles.

3. Introduction

MK-1308 (quavonlimab, but will be referred to as MK-1308 throughout the protocol) is a humanized, antagonist monoclonal antibody that binds Cytotoxic T-Lymphocyte-Associated Antigen 4 and blocks its interaction with its ligands, CD80 (B7.1) and CD86 (B7.2). This human immunoglobulin G1 antibody is being developed to combine with Keytruda® (pembrolizumab/anti-PD-1) to increase anti-tumor efficacy in participants with various tumor indications.

3.1 Study Rationale

Clinical studies utilizing the combination of Yervoy® (ipilimumab/anti-CTLA4 mAb) and Opdivo® (nivolumab/anti-PD1 mAb) have demonstrated improved efficacy over monotherapy in advanced melanoma. The Yervoy/Opdivo combination was initially approved by the FDA as a treatment for patients with BRAF V600 wild-type unresectable or metastatic melanoma, based on findings from the Phase 2 CheckMate-069 study [Postow, M. A., et al 2015] then expanded to include patients, regardless of BRAF mutational status, based on data from the Phase 3 CheckMate-067 trial, in which PFS and OS were co-primary endpoints [U.S. Prescribing Information 2017] [Larkin, J., et al 2015]. Additionally, combination treatment with lower dose ipilimumab (1 mg/kg) and pembrolizumab (2 mg/kg) in advanced melanoma in a Phase 1 study (KEYNOTE-029) demonstrated an estimated 1-year PFS of 69% (95% CI 60–75) and an estimated 1-year OS of 89% (95% CI 83–93) [Long, G. V., et al 2017]. Moreover, a single institution Phase 2 study in patients with PD-1/L1-refractory advanced melanoma recently showed a 50% ORR with ipilimumab combined with pembrolizumab [Olsonm, D., et al 2018].

This combination has also shown promising efficacy in NSCLC based on data from the Phase 1 CheckMate-012 study, prompting initiation of the Phase 3 CheckMate-227 study. The CheckMate-012 study suggested that lower and less frequent dosing of ipilimumab provided an acceptable safety profile with improved efficacy over nivolumab alone in 1L NSCLC [Hellmann, M. D., et al 2016]. Evidence for combination efficacy in the 2L SCLC population has also been reported from the Phase 1 CheckMate-032 study [Antonia, S. J., et al 2016], prompting the initiation of Phase 3 studies for nivolumab and nivolumab plus ipilimumab as maintenance therapy after first-line chemotherapy (CheckMate 451) and for nivolumab versus chemotherapy as second-line therapy (CheckMate 331) in SCLC.

Based on the results of these promising studies, MK-1308 is being developed in combination with pembrolizumab for the treatment of solid tumors. This is the first-in-human trial of MK-1308 and it is designed to assess the safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary efficacy of escalating doses of MK-1308 when used in combination and in coformulation (MK-1308A) with pembrolizumab in participants with advanced solid tumors. In the dose confirmation phase, Arms A, B, C and E will explore different dosing schedules of the MK-1308 plus pembrolizumab combination and include only participants newly diagnosed with Stage III/IV NSCLC. Arm D will explore this combination in 2L SCLC. Arms F and Arm G will explore the anti-tumor activity of MK-1308 with or without pembrolizumab in participants with advanced melanoma that is refractory to anti-PD-1/PD-L1. Arms I and K will explore the new coformulated product,

MK-1308A (25 mg MK-1308 + 400 mg pembrolizumab), in participants with advanced solid tumors. Arm K will study PK in participants from China.

Details regarding specific benefits and risks for participants participating in this clinical trial may be found in the IB and informed consent documents.

3.2 Background

Refer to the MK-1308 and pembrolizumab IBs for detailed background information.

3.2.1 Pharmaceutical and Therapeutic Background

In recent years, the field of cancer immunotherapy has developed a better understanding of mechanisms by which tumors can limit an immune response. The tumor microenvironment can escape immunosurveillance by possessing various immunosuppressive effects, allowing escape from immune detection and elimination. In particular, T-cells are kept from achieving activation when cell surface inhibitory receptors are engaged, prohibiting T-cell function. The most notable of these receptors are PD-1 and CTLA4, both of which have been demonstrated to be viable therapeutic targets through clinical investigation.

3.2.1.1 MK-1308 Background

MK-1308 is a humanized, antagonist mAb that binds Cytotoxic CTLA4 and blocks its interaction with both of its ligands, CD80 (B7.1) and CD86 (B7.2). This human IgG1 antibody is being developed to combine with Keytruda® (pembrolizumab/anti-PD-1) and other therapies to increase anti-tumor efficacy in patients with various tumor indications.

Cytotoxic T-Lymphocyte-Associated Antigen-4 is a negative regulator of T-cell function and proliferation. It is found on the surface of activated T-cells and regulatory T-cells (Tregs) as a single-pass transmembrane protein belonging to the immunoglobulin superfamily. Cytotoxic T-Lymphocyte-Associated Antigen-4 was identified as a second receptor for both CD80 and CD86 and shares some structural homology with the activating co-receptor, CD28. Unlike CD28, which is expressed on naïve T-cells, the cell surface expression of CTLA4 is both transient and tightly regulated. The opposing responses mediated by these 2 receptors are capable of coordinating the strength of the immune system's response.

As part of the adaptive immune response, T-cells are central to mounting a defense against tumor growth. Activation of T-cells is achieved via the dual engagement of both the T-cell receptor and CD28 receptor on the T-cell to mount a full immunogenic response. CD28 binds to either CD80 or CD86 molecules expressed on antigen presenting cells, leading to T-cell-specific expression and presentation of CTLA4, which then competes with CD28 to bind either of these activating molecules, thereby dampening the activation signal for the T-cell, moving it to a more tolerogenic state. Therefore, blocking this immunomodulatory checkpoint, allowing T-cells to remain active, would allow the immune system to mount a more competent and durable anti-tumor response.

Cytotoxic T-Lymphocyte-Associated Antigen-4 suppression is thought to be primarily at sites of T-cell activation, eg, secondary lymph organs rather than within the tumor microenvironment. However, inhibition of CTLA4 results in substantial increases of T-cell infiltrates within tumor tissues. This contrasts with the presumed inhibition of T-cell function

via PD-1 engagement which occurs within the tumor microenvironment between T-cells interacting with both antigen presenting cells and the tumor cells themselves. Differences in mechanism and expression of these receptors and their ligands suggest that these differential mechanisms of action may underlie the observed clinical benefit when utilized as combination therapy above their respective monotherapies.

The humanized anti-human CTLA4 antibody is being proposed for development in combination with MSD's anti-PD-1 mAb, pembrolizumab. Two human mAbs targeting CTLA4, ipilimumab (IgG1) and tremelimumab (IgG2) have been and continue to be evaluated in the clinic for the treatment of various oncology indications. Ipilimumab is approved for melanoma patients alone and in combination with the anti-PD-1 antibody. Ipilimumab demonstrates efficacy with doses from 1 to 10 mg/kg, with lower toxicity rates at lower doses. In Checkmate 227, the Phase 3 study of the combination in NSCLC, ipilimumab is being administered at a 1 mg/kg dose every 6 weeks (Q6W) [ClinicalTrials.gov 2017]. The combination of ipilimumab and nivolumab is being actively pursued in multiple cancer types.

MSD has conducted a Phase 1b study of pembrolizumab at 2 mg/kg every 3 weeks (Q3W) in combination with ipilimumab at 1 mg/kg Q3W x 4 doses in participants with advanced melanoma (KN-029) [Long, G. V., et al 2016]. Results of a melanoma expansion cohort (N=153) showed that the combination was reasonably well tolerated with 38% treatment-related Grade 3/4 AEs and highly efficacious with a 57% ORR. This study has demonstrated that CTLA4 blockade in combination with pembrolizumab is potentially beneficial to patients.

3.2.1.2 MK-1308A Background

MK-1308A is a novel coformulation of 25 mg MK-1308 and 400 mg pembrolizumab, 17.5-mL fill in a 20-mL single vial. The rationale to develop this single entity product as a FDC includes the following points:

1. There is an advantage to using FDCs when there is an identifiable patient population for whom treatment with a specific combination of agents in a fixed ratio of doses has been shown to be safe and effective, and when all of the agents contribute to the overall therapeutic effect [World Health Organization 2005].
2. As other anti-CTLA4 agents have not shown significant efficacy when administered as monotherapy, the Sponsor does not plan to develop MK-1308 as a monotherapy agent.
3. Data from the dose confirmation phase of this trial (MK-1308-001) show that only 12 (6.7 %) of the 179 patients enrolled to Arms A, B, C and E discontinued the combination regimen of MK-1308 + pembrolizumab due to toxicity and subsequently started pembrolizumab monotherapy. Moreover, most of these patients had recurrent toxicities of equal or worse grade following resumption of pembrolizumab monotherapy, suggesting holding the combination and restarting only pembrolizumab is not protective.
4. Pembrolizumab is available as a marketed product and can be used as on-label or off-label if MK-1308A requires discontinuation due to toxicity.

5. An FDC product is formulated in a single vial, which will result in time-conservation and reduced medication error in comparison to preparation of two independent products.

The objective in the coformulation phases of the study is to evaluate the safety, efficacy, and PK of the coformulated product, and to compare these data to that of the single, co-administered products given at the same dose and schedule.

3.2.1.3 Pembrolizumab (MK-3475) Background

Pembrolizumab is a potent humanized IgG4 mAb with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and PD-L2. Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1.

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 Ig superfamily member related to CD28 and CTLA4, which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [Talmadge, J. E., et al 2007] [Usubütün, A., et al 1998].

The structure of murine PD-1 has been resolved [Zhang, X., et al 2004]. PD-1 and family members are Type I transmembrane glycoproteins containing an Ig variable-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 ITIM, and an immunoreceptor tyrosine-based switch motif. After 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 CTLA4 as both molecules regulate an overlapping set of signaling proteins [Nobili, C., et al 2008] [Hiraoka, N. 2010]. As a consequence, the PD-1/L1 pathway is an attractive target for therapeutic intervention in a variety of cancers.

3.2.2 Preclinical and Clinical Trials

3.2.2.1 MK-1308

MK-1308 was found to behave comparably to clinical standards as assessed through various biochemical and cellular assays. The monovalent affinities of MK-1308 against human CTLA4 were comparable to one another and ~2-3-fold tighter compared to ipilimumab. MK-1308 showed comparable binding to human and cynomolgus CTLA4 as compared to ipilimumab.

The ability of the antibodies to block binding of human CTLA4 to its natural ligands, CD80 and CD86, was assessed by cell-based enzyme-linked immunosorbent assay (ELISA) using

CHO cells expressing human CTLA4. The determined mean inhibitory concentration (IC50) values for binding inhibition of MK-1308 were comparable to ipilimumab. Both ipilimumab and tremelimumab induced dose-dependent up-regulation of IL-2 production from Jurkat T-cells. MK-1308 also induced the up-regulation of IL-2 in a dose-dependent manner with a comparable potency to either clinical standard. Consistent with this finding, both ipilimumab and tremelimumab induced dose-dependent IFN-gamma production from CD4+ T-cells in a mixed lymphocyte reaction (MLR) based assay, utilizing activated CD4+ T-cells and allogenic differentiated monocytes to serve as DCs. MK-1308 induced the up-regulation of IFN-gamma in a dose-dependent manner with observed efficacy between ipilimumab and tremelimumab. The inclusion of pembrolizumab in combination with either MK-1308 or ipilimumab resulted in a substantial and synergistic increase in IFN-gamma production in the current MLR format.

In a humanized mouse model implanted with the Panc 08.13 pancreatic adenocarcinoma cell line, MK-1308 showed comparable single-agent anti-tumor efficacy to ipilimumab.

Refer to the current IB for more information.

3.2.2.2 Pembrolizumab (MK-3475)

Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated anti-tumor responses as a monotherapy in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, and colorectal carcinoma. Blockade of the PD-1 pathway effectively promoted CD8+ T-cell infiltration into the tumor and the presence of interferon-gamma, granzyme B, and perforin, indicating that the mechanism of action involved local infiltration and activation of effector T-cell (Teff) function in vivo [Okazaki, T., et al 2001] [Pölcher, M., et al 2010] [Ropponen, K. M., et al 1997] [Dudley, M. E., et al 2005] [Hunder, N. N., et al 2008] [Greenwald, R. J., et al 2005]. In-house experiments have confirmed the in vivo efficacy of PD-1 blockade as a monotherapy, as well as in combination with chemotherapy in syngeneic mouse tumor models.

Pembrolizumab has shown clinical activity in multiple tumor types. Please refer to the current label.

3.2.3 Ongoing Clinical Trials

3.2.3.1 MK-1308

The first human clinical trial with MK-1308 is MK-1308-001.

Additional ongoing trials evaluating MK-1308 include KEYNOTE-495, which is evaluating MK-1308 in combination with MK-3475 in participants with 1L NSCLC who have specific biomarkers and Substudy 02A: Safety and Efficacy of Pembrolizumab in Combination With Investigational Agents in Participants With Programmed Cell-death 1 (PD-1) Refractory Melanoma (MK-3475-U02A).

Please see the IB for the description of clinical data from these trials.

3.2.3.2 Pembrolizumab (MK-3475)

Over 300 interventional clinical studies involving pembrolizumab are currently ongoing in a number of advanced solid tumor indications as well as in hematological malignancies. For further details, please refer to the IB.

3.3 Benefit/Risk Assessment

As discussed in Section 3.2 and the IB, both MK-1308 and pembrolizumab, in combination, have shown promising efficacy in participants with solid tumors, and preliminary safety data of the combination of MK-1308 and pembrolizumab suggest toxicity is manageable.

The beneficial effects of pembrolizumab have been seen in several melanoma trials to date. Publications of a significantly positive benefit/risk ratio have been reported for melanoma in single-arm and randomized studies as monotherapy (KEYNOTE-001, KEYNOTE-002, KEYNOTE-006). The beneficial effects of pembrolizumab in combination with CTLA-4 blockade [ipilimumab] have been seen in several melanoma trials to date. Significantly positive benefit/risk ratio has been reported for melanoma in the Phase 1b study of pembrolizumab in combination with ipilimumab (KEYNOTE-029).

Given the relevance of improving and expanding treatment options for patients with advanced melanoma, there is an unmet medical need for novel combinations in this setting. The existing data suggest that CTLA4 blockade, in combination with PD-1 blockade, is a promising therapeutic strategy and the benefit: risk assessment for participants included in this study is considered to be favorable.

It cannot be guaranteed that participants in clinical trials will directly 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 who are at least 18 years of age with advanced solid tumors:

Objective	Endpoint
Primary	
• To determine the safety and tolerability of MK-1308 in combination with pembrolizumab and to establish a preliminary recommended Phase 2 dose (RPTD) when used in combination with pembrolizumab (Dose Escalation and Confirmation phases)	• Number of participants with ≥1 DLT • Number of participants with ≥1 AE • Number of participants discontinuing study treatment due to an AE

Objective	Endpoint
• To determine the safety and tolerability of MK-1308 as monotherapy (Efficacy Expansion phase)	• Number of participants with ≥1 AE • Number of participants discontinuing study treatment due to an AE
• To determine the safety and tolerability of MK-1308A (Coformulation phase)	• Number of participants with ≥1 AE • Number of participants discontinuing study treatment due to an AE • Number of participants with ≥1 DLT (Arms I)
• To evaluate ORR as assessed by BICR per RECIST 1.1 in the efficacy expansion phase (Arms F and G). RECIST 1.1 is adjusted to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ (see Section 5.4.1.1)	• Objective Response: CR or PR
Secondary	
• To characterize the PK profiles and incidence of ADA, as appropriate, of pembrolizumab, of MK-1308 as monotherapy, and of MK-1308 when used in combination and in coformulation with pembrolizumab in the dose escalation phase as well as in Arms A, B, C, D, E, F, G, and I. • To characterize PK profiles and incidence of ADA of both MK-1308 and pembrolizumab in Chinese participants in Arm K when the study drugs are administered as a coformulated product (MK-1308A).	• Pharmacokinetic parameters including AUC, C_{min}, C_{max} • Anti-drug antibody levels
• To evaluate ORR as assessed by investigator per RECIST 1.1 in the dose escalation phase, the dose confirmation phase, and in Arms I and K in the coformulation phase	• Objective response: CR or PR

Objective	Endpoint
• To evaluate DOR per RECIST 1.1 as assessed by BICR in the efficacy expansion phase (Arms F and G).	• DOR: The time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first (for responders only)
Tertiary/Exploratory	
CCI [redacted]	

5. Study Design

5.1 Overall Design

This is a first-in-human, multicenter, multi-arm, open-label, non-randomized, Phase 1 / 2 study of MK-1308 in combination with pembrolizumab in participants with a histologically or cytologically-confirmed diagnosis of an advanced solid tumor. The trial design and guidance of decision rules for dose escalation, dose confirmation, and efficacy expansion are shown in Figure 1 and Figure 2. The coformulation phase is presented in Figure 3.

This study will evaluate the safety, tolerability, PK, pharmacodynamics, and preliminary efficacy of MK-1308 in combination and in coformulation with pembrolizumab. Participants will be allocated to receive these agents using an interactive voice response system/integrated web response system (IVRS/IWRS).

After a screening period of up to 28 days, participants will be assigned to the dose escalation, dose confirmation, efficacy expansion phase, or coformulation phase. Each treatment cycle for dose escalation and confirmation is 3 weeks and for efficacy expansion and coformulation is 6 weeks. In the efficacy expansion and coformulation phases, each participant will be treated for up to 18 cycles (approximately 24 months) after initiation of treatment. Clinical follow-up will be at 30 days in the dose escalation and at 30 and 90 days in the efficacy expansion and coformulation phases after the last dose.

Details of all phases of the study are provided below.

For the purposes of making dose decisions from a safety perspective, participants will be considered evaluable for DLT if they have completed the following:

1. Dose escalation phase: DLT observation period of 6 weeks without a DLT or experienced a DLT during this period.
2. Dose confirmation phase: DLT observation period of 3 weeks without a DLT or experienced a DLT during this period.
3. Efficacy expansion phase: (Arm F only, up to 14 participants): DLT observation period of 6 weeks without a DLT or experienced a DLT during this period.
4. Coformulation phase (Arm I): DLT observation period of 6 weeks without a DLT or experienced a DLT during this period.

The dose decision rules are provided for a target number of participants evaluable for DLT. When the actual sample size differs from the target size, a Go-decision for dose escalation or dose confirmation for MK-1308 in combination with pembrolizumab (Cohort 1, 2, and 3, Arm A, B, C, D, E and F) will require that no more than one-fourth of the participants have a DLT. The doses chosen for evaluation for the MK-1308 and pembrolizumab combination are expected to have a DLT rate ≤10%. This is based on the known DLT rate of 10.7% in the KN-029 study (pembrolizumab combination with ipilimumab in melanoma) using a dose of ipilimumab of 1 mg/kg.

5.1.1 Dose Escalation Phase for MK-1308 and Pembrolizumab

The projected dose levels are provided in Table 4. A staged dose escalation phase will be instituted whereby the available safety, PK, and pharmacodynamics data from the first 6 participants for each cohort after completion of the DLT period (first 2 cycles) will be evaluated and discussed with the investigators at dose escalation meetings prior to making dose escalation decisions and enrolling additional participants. Initiation of MK-1308 treatment in participants enrolled within each new dose level will be staggered by at least 24 hours for the first 3 participants at that dose level.

Based on the emerging safety and/or efficacy signals, an intermediate dose level may be explored in consultation and agreement with the investigators and Sponsor.

Cohort 1 (n = 6 to 14) will enroll participants with advanced/metastatic **solid tumors**. On Cycle 1, Day 1, participants will receive a single monotherapy dose lead-in with MK-1308 at 25 mg by intravenous route of administration. On Cycle 2, Day 1, and for 3 subsequent cycles on Day 1 (Cycles 3 to 5), these participants will receive MK-1308 at 25 mg in combination with pembrolizumab at 200 mg on a Q3W schedule. For all subsequent cycles (starting with Cycle 6), all participants will receive pembrolizumab monotherapy on a Q3W schedule. A total of 6 participants may be enrolled initially. If ≤ 1 participant of the first 6 DLT-evaluable participants has a DLT during the first 2 cycles, Cohort 1 may be expanded to a total of 14 participants in order to obtain additional safety, PK, and pharmacodynamic data; a new cohort will be initiated at the next dose level; and 2 new dose confirmation arms (Arms A and B) at the same dose level will be initiated. If more than 1 DLT occurs in the first 6 DLT-evaluable participants, 6 new participants may be treated at a lower dose level consisting of a single monotherapy lead-in with MK-1308 at an estimated dose of 10 mg, which will be determined by the available safety, PK, and pharmacodynamic data.

Cohort 2 (n = 6 to 14) will enroll participants with advanced/metastatic **solid tumors except NSCLC**. Non-small cell lung cancer participants will be excluded from this cohort based on data from the CheckMate-012 study that shows that these participants have unacceptable DLT and discontinuation rates at the equivalent ipilimumab dose of 1 mg per kg [Hellmann, M. D., et al 2016]. On Cycle 1, Day 1, participants will receive a single monotherapy dose lead-in with MK-1308 at 75 mg by intravenous route of administration. On Cycle 2, Day 1, and for 3 subsequent cycles on Day 1 (Cycles 3 to 5), these participants will receive MK-1308 at 75 mg in combination with pembrolizumab at 200 mg on a Q3W schedule. For all subsequent cycles (starting with Cycle 6), all participants will receive pembrolizumab monotherapy on a Q3W schedule. A total of 6 participants may be enrolled initially. If ≤1 participant of the first 6 DLT-evaluable participants has a DLT, Cohort 2 may be expanded to a total of 14 participants in order to obtain additional safety, PK, and pharmacodynamic data and 3 new dose confirmation arms (Arms C, D, and E) at the same dose level will be initiated. If more than 1 DLT occurs in the first 6 DLT-evaluable participants, 6 new participants may be treated at a lower dose level or at a different dosing interval which will be determined by the totality of safety, PK, and pharmacodynamic data.

Cohort 3 (n = 6) will enroll participants with advanced/metastatic **solid tumors except NSCLC**. Non-small cell lung cancer participants will be excluded from this cohort. On Cycle 1, Day 1, participants will receive a single monotherapy dose lead-in with MK-1308 at 200 mg by intravenous route of administration. On Cycle 2, Day 1, and for 3 subsequent

cycles on Day 1 (Cycles 3 to 5), these participants will receive MK-1308 at 200 mg in combination with pembrolizumab at 200 mg on a Q3W schedule. For all subsequent cycles (starting with Cycle 6), all participants will receive pembrolizumab monotherapy on a Q3W schedule. If more than 1 DLT occurs in the first 6 DLT-evaluable participants, 6 new participants may be treated at a lower dose level or at a different dosing interval which will be determined by the totality of safety, PK, and pharmacodynamic data.

5.1.2 Dose Confirmation Phase for MK-1308 and Pembrolizumab

The purpose of dose confirmation is to gather additional safety, tolerability, PK, pharmacodynamic, and preliminary efficacy data of MK-1308 in combination with pembrolizumab. The dose confirmation phase will be initiated at selected dose levels once the safety profile of these dose levels in dose escalation has been characterized in the required number of participants specified above. A staged dose confirmation phase will be instituted for each arm whereby the safety, PK, and pharmacodynamic data from the first 14 participants for Arms A, B, C, and D and the first 6 participants of Arm E, and the safety profile beyond the DLT window for participants still on-therapy from the dose escalation phase will be evaluated and discussed with the investigators at dose escalation meetings prior to enrolling additional participants at that dose level. For subsequent dose levels (beyond 25 mg), a dose between 25 mg and 75 mg may be selected, based on the totality of data.

As described in detail below and in Figure 1, the arms of the dose confirmation phase will include: **first-line, advanced/metastatic NSCLC** (Arms A, B, C, E,) and **second-line (and beyond) advanced/metastatic SCLC** (Arm D). With respect to PD-L1 status, any tumor PD-L1 expression level is eligible for enrollment. Known tumor PD-L1 status is not required for study enrollment. However, if there are less than 10 participants with a PD-L1 tumor proportion score (TPS) ≥50% in any arm (as determined by centralized testing), additional participants with PD-L1 expression ≥50% will be added at the discretion of the Sponsor, for a total of 10 participants.

Arm A (n = 14 to 30) will enroll participants with a diagnosis of **advanced/metastatic NSCLC**. On Cycle 1, Day 1 and during all subsequent cycles, participants will receive MK-1308 at 25 mg in combination with pembrolizumab at 200 mg on a Q3W schedule. If ≤ 3 of the first 14 DLT-evaluable participants experience a DLT, after discussion of safety data with the Investigators, Arm A will be expanded to 30 participants. If more than 3 DLTs occur in the first 14 DLT-evaluable participants, enrollment of Arm A will not be expanded. Up to 16 participants may be enrolled initially to achieve the desired sample size of 14 DLT-evaluable participants.

Arm B (n = 14 to 30) will enroll participants with a diagnosis of **advanced/metastatic NSCLC.** On Cycle 1, Day 1, participants will receive MK-1308 at 25 mg in combination with pembrolizumab at 200 mg. On all subsequent cycles, pembrolizumab will be given on a Q3W schedule at a dose of 200 mg and MK-1308 will be given on a Q6W schedule at a dose of 25 mg. If ≤ 3 of the first 14 participants experience a DLT, after discussion of safety data with the investigators, Arm B will be expanded to 30 participants. If more than 3 DLTs occur in the first 14 DLT-evaluable participants, enrollment of Arm B will not be expanded. Up to 16 participants may be enrolled initially to achieve the desired sample size of 14 DLT-evaluable participants.

Arm C (n = 14 to 30) will enroll participants with a diagnosis of **advanced/metastatic NSCLC.** On Cycle 1, Day 1, participants will receive MK-1308 at 75 mg in combination with pembrolizumab at 200 mg. On all subsequent cycles, pembrolizumab will be given on an every Q3W schedule at a dose of 200 mg and MK-1308 will be given on a Q6W schedule at a dose of 75 mg. If ≤ 3 of the first 14 participants experience a DLT, after discussion of safety data with the investigators, Arm C will be expanded to 30 participants. If more than 3 DLTs occur in the first 14 DLT-evaluable participants, enrollment of Arm C will not be expanded. Up to 16 participants may be enrolled initially to achieve the desired sample size of 14 DLT-evaluable participants.

Arm D (n = 14 to 30) will enroll participants with **advanced/metastatic SCLC**. On Cycle 1, Day 1, participants will receive MK-1308 at 75 mg in combination with pembrolizumab at 200 mg. On all subsequent cycles, pembrolizumab will be given on a Q3W schedule at a dose of 200 mg and MK-1308 will be given on a Q6W schedule at a dose of 75 mg. If ≤ 3 of the first 14 participants experience a DLT, after discussion of safety data with the investigators, Arm D will be expanded to 30 participants. If more than 3 DLTs occur in the first 14 DLT-evaluable participants, enrollment of Arm D will not be expanded. Up to 16 participants may be enrolled initially to achieve the desired sample size of 14 DLT-evaluable participants.

Arm E (n = 6 to 14) will enroll participants with a diagnosis of **advanced/metastatic NSCLC**. On Cycle 1, Day 1 and during all subsequent cycles, participants will receive MK-1308 at 75 mg in combination with pembrolizumab at 200 mg on a Q3W schedule. If ≤ 1 of the first 6 DLT-evaluable participants experience a DLT, after discussion of safety data with the Investigators, Arm E will be expanded to 14 participants. If more than 1 DLT occur in the first 6 DLT-evaluable participants, enrollment of Arm E will not be expanded. Up to 8 participants may be enrolled initially to achieve the desired sample size of 6 DLT-evaluable participants.

An efficacy interim analysis is planned for each arm in dose confirmation after the first 8 or 14 participants (depending on the enrollment rate) have finished the first tumor assessment. An arm may have enrollment terminated early if there are zero responders out of the first 8 evaluable participants in the arm, or less than 2 responders (CR, PR) out of the first 14 participants in the arm, and if so, the remaining sample size yet to be enrolled for the arm may be used by one or more arms in the dose confirmation phase at the discretion of the Sponsor.

5.1.3 Efficacy Expansion and Crossover Phases for MK-1308 and Pembrolizumab

The purpose of the efficacy expansion phase is to gather preliminary anti-tumor efficacy data for MK-1308 in combination with pembrolizumab as well as for MK-1308 monotherapy in the specific target population of PD-1/PD-L1 refractory melanoma.

An adaptive design with one or more safety and efficacy interim analyses with potential to stop the enrollment early for futility will be implemented. Details of the interim analyses are described below. Whenever both the MK-1308 combination arm (Arm F) and the MK-1308 monotherapy arm (Arm G) are open, 1:1 randomization will be implemented to facilitate the enrollment and reduce bias.

Pre- and on-treatment biopsies are required for approximately 10 participants in each of Arms F and G. However, if there are less than 10 in each of these arms at the end of the planned enrollment period then additional participants will be added at the discretion of the Sponsor, for a total of up to 30 participants.

Arms F and G is applicable only to sites in Australia, New Zealand, Israel, Canada, Chile, France, Poland, Italy, Greece, Sweden, Spain, and United States.

Arm F (n = up to 100): On Cycle 1, Day 1 and for all subsequent cycles, participants will receive MK-1308 at 25 mg in combination with pembrolizumab at 400 mg. Both MK-1308 and pembrolizumab will be given on a Q6W schedule continuously for up to 18 cycles (up to 24 months).

A safety interim analysis will be conducted when the first 6 DLT-evaluable participants have completed their DLT evaluation. Up to 8 participants may be enrolled initially to achieve the desired sample size of 6 DLT-evaluable participants. If the observed DLT rate is higher than 25%, the 400 mg Q6W pembrolizumab dosing may be replaced with pembrolizumab 200 mg Q3W in the newly enrolled participants (Arm H; not activated). The decision to switch from pembrolizumab 400 mg Q6W to 200 mg Q3W will be based on the totality of the safety data and not limited to DLTs. If needed, up to 14 participants will be evaluated for DLT and additional safety interim analyses will be conducted after the first safety interim analysis of 6 DLT-evaluable participants and before the final decision of the dose and frequency of the combination is determined. If the decision to switch from pembrolizumab 400 mg Q6W to 200 mg Q3W is made, existing participants who have already been treated with pembrolizumab 400 mg Q6W plus MK-1308 25 mg Q6W may also be switched to pembrolizumab 200 mg Q3W plus MK-1308 25 mg Q6W, after discussion with the Sponsor. As soon as the DLT and safety evaluation is complete and the dose and frequency are decided, randomization between Arm F and Arm G (described below) will begin. A total of 100 new participants in the pembrolizumab 200 Q3W plus MK-1308 25 mg Q6W will be planned for enrollment, taking into consideration the efficacy interim analysis, if an alternate dosing regimen is chosen.

Note: The DLT period with the first 6 subjects concluded with no toxicity concerns. Arm H is not required and will not be activated.

Regardless of the dosing regimen chosen, an efficacy interim analysis will be conducted approximately 9 weeks after the first dose of the 20th participant. If at least 4 out of the first 20 participants (ie, at least 20%) experience a response, Arm F will continue to enroll a maximum of 80 additional participants for a total of 100 participants at the same dose level. Enrollment to Arm F may not be paused to wait for results of the efficacy interim analysis. If fewer than 20% responses are observed, the totality of the data will be evaluated to decide whether or not to continue enrollment in Arm F.

Arm G (n = up to 40): On Cycle 1, Day 1 and for all subsequent cycles, participants will receive MK-1308 at 25 mg as monotherapy on a Q6W schedule continuously for up to 18 cycles (up to 24 months). If after receiving at least 2 cycles of MK-1308 monotherapy, participants have radiographical-progressive disease that is centrally verified by BICR, they will be eligible to crossover to combination therapy with pembrolizumab.

An efficacy interim analysis will be conducted approximately 9 weeks after the first dose of the 20th participant in Arm G. If at least one response is observed out of the first 20 participants **AND** Arm F did not stop enrollment early at the efficacy interim analysis, Arm G enrollment will continue to enroll a maximum of 20 additional participants for a total of 40 participants. If there are zero responders out of the first 20 evaluable participants in Arm G **OR** a decision was made to stop the enrollment of Arm F, enrollment of Arm G will stop. Enrollment to Arm G may be paused to wait for results of the efficacy interim analysis.

Crossover to Combination Therapy from Arm G

Participants who show BICR-verified radiographical-progressive disease in Arm G will be eligible to receive combination therapy with pembrolizumab after consultation with the Sponsor. The specific regimen into which participants will cross over will be determined by the safety analysis conducted after the first 6 participants in Arm F complete the DLT period. If the Q6W pembrolizumab dosing regimen is deemed safe, then Arm G participants will cross over to this regimen.

Crossover to combination therapy will only be allowed after at least 2 treatments of monotherapy have been completed. Note: Disease progression must be assessed by imaging study using RECIST 1.1 and be sent to CIV for expedited central verification of progression by BICR. CIV will communicate the results to the study site and Sponsor via email. The imaging for BICR-verified progression will be used to establish a new baseline for the crossover phase if the imaging is performed within 28 days prior to first dose of combination therapy.

Participants who cross over to combination therapy will start with C1D1 activities per the SOA and should undergo all scheduled activities for the new Arm.

Participants who crossed over to combination therapy will be eligible to receive a maximum of 24 months of treatment from the start of combination treatment.

5.1.4 Coformulation Phase for MK-1308A (Arms I and K)

The purpose of the coformulation phase is to evaluate safety, PK, and efficacy for MK-1308A, a coformulation of 25 mg MK-1308 and 400 mg pembrolizumab, 17.5-mL fill in a 20-mL vial. The coformulation PK data will be compared to the data generated in the efficacy expansion phase when these drug products were individually co-administered at the same dose level and schedule. Arm I is applicable only to sites in Israel, New Zealand, and Australia. Arm K is applicable only to sites in mainland China.

Arm I (n= up to 20) will enroll participants with advanced/metastatic solid tumors. Participants will receive MK-1308A on a Q6W schedule starting on Cycle 1, Day 1 for up to 18 cycles (~ 24 months).

Arm K (n= up to 20) will enroll participants who reside in China with advanced solid tumors. On Cycle 1, Day 1 and for all subsequent cycles, participants will receive MK-1308A on a Q6W schedule continuously for up to 18 cycles (up to 24 months).

Data from Arm K will be used to demonstrate acceptable safety and PK of MK-1308A in Chinese participants and will inform the use of MK-1308A in China in future studies,

independent of tumor type. Chinese participants who reside in China will only enroll in Arm K.

MK-1308A may be considered as tolerant if one or less participant of the first 3 experience a DLT, or if 2 or less participants of the first 6 experience a DLT (1/3 or ≤ 2/6) for each sub-cohort (Table 1).

Table 1 Toxicity Assessment

Number of Toxicities	Number of Participants Treated at Current Dose	
	n=3	n=6
0	S	S
1	S	S
2	DU	S
3	DU	DU
4		DU
5		DU
6		DU
S=stay at the same dose; DU=De-escalate; the current dose is unacceptable. Modified mTPI table based on target DLT rate of 30% and equivalent DLT interval of (0.25, 0.33).		

Treatment Allocation

Treatment allocation for dose escalation, dose confirmation, and coformulation Arms I and K will be accomplished by non-random assignment. During the dose confirmation phase when more than 1 treatment arm is open for enrollment of NSCLC participants, IVRS/IWRS will distribute successive participants across all open treatment arms in each phase to minimize selection bias. Each new arm (if applicable) will open for enrollment without delay once the DLT observation period of the previous dose cohort is completed and a dose escalation or cohort expansion decision is made. In the efficacy expansion phase, randomization by IVRS/IWRS will be implemented with equal randomization ratio whenever at least two of the Arms F and G are open for enrollment. (Note: this is a true randomization which is different from the assignment methodology in dose confirmation).

ORR as assessed by the investigator is a secondary objective in the dose escalation phase, dose confirmation phase, and coformulation phase (Arms I and K). The progression-free survival according to RECIST v1.1, as well as overall survival, will be evaluated as exploratory endpoints. In the efficacy expansion and coformulation phases, ORR and PFS will also be assessed by iRECIST.

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 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 the tumor

assessment is repeated 4 to 8 weeks later in order to confirm progressive disease by iRECIST per site assessment.

Adverse events will be evaluated by the investigator, according to criteria outlined in the NCI CTCAE, Version 4.03, to establish the safety and tolerability of MK-1308 when administered as monotherapy, in combination with pembrolizumab, or in coformulation as per the primary objective of this study.

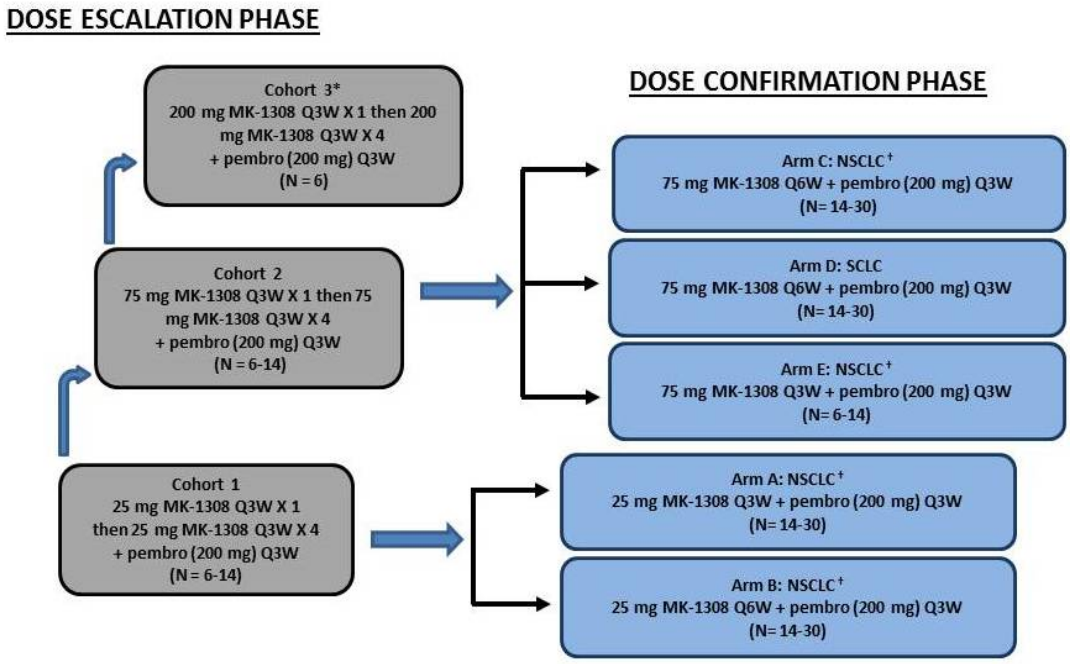
There will be no intra-participant dose escalation for participants enrolled in this study. The Sponsor will evaluate DLTs when at least 10 subjects have completed the DLT period to confirm the safety of Arm I. Enrollment will not be paused while this evaluation is performed. The definition of DLTs and criteria for dose modification of MK-1308 are outlined in Section 7.1.1 and Section 7.2.1.

Participants may receive study treatment after initiation of combination treatment with MK-1308 plus pembrolizumab for up to 18 cycles (Q6W) or 35 cycles (Q3W), for a total of 24 months. 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 trial treatment or procedure requirements, participant completes treatment, or administrative reasons requiring cessation of treatment, at which point they will be discontinued from the study.

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

5.1.5 Trial Diagram

Figure 1 Trial Design for Dose Escalation and Dose Confirmation



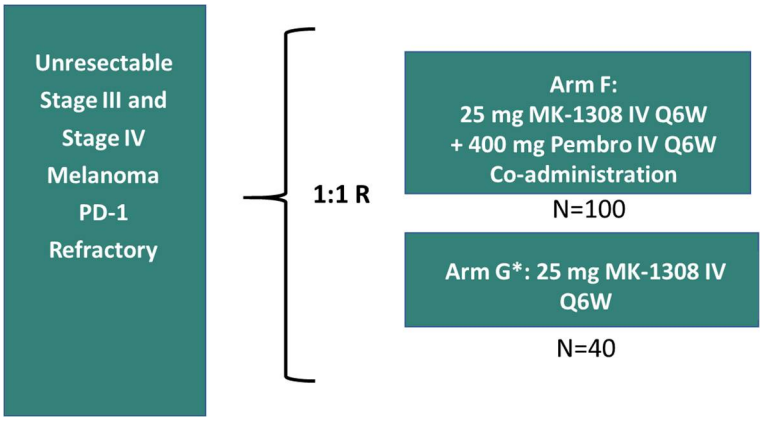
In the dose escalation phase: dosing of pembrolizumab begins at Cycle 2 Day 1 following the monotherapy lead-in dose with MK-1308.

In the dose confirmation phase: dosing of pembrolizumab begins at Cycle 1 Day 1.

* A dose level of MK-1308 between 75 mg and 200 mg may be selected based on the totality of data.

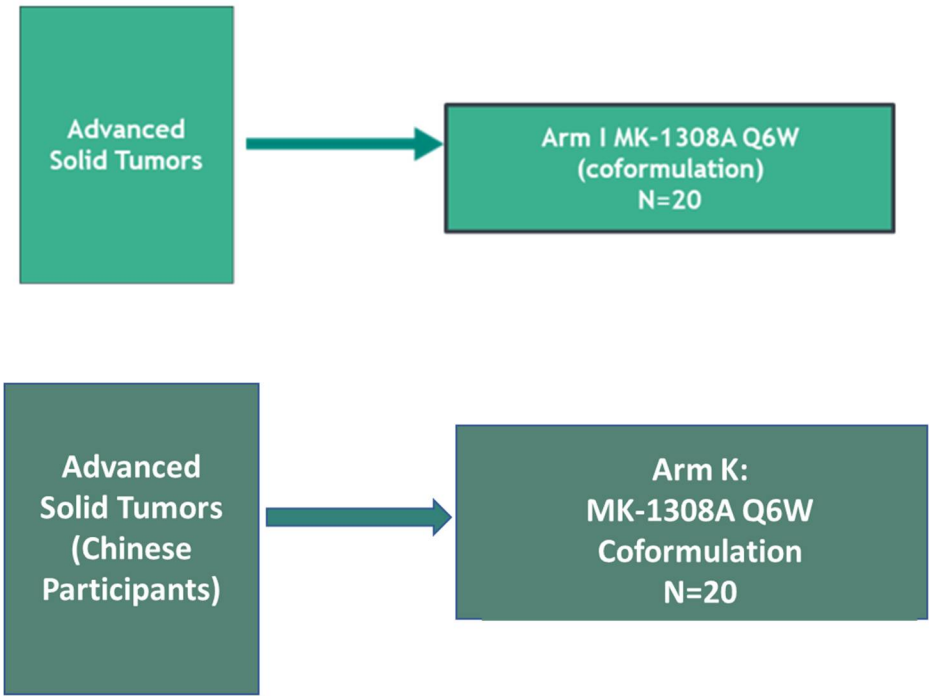
† An interim efficacy analysis will be performed after the first 8 or 14 participants. If there are 0 responses (CR, PR) in the first 8 evaluable participants, or if there is ≤1 response (CR, PR) in the first 14 evaluable participants, enrollment of the arm may be stopped early (if the enrollment is not yet complete). A decision will be made at the Sponsor's discretion whether the remaining sample size originally planned for the arm may be allocated to one or more arms in dose confirmation phase if the enrollments are open.

Figure 2 Trial Design for Efficacy Expansion Phase (Arm F and G)



*If participants have PD, they may cross over to Arm F, depending on the rules outlined in Section 5.1.

Figure 3 Trial Designs for Coformulation Arms I and K



5.2 Number of Participants

This study is expected to enroll approximately 348 participants.

5.3 Beginning and End of Study Definition

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent. The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

5.3.1 Clinical Criteria for Early Trial Termination

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

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

Ample notification will be provided in the event of decision to no longer supply MK-1308 or pembrolizumab.

5.4 Scientific Rationale for Study Design

5.4.1 Rationale for Endpoints

5.4.1.1 Efficacy Endpoints

For the efficacy expansion (Arms F and G) phase, ORR assessed by BICR based on RECIST 1.1 is the primary efficacy endpoint. The DOR based on RECIST 1.1 as assessed by BICR is a secondary efficacy endpoint for Arms F and G. The ORR assessed by investigator based on RECIST 1.1 is a secondary efficacy endpoint for the rest of the study. Exploratory endpoints include PFS and OS. In addition, ORR and PFS based on irRECIST (in the dose escalation phase and the dose confirmation phase) and iRECIST (in the efficacy expansion and coformulation phases) are exploratory endpoints.

Tumor responses are evaluated using RECIST 1.1, adjusted to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ followed by irRECIST or iRECIST. Response confirmation per RECIST 1.1 is required.

The irRECIST accounts for the unique tumor response characteristics seen with immunotherapeutic agents. Immunotherapeutic agents such as MK-1308 and pembrolizumab may produce anti-tumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard RECIST may, thus, not provide an accurate response assessment of immunotherapeutic agents. These findings support the need to apply a modification to RECIST that takes into account the unique patterns of atypical response in immunotherapy and enables treatment beyond initial radiographic progression. irRECIST will be used by BICR and investigators to assess tumor response and progression and make treatment decisions in the dose escalation phase and the dose confirmation phase.

iRECIST assessment has been developed and published by the RECIST Working Group, with input from leading experts from industry and academia, along with participation from the US Food and Drug Administration and the European Medicines Agency [Seymour, L., et al 2017]. The unidimensional measurement of target lesions, qualitative assessment of non-target lesions, and response categories are identical to RECIST 1.1, until progression is seen by RECIST 1.1. However, if a participant is clinically stable, additional imaging may be performed to confirm radiographic progression. For the efficacy expansion phase, iRECIST will be used by investigators to assess tumor response and progression and make treatment decisions, as per current health authority guidance.

5.4.1.2 Safety Endpoints

The primary safety objectives of this trial include characterizing the safety and tolerability of MK-1308 when used in combination with and in coformulation with pembrolizumab in participants with advanced solid tumors. The primary safety analyses will be based on participants who experience toxicities as defined by CTCAE, Version 4.03.

The attribution to drug, time-of-onset, duration of the event, its resolution, and any concomitant medications administered will be recorded. Safety data will include, but is not

limited to, AEs, SAEs, fatal AEs, and laboratory changes. Furthermore, specific events will be collected and designated as events of clinical interest (ECIs) as described in Section 9.3.7.

5.4.1.3 Pharmacokinetic Endpoints

A secondary objective of this trial is to characterize the PK profile of MK-1308 and pembrolizumab. The serum concentrations of each antibody will be used to determine PK parameters (eg, C_{max}, AUC) for MK-1308 and pembrolizumab. Furthermore, the results of these analyses will be used in conjunction with pharmacodynamics, safety, and ADA endpoints to help assess dosing strategies for MK-1308.

5.4.1.4 Pharmacodynamic Endpoints

A direct receptor occupancy assay to measure target engagement cannot be used as CTLA4 expression on the cell surface of T-cells is transient and tightly regulated. Therefore, post-treatment changes in absolute leukocyte counts (ALC) and expression of T-cell activation markers (for example Ki67, ICOS, and HLA-DR) will be assessed in peripheral blood based on the proposed effect of CTLA4 blockade in the immune priming phase to increase activation and proliferation of T-cells.

5.4.1.4.1 Anti-Drug Antibody Assessment

Formation of ADAs can potentially confound drug exposures at therapeutic doses, and prime for subsequent infusion-related toxicity. Anti-drug antibody response at the beginning of each cycle will be determined to understand drug metabolism, exposure, and safety. Anti-drug antibody response to MK-1308 and pembrolizumab will be evaluated in validated immunogenicity assays.

5.4.1.4.2 Exploratory Sample for T-cell Response

A whole blood sample will be collected at the end of treatment to perform an exploratory analysis to assess reactivity of T-cells to MK-1308 and pembrolizumab sequences. The procedure for collecting and shipping the blood to MSD will be provided in the Procedures Manual. This will not be performed for Arm K.

5.4.1.4.3 Serum for Cytokine Testing

Because treatment with MK-1308 can result in immune stimulation and resulting potential for cytokine release, serum cytokines may be monitored as needed to provide supplementary information to assist in the evaluation of any safety events. This will not be performed for Arm K.

5.4.1.5 Planned Exploratory Biomarker Research

(This is not applicable for Arm K.)

Cancer immunotherapies represent an important and novel class of anti-tumor agents. The mechanism of action of these exciting new therapies is, however, not completely understood and much remains to be learned regarding how best to leverage these new drugs to treat patients. To aid future patients, it is important to investigate the determinants of response or

resistance to cancer immunotherapy, as well as determinants of AEs in the course of our clinical trials. These efforts will identify novel predictive/ pharmacodynamic biomarkers and generate information that will better guide single agent and combination therapy with immuno-oncology drugs. To identify novel biomarkers, this study will collect biospecimens (blood components, tumor material, etc.) to support analyses of cellular components (eg, protein, DNA, RNA, metabolites) and other circulating molecules. Investigations may include but are not limited to:

- 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 (mutations, methylation status, microsatellite instability [MSI], etc.). 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. Genome-wide approaches may be used for this effort. Note that in order to understand tumor-specific mutations, it is necessary to compare the tumor genome with the germline genome. Microsatellite instability may also be evaluated as this is an important biomarker for some cancers (ie, colorectal cancer). Circulating tumor DNA and/or RNA may also be evaluated from blood samples.
- Germline (blood) genetic analyses (eg, Single Nucleotide Polymorphism (SNP) analyses, whole exome sequencing, whole genome sequencing): This research will 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 DNA variation across the genome in order to interpret tumor-specific DNA mutations. In addition to studying variation across the human genome, gene variants of CTLA4 may be investigated for SNP analysis and correlation with various endpoints. Finally, MSI may be evaluated as this is an important biomarker for some cancers (ie, colorectal cancer).
- Tumor and blood RNA analyses: Both genome-wide and targeted messenger RNA (mRNA) expression profiling and sequencing in tumor tissue and in blood may be performed to define gene signatures that correlate with clinical response to treatment with MK-1308, pembrolizumab, or other immunotherapies. Immunotherapies induce a response in tumors that likely reflects an inflamed/immune phenotype. Specific immune-related gene sets (such as those capturing interferon-gamma transcriptional pathways) may be evaluated and new signatures may be identified. Individual genes related to the immune system may also be evaluated (eg, IL-10). MicroRNA profiling may also be pursued as well as exosomal profiling.
- Proteomics, metabolomics and 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) device has been developed for use with pembrolizumab in NSCLC. Preliminary data indicate that

this association may also be true in additional cancer types (ie, triple-negative breast cancer, head and neck cancer, and gastric cancer). Additional tumor or blood-derived proteins may also correlate with response to pembrolizumab. Tumor tissue may, therefore, be subjected to proteomic analyses using a variety of platforms that could include but are not limited to immunoassays and liquid chromatography/mass spectrometry. This approach could identify novel protein biomarkers that could aid in patient selection for pembrolizumab therapy.

- Blood for immunophenotyping: Real-time biomarker analysis of Ki67, HLA-DR immune activation markers on CD4/CD8 T-cells will be performed to aid RPTD analysis. Analysis of peripheral blood for mononuclear cells will employ higher dimensional cytometry panel(s) for more in-depth analysis of additional activation markers. The procedure for collecting and shipping the blood to MSD will be provided in the Procedures Manual.
- Other blood-derived biomarkers: In addition to expression on tumor tissue, PD-L1 and other tumor-derived proteins RNA and/or DNA can be shed from tumors and released into the blood. Assays such as enzyme-linked immunoassay that measure proteins, those assessing circulating tumor DNA, RNA and/or exosomes may also be evaluated from blood samples. Correlation of these biomarkers 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 biomarkers. This research would serve to develop such assays for future clinical use.

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

- Recent research suggests that the diversity of bacteria in the GI tract (microbiome) might be associated with response to checkpoint inhibition therapy and development of irAEs [Vetizou, M., et al 2015] [Carbonnel, F., et al 2017] [Lynch, S. V. 2016] [Dubin, K., et al 2016]. For example, members of Bacteroides phylum may be protective against drug-induced colitis. To evaluate the potential for such association in this study, stool will be collected during the Dose Escalation and Dose Confirmation phases and the diversity and strains of bacteria comprising the gut microbiome may be evaluated in the context of irAEs, clinical response to MK-1308, and changes to the diversity of the microbiome that result from the study treatment.

Planned Genetic Analysis

Genetic variation may impact a participant's response to therapy, susceptibility to and severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a sample will be collected for DNA analysis from consenting participants.

DNA samples will be used for research related to the study treatment(s), the disease under study, and related diseases. They may also be used to develop tests/assays including diagnostic tests related to the disease under study, related diseases, and study drug(s).

Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome [or analysis of the entire genome] (as appropriate).

DNA samples will be analyzed for variation across the entire genome. Analyses may be conducted if it is hypothesized that they may help further the understanding of the clinical data.

The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to understand study disease or related conditions.

In addition to studying variation across the human genome, HLA will specifically be investigated for MK-1308 in combination with pembrolizumab and other treatments.

5.4.1.6 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 Future Biomedical Research are presented in Appendix 6 – Collection and Management of Specimens for Future Biomedical Research.

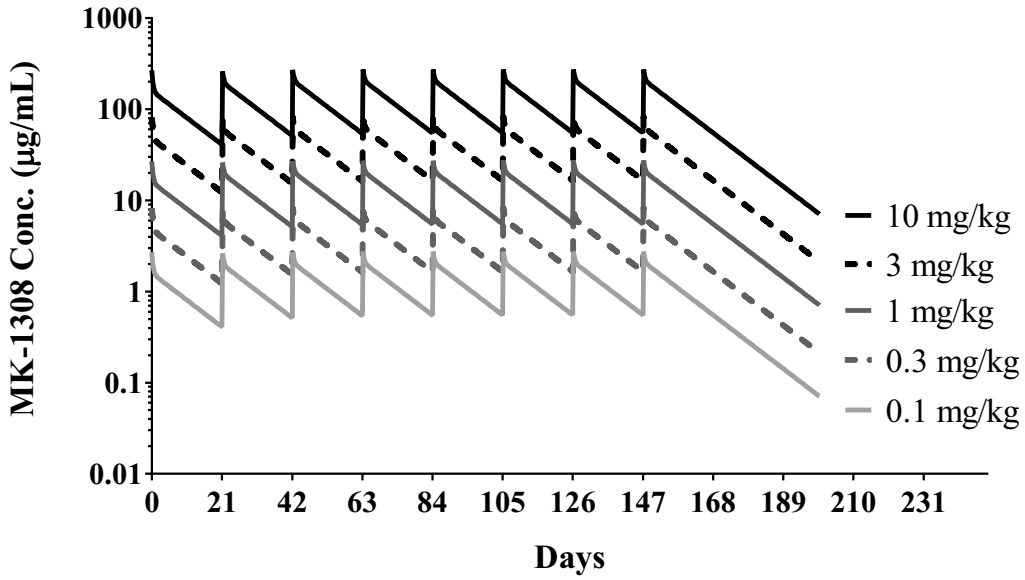
5.5 Justification for Dose

5.5.1 Starting Dose for This Trial

The first-in-human dose projection for MK-1308 was developed using an integrated approach based on the experimental no-observed-adverse-effect-level (NOAEL) from nonclinical Good Laboratory Practice (GLP) safety studies in cynomolgus monkeys (a relevant species), data obtained from various in vitro experiments, PK studies in cynomolgus monkeys (a relevant species), and using recent FDA guidelines for antibody-based immunotherapies [Saber, H., et al 2016]. Data and sources used for the comparison and analyses include: (1) the protein sequence of human and cynomolgus monkey CTLA4; (2) mRNA expression profiles in human and cynomolgus monkey; (3) the binding affinity of MK-1308 to human and cynomolgus monkey CTLA4; (4) the in vitro bioactivity of MK-1308 in human and cynomolgus monkey CTLA4; (5) the in vitro evaluation of cytokine release; (6) PK (exposure) in cynomolgus monkeys following administration of MK-1308; and (7) the results from the nonclinical safety studies in cynomolgus monkeys. MK-1308 was also found to be comparable to ipilimumab in biochemical and cellular assays, as detailed in Section 3.2, and had similar PK to ipilimumab in cynomolgus monkeys.

Predicted human MK-1308 exposure following administration of doses ranging from 0.1 to 10 mg/kg Q3W are shown in Figure 4. It is anticipated that the maximum concentration at steady-state ($C_{max, ss}$) following administration of the 0.3 mg/kg Q3W will not exceed ~8 µg/mL. This predicted steady-state concentration should provide an approximately 15-fold safety margin relative to the observed $C_{max, ss}$ of ~120 µg/mL at NOAEL (3 mg/kg MK-1308, Q1W) (Table 2). Additionally, based on the AUCτ,ss, the anticipated steady-state MK-1308 exposure at the FIH dose should provide an approximately 6-fold safety margin to the observed $AUC_{0\text{-}168h}$ (approximately equivalent to AUCτ,ss) in cynomolgus monkey at the NOAEL (Table 2).

Figure 4 Predicted Serum Concentration-time Profiles of MK-1308 in the Proposed Clinical Study at Doses of 0.3 mg/kg to 10 mg/kg MK 1308 When Administered by Intravenous Infusion Once Every 21 Days



Conc. = concentration

Table 2 Predicted Pharmacokinetic Parameters in Humans and the Relative Fold Differences at the NOAEL in Cynomolgus Monkeys

PK parameter	Units	Human (0.3 mg/kg; Q3W)	Cynomolgus monkey NOAEL (3 mg/kg Q1W)	Fold increase of human predictions over NOAEL in cynomolgus monkeys
$C_{max,ss}$	µg/mL	8.4	124	14.8
$C_{min,ss}$	µg/mL	1.75	39.4	22.5
$AUC_{\tau,ss}$	µg/mL×h	1800	10,200	5.67[1]

$AUC_{\tau,ss}$ = area under the curve at steady-state; $C_{max,ss}$ = maximum concentration at stead state; $C_{min,ss}$ = minimum concentration at stead state; NOAEL = no-observed-adverse-effect-level; PK = pharmacokinetic(s); Q1W = every week; Q3W = every 3 weeks

1. The fold increase in $AUC_{\tau,ss}$ was calculated as $AUC_{\tau,ss}$ (cynomolgus monkey, at NOAEL) / $AUC_{\tau,ss}$ (human, at FIH dose).

Furthermore, in the cynomolgus monkey PK study, exploratory biomarker analysis revealed no impact on T-cell markers for MK-1308 serum concentrations ≤ 10 µg/mL with a single IV bolus dose of 0.5 mg/kg MK-1308.

In vitro activity assays performed using human and cynomolgus monkey cell-based assay systems revealed no apparent potency differences for MK-1308. Also, no signal was observed in the cytokine release assay for MK-1308 concentrations up to 1000 µg/mL.

In an exposure-response model of the safety of ipilimumab monotherapy in melanoma participants, the model-predicted probability of experiencing a Grade 2 or more immune-related adverse events (irAEs) at the median $C_{min,ss}$ (5th, 95th percentiles) for the 0.3 mg/kg treatment group was approximately 9.8% (5.6, 14), and the corresponding probability of experiencing a Grade 3 or more irAE was approximately 3.3% (1.8, 4.9) [Feng, Y., et al 2014].

Based on these assessments, the FIH starting dose of 0.3 mg/kg MK-1308 is proposed. This dose is equivalent to a fixed dose of 25.5 mg MK-1308 for an 85-kg participant. Based on these assumptions the proposed clinical trial dose will start at 25 mg.

A fixed-dose regimen is chosen to be used in this study because it is expected to simplify the dosing regimen and potentially reduce dosing errors, as well as be more convenient for physicians. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities as well as reducing waste.

Given the similarity between ipilimumab and MK-1308, a published ipilimumab population PK model was used to identify a fixed-dose equivalent to 0.3 mg/kg MK-1308. The distribution of exposures from the 25 mg fixed-dose was predicted to considerably overlap those obtained with the 0.3 mg/kg dose. This comparison also demonstrated that the 25 mg fixed-dose regimen provided no substantive differences in PK variability (range of the distribution of individual exposures) as seen with weight-based dosing.

Similarly, the population pharmacokinetic model was used to identify that the 75 mg fixed-dose regimen is approximately equivalent to 1 mg/kg MK-1308. The rationale for the maximum dose studied in this trial is described in Section 5.5.2.

5.5.2 Maximum Dose/Exposure for This Trial

The maximum dose of MK-1308 will be determined based on the DLT rate during the dose escalation phase and data from the ongoing MK-1308 trial.

5.5.3 Rationale for Dose Interval and Trial Design

5.5.3.1 MK-1308 (Dose Escalation, Dose Confirmation, and Coformulation)

MK-1308 is being developed for the treatment of solid tumors. This is the first-in-human trial of MK-1308 and it is designed to assess the safety, tolerability, PK, and pharmacodynamics of escalating doses of MK-1308 when used in combination with pembrolizumab in participants with advanced/ metastatic solid tumors that have been refractory to conventional therapy, in first-line, treatment-naïve NSCLC, and in second-line SCLC. The effect of MK-1308 on tumor size will also be explored. First-line NSCLC participants are included in

this study in the dose confirmation phase based on the known excellent response rates and the US FDA approval of pembrolizumab monotherapy in participants with untreated NSCLC in the PD-L1 high population. This study will include participants with any PD-L1 tumor score based on the results of the Phase 1 CheckMate-012 study suggesting that participants with any tumor PD-L1 score may benefit from combination treatment with ipilimumab and nivolumab [Hellmann, M. D., et al 2016]. Second-line SCLC participants are included in this study in the dose confirmation phase based on the improved response rates observed in the Phase 1 CheckMate-032 study [Antonia, S. J., et al 2016], prompting the initiation of Phase 3 studies for nivolumab and nivolumab plus ipilimumab as maintenance therapy after first-line chemotherapy (CheckMate 451), and for nivolumab versus chemotherapy as second-line therapy (CheckMate 331) in SCLC.

It is reasonable to expect MK-1308 to be consistent with that of other humanized mAbs that typically have a low clearance and a limited volume of distribution. Using a population PK model of ipilimumab, distribution of exposures from the 25 mg MK-1308 fixed-dose considerably overlap that obtained with the 0.3 mg/kg weight-based ipilimumab dose and exposures from the 75 mg MK-1308 fixed-dose considerably overlap those obtained with the 1.0 mg/kg weight-based ipilimumab dose [Feng, Y., et al 2014]. Similar to pembrolizumab, a fixed-dose regimen of MK-1308 is expected to reduce complexity in the logistical chain at treatment facilities and reduce waste. The goal in introducing the lower doses of 25 mg MK-1308 at the schedule of either Q3W or Q6W is to determine if a similar response rate can be achieved at lower doses, which would be expected to result in a reduction in immune-related toxicities. The goal in evaluating the 75 mg MK-1308 dose at the Q6W interval is to achieve the expected response rates with similar acceptable toxicity and discontinuation rates based on the Phase 1 CheckMate-012 results in the NSCLC population [Hellmann, M. D., et al 2016].

Details regarding specific benefits and risks for participants participating in this clinical trial may be found in the IB and informed consent documents.

MK-1308 (Efficacy Expansion Phase)

Participants with advanced melanoma that is refractory to PD-1/L1 are included in this study in the efficacy expansion phase based on the following evidence: 1) improved response rates after ipilimumab/nivolumab compared with ipilimumab monotherapy in treatment-naïve advanced melanoma in the CheckMate 067 study; 2) improved response rates after treatment with ipilimumab/pembrolizumab (Keynote-029); and 3) the results from an MSD -single institution collaborative study in a similar melanoma population [Wolchok, J. D., et al 2017] [Long, G. V., et al 2017] [Olsonm, D., et al 2018]. An interim analysis of MK-1308 safety, anti-tumor activity, PK and pharmacodynamic biomarker data was performed for the dose escalation and dose confirmation phases of the study based on an 07-NOV-2018 database lock. The ORR by BICR with confirmation of MK-1308 25 mg administered every 6 weeks in the advanced 1L NSCLC population (Arm B) was similar to the ORR at the 75-mg dose level given every 6 weeks (33% versus 22%) at this data cutoff date. The target dose-limiting toxicity rate was not reached in any of the Cohorts 1, 2, or 3; however, a higher toxicity rate correlated with a higher MK-1308 dose among several different AE characteristics including drug-related AEs, Grade 3-5 AEs, serious AE (SAE), and AEs leading to treatment discontinuation or modification. The Grade 3-5 AE rate was 29% in Cohort 1, 71% in Cohort 2, and 100% in Cohort 3. In the dose confirmation phase, a lower MK-1308 dose and

a longer treatment interval had a more favorable toxicity profile (45% in Arm B, 48% in Arm A, 53% in Arm C and 86% in Arm E). Time to first Grade 3-5 AE was more rapid at a higher MK-1308 dose and with more frequent dosing (7 months in Arm B, 5.2 months in Arm A, 5.6 months in Arm C and 1.1 month in Arm E). The most common AEs were fatigue (24.9%), pruritus (24.4%), rash (23.5%), decreased appetite (22.5%), AST increased (19.2%), ALT increased (17.4%), diarrhea (16.4%), and hypothyroidism (16%). In totality, the efficacy, safety, and PK data indicated that a dose of 25 mg given every 6 weeks was most tolerable.

MK-1308A (Coformulation Phase)

The dose composition and schedule of MK-1308A is 25 mg/400 mg (MK-1308/pembrolizumab) to be administered every 6 weeks. This formulation and dosing regimen were chosen after data analyses of 215 participants in the dose escalation and dose confirmation phases of the study who were given varying dose levels of MK-1308 (25, 75, and 200 mg every 3 or 6 weeks) and a fixed dose of MK-3475 (200 mg every 3 weeks). Evaluation of the safety, tolerability, PK, pharmacodynamics, and efficacy analysis of this part of the study showed that 25 mg MK-1308 every 6 weeks in combination with MK-3475 every 3 weeks was equally efficacious but safer than the 75 mg and 200 mg MK-1308 dose levels. MK-1308A is being evaluated in this study in advanced solid tumors.

5.5.3.2 Pembrolizumab (MK-3475)

The planned dose of pembrolizumab for this trial is 200 mg every 3 weeks (Q3W) followed by 400 mg Q6W. The current approved dosing regimens of pembrolizumab for IV administration are 200 mg Q3W and 400 mg Q6W for adults.

200 mg Q3W

Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is an appropriate dose of pembrolizumab for adults across all indications. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies in melanoma and NSCLC indications demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg Q2W representing an approximate 5- to 7.5-fold exposure range (refer to IB, Section 5.2.2)
- Population PK analysis showing that both fixed dosing and weight-based dosing provides similar control of PK variability with considerable overlap in the distributions of exposures, supporting suitability of 200 mg Q3W
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications
- Pharmacology data showing full target saturation in both systemic circulation (inferred from PK data) and tumor (inferred from PBPK analysis) at 200 mg Q3W

400 mg Q6W

A 400 mg Q6W dosing regimen of pembrolizumab is expected to have a similar benefit-risk profile as 200 mg Q3W, in all treatment settings where 200 mg Q3W pembrolizumab is currently approved [Lala, M., et al 2020]. Specifically, the dosing regimen of 400 mg Q6W for pembrolizumab is considered adequate based on modeling and simulation analyses, given the following rationale:

- PK simulations demonstrating that in terms of pembrolizumab exposures:
  - Average concentration over the dosing interval (C_{avg}) [or area under the curve (AUC)] at 400 mg Q6W are similar to the approved 200 mg Q3W dose, thus bridging efficacy between dosing regimens.
  - Trough concentrations (C_{min}) at 400 mg Q6W are generally within the range of those achieved with 2 mg/kg or 200 mg Q3W, in majority (>99%) of participants.
  - Peak concentrations (C_{max}) at 400 mg Q6W are well below the C_{max} for the highest clinically tested dose of 10 mg/kg Q2W, supporting that the safety profile for 400 mg Q6W should be comparable to the established safety profile of pembrolizumab.
- Exposure-Response for pembrolizumab has been shown to be flat across indications, and OS predictions in melanoma and NSCLC show that efficacy at 400 mg Q6W is expected to be similar to 200 mg or 2 mg/kg Q3W, given the similar exposures; thus 400 mg Q6W is expected to be efficacious across indications.

6. Study Population

Male and female participants with advanced or metastatic solid tumors who are at least 18 years of age on the day of signing consent will be enrolled in this trial.

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

6.1 Inclusion Criteria

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

Type of Participant and Disease Characteristics
Male and female participants who are at least 18 years of age on the day of signing consent will be enrolled.

1. For **Dose Escalation Phase**: Have any histologically- or cytologically-confirmed advanced/metastatic solid tumor (except NSCLC for Cohorts 2 and 3) by pathology report and have received, been intolerant to, been ineligible for or refused all treatment known to confer clinical benefit.
2. For **Dose Confirmation Phase**, **Arms A, B, C, and E**: Have newly diagnosed histologically or cytologically-confirmed Stage IIIB/Stage IV NSCLC:

   The participant must not have received prior systemic treatment for advanced NSCLC or must have received previous neoadjuvant and adjuvant chemotherapies ≥6 months before dosing of study drug if prior systemic treatment was given for early-stage

disease. Diagnosis must be stated in a pathology report and pathologically confirmed at the study site by the investigator.

Note: Site must confirm that EGFR and ALK directed therapy is not indicated as primary therapy (document absence of tumor activating (sensitizing) EGFR mutations AND absence of ALK gene rearrangements).

If participant's tumor is known to have a predominantly squamous histology, molecular testing for EGFR mutation and ALK translocations is not required, as this is not part of current diagnostic guidelines.

3. For **Dose Confirmation Phase, Arm D:** Have histologically- or cytologically-confirmed metastatic (Stage III/IV) SCLC with progressive disease after at least one platinum-based chemotherapy regimen. Participants with platinum-sensitive (relapse ≥90 days after chemotherapy) or platinum-resistant (relapse <90 days after or during chemotherapy) disease are eligible. Diagnosis must be stated in a pathology report and pathologically confirmed at study site by the investigator.
4. Have measurable disease by RECIST 1.1 as assessed by the local site investigator/radiology. Target lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
5. Have a performance status of 0 or 1 on the Eastern Cooperative Oncology Group Performance Scale.
6. Demonstrate adequate organ function as defined by the following table (Table 3). All screening labs should be performed within the screening period.

Table 3 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count	>1,500/mcL
Platelets [a]	>100,000/mcL
Hemoglobin [a]	≥9 g/dL or ≥5.6 mmol/L without a red blood cell transfusion within 2 weeks of randomization
Renal	
Serum Creatinine or CrCl (measured or calculated [b]) or GFR in place of CrCl	≤1.5 X ULN or ≥30 mL/min for participant with creatinine levels >1.5 X ULN
Hepatic [c]	
Total bilirubin (serum)	≤1.5 X ULN or Direct bilirubin ≤ 1.5 X ULN for participants with total bilirubin levels >1.5 X ULN If there is no institutional ULN, then direct bilirubin must be <40% of total bilirubin to be eligible. Note: In no case can the total bilirubin exceed 3 x ULN.
AST (SGOT) and ALT (SGPT)	≤2.5 X ULN or ≤5 X ULN for participants with liver metastases

System	Laboratory Value
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5 X ULN unless participant is receiving anticoagulant therapy
Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants

Note: This table includes eligibility-defining laboratory value requirements for treatment. All screening lab tests must be reviewed by the Investigator or qualified designee and be acceptable prior to randomization.

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

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

[b] Creatinine clearance (CrCl) should be calculated per institutional standard. If no local guideline is available,creatinine clearance should be calculated using the Cockcroft-Gault Method: CrCl = [(140-age) * weight (kg) * (0.85 for females only)] / (72 * serum creatinine)

[c] An exception to this criteria is Gilbert's Syndrome

7. A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP
  OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year) or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5 during the intervention period and for at least 120 days after the last dose of pembrolizumab or MK-1308A, whichever comes last. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention.
    - A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 24 hours for urine and within 72 hours for serum before the first dose of study intervention.
    - If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
- Additional requirements for pregnancy testing during and after study intervention are in Section 9.5.5.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.
- Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

8. Female participants of childbearing potential must be willing to use an adequate method of contraception, as outlined in Appendix 5 – Contraceptive Guidelines, for the course of the study through 120 days after the last dose of study medication.
   Note: Abstinence is acceptable if this is the usual lifestyle preferred contraception for the participant.
9. Male participants with a female partner(s) of childbearing potential must agree to use an adequate method of contraception as outlined in Appendix 5 – Contraception during the treatment period plus an additional 120 days after the last dose of study treatment and refrain from donating sperm during this period.
   Note: Abstinence is acceptable if this is the usual lifestyle preferred contraception for the participant.
10. Has voluntarily agreed to participate by giving documented informed consent for the trial. The participant may also provide consent/assent for Future Biomedical Research. However, the participant may participate in the main trial without participating in Future Biomedical Research.
11. Must submit an evaluable baseline tumor sample for analysis (either a recent or archival tumor sample). Formalin-fixed, paraffin embedded tissue blocks are preferred to slides. If submitting unstained cut slides, freshly cut slides should be submitted to the testing laboratory within 14 days from when the slides are cut (Details pertaining to tumor tissue submission can be found in the Procedures Manual).
12. **For Efficacy Expansion Phase Arms F and G (Applicable countries only):**
    a. Have histologically/cytologically-confirmed unresectable Stage III or Stage IV melanoma per American Joint Committee on Cancer (AJCC) staging system version 8, not amenable to local therapy.
    b. Have at least 1 measurable lesion by CT or MRI per RECIST 1.1 by BICR. Cutaneous lesions and other superficial lesions are not considered measurable lesions for the purposes of this protocol but may be considered as non-target lesions.

       Note: Lesions that are in an area that has been previously irradiated should not be considered measurable unless there has been documented growth of the lesions since the completion of radiation.
    c. Participants with unresectable Stage III or IV disease must have progressed on-treatment with an anti-PD-1/L1 monoclonal antibody (mAb) administered either as monotherapy, or in combination with other checkpoint inhibitors or other therapies (combinations with anti-CTLA-4 agents will not be allowed).

       PD-1 treatment progression is defined by meeting all of the following criteria:

       1. Has received at least 2 doses of anti-PD-1/L1 mAb.
       2. Has demonstrated disease progression after PD-1/L1 as defined by RECIST v1.1.

3. The initial evidence of disease progression is to be confirmed by a second assessment ≥4 weeks from the date of the first documented PD, in the absence of rapid clinical progression [Seymour, L., et al 2017].
    - Note: Progressive disease is confirmed according to iRECIST.
4. Progressive disease must have been documented within 12 weeks from the last dose of anti-PD-1/L1 mAb.
5. Participants who have received targeted therapies as 1L treatment then progressed on anti-PD-1/ PD-L1 may enroll in this study.
6. Participants who have received prior neoadjuvant or adjuvant treatment may enroll in this study.
7. Early treatment discontinuation (prior to first response evaluation) on initial anti-PD-1/L1 therapy due to treatment intolerance will not be considered PD-1/PD-L1 refractory.

d. Participants who receive anti-PD-1 therapy as adjuvant treatment following complete resection of Stage III or Stage IV melanoma (Stage II may be eligible with Sponsor consultation) and have disease recurrence (unresectable loco-regional disease or distant metastases) while on active treatment or within 6 months of stopping anti-PD-1 are eligible. For these participants, the following applies: 1) a second assessment to confirm disease progression beyond recurrence is not required (eg, iRECIST is not required); 2) they must have received at least 2 prior doses of anti-PD-1/ PD-L1 mAb.

e. Have submitted pre-trial imaging: The site's study team must have reviewed pre-trial images that are of diagnostic quality from at least 3 scans (only the first 2 scans are needed for the recurrent adjuvant population and in the setting of rapid clinical progression after consultation with and approval from the Sponsor. The reason for rapid clinical progression must be documented in the participant's study record.) to determine that radiographic progression has occurred per RECIST 1.1 following initiation of an anti-PD-1/ PD-L1 agent (see Section 9.2.1 for further details).

   The visits for the 3 scans are as follows:

   1. First scan = baseline scan before previous anti-PD-1/ PD-L1 treatment was given
   2. Second scan = scan showing progression on prior anti-PD-1/ PD-L1 treatment per RECIST 1.1
   3. Third scan = scan confirming progression (iCPD) on prior anti-PD-1/ PD-L1 treatment per iRECIST

      Note: The second scan indicating PD (for adjuvant participants) and the third scan indicating iCPD (for all other participants) can be used as the baseline scan for the MK-1308 study, after consultation with and approval from the Sponsor. The reason for rapid clinical progression must be documented in the participant's study record.

The site must have received confirmation that the pre-trial images are of acceptable diagnostic quality by central imaging prior to enrollment.

f. BRAF V600 mutation-positive melanoma participants should have received targeted therapy for advanced or metastatic disease (eg, BRAF/MEK inhibitor, alone or in combination) prior to enrolling on this study; however, they are not required to progress on this treatment prior to enrollment. Exceptions may be made only for countries where these inhibitors are not available, after Sponsor consultation.

g. Participants with BRAF V600E mutant melanoma who have NOT received a BRAF inhibitor (either as adjuvant therapy or in the metastatic disease setting) are eligible for the study ONLY if they meet the following criteria:

   1. LDH < local ULN
   2. No clinically significant tumor related symptoms in the judgment of the investigator
   3. Absence of rapidly progressing metastatic melanoma in the judgment of the investigator

h. Approximately 10 participants each from Arms F and G will have 2 mandatory biopsies; one prior to C1D1 and one on-treatment during Cycle 1 (Week 4, ±7 days), as detailed in the Procedure Manual.

13. **For the Coformulation Phase - Arm I (Applicable countries only)**:

   a. Have any histologically- or cytologically-confirmed advanced/metastatic solid tumor by pathology report and have received, been intolerant to, been ineligible for or refused all treatment known to confer clinical benefit.

   b. Must meet all requirements for Inclusion Criteria 4 through 11.

14. **For the Coformulation Phase - Arm K (China only):**

   a. Have any histologically- or cytologically-confirmed advanced/metastatic solid tumor by pathology report and have received, been intolerant to, been ineligible for, or refused all treatment known to confer clinical benefit.

   b. Be a Chinese participant residing in China.

   Note: Chinese participants residing in China are not eligible for any other study arm.

   c. Must meet all requirements for Inclusion Criteria 4 through 10.

6.2 Exclusion Criteria

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

1. For all phases of the study: Has received previous treatment with another agent targeting CTLA4.
2. For the Dose Confirmation Phase: Has received previous treatment with another agent targeting PD-1, PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (eg, OX-40, CD137).

3. Has had chemotherapy, definitive radiation, or biological cancer therapy within 4 weeks (2 weeks for palliative radiation) prior to the first dose of study therapy or has not recovered to CTCAE Grade 1 or better from any AEs that were due to cancer therapeutics administered more than 4 weeks earlier (this includes participants with previous immunomodulatory therapy with residual irAEs).

   Note: Participants receiving ongoing replacement hormone therapy for endocrine irAEs will not be excluded from participation in this study if the associated AE has recovered to CTCAE Grade 1 with replacement hormone therapy prior to the first dose of study therapy.

4. Has received lung radiation therapy of >30 Gy within 6 months before the first dose of study treatment.

   Note: Participants must have recovered from all radiation-related toxicities to Grade 1 or less, not require corticosteroids, and not have had radiation pneumonitis.

   Note: If the participant has received prior lung radiation, the radiated lesion must not be included as a target lesion for RECIST 1.1 measurements or must show signs of progression before study start.

5. Is currently participating and receiving study therapy in a study of an investigational agent or has participated and received study therapy in a study of an investigational agent or has used an investigational device within 28 days of administration of MK-1308.

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

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

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

7. **For Cohorts 1-3 and Arms A through E ONLY**: Has known untreated central nervous system (ie, brain and/or spinal cord) metastases. Has known carcinomatous meningitis.

   Note: Participants with brain metastases may participate only if they satisfy all of the following:

   - Completed treatment (eg, whole brain radiation treatment [WBRT], stereotactic radiosurgery, or equivalent) at least 14 days prior to the first dose of trial treatment,
   - Have no evidence of new or enlarging brain metastases confirmed by post-treatment repeat brain imaging (using the same modality) performed at least 3 weeks after pre-treatment brain imaging, and
   - Are neurologically stable without the need for steroids for at least 7 days before first dose of trial treatment as per local site assessment.

- Participants with small (<1 cm) asymptomatic brain metastases may participate without satisfying the above requirements however they must be followed with regularly scheduled brain MRI scans throughout the study.

8. Has received any prior immunotherapy and was discontinued from that treatment due to a Grade 3 or higher irAE.
9. Previously had a severe hypersensitivity reaction to treatment with a monoclonal antibody or has a known sensitivity to any component of pembrolizumab.
10. Has any active infection requiring therapy.
11. Has a history of interstitial lung disease.
12. Has a history of (noninfectious) pneumonitis that required steroids or current pneumonitis.
13. Has a history of inflammatory bowel disease.
14. 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.

    Note: Participants with asthma or chronic obstructive pulmonary disease that require intermittent use of bronchodilators, inhaled steroids, or local steroid injections are not excluded from the study.
15. Has clinically significant cardiac disease, including unstable angina, acute myocardial infarction within 6 months from Day 1 of study drug administration, or New York Heart Association Class III or IV congestive heart failure. Medically controlled arrhythmia stable on medication is permitted.
16. Has received a live or live attenuated vaccine within 28 days of planned treatment start. Seasonal flu vaccines that do not contain live virus are permitted.
    Refer to Section 7.7 for information on COVID-19 vaccines.
17. Participants with known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies) and/or active hepatitis B or C, and/or positive HBsAg and HBV-DNA. Active hepatitis C is defined by a positive Hep C Ab result and quantitative HCV RNA results greater than the lower limits of detection of the assay.

    Note: Hepatitis B and hepatitis C testing is required at screening as indicated in Section 2 –Schedule of Events.
18. 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.

19. Has known psychiatric or substance abuse disorders that would interfere with the participant's ability to cooperate with the requirements of the trial.
20. Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the study, starting with screening and for up to 120 days following cessation of pembrolizumab or MK-1308A.
21. Has not fully recovered from any effects of major surgery without significant detectable infection. Surgeries that required general anesthesia must be completed at least 2 weeks before first study drug administration. Surgery requiring regional/epidural anesthesia must be completed at least 72 hours before first study drug administration and participants should be recovered.
22. Is taking chronic systemic steroids in doses >10 mg daily of prednisone or equivalent within 7 days prior to the first dose of trial treatment.
23. Has symptomatic pleural effusion (for example cough, dyspnea, pleuritic chest pain). A participant who is clinically stable following treatment for these conditions (including therapeutic thoraco- or paracentesis) is eligible.
24. **For Arm F and G (Efficacy Expansion Phase) and Arm K (Coformulation Phase) ONLY:**
    a. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least 4 weeks before the first dose of study treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases confirmed by repeat imaging, and have not required steroids for at least 14 days before study treatment.

       Note: Participants with asymptomatic, previously untreated brain metastases may not participate.

    b. Has not had resolution of anti-PD-1 antibody-related AEs, including immune-mediated AEs back to Grade ≤1 or baseline (not applicable to Arm K).
    c. Has not discontinued steroid treatment for an irAE for at least 2 weeks prior to the first dose of study drug (not applicable to Arm K).
    d. Has ocular melanoma (not applicable to Arm K).
    e. Has mucosal melanoma (not applicable to Arm K).
25. Has had an allogenic tissue/solid organ transplant.

6.3 Lifestyle Restrictions

6.3.1 Meals and Dietary Restrictions

Participants should maintain a normal diet unless modifications are required to manage AEs such as diarrhea, nausea, or vomiting, detailed in Section 7.7.1.

6.3.2 Caffeine, Alcohol, and Tobacco

There are no restrictions on caffeine, alcohol, and tobacco.

6.3.3 Activity

There are no restrictions on activity.

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized 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

Participants discontinuing within the DLT window due to reasons unrelated to study treatment will not be considered evaluable for DLTs and may be replaced. Participants with a DLT within the DLT window should not be replaced. Participants who receive less than 90% of the total MK-1308 (or pembrolizumab) infusion in Cycle 1 (eg, if the infusion had to be discontinued due to an infusion reaction) and did not experience a DLT may be replaced (not applicable for Arm I). See Section 10.5.1 for description of safety analysis population.

If a participant experiences a DLT, trial treatment should be discontinued. However, if the participant is deriving clinical benefit from the trial treatment, the participant may be allowed to continue after discussion between the Sponsor and the Investigator.

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 4.

Table 4 Study Treatments

Dose Escalation Phase[a]						
Study Treatment Name	**Dosage Formulation**	**Dose Unit Strength**	**Regimen/ Treatment Period**	**Dose Frequency**	**Route of Administration**	**Sourcing**
MK-1308	Solution for infusion	25 mg 100 mg/ 2 mL vial	Escalation/ Day 1 of each cycle × 5 doses.	Q3W	IV infusion	Provided centrally by Sponsor
	Solution for infusion	75 mg 100 mg/ 2 mL vial	Escalation/Day 1 of each cycle × 5 doses.	Q3W		
	Solution for infusion	200 mg 100 mg/ 2 mL vial	Escalation/Day 1 of each cycle × 5 doses.	Q3W		
Pembrolizumab (MK-3475)	Solution for infusion	200 mg 100 mg/ 4 mL vial	Escalation/Day 1 of each cycle starting at Cycle 2[a]	Q3W	IV infusion	
Dose Confirmation Phase[a]						
Study Treatment Name	**Dosage Formulation**	**Dose Unit Strength**	**Regimen/ Treatment Period**	**Dose Frequency**	**Route of Administration**	**Sourcing**
MK-1308	Solution for infusion	25 mg	Confirmation/Arm A- Day 1 of each cycle	Q3W	IV infusion	Provided centrally by Sponsor
		100 mg/ 2 mL vial	Confirmation/ Arm B- Day 1 of every other cycle	Q6W		
	Solution for infusion	75 mg	Confirmation/Arms C and D- Day 1 of every other cycle	Q6W	IV infusion	
		100 mg/ 2 mL vial	Confirmation/Arm E- Day 1 of each cycle	Q3W		
Pembrolizumab (MK-3475)	Solution for infusion	200 mg 100 mg/ 4 mL vial	Confirmation/ Day 1 of each cycle starting at Cycle 1[a]	Q3W	IV infusion	
Efficacy Expansion Phase[b]						
Study Treatment Name	**Dosage Formulation**	**Dose Unit Strength**	**Regimen/ Treatment Period**	**Dose Frequency**	**Route of Administration**	**Sourcing**
MK-1308 + pembro Co-administration admixture	Solution for infusion	25 mg MK-1308 + 400 mg pembro 25 mg / 0.5 mL vial MK-1308 + 100 mg/ 4 mL vial pembro	Efficacy expansion phase/ Arm F- Day 1 of every cycle, Option 1	Q6W	IV infusion	Provided centrally by Sponsor
MK-1308	Solution for infusion	25 mg MK-1308 100 mg/ 2 mL vial or 25 mg/ 0.5 mL vial	Efficacy expansion phase/ Arm G - Day 1 of every other cycle	Q6W	IV infusion	

Coformulation Phase[c]						
Study Treatment Name	**Dosage Formulation**	**Dose Unit Strength**	**Regimen/ Treatment Period**	**Dose Frequency**	**Route of Administration**	**Sourcing**
MK-1308A	Solution for infusion	25 mg MK-1308 + 400 mg pembro	Coformulation Phase (Arms I, K)	Q6W	IV infusion	Provided centrally by Sponsor
		25 mg MK-1308 + 400 mg pembro/ 17.5 mL vial				
Pembrolizumab (MK-3475)[d]	Solution for infusion	200 mg	Coformulation Phase (Arm I)	Q3W	IV infusion	Provided centrally by Sponsor
		400 mg		Q6W		
		100 mg/ 4 mLvial				

IV = intravenous; pembro = pembrolizumab; Q3W = every 3 weeks; Q6W = every 6 weeks.

a For dose escalation and dose confirmation, pembrolizumab will be administered as an IV infusion over 30 minutes. MK-1308 will be administered as an IV infusion over 30 minutes. MK-1308 will be administered 30 minutes after completion of pembrolizumab infusion on the days when pembrolizumab is administered. In the dose escalation phase of the study, pembrolizumab administration will start in Cycle 2 and in the dose confirmation phase pembrolizumab administration will start in Cycle 1. In addition to the dose levels detailed in this table, intermediate doses may also be evaluated in consultation and agreement with the investigators and Sponsor.

b For the efficacy expansion phase, Arm F pembrolizumab and MK-1308 will be co-administered in the same infusion bag over 30 minutes. For Arm G, MK-1308 will be administered alone. Participants in Arm F or G who cross over will receive the doses of MK-1308 and MK-3475 as determined by interim analysis at the time of crossover.

c For the coformulation phase, the solution will be infused over 30 minutes.

d In cases where toxicity is attributed to MK-1308A, participants may be re-initiated with pembrolizumab monotherapy at either 200 mg Q3W or 400 mg Q6W, after communication and agreement with the Sponsor.

All supplies indicated in Table 4 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.

7.1.1 Definition of Dose-limiting Toxicity

All toxicities will be graded using NCI CTCAE Version 4.03 based on the investigator assessment.

The DLT window of observation will encompass the first 2 cycles of treatment for dose escalation and the first 1 cycle for dose confirmation, efficacy expansion, and coformulation (Arm I only).

The occurrence of any of the following toxicities during the DLT window 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 non-hematologic 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 that requires a platelet transfusion
3. Any non-hematologic 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 rash without use of corticosteroids or anti-inflammatory agents per standard of care.
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 Section 9.3.7 for criteria)
5. Febrile neutropenia Grade 3 or Grade 4:
   - Grade 3 is defined as absolute neutrophil count ANC <1000/mm^3 with a single temperature of >38.3° C (101° F) or a sustained temperature of ≥38° C (100.4° F) for more than one hour
   - Grade 4 is defined as ANC <1000/mm^3 with a single temperature of >38.3° C (101° F) or a sustained temperature of ≥38° C (100.4° F) for more than one hour, with life-threatening consequences and urgent intervention indicated.
6. Prolonged delay (>2 weeks) in initiating Cycle 2 or Cycle 3 in Dose Escalation due to treatment-related toxicity; Prolonged delay (>2 weeks) in initiating Cycle 2 in Dose Confirmation due to treatment-related toxicity.
7. Any treatment-related toxicity that causes the participant to discontinue treatment during the DLT observation period.
8. Grade 5 toxicity.

7.2 Dose Modification (Escalation/Titration/Other)

7.2.1 Immune-Related Events and Dose Modification (Withhold, Treat, Discontinue)

Dose Modification and Toxicity Management for Immune-related AEs Associated with Pembrolizumab Monotherapy, Coformulations or IO Combinations

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

Attribution of Toxicity:

When study interventions are administered in combination, attribution of an adverse event to a single component is likely to be difficult. Therefore, while the investigator may attribute a toxicity event to pembrolizumab monotherapy, coformulations, or IO combinations, pembrolizumab monotherapy, coformulations, or IO combinations must be held according to the criteria in the Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events.

In these cases where the toxicity is attributed to pembrolizumab coformulations or IO combinations, re-initiation of pembrolizumab as a monotherapy may be considered after communication with an agreement by the Sponsor (not applicable to Arm K).

Holding Study Interventions:

When study interventions are administered in combination and if the AE is considered immune-related, pembrolizumab monotherapy, coformulations, or IO combinations should be held according to recommended Dose Modification criteria.

If the toxicity does not resolve or the criteria for resuming treatment are not met, the participant must be discontinued from pembrolizumab monotherapy, coformulations, or IO combinations.

Restarting Study Interventions:

Participants may restart pembrolizumab monotherapy, coformulations, or IO combinations as described below:

If the toxicities do resolve and conditions are aligned with what is defined in the Dose Modification and Toxicity Management Guidelines for irAEs, pembrolizumab monotherapy, coformulations, or IO combinations may be restarted at the discretion of the investigator.

Dose Modification and Toxicity Management Guidelines for irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations are provided in Table 5.

See Section 7.7.1 for supportive care guidelines, including use of corticosteroids.

Table 5 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab Monotherapy, Coformulations or IO Combinations

General instructions:
1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Pembrolizumab monotherapy, coformulations or IO combinations must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If pembrolizumab monotherapy, coformulations or IO combinations have been withheld, treatment may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring 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
	Recurrent Grade 2 or Grade 3 or 4	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.
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
AST / ALT Elevation or Increased Bilirubin	Grade 2 [a]	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 [b] or 4 [c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [d]	• 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 [d]		
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 [d]		

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis and renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
Ophthalmologic Uveitis, iritis, episcleritis	Grade 2	Withhold	• Administer corticosteroid eye drops to participants who develop uveitis, iritis, or episcleritis • Permanently discontinue study drugs for immune-mediated ocular disease that is unresponsive to local immunosuppressive therapy	• Monitor for signs and symptoms of ophthalmologic disorders
All Other irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue [e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

[a] AST/ALT: >3.0 to5.0 x ULN if baseline normal; >3.0 to 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 x ULN if baseline normal; >1.5 to 3.0 x baseline if baseline abnormal

[b] AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 to 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 x ULN if baseline normal; >3.0 to 10.0 x baseline if baseline abnormal

[c] AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal

[d] The decision to withhold or permanently discontinue pembrolizumab monotherapy, coformulations or IO combinations is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab monotherapy, coformulations or IO combinations may be resumed.

[e] Events that require discontinuation include, but are not limited to: Guillain-Barre Syndrome, encephalitis, myelitis, DRESS, SJS, TEN and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

(See Appendix 12.7.1 for France-specific criteria)

Dose modification and toxicity management of infusion reactions related to pembrolizumab, MK-1308, and MK-1308A

Pembrolizumab, MK-1308, and MK-1308A may cause severe or life-threatening infusion reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion. Dose modification and toxicity management guidelines on pembrolizumab-, MK-1308-, and MK-1308A-associated infusion reactions are provided in Table 6.

Table 6 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 minutes) prior to infusion of MK1308/pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further 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, refer to the Common Terminology Criteria for Adverse Events v4.03 (CTCAE) at http://ctep.cancer.gov		

Other Allowed Dose Interruption or Dose Delay

MK-1308, MK-1308A, or pembrolizumab may be interrupted/delayed for situations other than treatment-related AEs, ie, medical/surgical events or logistical reasons not related to study therapy. 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 participant's study record. This also applies to site-related holidays or unexpected closures due to other reasons, such as inclement weather.

7.3 Method of Treatment Assignment

Treatment allocation will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). There are 3 planned treatment cohorts (Cohorts 1, 2, and 3) in dose escalation and 5 planned treatment arms (Arms A, B, C, D, and E) in dose confirmation, 2 planned treatment arms in efficacy expansion (Arms F and G), and 3 planned treatment arms in the coformulation phase (Arms I and K). Participants will be allocated to 1 of 13 planned treatment cohorts/arms.

Treatment allocation will be accomplished by non-random assignment in dose escalation, dose confirmation, and coformulation phase. When more than one treatment arm is open for enrollment of participants with NSCLC during dose confirmation, IVRS/IWRS will

distribute successive participants across all open treatment arms within each phase to minimize selection bias. Each new arm will open for enrollment without delay once the DLT observation period of the previous dose cohort is completed and a dose escalation or cohort expansion decision is made. In the efficacy expansion phase, participants will be randomly assigned to either Arm F or Arm G with 1:1 randomization ratio until Arm G reaches the total sample size of 40.

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 3.2 – Background. 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

Interruptions from the protocol specified treatment for ≥12 weeks 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.

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 systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab, MK-1308, or MK-1308A
- Radiation therapy

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

  For all NSCLC and SCLC participants: Targeted external beam irradiation should not be used in the primary lung field where assessment for tumor is indicated.
- Live or live attenuated vaccines within 28 days before the first dose of study intervention and while participating in the study. Note: Killed vaccines are allowed. Note: Any licensed COVID-19 vaccine (including for Emergency use) in a particular country is allowed in the study as long as they are mRNA vaccines, adenoviral vaccines, or inactivated vaccines. These vaccines will be treated just as any other concomitant therapy. Investigational vaccines (ie, those not licensed or approved for Emergency Use) are not allowed.
- Systemic glucocorticoids may be used for the following purposes:
  - To modulate symptoms of an AE that is suspected to have an immunologic etiology

- To modulate symptoms of non-immune-related AEs (If more than 10 mg prednisone equivalent, this treatment should be discussed with the Sponsor)
- Premedication for IV contrast allergies
- Oral physiologic replacement (eg, prednisone < 10 mg/day) or treatment of COPD (standard dosing guidelines)

Note: Topical, ocular, intra-articular, or other local (non-systemic) use is allowed. Inhalation in the management of asthma or chronic obstructive pulmonary disease is also allowed.

Note: CBD oil and other THC-related medications are allowed, per institutional guidance.

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

7.7.1 Rescue Medications & Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 7.2.1 (Table 5). Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to MK-1308 or pembrolizumab.

Note: If after the evaluation of the event, it is determined not to be related to MK-1308 or pembrolizumab, the investigator does not need to follow the treatment guidance. Refer to Table 5 in Section 7.2.1 for guidelines regarding dose modification and supportive care.

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

7.7.1.1 Systemic Corticosteroid Use:

Systemic corticosteroids are permitted in the following situations:

- To mediate potential irAEs or non-immune AEs, as guided in Table 5
- As pre- or post-medication to prevent AEs associated with IV contrast material
- Brief, limited use of systemic corticosteroids (≤7 days) are permitted where such use is considered standard of care (eg, for chronic obstructive pulmonary disease exacerbation)

- For chronic systemic replacement, not to exceed 10 mg/day prednisone equivalent
- In addition, the following glucocorticoid use is allowed:
  - For topical use or ocular use
  - For intra-articular joint use
  - For inhalation in the management of asthma or COPD

Physiologic replacement doses of steroids (for example, prednisone 5 to 10 mg daily) are permitted while on study, as is the use of local (non-systemic) steroids.

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.

7.10 Standard Policies

For trials using Controlled Substances, all Federal, State, Province, Country, etc. regulations must be adhered to in regard to the shipping, storage, handling and dispensing of controlled substances. Additionally, the investigator should have the appropriate controlled drug license(s) as mandated by Federal, State, Province, Country, etc. laws in which the trial is being conducted.

8. Discontinuation/Withdrawal Criteria

8.1 Discontinuation of Study Treatment

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

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

Participants may discontinue study treatment at any time for any reason or be dropped from the study treatment at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study treatment by the investigator or 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.
- Unacceptable AE(s).
- Intercurrent illness that prevents further administration of study treatment.
- Confirmed radiographic disease progression outlined in Section 9.2.1 (exception if the Sponsor approves treatment continuation).
- Investigator's decision to discontinue the participant
- Any study intervention-related toxicity specified as a reason for permanent discontinuation as defined in the guidelines for dose modification due to AEs in Section 7.2.
- Progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment
- The participant has a confirmed positive serum pregnancy test.
- Noncompliance with trial treatment or procedure requirements.
- The participant completes study treatment (ie, up to 24 months of MK-1308/pembrolizumab/MK-1308A, as applicable).
- Administrative reasons.

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

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

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 including 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, as well as specific details regarding withdrawal from Future Biomedical Research are outlined in Section 9.1.9 – Withdrawal/Discontinuation.

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

The maximum amount of blood collected from each participant including any extra assessments that may be required, will not exceed 550 mL over any 8-week period.

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

9.1 Administrative and General Procedures

9.1.1 Informed Consent

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

9.1.1.1 General Informed Consent

Informed consent given by the participant or their legally acceptable representative must be documented on a consent form. The form must include the study protocol number, study protocol title, dated signature, and agreement of the participant (or his/her legally acceptable representative) and of the person conducting the consent discussion.

A copy of the signed and dated informed consent form should be given to the participant (or their legally acceptable representative) before participation in the study.

The initial ICF, any subsequent revised 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 study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's or the participant's legally acceptable representative's dated signature.

If the investigator recommends continuation of study intervention beyond disease progression, the participant or their legally acceptable representative will be asked to provide documented informed consent.

Specifics about the study and the study population are to be included in the study informed consent form.

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 medically qualified designee will explain the FBR consent to the participant, or the participant's legally acceptable representative, answer all of his/her questions, and obtain documented informed consent before performing any procedure related to FBR. A copy of the informed consent will be given to the participant before performing any procedure related to FBR.

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 study. The card will contain study-site contact information (including direct telephone numbers) to be used 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 documented informed consent. At the time of intervention allocation/randomization, site personnel will add the treatment/randomization number to the participant identification card.

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

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 including smoking 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 important. Details regarding the disease for which the participant has enrolled in this study will be recorded separately and not listed as medical history.

If a medical condition is diagnosed at the time of screening due to the physical examination, laboratory tests, radiologic assessment, other assessment, and/or a combination of these evaluations, the medical condition is to be recorded as a baseline condition along with the participant's other medical history unless due to any protocol-specified intervention (eg, procedure, washout or run-in treatment including placebo run-in).

9.1.4.1 Advanced Solid Tumor (ST), NSCLC, SCLC, and Melanoma History

The investigator or qualified designee will obtain information regarding the participant's advanced ST, NSCLC, SCLC, and melanoma. This information will include but is not limited to the presentation at primary diagnosis, date of and stage at primary diagnosis, date of and stage at most recent recurrence and location of metastases at screening (if applicable).

9.1.5 Prior and Concomitant Medications Review

9.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use and record prior medication taken by the participant within 28 days before the first dose of study treatment.

9.1.5.1.1 Prior Treatment for Advanced Solid Tumor Cancer

The investigator or qualified designee will review and report all prior treatments for advanced solid tumor including systemic treatments, radiation, and surgeries.

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.

All new anticancer therapy initiated after the study start must be recorded in the electronic case report form (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 Mandatory 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. Each participant will be assigned only one screening number. Screening numbers must not be re-used for different participants.

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

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

9.1.7 Assignment of Treatment/Randomization Number

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

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

9.1.8 Treatment Administration

Trial treatment should be administered on the day of treatment allocation/randomization or as close as possible to the date on which the participant is allocated/assigned. Administration of trial medication will be monitored by the investigator and/or trial staff at study visits. The total volume of trial treatment infused will be compared to the total volume prepared to determine compliance with each dose administered.

The instructions for preparing and administering MK-1308, pembrolizumab, and MK-1308A will be provided in the Pharmacy Manual.

Study Treatment should begin within 3 days of assignment of randomization number.

9.1.8.1 Timing of Dose Administration

Study intervention(s) will be administered by the investigator and/or study staff according to the specifications within the Pharmacy Manual. Details of administering the individual components are discussed below.

9.1.8.1.1 Timing of Dose Administration of MK-1308/MK-1308A

MK-1308 will be administered at the dose specified in the specific arm of the study using 30-minute IV infusion either every 3 weeks or every 6 weeks. MK-1308 will be administered 30 minutes after completion of pembrolizumab infusion on the days when pembrolizumab is administered.

For Arm F, MK-1308 will be co-administered as an admixture with pembrolizumab over a 30-minute time period.

For Arms I and K, MK-1308A will be administered over a 30-minute time period.

9.1.8.1.2 Timing of Dose Administration of Pembrolizumab

Pembrolizumab will be administered at a dose of 200 mg using a 30-minute IV infusion every 3 weeks during dose escalation and dose confirmation phase. In the efficacy expansion phase, Arm F, pembrolizumab will be co-administered as an admixture with MK-1308 at a dose of 400 mg every 6 weeks. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (ie, infusion time is 30 minutes -5 min/+10 min).

The Pharmacy Manual contains specific instructions for MK-1308, pembrolizumab, and MK-1308A reconstitution, preparation of the infusion fluid, and administration.

Every effort should be made to begin the first dose of study treatment on the day a participant is enrolled, but if this is not achieved, trial therapy should be initiated no later than 3 days from the date of allocation. All subsequent cycles of study treatment may be administered up to 3 days before or 3 days after the scheduled Day 1 of each cycle due to administrative reasons per the investigator's judgment. All study treatments will begin on Day 1 of each cycle after all pre-dose study procedures and assessments have been completed as detailed in the SoA. The reason for any variability in administration outside of the protocol-specified window should be documented in the participant's chart and recorded on the eCRFs.

9.1.8.2 Trial Communication Plan Summary

Safety data from individual participants will be closely followed by the principal investigator and the Sponsor on an ongoing basis and shared at regular safety teleconferences (typically once per week). The safety and tolerability of all participants, including those undergoing DLT evaluation, as well as those who have completed DLT evaluation, will be reviewed prior to the start of the next cohort. The Sponsor and principal investigators will assess the appropriateness of dose escalation/dose confirmation and assess safety and tolerability at the completion of each cohort/arm, and prior to the opening of enrollment for the next

cohort/arm. The subsequent dose level to be tested in the next cohort/arm of participants will be communicated to the investigator or designee following each dose escalation/dose confirmation decision meeting. A memorandum will be sent to each site to communicate the specified next dose level. Participants will be enrolled and allocated via IVRS according to the dose escalation and confirmation guidelines outlined in Section 5.1. The dose at each cohort will be specified via IVRS. Cohorts will be opened or closed through IVRS to assure correct dosing in each cohort.

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 study, 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, Serious Adverse Events and Other Reportable Safety 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@msd.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 evaluations and trial assessments
- Imaging equipment – as required for response assessments
- Electrocardiogram (ECG) equipment – as required for trial assessments
- Infusion pumps – as required for MK-1308, pembrolizumab administration
- Refrigerators and freezers – as required to store study treatments and laboratory samples

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

9.2 Efficacy Assessments

9.2.1 Tumor Imaging and Assessment of Disease

In addition to survival, efficacy will be assessed based on imaging evaluation of changes in tumor burden over time, until the participant is discontinued from the trial or goes into survival follow-up. The process for image collection and transmission to the CIV can be found in the SIM. Tumor imaging should be acquired by CT (strongly preferred). Refer to the Imaging Manual for additional guidance. MRI should be used when CT is contraindicated or for imaging in the brain. For the abdomen and pelvis, contrast-enhanced MRI may be used when CT with iodinated contrast is contraindicated, or when mandated by local practice. The same imaging technique regarding modality and use of contrast should be used in a participant throughout the study to optimize the visualization of existing and new tumor burden. Required anatomical images as well as the process for image collection and transmission to the CIV can be found in the SIM. Note: for the purposes of assessing tumor imaging, the term “investigator” refers to the local investigator at the site and/or the radiological reviewer at the site or at an offsite facility.

All tumor imaging (scheduled and unscheduled) should be submitted to the CIV for analysis. In addition, if the investigator obtains additional imaging, including other modalities, that are obtained at an unscheduled time point to determine if the participant has progressed as well as imaging obtained for other reasons but captures radiologic progression, all of these imaging scans should be sent to the CIV. All scheduled images for all study participants from the sites will be submitted to the CIV. In addition, images (including via other modalities) that are obtained at an unscheduled time point to determine disease progression, as well as imaging obtained for other reasons, but which show radiologic progression, should also be submitted to the CIV.

9.2.1.1 Initial Tumor Imaging

Initial tumor imaging at Screening must be performed within 28 days prior to the date of first dose. The site study team must review screening images to confirm the participant has measurable disease per RECIST 1.1. For the efficacy expansion phase Arms F and G, BICR confirmation of measurable disease based on RECIST 1.1 is required prior to allocation/randomization.

Scans performed as part of routine clinical management are acceptable for use as screening tumor imaging if they are of diagnostic quality and performed within 28 days prior to the date of first dose of study medication.

For SCLC, thyroid cancer, and melanoma participants: Brain MRI is required at Screening.

For efficacy expansion phase Arms F and G: Sites must submit 2 or 3 pre-trial scans to the CIV and receive a scan acceptance email from the CIV before randomizing the participant (See Inclusion criterion 12e for details).

9.2.1.2 Brain Imaging

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 3 weeks (4 weeks for the melanoma participants) prior to the first dose of trial treatment. Any neurologic symptoms must have returned to baseline and participants must have no evidence of new or enlarging brain metastases and have not used steroids for brain metastases for at least 7 days (14 days for the melanoma participants) prior to trial initiation as per local site assessment. This exception does not include carcinomatous meningitis, as participants with carcinomatous meningitis are excluded regardless of clinical stability.

For participants with stable brain metastases enrolled in the trial, the baseline brain image must be submitted to the CIV to be held for possible future analysis. For any participant with known stable brain metastases at baseline and who achieves a CR during trial treatment, follow-up brain imaging is required for confirmatory assessment of CR. This image will be submitted for independent central radiologic review.

Participants with small cell lung, thyroid cancer, and melanoma (without a history of stable brain metastases) must undergo a brain scan within 28 days prior to the first dose of trial treatment, with local confirmation that no new or untreated brain metastases are present. For those participants with these tumor types subsequently enrolled in the trial, this baseline brain scan should be submitted to the CIV, but independent central radiologic confirmation of a lack of brain metastases is not required.

For all parts except Arms F and G: Participants with small (<1 cm) asymptomatic brain metastases must be followed with regularly scheduled brain MRI scans throughout the study. For Arms F and G: Participants with asymptomatic, previously untreated brain metastases may not participate.

If a participant develops a new brain metastasis during treatment, the following steps will be taken:

- Participants with symptomatic brain metastases will be removed from study treatment.
- Participants with asymptomatic brain metastases (no need for steroids, no symptoms and signs indicating clinically significant progression of disease, no decline in ECOG performance status) can continue on study treatment under the following conditions:
    - If no immediate WBRT, both systemic lesions and brain lesions, can be followed by iRECIST.

- If immediate WBRT is chosen, the brain lesions will be non-evaluable for iRECIST.
- Brain MRI will be required at each subsequent image assessment.

9.2.1.3 Imaging for Bone Metastases

For any participant with clinical symptoms suggesting bone metastases, bone imaging (eg, bone scan or PET scan) should be performed to identify possible bone metastases. If bone metastases are identified that have not been imaged on the CT/MRI performed for Initial Tumor Imaging (Section 9.2.1.1), then additional baseline and all subsequent tumor imaging studies should include such lesions in the imaging field.

9.2.1.4 Tumor Imaging During the Study

The first on-trial imaging assessment should be performed at 9 weeks (±7 days) from the date of first dose of study drug. Subsequent tumor imaging should be performed every 9 weeks (63 days ±7 days) or more frequently if clinically indicated. After 54 weeks, participants who remain on-treatment will have imaging performed every 12 weeks (84 days ±7 days), or sooner if clinically indicated, for all cohorts. Imaging timing should follow calendar days from treatment initiation and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until disease progression is identified by the investigator, unless the investigator elects to continue treatment and follow irRECIST in the dose escalation phase and the dose confirmation phase (see Section 9.2.1.8) or iRECIST in the efficacy expansion and coformulation phases (see Section 9.2.1.9), the start of new anticancer treatment, withdrawal of consent, death, or notification by the Sponsor, whichever occurs first. All supplemental imaging must be submitted to the CIV.

Per RECIST 1.1 (Section 9.2.1.7), PR and CR should be confirmed by a repeat imaging assessment. The tumor imaging for confirmation of response may be performed ≥4 weeks after the first indication of response or at the next scheduled scan (ie, 9 weeks later), whichever is clinically indicated. Participants will then return to regular scheduled imaging every 9 weeks, 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.

On-study brain imaging should be performed if clinically indicated or to confirm CR (if other lesions indicate CR and brain lesions existed at Screening).

Per iRECIST (Section 9.2.1.9), disease progression should be confirmed by the site 4 to 8 weeks after site-assessed first radiologic evidence of progressive disease in clinically stable participants. Participants who have unconfirmed disease progression may continue on treatment at the discretion of the site investigator until progression is confirmed by the site. Participants who obtain a confirmation scan do not need to undergo the next scheduled tumor imaging if it is <4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point if clinically stable. Participants who have confirmed disease progression as assessed by the site will discontinue the treatment. Exceptions are detailed in Section 9.2.1.9.

For participants in Arm G, in order to be eligible to crossover, site-assessed radiographic PD must be verified by BICR. When the investigator identifies radiographic progression per RECIST 1.1 for participants in Arm G, the imaging should be submitted to CIV. Tumor imaging should be used as a new baseline for the participant for VOP by BICR. The CIV will perform expedited review and communicate the VOP results to the study site and Sponsor via email. In clinically stable participants, imaging should continue until PD has been verified by BICR (if initial site-assessed PD was not verified by BICR, each subsequent scan must be submitted to CIV with verification of PD request until PD has been verified by BICR).

9.2.1.5 End of Treatment and Follow-up Tumor Imaging

For participants who discontinue trial treatment, tumor imaging should be performed at the time of treatment discontinuation (±4 week window). If a previous scan was obtained within 4 weeks prior to the date of discontinuation, then a scan at treatment discontinuation is not mandatory. For participants who discontinue trial treatment due to documented disease progression, this is the final required tumor imaging if the investigator elects not to implement irRECIST or 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 calculated from the date of first dose (see Section 9.2.1.4) until the start of a new anticancer treatment, disease progression, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first.

9.2.1.6 Crossover Phase Tumor Imaging

For Arm G participants who are eligible to crossover to combination therapy (Arm F), the crossover screening imaging (new baseline) should be performed within 28 days prior to the first dose as new baseline imaging. The imaging for BICR-verified progression (while in Arm G) can be used as screening imaging if it's performed within 28 days prior to first dose of combination therapy. Note: When the investigator identifies radiographic progression per RECIST 1.1 for participants in Arm G, the imaging should be submitted to CIV for VOP by BICR. The CIV will perform expedited review and communicate the VOP results to the study site and Sponsor via email. In clinically stable participants, imaging should continue until PD has been verified by BICR (if initial site-assessed PD was not verified by BICR, each subsequent scan must be submitted to CIV with verification of PD request until PD has been verified by BICR). In order to be eligible to crossover, PD must be verified by BICR.

Participants who crossed over to combination therapy will be eligible to receive a maximum of 24 months of treatment ,starting with C1D1 from the start of combination treatment and the imaging schedule will follow that described in Section 9.2.1.4.

9.2.1.7 RECIST 1.1 Assessment of Disease

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

9.2.1.8 irRECIST Assessment of Disease (Dose Escalation Phase and Dose Confirmation Phase)

The irRECIST accounts for the unique tumor response characteristics seen with immunotherapeutic agents. Immunotherapeutic agents such as MK-1308 and pembrolizumab may produce anti-tumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard RECIST may, thus, not provide an accurate response assessment of immunotherapeutic agents. These findings support the need to apply a modification to RECIST that takes into account the unique patterns of atypical response in immunotherapy and enables treatment beyond initial radiographic progression.

Participants in the dose escalation phase and the dose confirmation phase who have initial evidence of radiological progressive disease by RECIST after starting study treatment, should, at the discretion of the investigator, continue on study treatment until repeat imaging is obtained ≥4 weeks later to confirm progressive disease (irRECIST participant management). This clinical judgment should be based on the participant's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease, including worsening of laboratory values;
- No decline in ECOG performance status;
- Absence of rapid clinical progression of disease; and
- Absence of progressive tumor at critical anatomical sites (eg, spinal cord compression).

Any participant deemed clinically unstable should be discontinued from trial treatment and is not required to have repeat imaging for progressive disease confirmation.

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

Progressive disease will be confirmed at repeat imaging if ANY of the following occur by irRECIST:

- Tumor burden remains ≥20% and there is at least a 5 mm absolute increase compared to the nadir;
- Non-target disease resulting in initial progressive disease is qualitatively worse;
- New lesion resulting in initial progressive disease is qualitatively worse;
- Additional new lesion(s) are identified since the last evaluation; OR
- Additional new non-target progression is identified since the last evaluation.

If repeat imaging confirms progressive disease due to any of the scenarios listed above, participants should be discontinued from study treatment. A participant with confirmed radiologic progression may continue to receive study treatment, after consultation with the Sponsor, if the investigator deems the participant is receiving clinical benefit or value from treatment.

Progressive disease will not be confirmed at repeat imaging if ALL of the following occur by irRECIST:

- Tumor burden is <20% or there is a <5 mm absolute increase compared to the nadir;
- Non-target disease resulting in initial progressive disease is stable or qualitatively improved;
- New lesion resulting in initial progressive disease is stable or qualitatively improved;
- No incremental new lesion(s) are identified since the last evaluation; AND
- No incremental new non-target progression is identified since the last evaluation.

If repeat imaging does not confirm progressive disease by irRECIST and the participant continues to be clinically stable, treatment may continue and follow the regular imaging schedule.

9.2.1.9 iRECIST Assessment of Disease (Efficacy Expansion Phase and Coformulation Phase)

iRECIST is based on RECIST 1.1 but adapted to account for the unique tumor response seen with immunotherapeutic drugs. During the efficacy expansion and the coformulation phases, iRECIST will be used by the investigator to assess tumor response and progression, and make treatment decisions instead of irRECIST, to be consistent with MSD's newest standard. When clinically stable, participants in the efficacy expansion phase should not be discontinued until progression is confirmed by the investigator, working with local radiology, according to the rules outlined in Appendix 8. This allowance to continue treatment despite initial radiologic PD takes into account the observation that some participants can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. These data will be captured in the clinical database.

Clinical stability is defined as the following:

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

Any participant deemed clinically unstable should be discontinued from study treatment at 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 CIV for potential retrospective BICR. In order to continue to receive study intervention after initial radiologic PD, the participant must sign an additional informed consent form (see Section 9.1.1.1).

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.

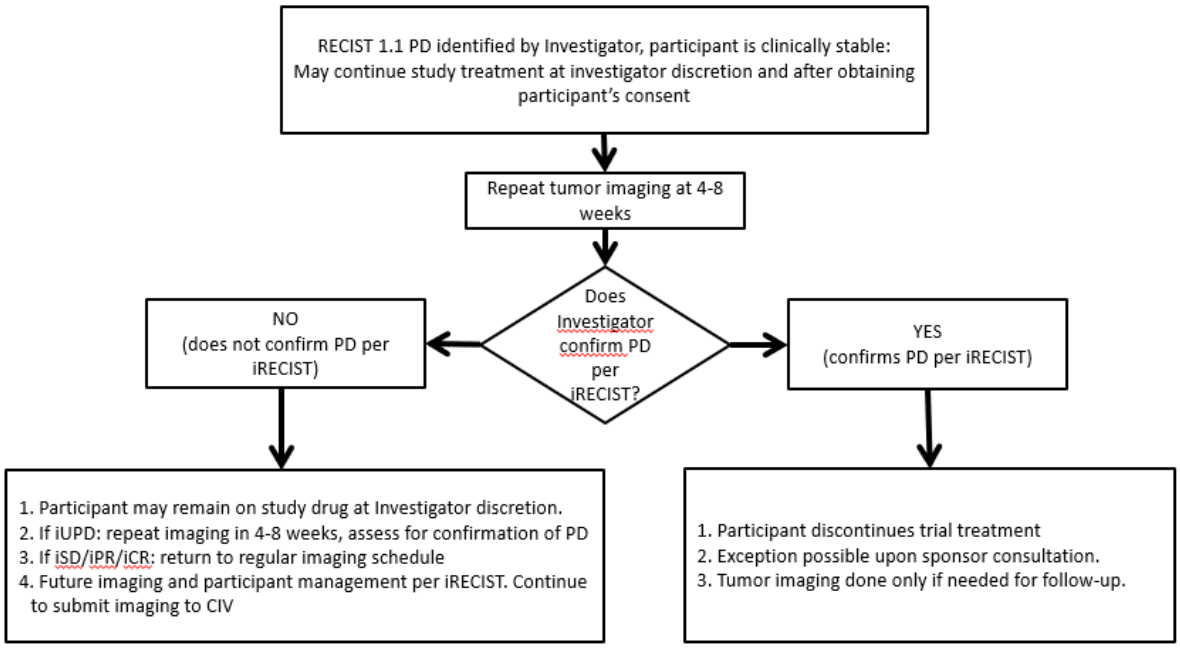
If a participant has confirmed radiographic progression as defined in Appendix 8, study treatment should be discontinued; however, if the participant is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered following consultation with the Sponsor. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 2.3 and submitted to the CIV.

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 and illustrated as a flowchart in Figure 5.

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 per investigator assessment	Repeat imaging at 4 to 8 weeks to confirm PD per iRECIST	May continue study treatment at the discretion of the investigator and after obtaining participant's consent	No additional imaging required	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 imaging required.	Not applicable
Repeat tumor imaging shows iUPD by iRECIST per investigator assessment.	Repeat imaging at 4 to 8 weeks to confirm PD.	Continue study treatment at the investigator's discretion.	No additional imaging required	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.	No additional imaging required	Discontinue treatment
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.				

Figure 5 Imaging and Treatment for Clinically Stable Participants After First Radiologic Evidence of PD Assessed by the Investigator



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

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

Progression of the cancer under study is not considered an 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 participant provides documented informed consent, but before intervention allocation/randomization, must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event cause the participant to be excluded from the study, or is the result of a protocol-specified intervention, including, but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

- All AEs from the time of intervention allocation/randomization through 30 days for the dose escalation phase, and through 90 days for the efficacy expansion and coformulation phases, after cessation of study intervention must be reported by the investigator.
- All AEs meeting serious criteria, from the time of intervention allocation/randomization through 90 days after cessation of study intervention or 30 days after cessation of study intervention if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator.
- All pregnancies and exposure during breastfeeding, from the time of intervention allocation/randomization through the time required to eliminate systemic exposure after cessation of study intervention as described in Sections 6.1 and 9.5.5, or 30 days after cessation of study intervention if the participant initiates new anticancer therapy must be reported by the investigator.
- Additionally, any SAE brought to the attention of an investigator at any time outside the time specified above must be reported immediately to the Sponsor if the event is considered related to study intervention.

Investigators are not obligated to actively seek AE or SAE in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the event is considered 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.

Exception: A positive pregnancy test at the time of initial screening is not a reportable event unless the participant has received study intervention.

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 and SAE

Care will be taken not to introduce bias when detecting AE and/or SAE. 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 nonserious 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

- Prompt notification (within 24 hours) by the investigator to the sponsor of SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, ie, per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators, as necessary.
- 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

Efficacy Endpoints as outlined in this section will not be reported to the Sponsor, as described in Section 9.3.1.

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

The Sponsor will ensure that unblinded aggregated efficacy endpoint events and safety data are monitored to safeguard the participants in the study.

9.3.6 Pregnancy and Exposure During Breastfeeding

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

All reported pregnancies must be followed to the completion/termination of the pregnancy.

Any pregnancy complication will be reported as an AE or SAE.

The medical reason (example: maternal health or fetal disease) for an elective termination of a pregnancy will be reported as an AE or SAE. Prenatal testing showing fetus will be born with severe abnormalities/congenital anomalies that leads to an elective termination of a pregnancy will be reported as an SAE for the fetus.

Pregnancy outcomes of ectopic pregnancy, 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 purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for MK-1308 or MK-1308A by ≥150% (eg, ≥1.5 times the indicated dose) based on the known dose-related toxicities of ipilimumab and for pembrolizumab ≥1000 mg. No specific information is available on the treatment of overdose of MK-1308, MK-1308A, or pembrolizumab. In the event of overdose, MK-1308, MK-1308A, or pembrolizumab 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 laboratory procedures/assessments to be performed in this trial are provided below. The total amount of blood/tissue to be drawn/collected over the course of the trial (from pre-trial to post-trial visits) can be found in Section 9.

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

9.5.1 Physical Examinations

The investigator or qualified designee will perform a complete physical exam including neurologic assessment during the screening period. Clinically significant abnormal findings should be recorded as medical history. The time points for full physical exam and directed physical examination are described in Section 2 – Schedule of Activities (SoA). After the first dose of trial treatment new clinically significant abnormal findings should be recorded as AEs.

9.5.2 Vital Signs

The investigator or qualified designee will obtain vital signs at screening, prior to the dosing of each treatment (MK-1308, MK-3475, or combo admixture), and at the end of infusion. Vital signs should also be collected at the End of Treatment Visit and Safety Follow-up (30-day and 90-day) Visits. Vital signs include temperature, pulse, respiratory rate, and blood pressure. Weight will be measured on Day 1 of each cycle (can be done at any time on Day 1 of each cycle). Height will be measured at the Screening visit only.

9.5.3 Electrocardiograms

Standard 12-lead ECGs will be performed using local standard procedures. The timing of ECGs is specified in the SoA in Section 2. Clinically significant abnormal findings at Screening should be recorded as medical history. Additional ECGs should be performed when clinically necessary.

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.

For dose escalation and dose confirmation only, laboratory safety tests (hematology and chemistries) for screening period should be performed within 14 days prior to the first dose of trial treatment.

For efficacy expansion and coformulation phases, laboratory safety tests (hematology and chemistries only) should be performed and reviewed by the investigator or staff designee for eligibility within 72 hours prior to the first dose of trial treatment. All other required screening laboratory tests (including hepatitis, ACTH, cortisol, and thyroid function testing) may be performed anytime within 28 days prior to first dose. If the participant has had prior anti-PD-1 or PD-L1 treatment, the ACTH, cortisol and thyroid test results must be reviewed prior to C1D1 dosing. Laboratory safety tests conducted within 72 hours of C1D1 do not need to be repeated prior to C1D1 dosing.

Laboratory test results must be reviewed by the investigator or qualified designee and found to be acceptable prior to administration of each subsequent dose of trial treatment. However, in the event thyroid function test results after Cycle 1 are not available prior to scheduled dosing, review of thyroid function tests (T3, T4, and TSH), ACTH and cortisol results after dosing is acceptable. 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 the normal range.

9.5.5 Pregnancy Testing

Pregnancy testing:

- Pregnancy testing requirements for study inclusion are described in Section 6.1.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted at every cycle (Q6W), prior to dosing, during intervention.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted at the end of relevant systemic exposure.
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.

9.6 Pharmacokinetics

Sample collections are planned for PK and ADA analysis for MK-1308 and pembrolizumab according to the SoA described in Section 2. Blood samples will be obtained to measure the PK of serum MK-1308 given as monotherapy and in combination with and in coformulation with pembrolizumab. If feasible, PK data of MK-1308 monotherapy and in combination and coformulation with pembrolizumab will be analyzed using nonlinear mixed effects modeling. A population PK analysis of MK-1308 may be performed to characterize PK parameters (ie, clearance, volume of distribution [V]) and evaluate the effect of extrinsic and intrinsic factors to support the proposed dosing regimen.

Pharmacokinetic data may also be used to explore the exposure-response relationships for MK-1308 anti-tumor activity/efficacy in combination with pembrolizumab, as well as safety in the proposed participant population. The results of these analyses, if performed, will be reported separately.

PK and ADA samples may be disposed of in accordance with sample destruction procedures once the PK and ADA data are finalized.

9.6.1 Blood Collection for Serum MK-1308

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

Pharmacokinetic samples should be drawn according to the PK collection schedule for all participants. Every effort should be taken to collect samples at 30 days after end of study intervention.

9.6.2 Blood Collection for Serum Pembrolizumab

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

Pharmacokinetic samples should be drawn according to the PK collection schedule for participants who receive pembrolizumab. Every effort should be taken to collect samples at 30 days after end of study intervention.

9.6.3 Blood Collection for Anti-Pembrolizumab Antibodies

Sample collection, storage and shipment instructions for serum samples will be provided in the Procedures Manual. Anti-pembrolizumab antibody samples should be drawn according to the ADA collection schedule for participants who receive pembrolizumab. Simultaneous PK sampling is required for interpretation of ADA analysis. Every effort should be taken to collect samples at 30 days after end of study intervention for ADA. Simultaneous PK sampling is required for interpretation of ADA analysis.

9.6.4 Blood Collection for Anti-MK-1308 Antibodies

Sample collection, storage and shipment instructions for serum samples will be provided in the Procedures Manual. Anti-MK-1308 antibody samples should be drawn according to the ADA collection schedule for participants who receive MK-1308. Simultaneous PK sampling is required for interpretation of ADA analysis. Every effort should be taken to collect samples at 30 days after end of study intervention for ADA. Simultaneous PK sampling is required for interpretation of ADA analysis.

9.7 Pharmacodynamics

A direct receptor occupancy assay to measure target engagement cannot be used as CTLA4 expression on the cell surface of T-cells is transient and tightly regulated. Therefore, post-treatment changes in ALC and expression of T-cell activation markers (for example Ki67, ICOS, and HLA-DR) will be assessed in peripheral blood based on the proposed effect of CTLA4 blockade in the immune priming phase to increase activation and proliferation of T-cells.

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

9.8 Future Biomedical Research Sample Collection

The following specimens are to be obtained as part of Future Biomedical Research (Not applicable for Arm K):

- Leftover main study tumor
- Leftover cells from mononuclear cells biomarker analysis
- Leftover serum from serum cytokine
- Leftover DNA from genetic analysis and T-cell repertoire
- Leftover RNA
- Leftover plasma from ctDNA
- Leftover and/or derivative from stool for biomarker analysis (Dose Escalation and Confirmation phases only)

9.9 Biomarkers

(This is not applicable to Arm K in China.)

Collection of samples for other biomarker research is also part of this study. The following samples for biomarker research are required and will be collected from all participants in this study as specified in the SoA. Sample collection, storage and shipment instructions for these samples will be provided in the Procedures Manual:

- Serum for cytokine measurements
- Blood for TCR repertoire
- Blood for RNA analyses
- Peripheral blood for immunophenotyping biomarker analyses
- Peripheral blood for mononuclear cells biomarker analysis
- Whole blood for exploratory T-cell response
- Blood for genetic analysis and HLA genotyping
- Tumor tissue
- Blood for ctDNA
- Stool microbiome collection (dose escalation, confirmation, and expansion phases only)

Pre- and on-treatment tumor tissue will be collected for additional biomarker analysis from approximately 10 participants each in Arms F and G. For these participants, an archival tumor sample is also requested, if feasible, from a time point before receiving any prior immune-oncology treatment. New biopsies of tumor tissue will be obtained from these participants at Screening (following confirmation of all other eligibility assessments) and at 4 weeks after C1D1 (±7 days). Tumor tissue from Screening should be accurately marked so

the same lesion site can be used for the on-treatment biopsy. If not possible, the Sponsor should be notified of the location.

9.9.1 Planned Genetic Analysis Sample Collection

This sample should be drawn for HLA genotyping and for planned analysis of the association between genetic variants in DNA and drug response. Data analysis will be limited to HLA if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for future biomedical research if the participant signs the FBR consent. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.

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 be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1. Screening procedures may be repeated after consultation with the Sponsor.

Documented informed 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:

- For dose escalation and dose confirmation, safety laboratory tests are to be performed within 14 days prior to the first dose of trial treatment. If these tests are performed within 72 hours of C1D1, they do not need to be collected earlier in screening.
- For efficacy expansion and coformulation phases, laboratory safety tests (hematology and chemistries) should be performed and reviewed by the investigator or staff designee for eligibility within 72 hours prior to the first dose of trial treatment. **All other required laboratory tests can be performed anytime within the 28-day screening period.**
- Evaluation of ECOG must be performed within 3 days (72 hours) prior to the first dose of trial treatment.
- For women of reproductive potential, a urine or serum pregnancy test will be performed within 24 hours for urine and within 72 hours for serum prior to the first dose of trial treatment and prior to each subsequent dose. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory).
- Archival or newly obtained tumor sample collection is required to be submitted within 28 days prior to the first dose of trial treatment.

- Participants may be re-screened up to 2 times with consultation and approval of the Sponsor.

9.10.2 Treatment Period

Visit requirements are outlined in Section 2.0 – Schedule of Activities (SoA). Specific procedure-related details are provided above in Section 9.1 – Administrative and General Procedures.

9.10.3 Discontinued Participants Continuing to be Monitored in the Study

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. For the efficacy expansion and coformulation phases, a second mandatory Safety Follow-up Visit should be conducted approximately 90 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 visits should be recorded (up to 90 days following end of treatment). Participants with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anticancer therapy, whichever occurs first. All AEs from the time of treatment allocation/randomization through 90 days following cessation of study treatment must be reported by the investigator. All AEs meeting serious criteria, from the time of treatment allocation/randomization through 90 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy, whichever is earlier must be reported by the investigator.

9.10.4 Post-Study

Participants will be required to return to clinic approximately 30 days after the last dose of study treatment for the post-trial visit. If the post-trial visit occurs less than 30 days after the last dose of study treatment, a subsequent follow-up phone call should be made at 30 days post the last dose of study treatment to determine if any AEs have occurred since the post-trial clinic visit.

For the efficacy expansion and coformulation phases, participants also will be required to return to clinic approximately 90 days after the last dose of study treatment for a post-trial visit. If the post-trial visit occurs less than 90 days after the last dose of study treatment, a subsequent follow-up phone call should be made at 90 days post the last dose of study treatment to determine if any AEs have occurred since the 30-day post-trial clinic visit.

9.10.5 Survival Follow-up

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 trial, whichever occurs first.

9.10.6 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 eDMC review, interim and/or final analysis. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor-defined time period will be contacted for their survival status (excluding participants who have previously recorded a 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. CCI [redacted]

10.1 Statistical Analysis Plan Summary

This section contains a brief summary of the statistical analyses for this trial. Full details are in the Statistical Analysis Plan, Section 10.2 through Section 10.12.

Study Design Overview	Phase 1 / 2 trial of MK-1308 in combination with pembrolizumab in participants with advanced/metastatic solid tumors.
Analysis Populations	Safety (Primary): All-Participants-as-Treated (APaT), DLT-evaluable population for DLT analysis PK (Secondary): Per-Protocol (PP) Efficacy (Primary in the efficacy expansion phase, and secondary for the other phases): APaT population

Primary Endpoint(s)	Safety: • Number of participants with at least 1 DLT • Number of participants with ≥1 AE • Number of participants discontinuing study treatment due to an AE Efficacy (efficacy expansion phase): • Objective Response Rate (ORR) defined as the portion of participants with CR or PR as assessed by BICR based on RECIST 1.1, adjusted to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ)
Secondary Endpoints	ORR as assessed by the investigator based on RECIST 1.1 (dose escalation phase, dose confirmation phase, and Arm I and K in the coformulation phase): DOR as assessed by BICR based on RECIST 1.1 (efficacy expansion phase): • The time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first (for responders only) PK profile and ADA of MK-1308 monotherapy and MK-1308 in combination with pembrolizumab; PK parameters of pembrolizumab in combination with MK-1308; PK profiles of MK-1308 and pembrolizumab when drugs are sequentially administered, co-administered and coformulated as MK-1308A. • AUC, C_{min}, C_{max} • Anti-drug antibody levels
Statistical Methods for Efficacy/Immunogenicity/ Pharmacokinetic Analyses	ORR will be summarized by treatment arm along with a 95% confidence interval. Descriptive summary statistics will be provided for DOR. Time-to-event analysis and Kaplan-Meier estimates may be provided for DOR in addition to the descriptive summary statistics if there are at least 10 responders. PK parameters of study medicines will be summarized by planned visit and time for each dose cohort.

Treatment Assignment	Participants will be allocated to receive MK-1308 in combination with pembrolizumab (Arms A-F), or MK-1308 monotherapy (Arm G), or the coformulation product MK-1308A (Arm I and K) using an IVRS/IWRS. Treatment assignments in the dose escalation phase, dose confirmation phase and coformulation phase are non-random. Treatment assignments in the efficacy expansion phase will utilize random assignment whenever there is more than 1 treatment arm open.
Statistical Methods for Safety Analyses	Summary statistics will be provided for the safety endpoints as appropriate.
CCI [redacted]	
Sample Size and Power	The sample size in Cohorts 1, 2, 3 and Arms A, B, C, D, E of this study depends on the observed DLT profiles of MK-1308 in combination with pembrolizumab. Maximum sample size will be 100 in Arm F and 40 in Arm G. Target sample size will be 20 in Arm I, and 20 in Arm K. A target sample size of 348 participants will be used for study planning purposes.

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 in dose escalation, dose confirmation and coformulation phase will

not be randomized. Participants in the efficacy expansion phase will be randomized between Arms F and G.

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 per BICR based on RECIST 1.1 is the primary efficacy endpoint in the efficacy expansion phase. ORR per investigator based on RECIST 1.1 is a secondary endpoint for the dose escalation, dose confirmation, and Arms I and K in the coformulation phase. An objective response is a CR or PR with confirmation. ORR is defined as the portion of participants with CR or PR.

DOR is a secondary endpoint in the efficacy expansion. For participants who demonstrate CR or PR, DOR is defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first.

CCI

PK endpoints include serum concentrations of MK-1308 and pembrolizumab, as well as derived PK parameters including AUC, C_{min}, and C_{max}. The primary PK parameters for the coformulation phase of MK-1308A would be AUC.

Incidence of ADA is a secondary endpoint.

10.4.2 Safety Endpoints

The primary safety endpoint is number of participants with at least one DLT. In addition, safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests, and vital signs.

A description of safety measures is provided in Section 9.3.

10.5 Analysis Populations

10.5.1 Safety Analysis Populations

The APaT population will be used for the analysis of safety data in this study. The APaT population consists of all participants who received at least 1 dose of study medicine.

DLT-evaluable population: Participants in the APaT population who finished the DLT observation period in the dose escalation phase or DLT observation period in the dose confirmation phase, Arm F in efficacy expansion phase (first 14 participants only), or Arm I without a DLT, or experienced a DLT during the DLT evaluation period will be included in the DLT evaluation. If a participant is replaced due to receiving less than 90% of MK-1308

(or pembrolizumab) in the first cycle, the participant will not be included in the DLT-evaluable population.

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

10.5.2 Pharmacokinetic Analysis Populations

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

10.5.3 Efficacy Populations

The APaT population will be the primary analysis population for ORR, PFS and OS. The APaT population consists of all participants who received at least 1 dose of study medicine. The Full Analysis Set (FAS) population will be a supportive analysis population for the ORR analyses. It consists of all participants with a baseline scan that demonstrated measurable disease, and who were administered at least 1 dose of study medicine. Efficacy data occurred during the crossover phase in Arm G will be excluded from the primary efficacy analyses of Arm G or F and may be used in exploratory analyses. For the primary analysis on group comparison between Arm F and Arm G, only the concurrent randomized participants from Arm G and Arm F will be included. Exploratory analyses may be conducted by including all Arm G participants for the group comparison to support the use of pembrolizumab as part of the combination regimen. Detailed plans of the exploratory analyses will be summarized in the sSAP.

10.6 Statistical Methods

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

10.6.1 Statistical Methods for Efficacy Analysis

Objective response rate will be summarized by arm along with a 95% confidence interval. Confidence interval would be calculated using the Clopper–Pearson method. The Miettinen and Nurminen method [Miettinen, O. 1985] will be used for comparison of the ORR between Arm F and Arm G.

Duration of Response will be summarized either using descriptive summary statistics or Kaplan-Meier estimates, depending on the number of responders.

Time to response and best overall response will also be summarized.

CCI [redacted]

10.6.2 Statistical Methods for Safety Analysis

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

Adverse events will be summarized by counts and frequencies for each arm. Laboratory tests, vital signs, and other safety endpoints will be summarized as appropriate.

Dose-limiting toxicities will be listed and summarized for each arm.

10.6.3 Summaries of Baseline Characteristics, Demographics and Other Analyses

10.6.3.1 Demographic and Baseline Characteristics

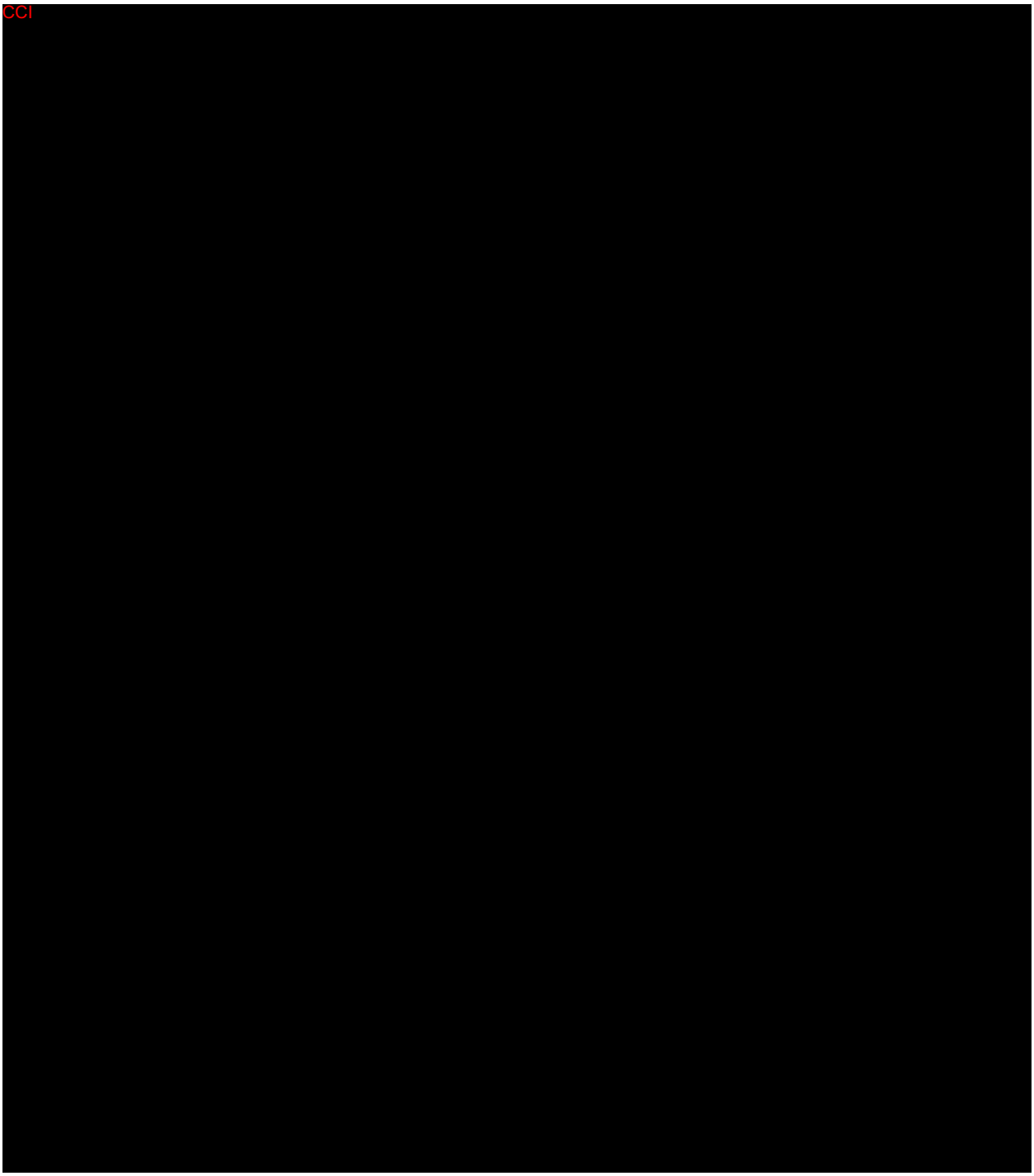
Demographic variables, baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized.

10.6.3.2 Pharmacokinetic and Pharmacodynamic Modeling Analysis

Pharmacokinetic and pharmacodynamic parameters of MK-1308 monotherapy and MK-1308, administered in combination and in coformulation with pembrolizumab, will be summarized by planned visit and time for each dose cohort/arm.

CCI [redacted]

CCI



CCI

[redacted]

10.9 Sample Size and Power Calculations

The overall sample size in Cohorts 1 through 3, Arm A, B, C, D and E in this study depends on the observed safety profiles of MK-1308 in combination with pembrolizumab. The maximum sample size is 100 in Arm F and 40 in Arm G. For MK-1308A, the coformulated product, the target sample size is 20 in Arm I, and 20 in Arm K. A target total sample size of 348 participants will be used for study planning purposes. CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

10.10 Subgroup Analyses

Subgroup analysis of ORR in PD-1/L1-refractory melanoma participants in the efficacy expansion phase will be conducted within each category of the following variables:

CCI

[redacted]

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.

11. References

[Antonia, S. J., et al 2016]	Antonia SJ, Lopez-Martin JA, Bendell J, Ott PA, Taylor M, Eder JP, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (checkmate 032): a multicentre, open-label, phase 1/2 trial. Lancet Oncol. 2016 Jul;17(7):883-95.	[04MGJJ]
[Carbonnel, F., et al 2017]	Carbonnel F, Soularue E, Coutzac C, Chaput N, Mateus C, Lepage P, et al. Inflammatory bowel disease and cancer response due to anti-CTLA-4: is it in the flora? Semin Immunopathol. 2017 Apr;39(3):327-331.	[04QZ9M]
[Chemnitz, J. M., et al 2004]	Chemnitz JM, Parry RV, Nichols KE, June CH, Riley JL. SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T cell stimulation, but only receptor ligation prevents T cell activation. J Immunol 2004;173:945-54.	[00VMPN]
[ClinicalTrials.gov 2017]	ClinicalTrials.gov. A trial of nivolumab, or nivolumab plus ipilimumab, or nivolumab plus platinumdoublet chemotherapy, compared to platinum doublet chemotherapy in patients with stage IV Non Small Cell Lung Cancer (NSCLC) (CheckMate 227) [Internet]. Washington: U.S. Department of Health & Human Services; 2017. Available from: https://clinicaltrials.gov/ct2/show/NCT02477826.	[04NBYZ]
[Dubin, K., et al 2016]	Dubin K, Callahan MK, Ren B, Khanin R, Viale A, Ling L, et al. Intestinal microbiome analyses identify melanoma patients at risk for checkpoint-blockade-induced colitis. Nat Commun. 2016 Feb 2;7:10391.	[04QZ9Y]

[Dudley, M. E., et al 2005]	Dudley ME, Wunderlich JR, Yang JC, Sherry RM, Topalian SL, Restifo NP, et al. Adoptive cell transfer therapy following non-myeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma. J Clin Oncol 2005;23(10):2346-57.	[00VMPR]
[Feng, Y., et al 2014]	Feng Y, Masson E, Dai D, Parker SM, Berman D, Roy A. Model-based clinical pharmacology profiling of ipilimumab in patients with advanced melanoma. Br J Clin Pharmacol. 2014 Jul;78(1):106-17.	[04KGQ7]
[Greenwald, R. J., et al 2005]	Greenwald RJ, Freeman GJ, Sharpe AH. The B7 family revisited. Annu Rev Immunol 2005;23:515-48.	[00VMQL]
[Hellmann, M. D., et al 2016]	Hellmann MD, Rizvi NA, Goldman JW, Gettinger SN, Borghaei H, Brahmer JR, et al. Nivolumab plus ipilimumab as first-line treatment for advanced non-small-cell lung cancer (CheckMate 012): results of an open-label, phase 1, multicohort study. Lancet Oncol. 2016 Dec 2. [Epub ahead of print].	[04KYCW]
[Hiraoka, N. 2010]	Hiraoka N. Tumor-infiltrating lymphocytes and hepatocellular carcinoma: molecular biology. Int J Clin Oncol 2010;15(6):544-51.	[00VMPT]
[Hunder, N. N., et al 2008]	Hunder NN, Wallen H, Cao J, Hendricks DW, Reilly JZ, Rodmyre R, et al. Treatment of metastatic melanoma with autologous CD4+ T cells against NY-ESO-1. N Engl J Med 2008;358(25):2698-703.	[00VMPX]
[Lala, M., et al 2020]	Lala M, Li TR, de Alwis DP, Sinha V, Mayawala K, Yamamoto N, et al. A six-weekly dosing schedule for pembrolizumab in patients with cancer based on evaluation using modelling and simulation. Eur J Cancer. 2020;131:68-75.	[05GNZM]
[Larkin, J., et al 2015]	Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med. 2015 Jul 2;373(1):23-34.	[049ZWX]

[Long, G. V., et al 2016]	Long GV, Atkinson V, Cebon JS, Jameson MB, Fitzharris BM, McNeil CM, et al. Pembrolizumab (pembro) plus ipilimumab (ipi) for advanced melanoma: Results of the KEYNOTE- 029 expansion cohort [abstract]. Abstracts of 2016 ASCO Annual Meeting; 2016 June 3-7; Chicago, Illinois: ASCO; 2016. p. 2.	[04NBYY]
[Long, G. V., et al 2017]	Long GV, Atkinson V, Cebon JS, Jameson MB, Fitzharris BM, McNeil CM, et al. Standard-dose pembrolizumab in combination with reduced-dose ipilimumab for patients with advanced melanoma (KEYNOTE-029): an open-label, phase 1b trial. Lancet Oncol. 2017 Sep;18:1202-10.	[04ZN95]
[Lynch, S. V. 2016]	Lynch SV, Pedersen O. The Human Intestinal Microbiome in Health and Disease. N Engl J Med. 2016 Dec 15;375(24):2369-2379.	[04PZSF]
[Miettinen, O. 1985]	Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med. 1985 Apr-Jun;4(2):213-26.	[04J96G]
[Nobili, C., et al 2008]	Nobili C, Degrate L, Caprotti R, Franciosi C, Leone BE, Trezzi R, et al. Prolonged survival of a patient affected by pancreatic adenocarcinoma with massive lymphocyte and dendritic cell infiltration after interleukin-2 immunotherapy. Report of a case. Tumori 2008;94(3):426-30.	[00VMP9]
[Okazaki, T., et al 2001]	Okazaki T, Maeda A, Nishimura H, Kurosaki T, Honjo T. PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine. Proc Natl Acad Sci U S A 2001;98(24):13866-71.	[00VMQ6]
[Olsonm, D., et al 2018]	Olson D, Luke JJ, Hallmeyer S, Bajaj M, Carll T, Krausz T, et al. Phase II trial of pembrolizumab (pembro) plus 1 mg/kg ipilimumab (ipi) immediately following progression on anti-PD-1 Ab in melanoma (mel). Presented at: 2018 American Society of Clinical Oncology (ASCO) Annual Meeting; 2018 Jun 1-5; Chicago, IL. J Clin Oncol. 2018;36(15 suppl). Abstract no. 9514.	[04ZM7X]

[Pölcher, M., et al 2010]	Pölcher M, Braun M, Friedrichs N, Rudlowski C, Bercht E, Fimmers R, et al. Foxp3(+) cell infiltration and granzyme B(+)/Foxp3(+) cell ratio are associated with outcome in neoadjuvant chemotherapy-treated ovarian carcinoma. Cancer Immunol Immunother 2010;59(6):909-19.	[00VMQ8]
[Postow, M. A., et al 2015]	Postow MA, Chesney J, Pavlick AC, Robert C, Grossmann K, McDermott D, et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. N Engl J Med. 2015 May 21;372(21):2006-17.	[049PTM]
[Riley, J. L. 2009]	Riley JL. PD-1 signaling in primary T cells. Immunol Rev 2009;229:114-25.	[00VMQ9]
[Ropponen, K. M., et al 1997]	Ropponen KM, Eskelinen MJ, Lipponen PK, Alhava E, Kosma V-M. Prognostic value of tumour-infiltrating lymphocytes (TILs) in colorectal cancer. J Pathol 1997;182(3):318-24.	[00VMQT]
[Saber, H., et al 2016]	Saber H, Gudi R, Manning M, Wearne E, Leighton JK. An FDA oncology analysis of immune activating products and first-in-human dose selection. Regul Toxicol Pharmacol. 2016 Nov;81:448-456.	[04LBFS]
[Seymour, L., et al 2017]	Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekar S, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol. 2017 Mar;18(3):e143-52.	[04P9RV]
[Sheppard, K-A, et al 2004]	Sheppard K-A, Fitz LJ, Lee JM, Benander C, George JA, Wooters J, et al. PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3zeta signalosome and downstream signaling to PKCtheta. FEBS Lett. 2004;574:37-41.	[00VMQC]
[Talmadge, J. E., et al 2007]	Talmadge JE, Donkor M, Scholar E. Inflammatory cell infiltration of tumors: Jekyll or Hyde. Cancer Metastasis Rev 2007;26(3-4):373-400.	[00VMPH]

[U.S. Prescribing Information 2017]	U.S. Prescribing Information: OPDIVO (nivolumab) injection, for intravenous use: 2017.	[04NZJ8]
[Usubütün, A., et al 1998]	Usubütün A, Ayhan A, Uygur MC, Özen H, Toklu C, Ruacan S. Prognostic factors in renal cell carcinoma. J Exp Clin Cancer Res 1998;17(1):77-81.	[00VMPJ]
[Vetizou, M., et al 2015]	Vetizou M, Pitt JM, Daillere R, Lepage P, Waldschmitt N, Flament C, et al. Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota. Science. 2015 Nov 27;350(6264):1079-84.	[04QZ9F]
[Wolchok, J. D., et al 2017]	Wolchok JD, Chiarion-Sileni V, Gonzalez R, Rutkowski P, Grob JJ, Cowey CL, et al. Overall survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med. 2017 Oct 5;377(14):1345-56.	[050PQN]
[World Health Organization 2005]	World Health Organization. WHO expert committee on specifications for pharmaceutical preparations: thirty-ninth report. Geneva (Switzerland): World Health Organization (WHO); 2005. Annex 5: guidelines for registration of fixed-dose combination medicinal products; p. 94-142. (WHO technical report series: 929).	[05KCK6]
[Zhang, X., et al 2004]	Zhang X, Schwartz J-CD, Guo X, Bhatia S, Cao E, Chen L, et al. Structural and functional analysis of the costimulatory receptor programmed death-1. Immunity 2004;20:337-47.	[00VMQJ]

12. Appendices

12.1 Appendix 1: Abbreviations and Trademarks

Abbreviation/Term	Definition
1L	First-line
2L	Second-line
ACTH	Adrenocorticotropic hormone
ADA	Anti-drug antibody
AE	Adverse event
ALC	Absolute leukocyte counts
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
APaT	All-participants-as-treated
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
AUC	Area under the curve
BCG	Bacille Calmette Guerin
hCG	human chorionic gonadotropin
BICR	Blinded Independent Central Review
BRAF	proto-oncogene B-raf
BUN	Blood urea nitrogen
CBD	Cannabidiol
CD3ζ	CD3 zeta
CFR	Code of Federal Regulations
CHO	Chinese hamster ovary
CIV	Central Imaging Vendor
C_{max}	Maximum concentration
$C_{max,ss}$	Maximum concentration at steady-state
C_{min}	Minimum concentration
$C_{min,ss}$	Minimum concentration at steady-state
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic obstructive pulmonary disease
CR	Complete response
CrCl	Creatinine clearance
CRF	Case report form
CRP	C-reactive protein
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CTLA4	Cytotoxic T-Lymphocyte-Associated Antigen-4
ctDNA	Circulating tumor deoxyribonucleic acid

Abbreviation/Term	Definition
DILI	Drug-induced liver injury
DLT	Dose-limiting toxicity
DOR	Duration of Response
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECI	Event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EGFR	Epidermal growth factor receptor
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOT	End of treatment
FAS	Full Analysis Set
FBR	Future biomedical research
FDA	Food and Drug Administration
FDAA	Food and Drug Administration Amendment Act
FDC	Fixed-dose combination
FIH	First-in-human
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony-Stimulating Factor
GFR	Glomerular filtration rate
GGT	Gamma glutamyl transferase
GI	Gastrointestinal
GLP	Good Laboratory Practices
GM-CSF	Granulocyte Macrophage Colony-Stimulating Factor
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HNSCC	Head neck squamous cell carcinoma
HRT	Hormonal replacement therapy
IB	Investigator's Brochure
IC50	Mean inhibitory concentration
ICF	Informed consent form
ICH	International Council on Harmonisation
iCPD	iRECIST confirmed radiographic progression
IEC	Independent Ethics Committee
IFNγ	Interferon-gamma
Ig	Immunoglobulin
IgV	Immunoglobulin variable
IHC	Immunohistochemistry

Abbreviation/Term	Definition
IL	Interleukin
IND	Investigational New Drug application
INR	International normalized ratio
IO	Immune-oncology
irAE	Immune-related adverse event
IRB	Institutional Review Board
iRECIST	Modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
ITIM	Immunoreceptor tyrosine-based inhibition motif
IUD	Intrauterine device
IV	Intravenous
IVD	In vitro diagnostic
IVRS	Interactive voice response system
IWRS	Integrated web response system
KL-6	Sialylated carbohydrate antigen KL-6
LDH	Lactate dehydrogenase
mAb	Monoclonal antibody
MASCC	Multinational Association of Supportive Care in Cancer chemotherapy, antiemetic therapy should follow Multinational Association of Supportive Care in Cancer (MASCC)
MLR	Mixed lymphocyte reaction
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MSI	Microsatellite instability
NCI	National Cancer Institute
NOAEL	No-observed-adverse-effect-level
NSAID	Nonsteroidal anti-inflammatory drug
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PBPK	Physiologically-based PK
PD	Progressive disease
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PET	Positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PKCθ	Protein kinase C-theta
PP	Per-protocol
PR	Partial response

Abbreviation/Term	Definition
PT	Prothrombin time
Q1W	Every week / once per week
Q2W	Every 2 weeks
Q3W	Every 3 weeks
Q6W	Every 6 weeks
RBC	Red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RPTD	Recommended Phase 2 dose
SAE	Serious adverse event
SCLC	Small cell lung cancer
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
SIM	Site Imaging Manual
SNP	Single nucleotide polymorphism
SoA	Schedule of Assessments
SP-D	Surfactant Protein D
SpO_2	Peripheral capillary oxygen saturation
sSAP	Supplementary Statistical Analysis Plan
SUSAR	Suspected unexpected serious adverse reactions
T3	Free triiodothyronine
T4	Free thyroxine
TCR	T-cell receptor
Teff	Effector T-cell
TMDD	Target-mediated drug disposition
TPS	Tumor proportion score
Treg	Regulatory T-cell
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
US	United States
V	Volume of distribution
VOP	Verification of progression
WBC	White blood cell
WOCBP	Woman of childbearing potential
ZAP70	Zeta-chain-associated protein kinase

12.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 13 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 13 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Hemoglobin Hematocrit RBC Count RBC Indices: MCV* MCH* MCHC %Reticulocytes*	WBC count with Differential: Absolute or Percentage (%) [1,*] Neutrophils: Absolute Lymphocytes Monocytes Eosinophils Basophils	Platelet count	
Chemistry	Albumin*	Calcium	Lactate Dehydrogenase (LDH)	Total Protein*
	Alkaline phosphatase (ALP)	Chloride*	Magnesium	
	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	CRP*	Phosphorous*	Uric Acid*
	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Creatinine	Potassium	*Sialylated carbohydrate antigen KL-6 (KL-6) (Japan only)*
	Bicarbonate (CO_2)[2]	Gamma glutamyl transpeptidase (GGT)*	Sodium	*Surfactant Protein D (SP-D)(Japan only)*
	Blood Urea Nitrogen (BUN)[3]	Glucose [nonfasting]	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the upper limit of normal)	
Routine Urinalysis	• Specific gravity • pH • Bilirubin, blood, glucose, ketones, protein by dipstick • Microscopic examination (if blood or protein is abnormal)			

Laboratory Assessments	Parameters
Other Screening Tests	• Serum or urine human chorionic gonadotropin (hCG) pregnancy test (for women of childbearing potential)[4] • Follicle-stimulating hormone (FSH), if indicated • Hepatitis B surface antigen [HBsAg] and/or hepatitis B (HBV-DNA), hepatitis C antibody (HepCAb and/or HCV RNA)[5] • Prothrombin time/international normalized ratio and activated partial thromboplastin time (aPTT/PTT)[6] • Thyroid function testing (free T4, total T4/FT4, T3/FT3, TSH), ACTH and Cortisol[7]
Other Tests, if indicated	• Follicle-stimulating hormone (FSH), Luteinizing hormone (LH), Testosterone, Prolactin, Thyroid peroxidase antibody (TPO), Thyroglobulin antibody (TGAb), Reverse T3 • ACTH (Cosyntropin) Stimulation Test

* Performed only if considered local standard of care.

1. Either absolute or percentage results may be reported at the initial visit. The same type of test results and normal ranges **must** be maintained for the remainder of the study.
2. If bicarbonate/CO_2 is not done as part of standard of care in your region then these tests do not need to be performed.
3. Blood urea nitrogen is preferred; if not available urea may be tested.
4. Women of childbearing potential only. Urine pregnancy test is preferred. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test is required.
5. Methodology of testing is at the discretion of the investigator. If the HBsAg and/or HepCAb is positive, this should be confirmed with specific RNA assays.
6. Coagulation factors (PT/INR and aPTT) should be tested as part of the screening procedures for all participants. If aPTT is not available PTT is acceptable Any participant receiving anticoagulant therapy should have coagulation factors monitored closely throughout the trial.
7. Total T3 is preferred; if not available free T3 or FT3 may be tested.

Investigators must document their review of each laboratory safety report.

12.3 Appendix 3: Study Governance Considerations

Code of Conduct for Clinical Trials

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD)

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (including all applicable data protection laws and regulations), and International Council for Harmonisation Good Clinical Practice (ICH-GCP), and also in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. All trial protocols are and will be assessed for the need and capability to enroll underrepresented groups. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD's clinical trials are conducted globally in many different countries and in diverse populations, including people of varying age, race, ethnicity, gender, and accounting for other potential disease related factors. MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel (or individuals acting on behalf of MSD) to assess the ability to successfully conduct the trial.

Where appropriate, and in accordance with regulatory authority guidance, MSD will make concerted efforts to raise awareness of clinical trial opportunities in various communities. MSD will seek to engage underrepresented groups and those disproportionately impacted by the disease under study. MSD will support clinical trial investigators to enroll underrepresented groups and expand access to those who will ultimately use the products under investigation.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if potential fraud, scientific/research misconduct, privacy incidents/breaches or Clinical Trial-related Significant Quality Issues are reported, such matters are investigated. When necessary, appropriate corrective and/or preventative actions are defined and regulatory authorities and/or ethics review committees are notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish the primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the pre-specified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing; in such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

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

All protocols and protocol amendments will be submitted by MSD for regulatory authority acceptance/authorization prior to implementation of the trial or amendment, in compliance with local and/or national regulations.

The protocol, protocol amendment(s), informed consent form, investigator's brochure, and other relevant trial documents must be reviewed and approved by an IRB/IEC before being implemented at each site, in compliance with local and/or national regulations. Changes to the protocol that are required urgently to eliminate an immediate hazard and to protect participant safety may be enacted in anticipation of ethics committee approval. MSD will inform regulatory authorities of such new measures to protect participant safety, in compliance with local and/or national regulations.

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible, as well as all applicable data protection rights. Unless required by law, only the investigator, Sponsor (or individuals acting on behalf of MSD), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

Financial Disclosure

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

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

Data Protection

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

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

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

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 participant to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. MSD, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow participants to identify potentially appropriate 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 (e.g., International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

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

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

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

e. Is a congenital anomaly/birth defect

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

f. Other important medical events:

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

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

Additional Events reported in the same manner as SAE

Additional Events which require reporting in the same manner as SAE

- In addition to the above criteria, 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 4.03. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.
  ● Grade 1: Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.
  ● Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
  ● Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.
  ● Grade 4: Life threatening consequences; urgent intervention indicated.
  ● Grade 5: Death related to AE.

Assessment of Causality

- Did the 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 experience 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 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 email 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

Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below):

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

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

For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

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 FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or 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

Contraceptives allowed during the study include[a]:

Highly Effective Contraceptive Methods That Have Low User Dependency[b] *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only subdermal contraceptive implant[c,d] • IUS[c,e] • Non-hormonal IUD • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) This 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. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Contraceptive Methods That Are User Dependent[b] *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen- containing) hormonal contraception[c,d] - Oral - Intravaginal - Transdermal - Injectable
• Progestogen-only hormonal contraception[c,d] - Oral - Injectable
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 intervention. 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.
[a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. [b] Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly). [c] Male condoms must be used in addition to female participant hormonal contraception. [d] If locally required, in accordance with CTFG guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation. [e] IUS is a progestin releasing IUD. Note: The following are not acceptable methods of contraception: - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM. - Male condom with cap, diaphragm, or sponge with spermicide. - Male and female condom should not be used together (due to risk of failure with friction).

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 Sample Collection 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 Future Biomedical Research.

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 (e.g., 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 a future biomedical research protocol and consent. 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@msd.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 (e.g., 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 (ie, 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@msd.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: Country-specific Requirements

12.7.1 France Requirements

Patients should be permanently discontinued from study treatment if any of the following AEs occur:

- Guillain-Barre Syndrome
- Encephalitis
- Steven-Johnson Syndrome
- Toxic-epidermal necrolysis
- Recurrent Grade 3 Diarrhea / Colitis

France-specific additions to Table 5: Dose Modification and Treatment Discontinuation Guidelines for Immune-Related Adverse Events Associated With Pembrolizumab, MK-1308, and MK-1308A (Section 7.2.1).

General instructions:

a. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
b. Pembrolizumab, MK-1308A, and MK-1308 must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last pembrolizumab treatment.
c. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
d. If pembrolizumab, MK-1308, and MK-1308A have been withheld, the study treatment may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

Immune-related AEs	Toxicity grade or conditions (CTCAE v5)	Action with pembrolizumab, MK-1308, and MK-1308A	irAE management with corticosteroid and/or other therapies	Monitoring and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper. • Add prophylactic antibiotics for opportunistic infections	• 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.
	Recurrent Grade 2, 3 or 4	Permanently discontinue		

Immune-related AEs	Toxicity grade or conditions (CTCAE v5)	Action with pembrolizumab, MK-1308, and MK-1308A	irAE management with corticosteroid and/or other therapies	Monitoring and follow-up
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.
	Recurrent Grade 3 or Grade 4	Permanently discontinue		
AST / ALT elevation or Increased Bilirubin	Grade 2 [a]	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 [b] or 4 [c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper.	

Immune-related AEs	Toxicity grade or conditions (CTCAE v5)	Action with pembrolizumab, MK-1308, and MK-1308A	irAE management with corticosteroid and/or other therapies	Monitoring and follow-up
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [d]	• 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 [d]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thioamides as appropriate.	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hypothyroidism	Grades 2, 3, 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care.	• Monitor for signs and symptoms of thyroid disorders.
Nephritis: grading according to increase creatine or acute kidney injury	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		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE, administer corticosteroids.	• Ensure adequate evaluation to confirm etiology or exclude other causes.
	Grade 3 or 4	Permanently discontinue		
	Persistent Grade 2	Withhold		
All Other immune-related AEs	Grade 3	Withhold or discontinue based on the type of event. [e]	• Based on severity of AE, administer corticosteroids.	• Ensure adequate evaluation to confirm etiology or exclude other causes.
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

Immune-related AEs	Toxicity grade or conditions (CTCAE v5)	Action with pembrolizumab, MK-1308, and MK-1308A	irAE management with corticosteroid and/or other therapies	Monitoring and follow-up

[a] AST/ALT: >3.0 - 5.0 x ULN if baseline normal; >3.0 - 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 - 3.0 x ULN if baseline normal; >1.5 - 3.0 x baseline if baseline abnormal

[b] AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 - 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 - 10.0 x ULN if baseline normal; >3.0 - 10.0 x baseline if baseline abnormal

[c] AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal

[d] The decision to withhold or permanently discontinue pembrolizumab, MK-1308, or MK-1308A is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab, MK-1308, or MK-1308A may be resumed.

[e] Events that require discontinuation include but are not limited to: Guillain-Barre Syndrome, encephalitis, Stevens-Johnson Syndrome, toxic-epidermal necrolysis, and recurrent Grade 3 diarrhea / colitis.

NOTE: For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab and/or MK-1308 is required, pembrolizumab and/or MK-1308 may be resumed when AE resolves to Grade ≤ 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

12.8 Appendix 8: 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 4 to 8 weeks later is obtained (using iRECIST for participant management; see Table 7 and Figure 5). 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].